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Contents

Protocols

Proposal

Original Papers

Corrigenda and Addenda

Protocol

A Randomized Controlled Trial Protocol to Evaluate the Effectiveness of an Integrated Care Management Approach to Improve Adherence Among HIV-Infected Patients in Routine Clinical Care: Rationale and Design

Heidi M Crane[1], MPH, MD; Rob J Fredericksen[1], PhD; Anna Church[1]; Anna Harrington[1]; Paul Ciechanowski[2], MD; Jennifer Magnani[1], MSW; Kari Nasby[1], MSW; Tyler Brown[1]; Shireesha Dhanireddy[1], MD; Robert D Harrington[1], MD; William B Lober[1], MD; Jane Simoni[1], PhD; Stevan A Safren[3], PhD; Todd C Edwards[4], PhD; Donald L Patrick[4], PhD; Michael S Saag[5], MD; Paul K Crane[1], MD; Mari M Kitahata[1], MD MPH

[1]Department of Medicine, University of Washington, Seattle, WA, United States

[2]Department of Psychiatry, University of Washington, Seattle, WA, United States

[3]Department of Psychology, Harvard University, Boston, MA, United States

[4]Department of Health Services, University of Washington, Seattle, WA, United States

[5]Department of Medicine, University of Alabama, Birmingham, Birmingham, AL, United States

Corresponding Author:
Heidi M Crane, MPH, MD
Department of Medicine
University of Washington
325 9th Ave, Box 359931
Seattle, WA, 98104
United States
Phone: 1 206 744 6649
Fax: 1 206 744 3693
Email: hcrane@uw.edu

Abstract

Background: Adherence to antiretroviral medications is a key determinant of clinical outcomes. Many adherence intervention trials investigated the effects of time-intensive or costly interventions that are not feasible in most clinical care settings.

Objective: We set out to evaluate a collaborative care approach as a feasible intervention applicable to patients in clinical care including those with mental illness and/or substance use issues.

Methods: We developed a randomized controlled trial (RCT) investigating an integrated, clinic-based care management approach to improve clinical outcomes that could be integrated into the clinical care setting. This is based on the routine integration and systematic follow-up of a clinical assessment of patient-reported outcomes targeting adherence, depression, and substance use, and adapts previously developed and tested care management approaches. The primary health coach or care management role is provided by clinic case managers allowing the intervention to be generalized to other human immunodeficiency virus (HIV) clinics that have case managers. We used a stepped-care approach to target interventions to those at greatest need who are most likely to benefit rather than to everyone to maintain feasibility in a busy clinical care setting.

Results: The National Institutes of Health funded this study and had no role in study design, data collection, or decisions regarding whether or not to submit manuscripts for publication. This trial is currently underway, enrollment was completed in 2015, and follow-up time still accruing. First results are expected to be ready for publication in early 2017.

Discussion: This paper describes the protocol for an ongoing clinical trial including the design and the rationale for key methodological decisions. There is a need to identify best practices for implementing evidence-based collaborative care models that are effective and feasible in clinical care. Adherence efficacy trials have not led to sufficient improvements, and there remains little guidance regarding how adherence interventions should be implemented into clinical care. By focusing on improving adherence within care settings using existing staff, routine assessment of key domains, such as depression, adherence, and substance use, and feasible interventions, we propose to evaluate this innovative way to improve clinical outcomes.

Trial Registration: Clinicaltrials.gov NCT01505660; http://clinicaltrials.gov/ct2/show/NCT01505660 (Archived by WebCite at http://www.webcitation/ 6ktOq6Xj7)

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KEYWORDS

adherence; randomized controlled trial; depression; substance use; alcohol use; intervention; HIV; care management

Introduction

Adherence to antiretroviral medications (ARVs) is a key determinant of outcomes including viral suppression and prevention of disease progression and death [1-9]. Unfortunately, poor adherence among persons living with human immunodeficiency virus (HIV/PLWH) is common with mean levels of adherence in clinical cohorts often 60% to 80% or less [3,10-13]. Substance use and mental illnesses such as depression are key predictors of poor adherence [3,10,14-36], common among PLWH [20,36-41] and may be crucial to identify and treat among those with poor adherence [42].

The importance of translating research on improving adherence into clinical practice has been noted [43]. Previous studies investigating a variety of adherence interventions have reported benefits, although often small [44-46]. Many focused on testing a single device, such as a pager or other electronic reminder system, or investigated the effects of time-intensive costly interventions that are not feasible in most clinical settings, and therefore failed to inform adherence in clinical care [44].

We sought to evaluate a collaborative care approach as a feasible intervention applicable to PLWH in care, including those with mental illness and substance use. Collaborative care approaches are multimodal interventions that typically involve a care manager who helps develop a shared definition of a problem, sets goals, develops specific action plans, offers problem solving and support, and facilitates appointments [47]. These interventions have shown value for people with depression and anxiety, heart failure, and chronically ill seniors [47-62]. While there is little experience with care management approaches among PLWH particularly as related to adherence, treatment of depression is an exception [63]. Many studies of care management models have been conducted as off-site studies separate from clinic settings, have incorporated extensive additional clinical research staff, or have included time-intensive interventions such as community outreach with home visits that may not be feasible to implement on a broad scale in clinical care [49-51,63].

We developed a randomized controlled trial (RCT) investigating an integrated clinic-based care management approach to improve outcomes. This approach is based on routine integration and systematic follow-up of a clinical assessment of patient-reported outcomes (PROs) targeting domains, including adherence, depression, and substance use, and adapts the previously tested care management approach used in the Program to Encourage Active, Rewarding Lives (PEARLS) study [50]. The health coach or care management role is provided by clinic case managers allowing the intervention to be generalizable to other HIV clinics with case managers. We hypothesize that our care management intervention will improve adherence compared with usual care. This paper describes the trial design and rationale for key methodological decisions.

Methods

Description of Trial and Intervention

Overview

We integrated a RCT into clinical care of PLWH. PLWH who reported inadequate adherence on the clinical assessment of PROs that is already being completed as part of routine clinical care visits were eligible for the RCT. Case managers in the clinic serve as the care managers for the intervention arm of the study. They are already part of the clinic and available to help PLWH when requested. However, in addition to these services, those in the intervention arm received a more structured and scheduled care management intervention, that included scheduled assessments and follow-up, a stepped-care approach, and, if needed, more intensive intervention such as problem solving therapy. A key difference between the intervention and usual care arms is that the case managers receive automatic email reminders of the need to follow-up with the patient at set intervals and conduct specific assessments facilitating a more systematic approach rather than ad hoc support.

Design

This prospective RCT is integrated into clinical care of PLWH at the University of Washington (UW) Harborview Madison HIV clinic (hereinafter “the UW HIV clinic”). Eligible patients are randomized to either a usual care arm or an intervention/enhanced support arm with a 1:1 ratio without blocking or stratification using a computer-based random number generator. Results of the randomization are applied to the database and tracking platform by a research coordinator who oversees the computer-based number generator and is not involved in enrollment and consent and has not met the participants. Patients are followed for 12 months as part of the trial.

Setting

The UW HIV clinic is the largest single provider of medical care to PLWH in the northwestern United States and provides care to approximately 2800 PLWH. The clinic provides primary care, on-site specialty care, financial and case management, and pharmacy services.

Clinical Assessment

We developed and implemented a clinical assessment platform for routine collection of PROs in clinical care, including instruments that measure medication adherence, drug and alcohol use, sexual risk behavior, and depression and anxiety

symptoms [64-68]. Examples of instruments collected as part of the clinical assessment include the 9-item Patient's Health Questionnaire (PHQ-9) measure of depression symptoms [69,70], medication adherence (several items with varying recall periods) [71,72], and substance use (Alcohol Use Disorders Identification Test Consumption Items and Alcohol, Smoking, and Substance Involvement Screening Test) [73-76]. We obtained input from outside clinical technology experts and conducted time-and-motion studies and qualitative semistructured interviews from key informants including patients, providers, and staff members to ensure implementation was not disruptive and inform the content of the assessment [65]. A primary goal was to ensure that the clinical assessment was completed on the day of and prior to provider visits to ensure that assessment feedback was available to providers at the time of the visit [77]. Patients at the UW HIV clinic complete the assessment every 4 to 6 months and assessment feedback is given to providers and case managers as a now established part of clinical care. This occurs for all patients regardless of whether or not they are in this trial.

Participants

Participants are 18 years of age or older, English-speaking PLWH with inadequate ARV adherence as measured by self-report using a single item on the clinical assessment given to all patient at Madison clinic asking about the number of missed doses during the prior 14 days. Eligible patients have access to either a home or cellphone and are in care at the UW HIV clinic for at least 6 months. Patients are ineligible if they are severely cognitively impaired or actively psychotic as these patients are not asked to complete the clinical assessment. To enhance generalizability and relevance to a broad spectrum of patients in routine care, patients are not excluded based on substance use or depression.

Intervention

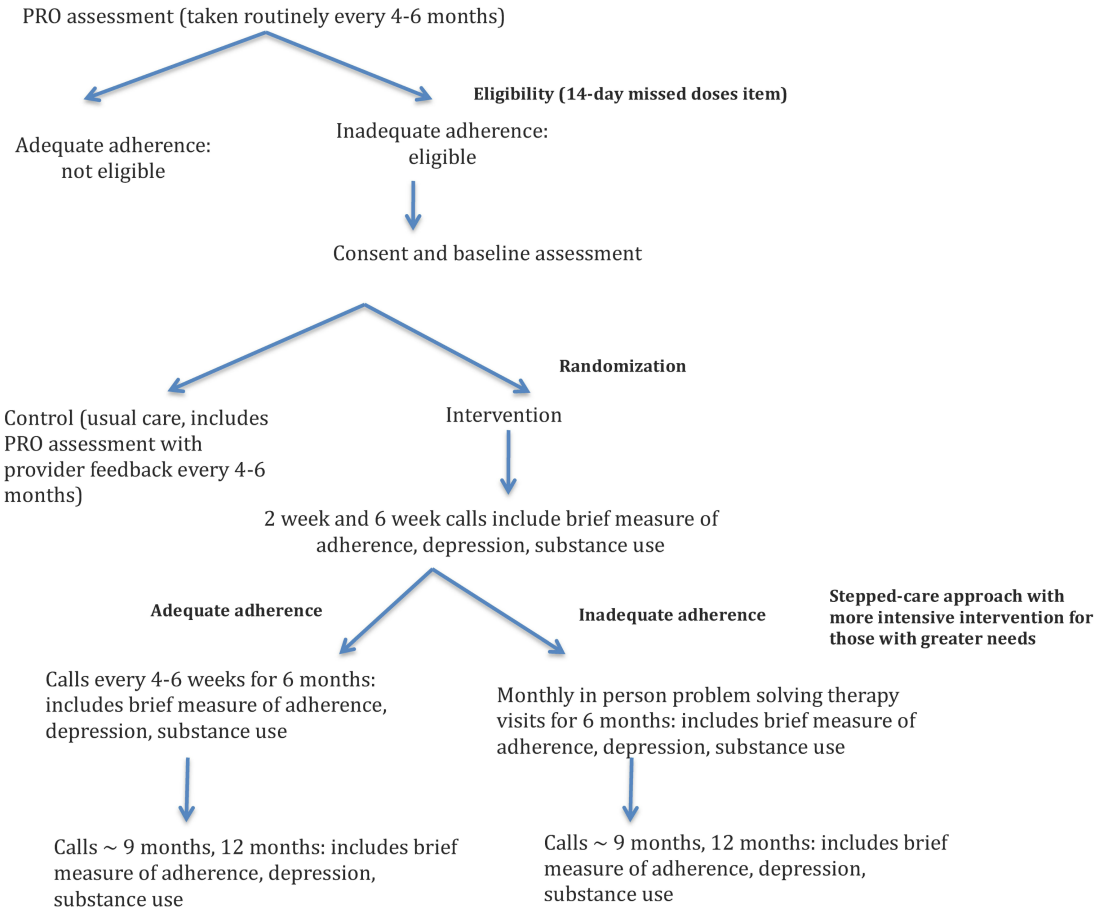
The intervention uses a care management approach that is incorporated into clinical care settings and has previously been shown to be useful in the care of patients with diabetes and epilepsy and more effective than providing PRO feedback alone [47,50,51,54]. Case managers are tasked with providing patient education and support, working with patients to develop a shared focus on specific problems with targeted goals and specific action plans. Our choice to incorporate case managers in this intervention allows them to focus on health domains case managers consider important, including adherence, depression, and substance use.

Case managers are available for patient or case manager-initiated interactions in both the usual care and intervention arms and each case manager has patients in both arms. In addition, the intervention arm uses automated email reminders for case managers to facilitate a more systematic approach targeting those who need it most. All patients in the intervention arm receive a structured 10 to 15 minute follow-up telephone call from their case manager 2 and 6 to 8 weeks after enrollment. A brief assessment including the depression, medication adherence, and substance use instruments from the clinical assessment that is given to all patients as part of clinical care visits is administered at the beginning of each call. Case managers then provide education and support based on responses, working with patients to develop targeted goals and plans. After a second call, a stepped-care approach is used for those patients identified as needing more intensive interventions (Figure 1).

Patients in the intervention arm who continue to report inadequate adherence after 6 weeks receive a more intensive intervention based on the PEARLS approach, which includes (1) problem solving therapy, (2) social and physical activation, (3) pleasant events scheduling, and (4) patient support and education regarding ARV use. We modified this approach to facilitate clinical care integration and to accommodate daily experiences of PLWH. For example, we modified the list of possible pleasant events and activities taking into account the limited incomes of many patients. Motivational interviewing techniques are used to facilitate substance use reduction.

Problem solving therapy (PST) involves up to 6, approximately 40-minute sessions with the case manager over 6 months, typically in-person at the clinic. PST is a skills-enhancing behavioral treatment based on the assumption that the accumulation of problems in living cause and promote inadequate adherence (and other maladaptive behaviors and symptoms). PST is a skill-building method consistent with modern self-management support strategies used in managing chronic medical illness [78]. PST helps to define and clarify problems and provides a structured, realistic, and achievable approach to solve problems and meet individual goals. Everyone in the intervention arm including those doing well with adherence early on also receive follow-up "check-in" calls by the care manager with a brief assessment at approximately 9 and 12 months after enrollment.

Figure 1. Participant flow including eligibility, enrollment, and follow-up. PRO: patient-reported outcomes.



Training

Case managers received a 2-day training session at the beginning of the trial focused on motivational interviewing techniques and PST led by an HIV specialist, psychiatrists, and psychologists with expertise in training for PST and motivational interviewing. An intervention manual based on IMPACT, PATHWAYS, and PEARL collaborative care trials formed the basis of training on collaborative care, stepped-care principles, and PST [50,55,57]. Training included didactics, role-playing exercises, group discussion of the role-play activities, and observation of a videotaped demonstration. We have also done 1 booster session to date and record a small subset of sessions looking for a means of improvement.

Platform

One goal was to use the PRO platform to promote practice system changes to improve outcomes by facilitating systematic monitoring and follow-up, proactive care management, and information sharing with the entire team. Based on this goal, we used the open-source PRO platform [79] already integrated into the clinic to collect the clinical assessment and used for similar work in oncology and other clinics [64,66,80-84]. The platform notifies team members by pager when a patient's clinical assessment results suggest trial eligibility. Once enrolled and assigned to the intervention, the platform sends automatic email notifications to individual care managers when their patients are due for a call or PST session, tracks attempted and completed calls, and sends automatic reminders if calls or PST sessions are not completed. Care managers can use the platform to conduct brief phone-based assessments with patients at the beginning of follow-up calls. The platform incorporates skip patterns and eliminates paper-based forms. Finally, the platform facilitates rapid integration of care manager documentation including assessment results that can be directly entered into the UW HIV clinic's electronic health records (EHR) to notify other health care team members as needed. The platform reduces research coordination time for the trial and promotes the feasibility of the intervention in clinical care and further provides an easy way to track intervention fidelity in terms of care manager completion rates.

Outcomes

The primary trial outcome is change in adherence as measured by the clinical assessment, however changes in depression symptom severity is also important. Standard PHQ-9 scores range from 0 to 27 and are categorized as: none (0-4 points), mild (5-9 points), moderate (10-14 points), moderately-severe (15-19), and severe (≥20 points) depressive symptom severity [70]. PHQ-9 standard scores have curvilinear measurement properties with respect to the latent trait of depression defined by all the items, meaning that a constant difference in score implies different amounts of depression symptom severity at different depression severity levels [85]. In this situation, using continuous standard total scores in regressions can lead to confusing and even biased findings [86]. We therefore will generate scores using item response theory (IRT) as done previously [85]. IRT-based depression severity scores have

linear scaling properties with respect to the latent trait of depression defined by all the items [87]. These outcomes are based on clinical assessments integrated into routine care for all clinic patients and measured every 4 to 6 months, and do not include study specific measures. While using data from clinical care requires greater flexibility in terms of outcome timeframe windows, it allows data collection for primary outcomes to be completely distinct and independent of whether a patient was in the intervention or the usual care control arm.

Important secondary outcomes include antidepressant medication use, HIV-1 viral load (VL), alcohol and substance use, health-related quality of life, and symptom burden. Medications including antidepressant medication are collected as part of the EHR. Even medications filled by other pharmacies are captured because all prescriptions from the clinic are written within the EHR and then sent via the EHR to the correct pharmacy allowing a very high capture of medications including initiating a new antidepressant medication or increasing a dose of an existing antidepressant medication. VL values are measured as part of routine clinical care, and therefore timing varies. Cut-offs of <40 are considered undetectable although we also tend to repeat VL analyses using a cut-off of <400 to exclude viral blips. Health-related quality of life, symptom burden, and current drug and alcohol use are captured through the clinical assessment.

In addition, we will examine process outcomes, including provider diagnoses (depression, substance use) and referrals and visits with mental health counselors, substance use counselors, and health educators. Diagnoses including drug and alcohol use are captured in the EHR as is information regarding scheduled, kept, and cancelled visits as well as visit types. These outcomes are collected as part of routine care.

Incentives

There is no incentive for completing the clinical assessment as this is part of clinical care for all patients. Despite this, refusal rates have been low to date; the current refusal rate is 1%. There are no financial incentives for participating in this trial as the trial philosophy is assessing the impact of systematic approaches to care management to improve clinical care. Bus passes are available for participants who meet with their care manager on a day when they otherwise would not be in clinic.

Statistical Analyses

Clinical data will be used to assess differences between patients enrolled in the trial and eligible patients not enrolled. Primary analyses comparing outcomes in the usual care versus intervention arms will be performed on an intent-to-treat basis focused on 1 year after enrollment. Secondary analyses will be done on an as-treated basis with censoring if patients do not complete follow-up. We have previously found missing rates of <4% for clinical assessment items [64] but will use multiple imputation approaches to address this if necessary. Descriptive analyses compare patients in the intervention and usual care arms on demographic and clinical variables, including depression status, adherence, substance abuse, use of mental health services, and use of antidepressant medications to assess whether groups are balanced at baseline. Depending on the distribution, we will likely use linear mixed-effects models [88,89] to assess differences in adherence levels taking into account within-subject correlations between adherence levels over time and the influence of potential confounding covariates. We will look for influential outliers in the regression model and we will explore nonlinear transformations of the outcome measure to see if the linearity assumption is violated. We will check an unstructured version of the working correlation matrix to ensure that our default working correlation, exchangeable, is properly specified. Selection of variables for inclusion in the models will be based on likely confounding factors based on the literature to date, coupled with inclusion of variables observed to be strong risk factors for the outcome and are therefore potential "precision variables" to improve statistical efficiency. Model fit will be assessed with R^2, we will report the ratio between the variance that is accounted for by the random effects and the residual variance, and we will determine whether the linear mixed-model's distributional assumptions are met [90]. We will examine effect modification of the pattern of change in adherence over time between groups by depression and substance abuse status. We will also examine baseline characteristics as potential moderators of intervention effects [91,92]. We will compare loss-to-follow-up rates in the 2 groups. If these rates exceed 5% or differ between groups, we will use baseline assessment data and clinical information data to assess for potential bias. Sensitivity analyses will be conducted to determine the impact of dropout [93,94] and spillover effects and to evaluate additional longer timeframes. We will examine the impact of the intervention on visit frequency with case managers in both the intervention and usual care arms looking for potential spillover effects of the intervention on the usual care arm. Our last sensitivity analysis will be an "as treated" analysis, using inverse probability of treatment weights. This will account for the possibility of differential switching between groups (ie, drop out) as a form of contamination and can assist in the interpretation of the primary endpoint. However, we intend to use the intention to treat analysis as the primary study endpoint, as we see the benefits of randomization for confounder control as exceeding the risks of validity posed by contamination. We thus follow recommendations of a Cochrane review: randomized design, follow patients for >5 months, analyze patients in the groups to which they were randomized, and control for baseline values or use differences between follow-up and baseline values as the main outcome [95].

Sample Size

We based sample size estimates on a two-tailed significance level (alpha) of .05 and power (1-beta) of .80 [96]. With 115 individuals in each arm (N=230), we would be able to detect even a 4% increase in adherence in the intervention arm. We expect a loss to follow-up rate between 8% and 10%, but conservatively account for a 15% loss to follow-up rate and increased our overall sample size target to 270. Power for this type of trial should be sufficient to identify small to moderate effects [97] (defined as effect sizes of 0.2-0.5 [98]). Even if we have a higher than expected loss to follow-up rate of 15%, we will have sufficient power to detect effect sizes of 0.35, well within the small-to-moderate effects continuum and in line with the magnitude of effects seen in other adherence intervention

studies [44,99,100]. We expect several of our outcomes will be more responsive to change than overall adherence particularly many of the binary process outcomes. We will have more than sufficient power to detect differences in those outcomes. While we plan to attempt to enroll 270 individuals, one of the outcomes of interest is the willingness of patients to participate in these types of interventions. Therefore, we are also specifically interested in whether it is feasible to enroll this many individuals from a clinical care setting in a reasonable amount of time.

Trial Registration, Ethics, Consent, and Institutional Review Board Approval

This trial is registered in clinicaltrials.gov (NCT01505660) and received approval from UW Human Subjects Division (UW #41128). Informed consent to participate in the study was obtained from each participant. They are not pressured to participate and participation or not does not impact their ability to receive care at the clinic.

Results

The National Institutes of Health funded this study and had no role in study design, data collection, or decisions regarding whether or not to submit manuscripts for publication. This trial is currently underway with follow-up time still accruing.

Discussion

Design

The key consideration in designing this trial was to adapt and test an evidence-based model of collaborative care [50] to enhance ARV adherence. We used existing clinical staff members in a manner that is streamlined and could be integrated into care. The intervention offers patients and health care delivery teams resources necessary to increase the use of evidence-based treatments to improve adherence, depression, and substance use. The case manager-based collaborative model is a system of care that can be integrated into clinical care settings to provide patient-centered care. The intervention was modeled on the PEARLS and PATHWAYS studies [50,51] based on the IMPACT study [57]. We made modifications to focus on adherence and care for PLWH and to ensure that the interventions were sufficiently streamlined to facilitate use in routine care.

Stepped-Care Approach

We are using a stepped-care approach allowing intervention intensity to be tailored to the patient's needs [101]. Earlier depression studies suggested incorporating additional interventions led to improvements and sustainability beyond that obtained by telephone care management alone [102-104]. Similarly, adherence studies have demonstrated a greater impact with added services targeting those with the highest needs [45]. This stepped-care approach allows us to target these interventions to those at greatest need and who are most likely to benefit rather than on everyone to maintain feasibility for incorporating into busy clinical care settings.

Telephone

While many care management protocols incorporate community outreach and home visits, these are not likely applicable to HIV care in the current funding environment. However, telephone-based care management approaches [53,54,104-107] have shown improvements in readmission rates and depression levels. Therefore, we included a brief telephone-based approach for the initial interactions (2 and 6 weeks), as well as later check-ins for those doing well, to enhance feasibility.

Intensity

We designed the intervention to be less intensive than previous care management trials [50,51,63] to enhance feasibility in clinical practice. Prior care management approaches often included home visits and frequent, hour-long sessions for everyone in the intervention group. We truncated these practices and are using phone-based check-in calls, and office- or phone-based visits for PST targeted to those with the greatest need. An advantage of using case managers to deliver the intervention is the ability to leverage existing patient-case manager relationships.

Adherence Measurement

Patients with inadequate medication adherence measured by the 14-day adherence item are eligible for inclusion. Although self-reported adherence has been critiqued for inaccuracies, these concerns have centered on over-reporting rather than under-reporting of adherence. Patients who report poor adherence are likely to truly have poor adherence. We chose the 14-day timeframe to include weekends, which are frequent times of missed doses and avoided longer time frames to limit recall errors and focus on current behavior.

Limitations

This intervention is being evaluated in English-speaking patients only. A Spanish language version of the clinical assessment is now offered at the UW HIV clinic, and an Amharic version has just been introduced. Another limitation is it includes only one clinic. Additional studies will be needed at other sites and in non-English speaking patients to determine if findings are generalizable. While we track the number of call attempts (successful and unsuccessful) and other contributions to staff time burden, our focus is not specifically on evaluating costs. The use of self-reported adherence as one of the primary outcomes may be considered a limitation. We have previously demonstrated high correlations between self-reported adherence and viral load, pharmacy refill data, and unannounced pill count data [108,109]. Furthermore, self-reported adherence data has been shown not to inflate effects of adherence interventions [44]. Self-reported adherence is one of several outcomes. We collect adherence in the clinical assessment from all patients as part of care as opposed to just in the intervention itself, reducing the likelihood of biased responses from those in the intervention group. The clinical assessment includes a normalizing statement, and we selected an intermediate timeframe to minimize concerns with recall bias. A prior meta-analysis has demonstrated that the ability to identify existing intervention effects are stronger when using adherence measures with longer recall periods (2 weeks or 1 month rather than 7 days or shorter) [44].

Another potential limitation is that providers and case managers can have patients in both usual care and intervention arms, and therefore may be subject to spillover effects, which could dilute the impact detected. Systematic changes such as automated email reminders of time to contact patients are not subject to spillover. Concern about spillover effects is one of the factors that led some investigators to evaluate nonintegrated approaches for delivering interventions. However, given the potential advantages of having a care manager with an established relationship with the patient, as well as designing an intervention that would be feasible within clinical care settings, we elected to conduct this intervention using existing clinic case management staff despite the potential for spillover effects. While this does not allow feasible blinding, the outcomes are assessed as part of routine care and not part of the trial.

Finally, the intervention is a comprehensive multifaceted approach, so we may be unable to isolate the critical factors necessary for success.

Strengths

A key strength is the adaption of an evidenced-based collaborative care intervention for use among PLWH with inadequate adherence. A collaborative care approach has long been recommended for improving adherence [110], as has a stepped-care approach targeting patients with particular difficulty to receive more intensive strategies [110]. We are attempting to maximize generalizability by conducting this study among a clinical care patient population. We identify patients from the clinical assessment given to the entire clinic population as part of routine care. This approach contrasts with the subset of patients who return mail-in surveys, which has often been the recruitment strategy for other care management studies. In particular, we do not exclude patients with substance abuse or depression. In fact, these two inter-related problems are key contributors to inadequate adherence in clinical care, and therefore this intervention addresses all three rather than focusing on inadequate adherence in isolation. Another strength is using care managers who are routinely part of HIV care settings as this makes it much more likely to be feasible for widespread use.

We integrated proactive telephone check-ins. There is considerable support for the efficacy of telephone-based interventions with a number of health problems in various patient populations [111]. Among PLWH, recent studies have focused on sexual risk reduction [112], interpersonal therapy for rural PLWH with depression [113], tobacco cessation [114], and adherence [115]. Potential advantages of telephone-based strategies include cost effectiveness and reducing barriers to care [116]. We optimized resource allocation by combining routine telephone check-ins with in-clinic, in-person PST for those who need a more intensive intervention.

Finally, using a Web-based PRO platform for data collection enhances fidelity, and allows automation of reminders to case managers and a more proactive systematized approach to routine follow-up.

Conclusion

Medication adherence is critically important for long-term outcomes among PLWH. There is a need to identify best practices for implementing evidence-based collaborative care models that are effective and feasible in clinical care. Adherence efficacy trials have not led to sufficient improvements, and there remains little guidance regarding how adherence interventions should be implemented into clinical care. By focusing on improving adherence within care settings using existing staff, routine assessment of key domains, such as depression, adherence, and substance use, and feasible interventions, we propose to evaluate this innovative way to improve clinical outcomes.

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Authors' Contributions

HC, RF, PC, JS, SS, PKC, and MMK made substantial contributions to the design of this trial. HC, RF, AC, AH, JM, KN, TB, SD, and RDH contributed to the acquisition of data from this trial. HC, RF, WBL, MSS all contributed to the development of the platform used for the clinical assessment in this study. HC, PKC, WBL, JS, SAS, MMK, MSS all contributed to the grant that resulted in funding for this trial. HC drafted the first draft of this manuscript with contributions from PKC, RF, and MMK. All authors have reviewed and revised the manuscript critically with important intellectual content. All authors have given final approval of this version of the manuscript to be published and agree to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

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Abbreviations

ARVs: antiretroviral medications
EHR: electronic health records
HIV: human immunodeficiency virus
IRT: item response theory
PEARLS: Program to Encourage Active, Rewarding Lives study
PHQ-9: Patient's Health Questionnaire
PLWH: persons living with HIV
PROs: patient-reported outcomes
PST: problem solving therapy
RCT: randomized controlled trial
UW: University of Washington
UW HIV: University of Washington Harborview Madison HIV
VL: viral load

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Protocol

Effects of Intranasal Oxytocin on Emotion Regulation in Insecure Adolescents: Study Protocol for a Double-Blind, Randomized Controlled Trial

Monika Szymanska[1], MSc; Carmela Chateau Smith[2], PhD; Julie Monnin[1,3], PhD; Patrice Andrieu[1], PhD; Frédérique Girard[4], PhD; Lucie Galdon[4], MD; Marie Schneider[4], MD; Lionel Pazart[5], MD, PhD; Sylvie Nezelof[1,4], MD, PhD; Lauriane Vulliez-Coady[1,4], MSc, MD, PhD

[1]Laboratory of Clinical and Integrative Neuroscience EA481, University of Franche-Comte, Besançon, France

[2]UFR SVTE, COMUE Bourgogne Franche-Comté, University of Burgundy, Dijon, France

[3]Clinical Investigation Center, CIC-IT 808, INSERM, University Regional Hospital, University of Franche-Comte, Besançon, France

[4]Department of Child and Adolescent Psychiatry, University Regional Hospital, Besançon, France

[5]Clinical Investigation Center, CIC-IT 1431, INSERM, University Regional Hospital, Besançon, France

Corresponding Author:
Monika Szymanska, MSc
Laboratory of Clinical and Integrative Neuroscience EA481
University of Franche-Comte
2 PL Leclerc
Besançon, 25000
France
Phone: 33 0787975526
Fax: 33 0787975526
Email: monika.szymanska@edu.univ-fcomte.fr

Abstract

Background: Emotional dysregulation and impaired attachment are potential contributors to the development of psychopathology in adolescence. This raises the question of whether oxytocin (OT), the paradigmatic “attachment hormone,” may be beneficial in such contexts. Recent evidence suggests that intranasal administration of OT increases affiliative behavior, including trust and empathy. OT may also facilitate social reciprocity by attenuating the stress response to interpersonal conflict. To date, few studies have investigated the effects of intranasal oxytocin (IN-OT) on neurophysiological emotion regulation strategies in healthy adolescents, particularly during parent-adolescent interaction. To understand these mechanisms, our study will examine the effects of IN-OT on emotion regulation in adolescents during parent-adolescent stressful interactions, and on each adolescent’s visual and neurophysiological strategies when visualizing attachment-related pictures. We hypothesize that IN-OT will influence psychophysiological outcomes under conditions of stress. We predict that IN-OT will momentarily increase feelings of safety and attenuate stress and hostile behavior during conflict situations. OT may also enhance attachment security by increasing comfort and proximity-seeking, and reducing neurophysiological hyperactivation.

Objective: The objective of this study is to evaluate the effects of IN-OT on insecure adolescents by studying their behavior and discourse during a disagreement with one of their parents. Their neurophysiological responses to pictures eliciting attachment-related emotions and their visual exploration strategies will also be investigated.

Methods: In this randomized, double-blind, placebo-controlled parallel-group design, 60 healthy male adolescents classified as insecurely attached will receive 24 international units (IU) of IN-OT versus placebo (PB), 45 minutes before the experimental tasks. Each adolescent will then be invited to engage in an experimental conflict discussion with one of his parents. The conflict session will be videotaped and coded for verbal and non-verbal interaction behavior, using the Goal-Corrected Partnership in Adolescence Coding System (GPACS). Each adolescent will then be asked to visualize attachment-related pictures on a screen. Eye-tracking (ET) and neurophysiological responses, including electrodermal activity (EDA) and heart rate (HR), will be recorded simultaneously and continuously during attachment-related picture viewing (Besançon Affective Picture Set-Adolescents, BAPS-Ado).

Results: Enrollment for the study was completed in May 2016. Data analysis commenced in July 2016. Study results will be submitted for publication in the winter of 2017.

Conclusions: OT is a complex molecule with many facets that are not yet fully understood. This experimental protocol will increase scientific and clinical knowledge of emotion regulation skills in insecure adolescents by assessing the impact of IN-OT on parent-adolescent interaction and on the visual processing of attachment-related emotions. Positive results could lead to therapeutic uses of IN-OT to treat emotion dysregulation in adolescence.

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KEYWORDS

intranasal oxytocin; attachment; adolescents; parent-adolescent interaction; randomized controlled trial

Introduction

Background

Adolescence is a period of psychobiological and social changes necessary to achieve psychological maturation and develop autonomy [1,2]. However, because of their history and temperament, some adolescents will have difficulty regulating their emotional reactivity, which could lead to emotional dysregulation and mental suffering when emotions are too intense or violent. This emotional dysregulation can be associated with psychopathology, such as depression [3], eating disorders [4], substance abuse [5], or antisocial and delinquent behavior [6]. In recent years, the impact of attachment bonds on adolescent emotional (dys)regulation has been seriously questioned.

Attachment has been defined as an innate psychobiological system that motivates people to seek proximity in times of distress [7-9]. The quality of this system is determined by early caregiving experiences and results in individual differences in attachment security. Harmonious attachment experiences can result in secure attachment, while disordered experiences can lead to insecure (ie, avoidant or anxious) or disorganized attachment [10]. Attachment patterns become part of the general interpersonal style that will influence strategies of closeness-distance regulation toward the attachment figure, as well as strategies of emotion regulation [11,12].

Despite the change in parent-child interaction during the process of adolescence, where more distance and more conflict linked with autonomy occur, parents remain a secure base for the adolescent in times of distress. It is expected that parents will continue to offer a protective base to help adolescents to regulate their emotions and to sustain a "goal-directed partnership" with them. This relationship context, in which adolescents might experience disagreement situations and develop a variety of emotional responses to deal with potentially elicited distress, is linked to the attachment style of the adolescent [13-16].

Social attachment interaction has health benefits, and its absence can be associated with both physical and mental illness, with broad consequences throughout the lifespan [17]. Researchers have shown that a securely attached adolescent reports less conflict with parents and fewer psychopathological symptoms [18-20]. During conflictual exchange, secure adolescents display collaborative communication, while also expressing anger and hostility. In this context, secure adolescents feel safe to communicate differences of opinions and vulnerabilities with trust and openness [14]. In contrast, insecurely attached, avoidant adolescents display deflecting and/or minimizing attachment strategies during interaction with their parents. They tend to manifest distracted and disengaged behavior and to elaborate on their disagreement, maintaining emotional distance, instead of reciprocity. Adolescents with ambivalent attachment may present entangled and/or oscillatory interactions. Here, the adolescent may manifest distressed or frustrated behavior when facing awkward reciprocity and parental inconstancy [21,22]. These two insecure attachment patterns could become risk factors for emotional dysregulation linked to a broad spectrum of psychopathology (eg, anxiety, depression, conduct disorders). Finally, disorganized parent-adolescent dyadic interaction is characterized by the inability to collaborate, marked by an unbalanced relationship, characterized by different profiles, such as role-confusion or hostile/passive patterns [23].

Recent findings suggest that a common neurobiological system appears to underlie attachment via release of various neuropeptides, the main one being oxytocin (OT) [24]. OT, synthesized in the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus, projects to the posterior pituitary [25], where it is released into the bloodstream causing a wide range of bodily effects [26-28]. Within the brain, OT can act as a neurotransmitter and/or neuromodulator in various limbic, midbrain, and hindbrain structures [29]. Its central neuromodulatory role in sexual behavior [30], lactation, and childbirth [31] is increasingly recognized. Due to its role in parent-child bonding [32], empathy [24,33,34], trust [35,36], and the promotion of social behavior [37], OT has earned a strong popular and scientific reputation as the "hormone of love" or "hormone of attachment" [38].

These discoveries have led researchers to investigate the effects of intranasal oxytocin (IN-OT) within the healthy [39-45] and clinical [46-49] population. However, it appears that IN-OT can be more beneficial for some individuals than for others, and that the effects of IN-OT seem to be moderated by contextual factors (eg, presence of stranger versus friend [50]), and individual factors (eg, differences in attachment [39,43,44,51-57]). Individual attachment differences have proved to be a strong modulator of OT action [49,55,56], and mediate stress-buffering effects in times of stress [58]. Interestingly, the effects of OT appear to be moderated by attachment anxiety level [40]. In highly preoccupied anxious individuals, OT appears to exacerbate interpersonal insecurity and to affect how the quality of maternal interaction is remembered. After IN-OT administration, highly preoccupied

individuals remembered their mothers as less caring and less close, while less anxiously attached individuals remembered their mothers as more caring and more close [40]. The level of attachment avoidance also seems to influence IN-OT effects. In highly avoidant individuals, IN-OT has been shown to increase constructive interaction [52]. For example, under the placebo (PB) condition, avoidant males trusted an unknown protagonist less, feared betrayal more, and decided less often to approach their protagonist cooperatively. However, these effects of attachment avoidance disappeared when males received IN-OT prior to decision-making. Participants high in attachment avoidance show more trust, lower betrayal aversion, and they cooperated more when given IN-OT rather than PB. Other findings [44] have shown that individual differences in attachment act as an endophenotype that moderates the effects of the OT system on social behaviors and cognition following social exclusion. OT appears to contribute to ongoing cooperation with a rejecting but initially cooperative partner, but only for those with low attachment avoidance [44]. Recent research [39] has shown that IN-OT increases communion skills in avoidantly attached individuals, who were especially likely to perceive themselves as more kind, warm, and gentle after receiving IN-OT than after receiving the PB. There was also a major effect of IN-OT on agency [59] in anxiously attached individuals, who showed a selective decrease in independent, self-confident behavior following IN-OT administration. This variability in IN-OT effects raises many questions and controversies regarding the effects of this hormone on social interaction, and especially on the influence of moderating factors. This lack of consensus together with many inconsistent results have led researchers [60-62] to openly question the true impact either of IN-OT in general or of its potential therapeutic effect [63]. Thus, to better understand the effects of OT and the impact of moderating factors on the mechanisms of socio-emotional interaction, we propose an original study protocol that provides new avenues of research into OT from both social and emotional perspectives.

Current Study

This study protocol seeks to examine the effects of IN-OT administration on emotion regulation strategies in insecure adolescents. A reliable protocol is crucially needed in the field of attachment and OT research, if we want to build a solid theoretical background for interpreting OT, before IN-OT can be proposed as adjuvant therapy in insecure adolescents with emotion dysregulation. We hypothesize that IN-OT will promote a “momentary” subjective experience of attachment safety and proximity-seeking in insecurely attached adolescents during dyadic stressful interaction. We suppose that both anxious and avoidant adolescents under treatment will communicate with their parents with more self-disclosure, and will manifest less negative (eg, controlled, hostile, odd) behavior than under the PB condition. We suppose that IN-OT will positively bias parent-adolescent interaction, especially for highly anxious individuals, because it should attenuate their chronic concerns about distress, separation, and abandonment. OT might support parent-adolescent interaction and emotion regulation for highly avoidantly insecure adolescents (often suspicious and defensive), who avoid expressing emotions in the family context. We hypothesize that, in general, insecurely attached adolescents under IN-OT will process attachment-related emotional information in a more accessible and open way compared to PB conditions. Compared to the PB, IN-OT will increase exploration of distress and comfort pictures (eg, first fixation duration; number and duration of fixations). During visualization of distress pictures, IN-OT will attenuate emotional arousal by decreasing neurophysiological reactivity (amplitude of specific skin conductance response, SCR), and should also decrease SCR and decelerate heart rate (HR).

The main objective is to evaluate the effect of IN-OT on the behavior and discourse of insecure adolescents during a disagreement (stressful situation) with one of their parents. This evaluation will be based on the average score on the scales (4 negative and 1 positive) of the Goal-Corrected Partnership in Adolescence Coding System (GPACS) (personal communication from K Lyons-Ruth, author of the GPACS). Secondary objectives will be to evaluate the effect of IN-OT versus PB on visual exploration strategies for images eliciting attachment-related emotions (ie, distress and comfort). This characterization will be based on the study of eye parameters (ie, total picture fixation time, and average number of fixations per emotion) assessed by a remote eye tracking (ET) device.

We are conducting a randomized, double-blind, placebo-controlled protocol in which insecure adolescent male participants received IN-OT or PB. The protocol was designed to investigate the effects of IN-OT on emotion regulation strategies, by testing whether attachment anxiety and avoidance moderate the effects of IN-OT during a conflict discussion with a parent, and during the visualization of attachment-related pictures.

Emotion (dys)regulation strategies will be evaluated through a multi-dimensional approach: ET and neurophysiological measurements including electrodermal activity (EDA) and HR. These neurophysiological measurements have recently received a great deal of attention as potential biological markers of individual differences in affective response [64,65]. HR reflects the continuous interplay between the sympathetic and the parasympathetic nervous systems and is regarded as a measure of autonomic flexibility and even as a biological marker of emotional response [65]. SCR, a form of EDA, is supposed to primarily reflect autonomic arousal, regardless of the state induced by the stimulus, whether negative or positive [64]. Changes in SCR represent activity within the sympathetic axis of the autonomic nervous system (ANS), measured by autonomic innervations of the skin sweat glands [66]. The neurobiological underpinnings of SCR are widespread and not exclusively related to the defense network. Likewise, HR is also under the control of the ANS [67]. Deceleration of HR is often shown in response to affective stimuli, and is more pronounced in reaction to negative stimuli [67]. HR deceleration seems to be more closely related to attentional processing regarding changes in affective states rather than to valence or arousal [68]. In summary, SCR and HR represent different neural systems, thus allowing us to assess more accurately the effects of OT in response to attachment-related emotions.

Methods

Type of Clinical Trial

We present a randomized, double-blind, placebo-controlled, parallel clinical trial protocol for IN-OT versus PB. We will argue in favor of a multi-method, multi-dimensional (individual and interpersonal strategies) approach to emotion-regulation assessment. We will use two types of attachment paradigms: a conflict discussion with the parent (attachment figure), and the visualization of standardized attachment-related emotional pictures (ie, distress, comfort, joy-complicity, and neutral stimuli) to assess behavioral, neuropsychological, and neurophysiological responses. Although some studies [69-72] have underlined the importance of investigating the effects of IN-OT on adult females, given the risk factors (eg, uterine contraction and menstrual cycle disturbance) for female adolescents in non-clinical environments, this experimental research will be conducted exclusively on healthy male adolescents.

Study Setting

This study will be conducted in Besançon, France at the University Regional Hospital, in the Department of Adolescent and Child Psychiatry.

Ethical Criteria

The study will be carried out in accordance with the principles of the Helsinki Declaration. This protocol is governed by French legislation concerning interventional biomedical research and was submitted to the local ethics committee (ie, Comité de Protection des Personnes-EST II) and approved in 2013 (number 2013-000029-29). The study was also approved by the French Agency for the Safety of Health Products (ie, Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM) in 2013. The trial is registered with the Clinical Trials Register (NCT02301715). An anonymous identification code will be attributed to each participant in the study, and the list identifying participating patients with their personal data will be stored by the investigator and kept strictly confidential.

Participants

For this study, 60 French-speaking male adolescents, aged 13 to 20 years, each accompanied by one parent, will be recruited from secondary schools in Besançon, France. Compensation will be given to each adolescent (a €20 gift voucher, Ticket Kadéos Universel, Edenred, France) and to the parent accompanying him (a €20 check).

Participant Recruitment

To assess eligibility, a pediatric psychiatrist will interview candidate participants using the Attachment Scale Interview (ASI) [73] to determine attachment style. Adolescents diagnosed as insecurely attached will be accepted in the study. Signed consent will be required from both parents and adolescents. The following inclusion and exclusion criteria will be used (Textbox 1).

Information and Consent

Information packs will be given to adolescents on the day of the first meeting. Information packs will contain two detailed study statements: one for parents, and one for the adolescent. The adolescent's consent form must be signed by both parents and by the adolescent. The participating parent must sign the parental consent form. The investigator will sign informed consent forms, with a copy for each participant, and the original stored by the investigator. Participants will be informed, in the participant's information leaflet, that the data generated by the study will be accessible only to the investigator, or to the relevant health authorities for official inspection.

Material

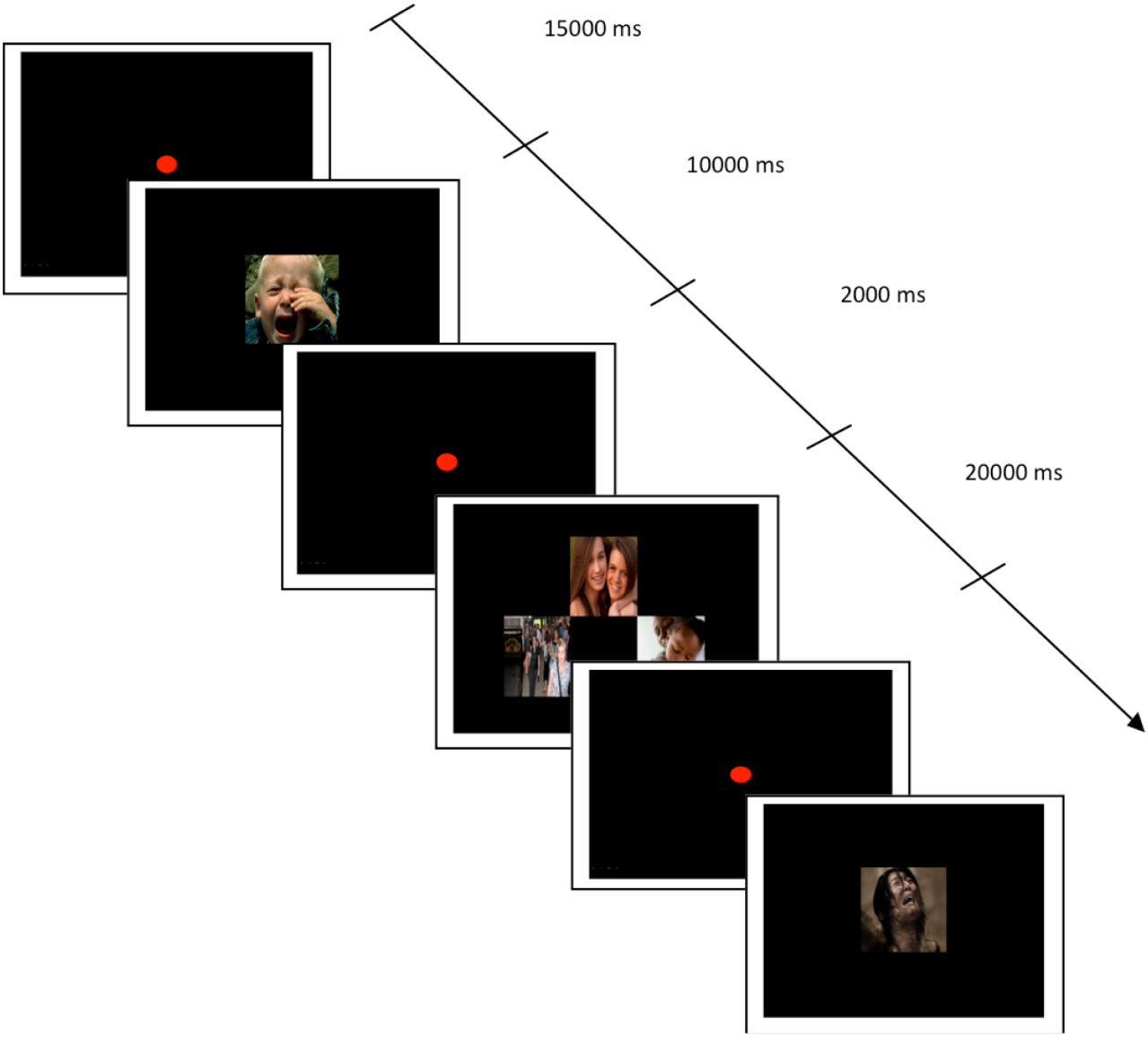
Oxytocin or Placebo Treatment

Syntocinon (NOVARTIS, Basel, Switzerland) is a synthetic, sterile, clear aqueous solution containing a cyclic nonapeptide, identical to endogenous OT released by the posterior lobe of the pituitary. The excipients are sodium acetate, glacial acetic acid, chlorbutanol, and ethanol. The PB will contain all the ingredients in the Syntocinon spray (saline solution) except for OT. Syntocinon and PB sprays, with identical ampoules and labels, will be prepared and randomly assigned by the research pharmacy at the University Regional Hospital Pharmacy of Besançon. Based on studies of IN-OT in adults [74], age-dependent dosage will be used, with age as a proxy for size and weight. Thus, younger participants (aged 13 to 15) will receive 16 international units (IU, 4 puffs of 4 IU), and older participants (aged 16 to 20) will receive 24 IU (6 puffs of 4 IU).

Textbox 1. Inclusion and exclusion criteria for participants.

- Inclusion
  - Results of Attachment Scale Interview (ASI): clinical diagnosis of insecure attachment
  - Male adolescent
  - Enrolled in high school or college
  - Not hospitalized
  - No current or past history of neurological or psychiatric illness, including substance abuse or dependence
  - Aged 13 to 20 years
  - Able to speak and understand French
  - Accompanied by a parent
  - Normal or adequately corrected vision
  - Affiliation to French social security
  - Not participating in any other ongoing trials
  - Informed signed consent of adolescent and both parents
- Exclusion
  - Results of ASI: clinical diagnosis of secure attachment
  - Female
  - Intellectual deficit
  - Severe neurological symptoms
  - Known allergies to OT or to preservatives in the nasal spray (in particular, E216, E218 and chlorobutanol hemihydrates)
  - Outside of age range
  - Not speaking French (either adolescent or parent)
  - Vision problems
  - Chronic disease (ie, liver failure, kidney failure, or cardiovascular disease)
  - Antihypertensive therapy
  - Smoking
  - Heavy alcohol use or drug use
  - Participation in another ongoing trial

Figure 1. Examples of stimulus displays of the four picture categories (distress, comfort, joy-complicity, and neutral).



Stimuli

The Besançon Affective Picture Set-Adolescents (BAPS-Ado) [75] will be used to elicit attachment-related emotions. The following categories of emotional stimuli will be used: (1) “distress” (n=20), (2) “comfort” (n=20), (3) “joy-complicity” (n=20), and (4) “neutral” pictures (n=20). The first category of pictures is scenes of distress (ie, faces expressing sadness or anguish, or scenes of loss and separation). The second category is comfort-related scenarios (ie, a parent comforting an infant or an adolescent after an episode of distress). The third is pictures of complicity (ie, joyful moments such as parent-child interaction, and partner or peer interaction). The fourth category is neutral scenes (ie, persons walking along a street or in the subway). Levels of color saturation (50%) and lightness (50%) will be adjusted with Adobe Photoshop (Adobe Photoshop Elements 6.0, Los Angeles, USA). The pictures measuring 11.80 cm in height and 11.50 cm in width will be equiluminant and subtended 10.98° (horizontal) x 11.26° (vertical) of visual angle at a viewing distance of approximately 60 cm. All pictures will be displayed on a black background. Pictures will be pseudo-randomized in blocks. Each block will contain 1 slide with a picture of distress, displayed for 10 seconds, with an inter-stimulus-interval of 2 seconds, followed by 1 slide containing 3 pictures (comfort, joy-complicity, and neutral) presented simultaneously and displayed for 20 seconds. Each block of pictures will be separated by an inter-stimulus interval of 10 seconds (Figure 1).

Eye-Tracking Apparatus

Eye-tracking (ET) data will be recorded using the Remote Eye-Tracking Device (RED), a non-invasive, contact-free, automatic ET and head movement compensation solution developed by SensoMotoric Instruments (SMI, Teltow, Germany). This system will capture data with temporal sampling at 250 Hz, spatial resolution of 0.03° and high accuracy of visual angle, 0.4°. The RED system will provide reliable binocular and pupil gaze data and allow subjects to wear glasses or contact lenses. The RED system, including Experiment Center 3.0 to control stimulus presentation, iView X 2.8 to control ET data

acquisition, and BeGaze to record data, will be interfaced with a Dell laptop. Pictures will be presented on a stand-alone 20 inch monitor (1680 by 1050 pixel screen resolution) placed approximately 60 cm in front of the participant.

Neurophysiological Measurement Apparatus

A BIOPAC 5 channel acquisition system (BIOPAC System Inc. Model MP 36, Goleta, CA) and a Dell Pentium computer will be used to collect neurophysiological data. AcqKnowledge 4.3 software (BIOPAC Systems, INC. Goleta, CA) will be used to obtain continuous recordings of the participant's neurophysiological responses (EDA and HR). Two electrodes (BIOPAC Systems Inc., Model EL 507), placed on the second phalanges of the index and middle fingers of the non-dominant hand [76] will be used to record EDA. The EDA data will be digitized at 1000 samples per second, with a gain of 1000. Low (35 Hz) and high (.05 Hz) pass filters will be applied.

Electrocardiograms (ECG) will be collected, together with cardiac impedance, using a two-electrode (2560, 3 M RED DOTTM) configuration with the bio-impedance module for ground referencing. The electrodes will be connected to a BIOPAC ECG module with the gain set to 1000. The waveform will be used to estimate HR using the AcqKnowledge "Hemodynamics" function. HR will be calculated from the R-R intervals in an ECG.

Attachment Style Assessment

Attachment will be assessed using a modified ASI, with questions adapted to be applicable to adolescents. This interview elicits the adolescent's current state of mind regarding the quality of relational experiences with parents and peers. The ASI determines the adolescent's ability to access and use social support with 3 confidants (ie, parents and peers). This tool assesses relationship quality, social support, and security of attachment style. Several dimensions (ie, mistrust, constraint of closeness, fear of rejection, self-reliance, desire for company, fear of separation, and anger) were coded to determine the attachment profile as either secure or insecure (ie, enmeshed, fearful, angry-dismissive or withdrawn).

Parent-Adolescent Interaction Assessment

The quality of the parent-adolescent interaction will be assessed with the French version of the GPACS. The development of the GPACS drew on prior literature describing behavioral manifestations of security, insecurity, controlling behavior, and behavioral disorganization among younger children toward their parents in stressful situations. It has already been used in several studies [77-79]. The GPACS coding system includes the rating of each interaction on 10 5-point scales from 1 (not at all) to 5 (very much). There are 2 positive scales (1) "Collaborative Communication" indexing cooperative goal-corrected partnership and parent/adolescent carefulness; and (2) "Caregiving Validation of Adolescent's Voice" indexing the caregiver's support for the adolescent. There are 8 negative scales characterizing 3 subtypes of disorganized interaction (ie, punitive, caregiving/role confusion, and disoriented behavior). These 8 scales are (1) parental punitive behavior (eg, angry, critical or mocking comments about the adolescent); (2) adolescent punitive behavior (eg, angry, critical or mocking comments about the parent); (3) adolescent disoriented-distractible behavior (eg, suddenly stopping in midsentence and "freezing" with hand in midair or pausing abruptly in mi-sentence); (4) parental disoriented behavior (eg, the same as adolescent disoriented behavior); (5) adolescent odd, out-of-context or contradictory behaviors, which may seem disjointed, startling, or inexplicable to an observer (eg, using a forced, high-pitched, or childish tone of voice, shifting into unusual, fantasy-based topics); (6) parent odd, out-of-context behavior (eg, using a forced, high-pitched, or childish tone of voice, wandering around the room, stiff, usually shifting away from the topic); (7) adolescent attempts to manage or take care of the parent or modulate the parent's behavior (eg, offering guidance, defusing tension with over-bright, entertaining behavior); and (8) parental role confusion (eg, asking for advice on topics typically discussed with partner or other adult).

Psychological Evaluation

To evaluate psychiatric traits in participants we will use an abbreviated version of the Beck Depression Inventory (BDI) [80], the Spielberger State-Trait Anxiety Inventory (STAI, Forms Y A and Y B) [81], and the Toronto Alexithymia Scale (TAS-20) [82].

The Beck Depression Inventory

BDI-II will be used as a depression-screening tool. The BDI-II is a self-assessment instrument with 21 items that assess the presence and severity of depressive symptoms. Each question is scored 0 (symptom absent), 1 (symptom present), 2 moderate symptom), or 3 (severe symptom). The total potential score is 63.

The Spielberger State-Trait Anxiety Inventory Forms Y A and Y B

This self-report assessment indicates the intensity of feelings of anxiety; it distinguishes between state anxiety (a temporary condition experienced in specific situations) and trait anxiety (a general tendency to perceive situations as threatening). Responses for the S-Anxiety scale will assess intensity of current feelings "at this moment" from 1 (not at all), 2 (somewhat), 3 (moderately so), to 4 (very much so). Responses for the T-Anxiety scale will assess frequency of feelings "in general" from 1 (almost never), 2 (sometimes), 3 (often), to 4 (almost always). The scale has been standardized in French.

The Toronto Alexithymia Scale

The TAS-20 [82] comprises 3 factors to assess difficulties in identifying and describing feelings, which are thought to reflect a deficit in cognitive processing and regulation of emotional states [83].

Eye-Tracking Measurements

The whole of each picture will be treated as a single area of interest (AOI). Prior to detailed statistical analyses, AOIs will be divided into 4 categories (distress, comfort, joy-complicity, and neutral) and each category will be analyzed separately. Fixations will be defined temporally and spatially, using a pre set minimum fixation duration of 80 milliseconds and a maximum dispersion value of 100 pixels. In order to explore different gaze patterns, various parameters (ie, fixation order,

first fixation duration, fixation duration, number of fixations, and entry time) will be analyzed in relation to attachment style.

The mean fixation order of an AOI category will be calculated by averaging the fixation order of each AOI in the same category of pictures. The mean first fixation duration (ms) in the AOI will be calculated by averaging first fixation duration for each AOI in the same category of pictures. The mean duration of a fixation (ms) in the AOI will be calculated by averaging the fixation duration for each AOI in the same category. The mean number of fixations will be calculated by averaging the number of fixations in each AOI category. The mean sum of fixation duration will be calculated by averaging the sums of duration of all fixations in an AOI category. The mean entry time for an AOI will be determined by averaging entry time for each AOI in the same category.

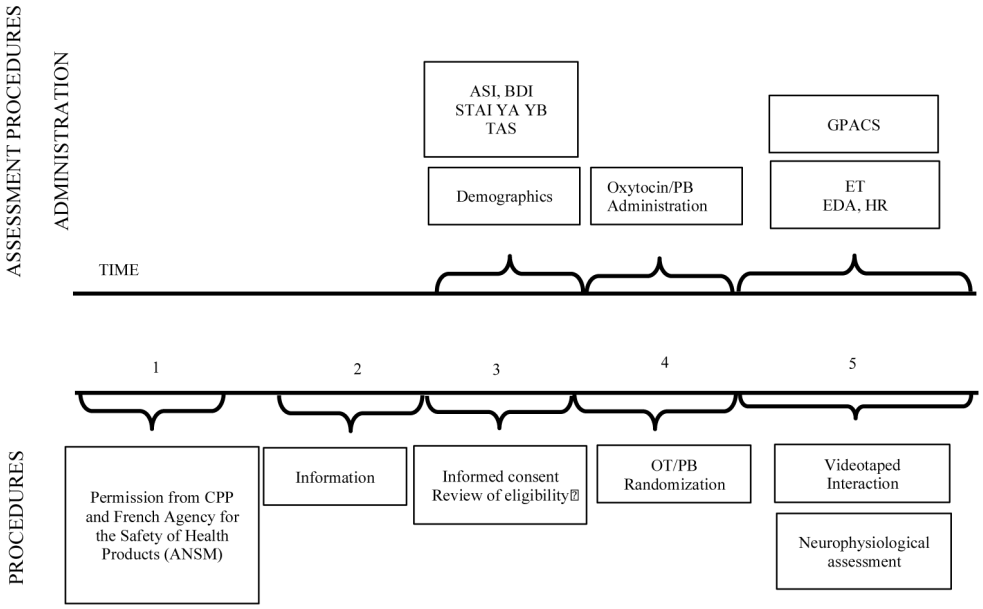
Neurophysiological Measurements

EDA will be measured by skin conductance level (SCL) and SCRs. The SCR will be defined as the maximum change in conductance (in µSiemens) in the 0.1 to 6 second window after stimulus onset. The change in neurophysiological response will be calculated by subtracting mean levels of neurophysiological response SCRs (ie, latency and amplitude) during the baseline from mean levels during each slide viewing, a practice commonly used in neurophysiological research [65,67]. HR will be calculated from the R-R intervals in the ECG.

Procedure

First, a psychologist will evaluate the participant's diagnostic eligibility. Attachment style will be determined using the ASI [74]. Participants who are classified as insecurely attached will return 1 week later for the OT trial (see Figure 2). Randomization will be centralized and performed after the inclusion of the eligible participants. Participants will be randomly assigned to receive either OT or PB intranasally, with both investigators and participants blind to condition. The randomization code will be kept secret by the pharmacy responsible for dispensing the corresponding medication. To reduce bias, randomization will be performed in blocks, with stratification for confounding factors (eg, age). Experiments will be conducted in a comfortable laboratory during the mid-afternoon hours, in accordance with previous research suggesting stability in the diurnal cycle of plasma OT [84]. Each adolescent will first be asked to choose a topic of disagreement to discuss during the parent-adolescent interaction. Then, 45 minutes before the interaction, the adolescent will be instructed to sit and self-administer 1 puff every 30 seconds, alternating nostrils. The adolescent will take each dose in front of the investigator, to assure correct administration and tolerability. The dosage and timing of the nasal spray administration were chosen based on published research on IN-OT, behavior, and emotions in humans [85], and results on cerebrospinal fluid levels after intranasal vasopressin administration [86]. Dyadic interaction will consist of a 5-minute free conversation and a 10-minute conflict discussion that will both be videotaped. The entire interaction session will be transcribed verbatim, and then coded offline for verbal interaction behavior with the GPACS by coders blind to the study hypotheses. After the dyadic stressful interaction, the adolescent will then be isolated in the ET room for 15 minutes, in order to adapt to experimental conditions. The adolescent will be seated in front of the screen in a comfortable viewing position. After this adaptation phase, the EDA electrodes will be fastened to the second phalanges of the index and middle fingers of the non-dominant hand and 2 ECG electrodes will be placed in a bipolar configuration on interior sides of the participant's wrists [87]. The RED will perform a 9-point calibration procedure. Once this calibration has been successfully accomplished, the 3 minute baseline responses will be recorded with the BIOPAC system. The participant will be informed that the test is due to start, and that he will freely observe a series of 80 pictures. The neurophysiological monitoring AcqKnowledge 4.3 software will be synchronized with Experiment Center 3.0 (RED SMI) software by event markers representing the beginning of each picture. The participant's eye movements and neurophysiological recordings (EDA and HR) will begin when the first red dot (approximately 0.95° of visual angle) appears. The task will last for about 15 minutes.

Figure 2. General study protocol.



Study Periods

Entry into the study (T0) is the first study period and will take place in agreement with the French Agency for the Safety of Health Products and the local ethics committee. The adolescents' parents agree to be included and sign the informed consent to enter into the clinical active phase of the study. The ASI results will be assessed, taking into account that an insecurity score on the ASI is a prerequisite for entry into the study. The intermediate study period (1 to 24 months, T1) will involve the inclusion criteria described in Textbox 1. In the third (end) study period (30 months, T2) the AOI parameters and neurophysiological data will be analyzed for the adolescent population. The GPACS analyses will be carried out for dyads included in the study. The results will be valorized.

Outcomes

Primary Outcome

The primary outcome is the evaluation of the changes in adolescent-parent interaction using GPACS in the OT versus PB conditions.

Secondary Outcome

The secondary outcome is the evaluation of the changes in oculomotor behavior and neurophysiological responses (ie, modification of EDA and HR [88]) in the OT versus PB conditions.

Safety Procedure

Side Effects

Findings show that IN-OT produces non-detectable subjective changes in recipients, and is not associated with adverse outcomes when delivered in doses of 18 to 40 IUs for short-term use in controlled research settings [89].

Withdrawal of Individual Participants

Participants may withdraw from the study at any time for any reason and without any sanction. Researchers, after consulting with the principal investigator and the study coordinator, may also interrupt the treatment program if, in their opinion, continuing this treatment is prejudicial to the patient's welfare. If a participant withdraws or is withdrawn from the study, follow-up at day 30 will be continued whenever possible.

Suspension of the Study

In cases where severe adverse events related to the administration of the treatment are suspected, the study will be interrupted and the researchers and coordinator will decide whether to continue.

Reporting of Adverse Events

Any adverse events reported spontaneously by the participant or observed by the researcher or the research team will be recorded on the case report form (CRF) designed for this purpose. The researcher will classify the intensity of said adverse events in accordance with a mild to severe scale, and the periodicity of the event will be classified by following a single occurrence to persistent scale (Textbox 2).

Textbox 2. The classification scheme for reporting the intensity and periodicity of adverse events.

1. Intensity
   a. Mild: some discomfort, but not as such as to interrupt normal daily activity.
   b. Moderate: sufficient discomfort to reduce or notably affect normal daily activity.
   c. Severe: causing incapacity to work or perform normal daily activities.
2. Periodicity
   a. Single occurrence: just one event of limited duration.
   b. Intermittent: various episodes of an event, each of limited duration.
   c. Persistent, unlimited: an event that has persisted over time and is of indefinite duration.

For each adverse event, its relation to the medication taken, in the researcher's opinion (definitive, probable, possible, improbable, none), as well as any action taken as a result, will be recorded on the data collection form. The occurrence of an adverse event that is fatal, potentially fatal or incapacitating, or that requires or prolongs hospitalization, or that provokes severe congenital anomalies will be recorded as a "severe" adverse event (SAE). All SAEs and unexpected adverse pharmacological reactions, defined as adverse events whose nature or intensity is not in accordance with any expected adverse event, will be reported by the researcher to the study coordinator by telephone, mail or fax as soon as is reasonably possible, but in any case within 24 hours of occurrence.

Data Analysis

Statistical Power, Establishment of Sample Size, and Safety

The calculation of sample size will be based on the average score on the 4 negative dimensions (items) of the GPACS between the group of adolescents who will receive treatment with OT and the group that will receive the PB. No clinical studies have used this scale in an attachment study, so this calculation is based on expert opinion (personal communication from K Lyons-Ruth, author of the GPACS). We estimate that a difference of 5 points for our main criterion is an interesting minimum clinical difference. Based on the supposition of a difference of 5 points for the OT group, a standard deviation value of 6.2 was calculated. We do not have the standard deviation of the values on our primary endpoint. However, we have the standard deviation of each negative item in the GPACS and summarized data from the original validation study of the GPACS. The variability of the values obtained for each of the 4 negative items were summed and we obtained a variability of 0.03 (SD 0.175). If we consider that the sum represents 3% of the total variability (co-variations to be added), then we arrive at a standard deviation of 6.2, a 90% power and an alpha level of 5% unilateral (superiority of trial against PB); therefore 54 patients should be included. Taking into account 10% of error and non-analyzable data, 60 patients should be included (ie, 30 patients per group). The overall significance level of statistical tests will be at 5%.

Statistics

To analyze the quantitative variables, parametric (Student *t*) or nonparametric (Wilcoxon) tests will be used, depending on the distribution of variables. The Shapiro-Wilk test will be used to test the normality of the distributions. Clinical and sociodemographic variables collected at the beginning of the study will be described using the mean (SD) for normally distributed continuous variables, and the median, for non-normally distributed variables. For qualitative variables, the chi-square or Fisher's test will be used to compare proportions between the two groups. Statistical analyses will be conducted and supervised by the Methodology and Biostatistics cell of the Centre of Investigation Clinic (CIC) in Besançon. All data will be analyzed using the SAS application. To estimate the clinical relevance of the findings, Cohen's effect size (Cohen's d) will be used for parametric outcomes (large effect ≥ 0.8) and *r* for non-parametric outcomes (large effect ≥.5).

Results

Enrollment for the study will be completed in May 2016. Data analysis will commence in July 2016. Study results are to be published in the winter of 2017.

Discussion

Principal Findings

In order to investigate the potential clinical implications of OT as an add-on treatment in psychotherapy, it is necessary to establish a well-designed, randomized, controlled protocol to assess the impact of OT on emotion regulation skills in adolescents. Research shows that OT might induce a momentary emotional state of trust and safety, while enhancing self-confidence. Administration of a single dose of OT might ameliorate emotional regulation skills in adolescents, and thus promote their capacity to connect with parents and peers. Given that adolescence is a critical period for the refinement of interpersonal and intrapersonal competences in close relationships, emotion regulation skills in conflict situations may have direct implications for experiences in close friendships and romantic relationships. Experimental research on OT and emotion regulation in adulthood has provided a scientific basis for the administration of OT, and has already had a positive impact on many short- and long-term health outcomes. The proposed research should contribute significantly to the understanding of the role of OT in emotion regulation, and represents a critical domain that might contribute significantly to improving health and well-being. This protocol could also be used in clinical interventions to increase positive life

outcomes for insecure adolescents. Additionally, IN-OT may hold promise for the therapeutic neuroenhancement of parent-adolescent close relationships.

A multi-dimensional approach should prove valuable in characterizing the intra- and inter-individual differences underlying both emotions and attachment, and their impact on social function. Studying attachment-related emotion regulation via oculomotor assessment and neurophysiological strategies during emotional picture viewing might provide additional evidence for the implicit defensive and/or approach strategies of emotion regulation.

Methods traditionally employed in emotion regulation studies [90] require conscious effort and self-monitoring processes from participants. In this study, participants will not be instructed to exert effortful regulation of their emotions. We seek to investigate emotion regulation mechanisms that will be automatically triggered by the stimulus itself and will take place without monitoring or awareness [91].

Limitations

This is the first correlational study of a healthy adolescent population that explicitly investigates the role of OT in stressful interaction, combined with analysis of oculomotor behavior and neurophysiological reactions in attachment-related pictures (the BAPS [75]). There are, however, some potential limitations (1) only one dose of OT is administered; (2) only the healthy male adolescent population is studied; and (3) only static images are used.

Future investigation should seek to determine the effects of higher doses, administered in both clinical and healthy populations. Researchers should also examine the effects of OT on emotion regulation with different types of social support (eg, peers or strangers). Dynamic stimuli could also be used for ET studies, as they provide more naturalistic interpersonal situations than static pictures. Gaze pattern modulation could then be analyzed over time. Given the central role of OT in human social relationships, further research should integrate longitudinal data on the biological and family and/or environmental systems, focusing on triadic interactions between the healthy male adolescent and both of his parents.

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Authors' Contributions

All authors contributed to the design and coordination of the study and have read, commented on, and approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AOI: area of interest
ASI: Attachment Scale Interview
BAPS-Ado: Besançon Affective Picture Set-Adolescents
BDI-II: Beck Depression Inventory-II
EDA: electrodermal activity
ECG: electrocardiogram
ET: eye tracking
GPACS: Goal-Corrected Partnership in Adolescence Coding System
HR: heart rate
IN-OUT: intranasal oxytocin
IU: international unit
OT: oxytocin
PB: placebo
RED: remote eye-tracking device
SAE: severe adverse event
SCL: skin conductance level
SCR: specific conductance response
TAS-20: Toronto Alexithymia Scale-20

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Protocol

Overcoming Perfectionism: Protocol of a Randomized Controlled Trial of an Internet-Based Guided Self-Help Cognitive Behavioral Therapy Intervention

Radha Kothari[1*], BSc (Hons), PhD; Sarah Egan[2*], BA (Hons), MS, PhD; Tracey Wade[3*], BSc (Hons), MClinPsych, PhD; Gerhard Andersson[4,5*], BA (Hons), MSc, PhD; Roz Shafran[6*], BA (Hons), DClinPsy, PhD

[1]Division of Psychology and Language Sciences, University College London, London, United Kingdom

[2]School of Psychology and Speech Pathology, Faculty of Health Sciences, Curtin University, Perth, Australia

[3]School of Psychology, Flinders University, Adelaide, Australia

[4]Department of Behavioural Sciences and Learning, Linkoping University, Linköping, Sweden

[5]Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

[6]Institute of Child Health Population, Policy and Practice Programme, University College London, London, United Kingdom

[*]all authors contributed equally

Corresponding Author:
Roz Shafran, BA (Hons), DClinPsy, PhD
Institute of Child Health Population, Policy and Practice Programme
University College London
4th Floor
30 Guilford Street
London
United Kingdom
Phone: 44 020 7905 2311 ext 2169
Fax: 44 020 7831 7050
Email: r.shafran@ucl.ac.uk

Abstract

Background: Perfectionism is elevated across, and increases risk for, a range of psychological disorders as well as having a direct negative effect on day-to-day function. A growing body of evidence shows that cognitive behavioral therapy (CBT) reduces perfectionism and psychological disorders, with medium to large effect sizes. Given the increased desire for Web-based interventions to facilitate access to evidence-based therapy, Internet-based CBT self-help interventions for perfectionism have been designed. Existing Web-based interventions have not included personalized guidance which has been shown to improve outcome rates.

Objective: To assess the efficacy of an Internet-based guided self-help CBT intervention for perfectionism at reducing symptoms of perfectionism and psychological disorders posttreatment and at 6-month follow-up.

Methods: A randomized controlled trial method is employed, comparing the treatment arm (Internet-based guided self-help CBT) with a waiting list control group. Outcomes are examined at 3 time points, T1 (baseline), T2 (postintervention at 12 weeks), T3 (follow-up at 24 weeks). Participants will be recruited through universities, online platforms, and social media and if eligible will be randomized using an automatic randomizer.

Results: Data will be analyzed to estimate the between group (intervention, control) effect on perfectionism, depression, and anxiety. Completer and intent-to-treat analyses will be conducted. Additional analysis will be conducted to investigate whether the number of modules completed is associated with change. Data collection should be finalized by December 2016, with submission of results for publication expected in mid-year 2017. Results will be reported in line with recommendations in the Consolidated Standards of Reporting Trials Statement for Randomized Controlled Trials of Electronic and Mobile Health Applications and Online TeleHealth (CONSORT-EHEALTH).

Conclusions: Findings will contribute to the literature on treatment of perfectionism, the effect of treating perfectionism on depression and anxiety, and the efficacy of Internet-based guided self-help interventions.

ClinicalTrial: ClinicalTrials.gov NCT02756871; https://clinicaltrials.gov/ct2/show/NCT02756871 (Archived by WebCite at http://www.webcitation.org/6lmIlSRAa)

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KEYWORDS

perfectionism; cognitive behavioral therapy; randomized controlled trial; Internet-based intervention; anxiety; depression

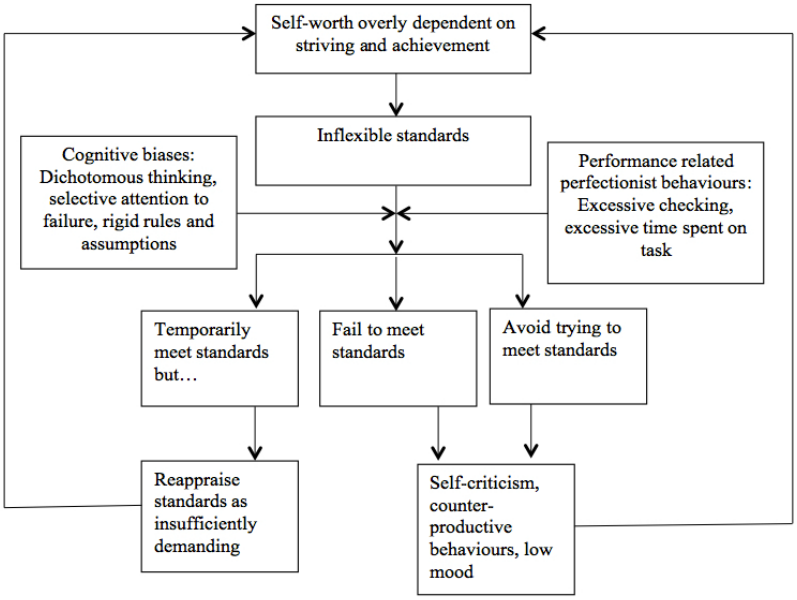
Introduction

Overview

Being a perfectionist has both positive and negative connotations. In day-to-day life, a moderate level of perfectionism is commonly associated with success and achievement, but perfectionism has been found to be elevated across, and associated with, a range of psychiatric disorders, including major depression, generalized anxiety disorder, obsessive compulsive disorder, bipolar disorder, posttraumatic stress disorder, panic disorder, eating disorders, body dysmorphic disorder, social anxiety disorder, chronic fatigue syndrome, and suicidal ideation and behavior [1,2]. Perfectionism has been found to increase risk for, and contribute to, the maintenance of eating disorders, anxiety disorders, and depression [3] and has been identified as a key maintenance factor in the transdiagnostic model and cognitive behavioral treatment of eating disorders [4]. Perfectionism can impede treatment progress and lead to poorer outcomes in treatment of patients with chronic pain [5], depression [6], and anorexia nervosa [7,8]. Perfectionism has also been associated with poor physical health and premature death [9,10].

The problems associated with perfectionism highlight the need for intervention, and with this in mind a cognitive behavioral maintenance model of perfectionism was developed by the Oxford Centre for Research on Eating Disorders, led by Christopher Fairburn. This cognitive behavioral analysis, particular to a specific form of perfectionism typically seen in clinical settings, characterizes *clinical perfectionism.* According to the cognitive behavioral account, people with clinical perfectionism are determined in the pursuit of their own personally demanding, rigid standards in at least one salient domain. These standards are pursued regardless of adverse consequences due to the individual's self-evaluation being almost entirely reliant on achievement and striving; individuals develop rigid standards and rules which come to dominate their lives, often expressed as "musts" and "shoulds," and continually strive for achievement and success to avoid the occurrence of their feared outcome, perceived failure. This in turn leads to behaviors that maintain clinical perfectionism such as avoidance, procrastination, repeated checking, and excessive thoroughness. The cognitive behavioral account goes on to suggest that an individual's assessment of whether they have met their standards is subject to well-established cognitive biases including dichotomous thinking, attention to negative rather than positive feedback, and discounting of success. This means that people with clinical perfectionism are likely to perceive themselves as having failed to meet their standards, leading them to be self-critical; experience emotional arousal at the thought of failure, anxiety, and low mood; and engage in further counterproductive behavior such as increased checking and thoroughness [11,12] (see Figure 1). For a full explanation and evaluation of the cognitive behavioral maintenance model of clinical perfectionism see Shafran et al [13].

Figure 1. The cognitive behavioral model of clinical perfectionism, reproduced from Cognitive Behavioural Treatment of Perfectionism [2].



Cognitive Behavior Therapy for Clinical Perfectionism

Based on the cognitive behavioral maintenance model of clinical perfectionism, a cognitive behavior therapy (CBT) protocol has been developed consisting of 10 modules typically delivered over 8 weeks. In line with the principles of CBT, emphasis is on maintenance over etiology. Cognitive behavioral techniques are used to challenge the cognitive biases, personal standards, and self-criticism that maintain clinical perfectionism and to broaden the client's attention and scheme for self-evaluation. Full details of CBT for clinical perfectionism can be found in the published manual [2].

There is a growing body of evidence to support the efficacy of using CBT to target perfectionism. A recent meta-analysis of 8 studies showed that CBT was effective at reducing symptoms of perfectionism, anxiety, and depression, with medium-to-large pre-post intervention effect sizes according to Cohen's [14] criteria for change [15]. Since publication, a further 4 studies have been added to the meta-analysis, showing large effect sizes for the reduction of symptoms of perfectionism and large effect sizes for the reduction of psychological disorders (Lloyd et al, unpublished thesis).

Internet-Based Self-Help Cognitive Behavior Therapy for Perfectionism

Given the increased need and desire for Internet-based interventions, an Internet-based version of CBT for perfectionism (where participants work independently without guidance from a therapist) has been developed and tested. An initial study found that Internet-based CBT for perfectionism led to significant decreases in perfectionism, anxiety, and depression [16]; however, a more recent study has found that although this Internet-based intervention led to a reduction in symptoms of perfectionism, it was less effective than the face-to-face version of the treatment in maintaining this change at a 6-month follow-up [17]. In addition, the Internet-based intervention did not affect levels of depression and anxiety.

Computer and Internet-based interventions are commonly associated with a number of advantages over face-to-face treatment, such as reduced cost to health care providers, increased patient anonymity, and increased convenience for the patient with regard to time and location of treatment [18-22]. Furthermore, the demand for psychological therapies outstrips availability, and Internet-based intervention can help fill this gap. However, Musiat and colleagues [21] found that individuals are more likely to use face-to-face therapy than Internet-based interventions. The authors of this study suggest that this might be due to the personal support that participants associate with face-to-face therapy, noting that personal support was rated the second most important factor when considering seeking help for mental health disorders, after the helpfulness of an intervention [21].

Being able to process thoughts and feelings in written form and developing a virtual relationship with a therapist were shown to be important to mental health users when receiving CBT delivered online by a psychologist [23]. A growing body of evidence suggests that Internet-based self-help interventions would benefit from a personal component of this nature, and Internet-based treatment of depression and anxiety has in fact been found to benefit from therapist guidance, leading to improved recovery rates and lower dropout rates [18,24]. A meta-analysis of randomized controlled trials (RCTs) of computer-based interventions for depression found that studies which included therapist support, or support from nonclinically trained guides, had medium effect sizes (d=0.78 and d=0.58, respectively), while the effect size for interventions without support was small (d=0.36) [25]. Given that a goal of Internet-based interventions is to increase availability, the effect size observed for nonclinically trained guides is encouraging, suggesting that guidance could be provided by individuals with minimal training. A more recent meta-analysis found a correlation between level of support and effect size of treatment, comparing interventions with no human contact; contact before the intervention only; contact mainly during the intervention; and contact before, during, and after the intervention. Average effect sizes were found to be 0.21, 0.44, 0.58, and 0.76, respectively [26]. This study aims to investigate whether additional guidance and feedback in the form of email (guided self-help) might also improve the effectiveness of an Internet-based version of CBT for perfectionism.

Methods

Setting and Intervention

This study is an RCT of an Internet-based guided self-help intervention for clinical perfectionism called *Overcoming Perfectionism* [27]. Recruitment, interventions, and measurement will take place online and through the website. This Internet-based version of the treatment has been adapted from the manual on perfectionism-specific CBT, *Cognitive Behavioural Treatment of Perfectionism* [2]. Content was made briefer and more focussed for the Internet-based intervention, and video was used. The intervention consists of 8 modules based on CBT techniques (see Table 1), and participants will be allowed 12 weeks to complete it and be provided with guidance and support.

Participants will still be given access to the intervention after this 12 weeks, but guidance will not be provided. Each module begins by providing psychoeducation and examples and then allows the participant to answer questions and complete relevant worksheets to create an idiosyncratic model of their own unhelpful perfectionism. In line with the principles of CBT, participants are encouraged to integrate their learning into their day-to-day lives by completing thought records, challenging cognitions, conducting surveys, and performing experiments in the form of between-session work.

Completed worksheets can be viewed by a guide who has been allocated to the participant and who is able to provide feedback and suggestions to the participant in the form of Internet-based written communication. Participants are also able to communicate directly with their allocated guide through the website, allowing them to ask questions or respond to the feedback that they have received.

Guidance and Feedback

Guidance and feedback will be provided by psychology undergraduates, graduates, master's students, PhDs, and trainee clinical psychologists. Guidance will be based upon the manual *Cognitive Behavioural Therapy of Perfectionism* [2], which guides will read as part of their training and refer back to when giving guidance. All guides will be provided with a range of sample responses for each module which they will study as part of their training and refer back to when providing feedback.

Guides will receive supervision throughout in 2 forms. First, all guidance and feedback written by guides will be checked by a qualified clinical (RS) or research psychologist (RK), who will help the guides develop their responses and consider different ways to support and encourage participants. In this way all participants will receive feedback that has been contributed to by at least 2 guides. This process will serve to provide guides with continuous training and supervision throughout and also to keep responses to participants consistent. The second aspect of supervision will be in the form of monthly supervision meetings during which guides will be supported with their case management and be able to discuss complex cases and challenges they may be experiencing as guides. The content of the feedback will be as closely aligned to the content of the therapy manual as possible [2].

Recommendations in the literature highlight a number of mechanisms of action through which feedback is effective, and these will be adopted when drafting feedback for participants [28]:

1. Guides will summarize and reflect information, thoughts, and experiences provided by participants, enabling participants to process their thoughts and feelings and reflect upon their experiences [29].

2. Feedback that is personally relevant is more likely to lead to deeper processing and is therefore more likely to be examined for its content [30]. Addressing recipients by their name is thought to sufficiently personalize feedback, but in addition to this guides will refer to specific experiences and examples that have been provided by participants when responding [31].

3. Cognitive theories highlight the importance of providing information that will support participants in changing their knowledge, thinking, and behavior, particularly if participants have misunderstood or mistaken elements of the intervention [32]. Guides will directly address the thought challenging, behavioral experiments, and other cognitive behavioral tasks that participants engage with to support them in thinking about the impact of the changes made and the potential for transferring their new skills to other situations. Guides will also support participants in the design of behavioral experiments so that participants gain the maximum benefit from challenging their behavior.

4. Adopting the principles of motivational interviewing can make personalized feedback effective in strengthening motivation for change [33]. Guides will remind participants of their goals and personal motivations for change, emphasizing the discrepancy between where they are and where they would like to be with regard to problematic behaviors and how much progress they have made since the start of the intervention, so as to support participants and strengthen continued engagement.

Participants will receive feedback and guidance as they complete each module and submit the relevant worksheets, with the average length of feedback for each worksheet being 1 to 2 paragraphs. Participants will also receive guidance if they specifically request help in understanding or completing modules and between session work.

Table 1. Modules and components of Overcoming Perfectionism, an Internet-based guided self-help intervention for perfectionism.

Module	Module Components
1. Understanding Perfectionism	1.1. What is unhelpful perfectionism?
	1.2. Why perfectionism continues
	1.3. Fact or fiction?
	1.4. “The harder you work, the better you'll do” Fact or fiction?
	1.5. Facts about perfectionism and performance
	1.6. Preparing for change
	1.7. Key take away
	1.8. Between-module work
2. Your Perfectionism Cycle	2.1. Between-module work
	2.2. A reminder
	2.3. The first steps
	2.4. Drawing your own diagram
	2.5. Between-module work
	2.6. Take-home message
3. Surveys and Experiments	3.1. Between-module work
	3.2. Perfectionism behaviors
	3.3. Surveys
	3.4. Reflect on the responses
	3.5. Behavioral experiments
	3.6. Different forms of behavioral experiments
	3.7. An added benefit
	3.8. Between-module work
	3.9. Take home message
4. New Ways of Thinking	4.1. Between-module work
	4.2. Changing thinking
	4.3. Imagining vivid future positive outcomes
	4.4. From all or nothing thinking to flexibility and freedom
	4.5. “Rules break, guidelines bend:” Turning rigid rules into guidelines
	4.6. Changing thinking styles
	4.7. Between-module work
	4.8. Key take away
5. Useful Skills for Managing Unhelpful Perfectionism	5.1. Procrastination
	5.2. Problem-solving
	5.3. Pleasant events
	5.4. Take home message
	5.5. Before the next module
6. Self-Criticism or Self-Compassion	6.1. How to respond
	6.2. Take home message
	6.3. Before the next module
7. Reexamining the Way We Examine our Self-Worth	7.1. Your self-worth
	7.2. Step 1. Recognizing that your self-worth can be independent of your achievements
	7.3. Step 2. Encouraging flexible and realistic goals
	7.4. Step 3. Spreading your self-worth across as many areas of your life as possible
	7.5. Step 4. Develop more balance in what you pay attention to daily
	7.6. Take home message
	7.7. Before the next module
8. Staying Well—Managing Unhelpful Perfectionism in the Long-Term	8.1. Improve your sense of self-worth
	8.2. Questions
	8.3. Thank you!

Participants

Participants will be recruited through university notice boards and online platforms, recruitment websites such as www.callforparticipants.com, and social media platforms such as Facebook and Twitter. Researchers will not approach potential participants directly, but rather interested individuals will be directed to the study website where they will be able to find out more about the study, read the information sheet, and give consent for participation. After registering online participants will complete screening measures, responses to which will determine their eligibility for inclusion. To be eligible for inclusion in this study, participants must be 18 years or older, fluent in English, and score 1 standard deviation above published norms on the "Concern over mistakes" subscale of the Frost Multidimensional Perfectionism Scale [34] (ie, a score of ≥29 [35]). Participants will be excluded if they report suicidal thoughts or intent. In this case participants will be telephoned by a clinical psychologist to be assessed for risk and signposted to the relevant services.

Participants with elevated levels of psychopathology will not be excluded from the study due to the established comorbidity between psychopathology and clinical perfectionism. Upon registering and providing informed consent, participants will be asked to complete a collection of screening measures to determine their eligibility for the study. If eligible, participants will be randomly allocated to the experimental group to complete the intervention or the control group (no intervention). Randomization of participants will be performed by a third party, unconnected to the study, who will create a randomization schedule using a Web-based randomizer [36]. Guides will be paired with participants who have been allocated to the treatment group after randomization. Participants who do not meet criteria for inclusion in the study will be sent a copy of *Overcoming Perfectionism: A Self-Help Guide Using Cognitive Behavioural Techniques* [11] and will be signposted to other services.

Sample Size

An a priori power calculation was conducted using a tool designed by Hedeker and colleagues which is appropriate for determining power for longitudinal designs [37], with a 2-tailed alpha of .05, 3 assessment points, a pre-post correlation for the primary outcome measure ("Concern over mistakes" subscale) of 0.61, and attrition rates of 50%. Both the pre-post correlation and expected attrition rate were based upon a similar RCT of a Web-based intervention for perfectionism [17]. A sample size of 40 enrolled participants per group, with 20 participants completing per group, would provide 80% power at 2-sided $P<.05$ to detect large effect size (0.80) difference between the control and intervention groups. This use of a large effect size was also based upon the previous RCT conducted by Egan and colleagues [17].

Measures

Overview

Self-report questionnaire measures of perfectionism, anxiety, and depression will be collected from all participants at 3 time points: (1) prior to any intervention as a baseline, (2) 12 weeks after the participant has been randomly assigned to the treatment or control group (to assess change), and (3) 24 weeks after being randomly assigned to the treatment or control group (to assess whether change is maintained at follow-up).

Participants in the experimental group will also complete a measure of clinical perfectionism weekly to monitor progress. Engagement with the website will be monitored through questions asking participants how much time they spent completing each module and the between session tasks.

Measures of Perfectionism

The Frost Multidimensional Perfectionism Scale (FMPS) self-report measure consists of 35 items grouped into 6 subscales: Concern over mistakes (eg, "I should be upset if I make a mistake"), Doubts about actions (eg, "I usually have doubts about the simple everyday things I do"), Personal standards ("I set higher goals than most people"), Parental expectations ("My parents set very high standards for me"), Parental criticism ("My parents never tried to understand my mistakes"), and Organization ("I try to be an organized person"). Participants respond on a 5-point scale ranging from 1 = "strongly disagree" to 5 = "strongly agree." The measure has been found to be both reliable and valid for use with nonclinical and clinical populations [34,38,39]. Participants will be considered eligible for inclusion in the study if they score 1 standard deviation above published means on the "Concern over mistakes" subscale (ie, a score of ≥29) [35]. This subscale is being used as the baseline and main outcome measure in line with previous RCTs investigating treatment of perfectionism [15,17]. The FMPS has been amended to reflect participant experience over the past month allowing us to measure change.

The Clinical Perfectionism Questionnaire self-report measure consists of 12 items reflecting participant experience over the past month (eg, "Have you pushed yourself really hard to meet your goals?" and "Have you raised your standards because you thought they were too easy?") [40]. Participants respond on a 4-point scale ranging from 1 = "not at all" to 4 = "all the time." This measure of clinical perfectionism was created by Fairburn, Cooper, and Shafran at the University of Oxford and has been found to have good reliability and validity in 2 community samples and an eating disordered sample [41]. The original version of this measure excluded perfectionism in the domain of eating, shape, and weight due to the design of the study in which it was developed, but for this study it has been amended to allow for perfectionism in this domain. As well as being administered at baseline, posttreatment, and at follow-up, a version of the measure amended to reflect participant experience over the past week will be administered to the treatment group weekly allowing us to monitor change.

Measures of Psychopathology

The Depression, Anxiety, and Stress Scales [42] is a 21-item self-report measure of depression, anxiety, and stress (eg, "I found myself getting upset by quite trivial things") rated on a 4-point scale ranging from "Did not apply to me at all" to "Applied to me very much or most of the time." It has been shown to be reliable and has been validated for use among clinical and community samples [42,43].

Ethical Considerations

Ethical approval for this study has been granted by the University College London Research Ethics Committee (Project ID: 6222:001). Professor Roz Shafran is the primary investigator on the trial.

Results

Methodology

Data will be analyzed using T2 (postintervention and primary endpoint at 12 weeks) as the outcome variable adjusted for observations at T1 (baseline) in order to estimate the between-group (intervention, control) effect on perfectionism, depression, and anxiety. The follow-up effect of the intervention will be investigated in the same way with T3 (follow-up, 24 weeks) replacing T2 observations. Both completer and intent-to-treat (ITT) analyses will be conducted. ITT analyses will use multiple imputation to manage missing data. An analysis will be conducted to investigate whether the number of modules completed is associated with change. Results will be reported in line with recommendations in the Consolidated Standards of Reporting Trials Statement for Randomized Controlled Trials of Electronic and Mobile Health Applications and OnLine TeleHealth (CONSORT-EHEALTH) [44].

Timeline

Ethical approval for this trial was granted in February 2015. Enrollment of participants began in July 2015. Data collection should be finalized by December 2016, with submission of results for publication expected in mid-year 2017.

Discussion

Overview

The aim of this study is to investigate whether CBT Internet-based guided self-help for perfectionism is effective at reducing perfectionism and symptoms of depression and anxiety. Perfectionism has been shown to be elevated across, and increase risk for, a range of psychological disorders, as well as having detrimental effects on day-to-day functioning directly. This is the first trial assessing the efficacy of an Internet-based self-help intervention for perfectionism that provides personalized feedback from a guide throughout. Outcomes will contribute to the literature on the treatment of perfectionism and providing guidance within Internet-based interventions.

Limitations

Participants are only eligible for inclusion in the study if they score 1 standard deviation above the reported mean on the "Concern over mistakes" subscale, taken from a study investigating perfectionism within a student population [35]. A limitation of this study is that perfectionism may be relatively high among college students, making our cut-off for inclusion higher than necessary. Participants will also be excluded from the study if they report suicidal ideation or behavior; however, a limitation of the study is that due to ethical considerations we are not able to directly assess suicidal ideation or behavior and are reliant on participants volunteering this information to their guide. Participants reporting mental health difficulties other than perfectionism will not be excluded due to the established relationship between perfectionism and elevated levels of psychopathology. This may lead to an additional level of variability within the sample, and variation in psychopathology may impact treatment adherence and/or effectiveness. Randomization of participants will minimize these effects, however, and participants will also be asked to report any mental health diagnoses to investigate any potential differences between the treatment and control groups.

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Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavior therapy
FMPS: Frost Multidimensional Perfectionism Scale
ITT: intention-to-treat
RCT: randomized controlled trial

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Protocol

Efficacy of Mobile Serious Games in Increasing HIV Risk Perception in Swaziland: A Randomized Control Trial (SGprev Trial) Research Protocol

Bhekumusa Wellington Lukhele[1], MPH; Patou Musumari[1], MD, PhD; Christina El-Saaidi[1], MPH; Teeranee Techasrivichien[1], MSc, PhD; S. Pilar Suguimoto[1], MD, PhD; Masako Ono Kihara[1], PhD; Masahiro Kihara[1], MD, PhD

Kyoto University, Department of Global Health and Socio Epidemiology, Kyoto University, Kyoto, Japan

Corresponding Author:
Bhekumusa Wellington Lukhele, MPH
Department of Global Health and Socio Epidemiology
Frontier Laboratory Bldg, 2nd Fl.
Kyoto University School of Public Health Yoshida Konoe-cho, Sakyo-ku
Kyoto, 6068501
Japan
Phone: 81 757534350 ext 4350
Fax: 81 757534349
Email: bhekumusa.lukhele.36x@st.kyoto-u.ac.jp

Abstract

Background: The human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) continue to be a major public health problem in Sub-Saharan Africa (SSA), particularly in Swaziland, which has the highest HIV prevalence in this region. A wide range of strategies and interventions have been used to promote behavior change, though almost all such interventions have involved mass media. Therefore, innovative behavior change strategies beyond mass media communication are urgently needed. Serious games have demonstrated effectiveness in advancing health in the developed world; however, no rigorous serious games interventions have been implemented in HIV prevention in SSA.

Objective: We plan to test whether a serious game intervention delivered on mobile phones to increase HIV risk perception, increase intention to reduce sexual partnerships, and increase intention to know own and partners HIV status will be more effective compared with current prevention efforts.

Methods: This is a two-arm randomized intervention trial. We will recruit 380 participants who meet the following eligibility criteria: 18-29 years of age, own a smartphone running an Android-based operating system, have the WhatsApp messaging app, live in Swaziland, and can adequately grant informed consent. Participants will be allocated into a smartphone interactive, educational story game, and a wait-list control group in a 1:1 allocation ratio. Subsequently, a self-administered Web-based questionnaire will be issued at baseline and after 4 weeks of exposure to the game. We hypothesize that the change in HIV risk perception between pre- and post-intervention assessment is greater in the intervention group compared with the change in the control group. Our primary hypothesis is based on the assumption that increased perceived risk of HIV provides cues to engage in protective behavior. Our primary outcome measure is HIV risk perceived mean change between pre- and post-intervention compared with the mean change in the wait-list control group at 4-weeks post-intervention. We will use standardized regression coefficients to calculate the effect of the intervention on our primary outcome with *P* values. We will conduct both intention to treat and as treated analysis.

Results: This study is funded by Hayao Nakayama Foundation for Science & Technology and Culture; Grant number H26-A2-41. The research and development approval has been obtained from Kyoto University Graduate School and Faculty of Medicine Ethics Committee, Japan, and Swaziland's Ministry of Health Ethics and Scientific committee. Results are expected in February 2017.

Conclusions: This study will provide evidence on the efficiency of a mobile phone interactive game in increasing HIV risk perception in Swaziland. Our findings may also be generalizable to similar settings in SSA.

Trial Registration: University Hospital Medical Information Network Clinical Trial Registry ID number (UMIN-CTR):UMIN000021781; URL:https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000025103 (Archived by WebCite at http://www.webcitation.org/6hOphB11a).

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KEYWORDS

eHealth; mHealth; gamification; Internet; HIV prevention; innovation

Introduction

It is estimated that 35.3 million people are living with human immunodeficiency virus (HIV) globally [1]. Sub-Saharan African (SSA) is the most affected region and the disease burden varies considerably between countries. In Swaziland, a land-locked, lower-middle income country surrounded by South Africa and Mozambique, HIV prevalence is estimated to be 26% among men and women of 15-49 years [2]. The overall HIV prevalence among the reproductive age population (18-49) has remained unchanged between 2006 and 2011 at 31% [3,4]. A recent, longitudinal, cohort study between December 2010 and June 2011 has estimated the incidence of HIV at 1.7% in men and as high as 3.1% in women [5]. Unprotected heterosexual transmission accounts for 94% of all new infections in the country [6]. More specifically, multiple concurrent partnerships have been identified as key drivers of HIV infection in Swaziland [6]. A recent qualitative study found that social and structural factors played a role in creating an enabling environment for high-risk sexual partnerships, and these factors included social pressure and norms, a lack of social trust, poverty and a desire for material goods, and geographical separation of partners [7].

Other key drivers have been highlighted in the Extended National Multi-sectoral HIV/AIDS Framework for 2014–2018 (eNSF) as: low rates of HIV testing (only 40% of people aged 15-49 had tested for HIV 12 months preceding a household survey) [8]; early sexual debut; low levels of medical male circumcision; and low HIV risk perception [8,9].

HIV is the leading public health concern in Swaziland [4]. National efforts have emphasized the scale-up of a combination of prevention approaches including: HIV testing and counseling, social behavior change communication, medical male circumcision, and HIV care and antiretroviral services. Despite this cocktail of prevention approaches, risky behaviors remain high. For example, Bicego and colleagues [4] note that there is still a low/late uptake of HIV testing services by men, which is consistent with late entry into care and treatment. Furthermore, according to the Swaziland Demographic Health Survey of 2006/07 and the Multiple Indicator Survey of 2010, the overall prevalence of multiple sexual partners remained unchanged at approximately 11% between 2006 and 2010 (data recalculated) [9,10]. On another note, the eNSF 2014-2018 points out that the Swaziland Social and Behavior Change strategy developed in 2010 has had limited success in facilitating desired levels of behavior change most importantly influencing personal HIV risk perception that focus on translating HIV awareness into protective action [8]. Beliefs about personal risk of HIV infection are central to motivate people to engage in behaviors that reduce their risk of HIV infection [11]. The Swaziland HIV testing and counseling guidelines includes HIV risk assessments to enhance self-perception of risk [12]. Models such as the Protection Motivation Theory and the Health Belief Model offer insights into the significance of perceived risk in adopting protective behavior. To date, there has been limited randomized control trials aimed at influencing how people perceived their risk of HIV in Swaziland.

Furthermore, anecdotal information suggests that there is information fatigue from the target audience in receiving HIV prevention messages from the mass media because most prevention campaigns have been dominantly delivered through mass media. One strategy that can break this perceived fatigue is the use of target audiences' mobile phones. In developing countries, decreasing costs and increasing mobile network coverage provide a wide range of opportunities for apps using mobile phones [13]. Although comprehensive up to date data for mobile phone usage in Swaziland is limited, mobile phone penetration is estimated at 87% [14]. Our consultative meeting with the only mobile carrier in Swaziland revealed that there are currently 206,880 smartphones on the mobile network (as of June 2015). Therefore, our study seeks to use serious games delivered via mobile smartphones to engage the target audience in creative ways to increase personalization of HIV risk.

In this study, we adopt the definition of Serious Games as proposed by Alvarez and Djaouti [15], "a computer application whose intended purpose is to coherently combine both serious aspects such as, but not limited to teaching, learning, communication, or information, with game playing aspects from video games." These combined serious aspects and playing aspects form a utilitarian scenario, which in computer terms uses a sound and graphics package, a story and appropriate rules, and is therefore distinct from simple entertainment [15]. Alvarez and Djaouti [15] summarize this definition by the following relationship:

Utilitarian scenario + gaming scenario => Serious Games.

Current literature suggests that serious games are effective in changing behavior. For example, a randomized trial (in the United States) designed to improve treatment adherence among 13- to 29-year-old patients with malignancies including acute leukemia, lymphoma, and soft-tissue sarcoma found that among 200 participants who were prescribed oral trimethoprim-sulfamethoxazole and 6-mercaptopurine, 16% indicted an increase in adherence for the serious games intervention group compared with the control group. Mixed-effect linear model analyses of chemotherapy metabolite concentrations showed that patients in the intervention group maintained significantly higher chemotherapy metabolite levels

over time than did patients in the control group (significant group × time interaction; P=.002)[16]. Additionally, another clinical trial conducted in the United States among 935 males who had sex with males between 18- and 24-years old aimed at reducing risky sexual behavior and sexual shame, found that exposure to a serious games intervention led to immediate shame reduction for those in the serious games intervention group compared with the control group (mean [M]=−0.08, standard deviation [SD]=0.51, n=437 compared with M=0.07, SD=0.54, n=484, respectively; the difference was statistically significant at $t_{(919)}$=4.24, P< .001) [17]. Despite the success of serious games in advancing health, no randomized intervention trials have been conducted in HIV prevention in SSA or in Swaziland. To address these research gaps, our goal is to design a serious game to increase HIV risk perception and use randomization to evaluate the efficacy of this intervention among 18- to 29-year-old people in Swaziland.

Methods

Study Design and Hypotheses

The Swaziland Serious Games–Based HIV Prevention Trial (SGprev trial) will be a 4-week, two-arm randomized intervention trial. Participants will be randomized into 2 groups (the intervention group and a wait-list control group) in a 1:1 allocation ratio (Figure 1) [18]. The intervention will be downloadable from our website, on the Google Play store, and in popular cellular shops around Swaziland. These cellular shops already serve as distribution sites for other mobile software and apps, such as antiviruses, Opera mini, and WhatsApp, and are thus very popular in Swaziland. Additionally, the game will also be available from kiosks in all tertiary institutions in the country. Downloading the game will not be synonymous with enrolling in the trial. After downloading the game, potential participants will be redirected or prompted to visit our website where information about the trial and eligibility screening will be provided.

We plan to test whether a serious game intervention delivered on mobile phones to increase HIV risk perception, increases the intention to reduce multiple sexual partnerships, intention to know own HIV status, and intention to know all sexual partners' HIV status will be more effective compared with current prevention efforts. Therefore, our hypotheses are that

1. The change in HIV risk perception between pre- and post-intervention assessment is greater in the intervention group compared with the change in the control group.

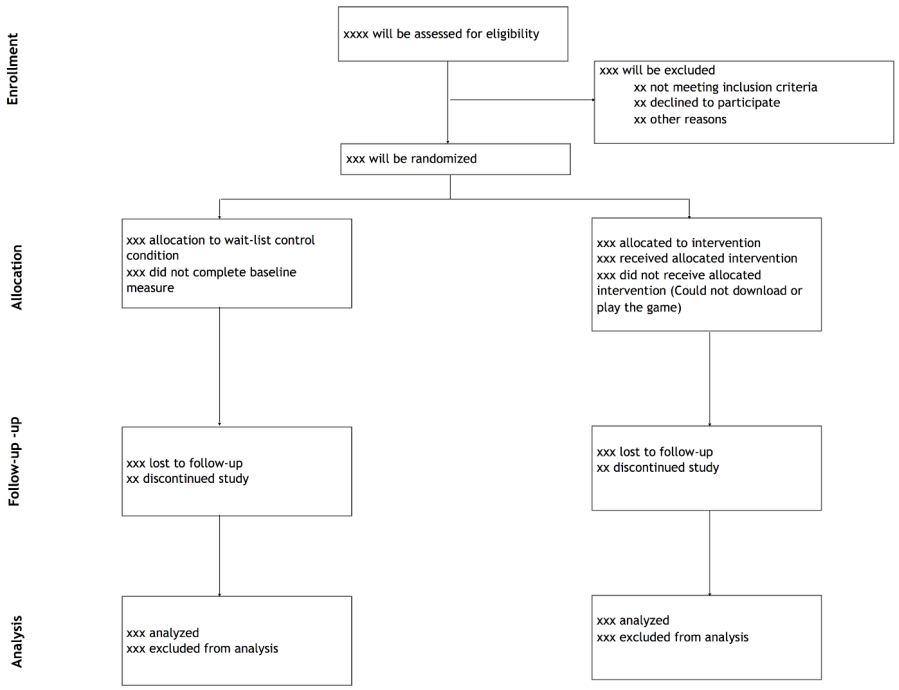
2. The change in HIV risk perception between pre- and post-intervention assessment will be greater among those reporting high HIV risk behavior in the intervention group compared with the control group.

3. The change in intention to have an HIV test between pre- and post-intervention assessment will be greater in the intervention group compared with the change in the control group.

4. The change in intention to reduce multiple concurrent partnerships between pre- and post-intervention assessment will be greater in the intervention group compared with the change in the control group.

5. The intervention group will report higher rate of condom use in the last sexual encounter compared with the control group.

Figure 1. CONSORT diagram for Swaziland serious games-based trial.



Participants, Setting, and Intervention

Our target population is Swazi males and females between 18- to 29-years old currently in Swaziland. Our intervention study targets people between 18- and 29-years old for the following reasons: (1) according to Bicego and colleagues [4], young people between this age group are most vulnerable to HIV because of their low HIV-testing behavior, (2) our primary study recruitment platform will be Facebook because the majority of mobile phone users in Swaziland also use Facebook, and (3) in our formative research (unpublished work, 2014) we found that this age group is likely to use smartphones and be literate on navigating the Internet compared with younger than 18-years-old or older than 29-years-old participants. Moreover, this age group is likely to find the SwaziYolo game entertaining.

Inclusion Criteria

For this study, we will include males and females if they meet the following criteria: (1) are between 18 and 29 years of age, (2) own a smartphone running an Android-based operating system, (3) currently have the WhatsApp messaging app, (4) currently live in Swaziland, and (5) are able to adequately grant informed consent.

Sampling Method

To recruit participants, we will post a targeted (based on our inclusion criteria), clickable banner advertisement on Facebook. After clicking on the advertisement, potential participants will be redirected to our website. Those who meet our eligibility criteria and have granted informed consent will be sent a unique trial verification code via text message and email. This unique trial verification code will be used to take our survey. Moreover, participants eligible for this trial will be entered into a lottery draw with a 1:100 chance of receiving US $20.

Study Setting

The Kingdom of Swaziland, situated in Southern Africa, is a small land-locked country, the area of Swaziland is estimated to be 17,364 km^2 with an estimated population of 1,146,050 (2006) [19]. According to Facebook there are currently approximately 160,000 people on Facebook, of those, 97,000 of them are man and women between the ages of 18- and 29-years old. Our primary recruitment site will be Facebook. Facebook is one of the most widely used social networking platforms in Swaziland and allows for targeted advertisements specifically to send people to our website. These two factors make Facebook an ideal platform to reach the Internet population in Swaziland. Participants do not need to be Facebook users to participate in the trial because our website can be assessed directly from the Internet. Participants will not be discouraged to share the study website link on other platforms, such as WhatsApp, Instagram, Email, and others.

Description of the Intervention

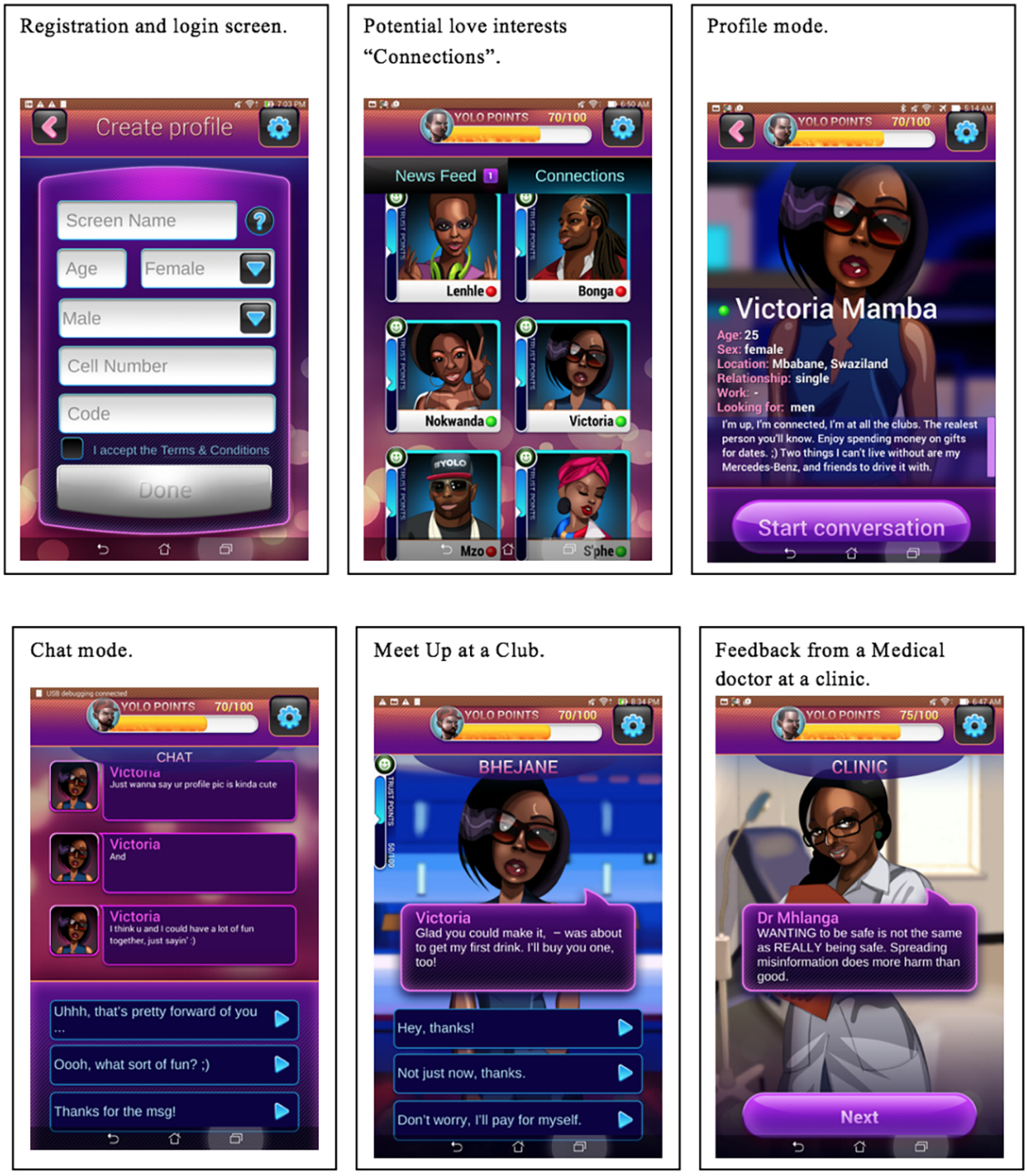
SwaziYolo (a smartphone game) is an interactive, educational story game that puts the player in the role of a young adult looking for love in Mbabane (the capital city of Swaziland), making important choices about relationships and sexual health (see Multimedia Appendix 1 for an overview of the steps taken in developing the intervention). The intervention is guided by cognitive-based approaches such as the Theory of Planned Behavior to target intentions to engage in HIV protective behavior [20-22] and the Health Belief Model to target perceived susceptibility of acquiring HIV infection [20]. While capitalizing on elements of serious games such as immersion, role-playing, and a dynamic storyline, the game exists in two major parts: the first is set in an imaginary social network called SwaziYolo, which is meant to resemble a combination of existing tools like Facebook, OKCupid, and Whatsapp. Here, players register (registration and login screen), view pictures (potential love interests “Connections” screen) and profiles of potential love interests (profile mode screen), and have Web-based chats (chat mode screen) with various characters. The other half of the game takes place in various made-up locations around Mbabane, such as nightclubs and cafes (meet up at a club screen) where players regularly go on dates referred to in the game as “meet-ups.” In both parts of the game, players are regularly required to choose between several courses of action to progress a conversation or storyline with a friend or love interest (chat mode screen). The decisions they make will influence the opinions and behavior of other characters, as well as the player’s own health and safety. Eventually, feedback is given based on choices made (feedback from a medical doctor at a clinic screen). In the game, the various character dialogues and scenes, will address the issues identified in our formative research such as HIV risk perception, raising knowledge of their own HIV status as well as a sexual partner’s HIV status, reducing multiple concurrent sexual partnerships, and consistent condom use.

The goal of the game is to maintain relationships with the characters, while staying healthy and happy. Once all the interactions with the characters have been completed, the game will give feedback on choices made and the risks those choices might carry. The game is expected to have an immense appeal to the youth, as an exciting new way to use their smartphones (see Figure 2 for the actual SwaziYolo screenshots). Participants in the wait-list control condition will complete the baseline and the immediate posttest measures as those in the SwaziYolo intervention condition, but will not play the game until the post-intervention assessment.

Game Play

Player’s curiosity to “know what happens when they make a choice” is key to user engagement. The game’s narrative is primarily concerned with matters of sexual health, especially as it relates to HIV. Players will usually find themselves in situations where they have to make important decisions about their health, for example, resisting the pressure to have unprotected sex. The game keeps track of how well a player’s relationship is going with other characters using “TRUST” ratings (intimacy ratings), and a “YOLO” rating: how safe (safe relates to making choices that do not expose player to HIV risk) they have been during the course of the game. While players enjoy game play, they are exposed to valuable learning situations and are encouraged to care more about the various characters. Some will give good advice, while others will find themselves in difficult situations where they ask other players for help and guidance.

Figure 2. SwaziYolo screenshots.



Sample Size Calculation

The trial will be powered on the primary outcome measure and based on comparison of the change in HIV risk perception score from pre- to post-intervention assessment in the intervention group at 4 weeks. A study conducted in Uganda estimated mean HIV risk perception of M=3.27, SD = 1.03, therefore, we used this estimation as our baseline mean and SD to calculate our effect size [21]. Assuming a moderate effect size of 0.477 (identified by Chu et al [22]), alpha (two-tailed)=0.05, beta=0.20, with 1:1 allocation ratio between both groups, and a SD of the outcome in the population of 1.03, the total sample required to sufficiently power the study would be 146 (73 for each group). Moreover, assuming a 30% loss to follow-up rate [15], we then inflated the sample by 30% to yield a sample of 190. After that, we considered gender differences and once more inflated the sample by a factor of 2 to give a final sample size of 380. Finally, to ensure a balance between males and females in both groups we will recruit 190 females and 190 males. The sample size was calculated using Web-based sample size calculation software [23,24].

Randomization

Upon confirmation of participants' trial registration, participants will be assigned another unique code called "game unlock code," which will be used for randomization using secure, remote,

Web-based computer software within 24 hours of recruitment. As stated in the research design, participants will be randomized into 2 groups; the intervention group and the wait-list control group in a 1:1 ratio. The data analysis team will be blinded in this study, however, participants will not be blinded.

Measurement Instrument

A self-administered structured Web-based questionnaire was created based on review of both Swazi and international literature. For example, questions relating to sociodemographic characteristics were adopted from the 2007 Swaziland Demographic Health Survey, and those related to risky sexual behavior and intention to change behavior were developed from our formative studies. Additionally, the Perceived Risk of HIV Infection Scale (PRHS; found to have excellent internal consistency Cronbach alpha=0.88) [11] will be used to assess the primary outcome of this study. Past research has used a variety of approaches to measure HIV risk perception including single likelihood assessments [21,25]. The 8-item PRHS scale incorporates items assessing cognitive assessments of risk (eg, chance of infection), as well as intuitive assessments (eg, feeling vulnerable, worry, gut feeling about likelihood), and salience of risk (eg, thought about risk, can picture it happening) to provide a more comprehensive measure of perceived risk of HIV infection, thus our choice to use this scale. The questionnaire will be converted into a Web-based format accessible via a link. Detailed variables assessed by the questionnaire are described in the section below and the questionnaire is presented in Multimedia Appendix 2. The trial tools were piloted among respondents known to the principal investigator, who will not be part of the main trial, in order to assess Web-based eligibility screening functionality; user verification; participant randomization functionality; questionnaire skip logic functionality; and the average length of time it takes to complete the questionnaire.

Primary Outcome Measure

Adding one or more comparison groups to a pre- and post-intervention assessment will result in a stronger intervention design than having a single intervention group to a pre- and post-intervention assessment [26]. Therefore, the primary intervention outcome will be the change in HIV risk perception score from pre- to post-intervention assessment in the intervention group compared with the change in the wait-list control group. High perception is considered to be the first stage toward behavioral change and has been associated with HIV protective HIV behavior [27,28]. HIV risk perception using the PRHS will be used to measure the primary outcome at baseline and at 4-weeks follow-up.

Secondary Outcomes Measure

The secondary outcomes for this intervention are self-reported intention to have an HIV test; intention to reduce multiple concurrent sexual partnerships; and an increase in reported condom use in the last sexual encounter (Table 1).

Table 1. Secondary outcome measures.

Measures	Baseline	Follow-up at 4 weeks
Sexual reproductive history		
Condom use in the last sex	X[a]	X
Number of sexual partners	X	X
Intent to change behavior		
Intention to test for HIV and know partners' HIV status	X	X
Intention to reduce multiple concurrent partnerships	X	X
Intention to use a condom	X	X
Steady sexual partner's history		
Has current sexual partner ever tested for HIV?	X	X
Knowledge of current partner's HIV status	X	X
Demographics		
Age	X	
Level of education	X	
Employment status	X	
Income level	X	
Marital status	X	
Ever tested for HIV	X	X
Contact information		
Cellphone number and email	X	
User experience		
Would you recommend the game to your friends?		X
How did you hear about this game?		X
Number of times player reached the end of the game		X
Level of satisfaction about the game		X

[a]Timing of assessment.

Data Collection Procedures

Baseline Data Collection

Participants will be recruited from Facebook users in Swaziland via a targeted Facebook advertisement. Potential participants will be directed to the study Web page where information about the intervention trial will be given and if willing, screening for eligibility will be done. After screening for eligibility, eligible individuals interested in participating in the trial will have an opportunity to ask detailed questions via free text message service offered by the WhatsApp app, Facebook messenger, or calling us. Sufficient time will be allowed for making an informed decision about participation in the study. Recruitment into this study will continue until our sample size is achieved.

After informed consent, a trial verification code will be sent to the participants via their mobile phones to prevent multiple identities in line with the CONSORT-EHEALTH guidelines 4a(ii) [29]. Upon confirmation of the unique verification code, participants will be enrolled in the trial and randomized into a control or intervention group. Subsequently, participants will be asked to answer the baseline Web-based questionnaire. In addition to study variables, contact information in the form of cellphone numbers will be collected at baseline to facilitate location of the research participants in the 1-month follow-up period [23,30]. The detailed questionnaire is outlined in Multimedia Appendix 2.

Four-Weeks Follow-Up Data Collection

Trial participants will be followed-up for 4 weeks, the game will collect log data and send this data to our servers when the participant goes on the Internet, this will allow us to assess the exposure to the intervention without over burdening our participants to manually send us their usage data. Data captured will be limited to login data. In addition to this, a Web-based questionnaire will be sent to participants at the end of the follow-up period. Participants who will miss their 4-week follow-up assessment will be actively traced though phone calls and text messages.

Data Management and Statistical Analysis

Data Quality Assurance

First, Web-based questionnaires must be usable even for less experienced and knowledgeable Internet users [31], therefore

we will exploit specific technical possibilities offered by open source Web-based questionnaires, such as visually highlighting buttons and predefined input fields. Additionally, we will use help features and input checks to assist participants when filling out the Web-based questionnaire. Beyond this, we will pilot test all filters and instructions given in the questionnaire. Second, to limit undesired multiple participation [32], either at baseline assessment or follow-up assessment, "sessions" will be used together with a verification code that participants will receive upon giving informed consent. Third, a specific problem that is faced by Web-based surveys is that respondents may "click through" the questionnaire, a phenomenon that becomes apparent when the interview is completed in less than the theoretical minimum time [31], therefore, the responses will be checked for plausibility and consistency and inconsistent records will be documented and censored from the final analysis.

Baseline Characteristics

Initially, descriptive statistics for the sample characteristics will be done for the intervention group and the wait-list control group to assess the distribution of important predictors of the outcome between both groups at baseline.

Primary Outcome Measure: HIV Risk Perception Score

First, we will use bivariate analysis to calculate the mean between baselines and follow-up. Next, to estimate the difference between the 2 groups, we will calculate the difference between the mean change of the intervention group and the mean change of the wait-list control group using two-sample paired *t* test. We will not perform interim analysis.

Secondly, in the case that, even after randomization, we observe some baseline differences, we will use multiple linear regression to adjust for those differences; where the outcome will be the follow-up score and the independent variables will be the intervention group, baseline scores, age, gender, marital status, level of education employment status, current monthly income, and number of times players played SwaziYolo. We will present our results in standardized regression coefficients for the intervention effect on the outcome variable as previously done for this type of hypothesis [25].

Although great effort will be put to minimize attrition, it is common for eHealth trials to typically have substantial attrition [26]. For this reason, our primary outcome analysis will prioritize analysis of the subjects who adhered to their group assignment and were sufficiently exposed to the intervention. Therefore, both pre-protocol analysis (as treated analysis) as well as intention to treat analysis will be done and both results will be reported. The approach of conducting both "intention to treat analysis" together with "as treated analysis" has been observed in literature for example, Weinstein and colleagues [33] followed this approach in their randomized trial comparing surgical versus nonoperative treatment for lumbar disk herniation.

Secondary Outcome Measures

Two-sample generalization McNemar's test will be done to assess whether a significant change occurred between the pre- and the post-intervention assessments for dichotomous variables such as: intention to know self and partners HIV status, intention to reduce multiple sexual partners, and intention to use a condom the next time a participant has sexual intercourse. Each of these, outcomes will be assessed separately (individually). In order to judge the change, we will calculate the proportions of the dichotomous variable pre- and post-intervention in both groups. After that, we will obtain the pre- and post-intervention difference percentage at a *P* value within group and a *P* value in the intervention versus waitlist control group. This technique is documented by Katz [26]. Additionally, we will conduct a subgroup analysis of those with low-risk perception who report no condom use at last sexual encounter. This subgroup analysis will give us a more nuanced insight of the effect of the intervention to the most as risk subgroup in our study.

Informed Consent

All participants will be required to give Web-based informed consent (Multimedia Appendix 3) before participation in the study. An online forum via Facebook and WhatsApp will be setup to allow participants to ask questions related to this research. They will be informed about the purpose of the study, its strict confidentiality, importance, and voluntary nature of their participation, their right to end the participation at any time without having to state a reason. Lastly, participants will be informed that the aggregated results (not individual case data) will be disseminated to improve the intervention package and general HIV prevention in Swaziland (see SGprev Trial information sheet in Multimedia Appendix 4).

Protection of Personal Information

The following measures will be taken to protect participant's personal information:

1. Permission will be sought from study participants to collect game usage data (login data) automatically.

2. All participants' data will be stored under encrypted servers to protect participants' information.

3. Participants' cellphone numbers will be stored in a password protected file and will not be used for purposes other than those outlined in this protocol. After the trial, all cellphone numbers will be deleted.

Expected Adverse Effects and Countermeasures

During or after the study, participants may develop psychological distress or embarrassment. All efforts to prevent this psychological distress or embarrassment will be put in place. If despite our efforts any psychological issue arises during the intervention and data collection, the research team will refer the participants' to the nearest counselor (who is well vest on psychological issues) for appropriate psychological care and support via text messaging or calling. Participants will be encouraged to self-report any feelings of distress or discomfort to the research team using Web-based tools such as the WhatsApp app, Facebook private message, or via our contact details provided in the study information sheet including a toll-free number for HIV counseling.

Data Storage

All data will be stored in the password-encrypted servers. Upon completion of the survey, all data will be exported to a password protected desktop computer at Kyoto University Department of Global Health and Socio-Epidemiology. Persons not part of the research team will not have any access to the collected data.

Incentive

A lottery draw at baseline with a 1:100 chance of receiving US $20 will be given to all participants at the end of data collection as an incentive for their time in taking part in this trial. This amount was chosen carefully not to cause undue influence to the target population in that it is not excessive and is fair considering the country's socioeconomic status.

Results

Current Status

The status of the study is in preinitiation stage. Results are expected in February 2017. We will present results as percentages, observed means with 95% confidence intervals, mean difference and 95% confidence intervals, standardized regression coefficients, and *P* values. All analysis will be performed using SPSS for Windows.

Ethical Considerations

The study will be conducted according to the principles outlined in the Declaration of Helsinki International Guidelines for Ethical Review of Epidemiological Studies (CIOMS, 1991 Geneva). Furthermore, the research and development approval has been obtained from Kyoto University Graduate School and Faculty of Medicine Ethics Committee, Japan, and Swaziland's Ministry of Health Ethics and Scientific committee. Caution will be taken to protect participant's privacy during the data collection, data handling, and data reporting.

Funding

Development of "SwaziYolo" serious game was funded by Hayao Nakayama Foundation for Science & Technology and Culture; Grant number H26-A2-41. The research implementation will be sponsored by the Department of Global Health and Socio-Epidemiology, Kyoto University, Japan.

Discussion

Overview

The risk of HIV infection is high among young people who practice risky sexual behavior, often they do not perceive their risk to be high, a phenomenon termed optimistic bias [11,27,28,34-36]. Some studies have reported that increased risk perception leads to subsequent increase in HIV protective behaviors, such as acceptance of HIV testing [37] or condom use [38]. The mechanism that increased perception leads to protective behavior is implicit in many behavioral theories as noted by Napper and colleagues [11]. Consequently, the joint United Nations Programme on HIV/AIDS (UNAIDS) guidance note on "social and behavior change programming" outlines risk perception as a thematic focus area for effective HIV prevention [39].

Trial Implications

In line with the guidance form UNAIDS, this trial will provide a robust and rigorous evaluation of the efficacy of mobile serious games in increasing HIV risk perception in a resource limited setting such as Swaziland. Findings from this study will be made available to Swaziland authorities and stakeholders working to improve HIV prevention in Swaziland. We envision that the results of this study will be highly relevant to HIV prevention interventions in Swaziland and will inform future innovative strategies for HIV prevention. We are hopeful that our results will be generalizable to other settings in SSA. To our knowledge this is the first randomized control trial of a mobile serious games–based study to increase HIV protective behaviors in Swaziland and SSA; therefore, our findings will be a timely contribution to literature.

Acknowledgments

We would like to acknowledge Formula D Interactive for development of the game and Net Storm Technologies for the website development. Further, we thank Mr Norihisa Wada for his advice and support.

Authors' Contributions

MK, MOK and BWL led study conception, intervention design, and methodology, statistical design, programing platform, and intervention user interface design, and will lead study implementation. CE participated in the study design and intervention development. PPM participated in the study conception, statistical design, and intervention development. TT and SPS participated in the study conception, design and statistic design, and intervention development. BWL will establish recruitment and randomization of participants. BWL and MK drafted the protocol, and all authors read and edited drafts of the protocol and approved the final protocol manuscript.

Conflicts of Interest

The authors declare that they have no competing interests. Though as stated earlier, BWL received funding for intervention development from Hayao Nakayama Foundation for Science & Technology and Culture, our funding agreement gives us full

control over primary data, statistical analysis, and the freedom to publish findings whether negative or positive, as is standard precaution to ensure potential competing interests are kept in check [21].

Multimedia Appendix 1

Intervention development.

[PDF File (Adobe PDF File), 33KB - resprot_v5i4e224_app1.pdf]

Multimedia Appendix 2

Pre- and post-intervention questionnaire for the SGpriv trial.

[PDF File (Adobe PDF File), 109KB - resprot_v5i4e224_app2.pdf]

Multimedia Appendix 3

Informed consent form.

[PDF File (Adobe PDF File), 22KB - resprot_v5i4e224_app3.pdf]

Multimedia Appendix 4

Trial information sheet.

[PDF File (Adobe PDF File), 112KB - resprot_v5i4e224_app4.pdf]

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Abbreviations

AIDS: acquired immune deficiency syndrome
eNSF: Extended National Multi-sectoral HIV/AIDS Framework for 2014–2018
HIV: human immunodeficiency virus
M: mean
PRHS: perceived risk of HIV infection scale
SSA: Sub-Saharan Africa
UNAIDS: United Nations Programme on HIV/AIDS

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Protocol

Pretravel Health Advice Among Australians Returning From Bali, Indonesia: A Randomized Controlled Trial Protocol

Chloe A Thomson[1,2], BSc, MInfDis; Robyn A Gibbs[2], BSc, MPH, PhD; Jane S Heyworth[1], BAppSc, GradDipHlthSc, MPH, PhD; Carolien Giele[2], BSc (Hons), RN, MPH; Martin J Firth[3], BSc; Paul V Effler[2,4], MPH, MD, FAFPHM

[1]School of Population Health, Faculty of Medicine and Dentistry, The University of Western Australia, Perth, Australia

[2]Communicable Disease Control Directorate, Department of Health, Western Australian Government, Perth, Australia

[3]Centre for Applied Statistics, School of Mathematics and Statistics, The University of Western Australia, Perth, Australia

[4]School of Pathology and Laboratory Medicine, Faculty of Medicine and Dentistry, The University of Western Australia, Perth, Australia

Corresponding Author:
Chloe A Thomson, BSc, MInfDis
School of Population Health
Faculty of Medicine and Dentistry
The University of Western Australia
Clifton Street Building
35 Stirling Highway
Perth, 6009
Australia
Phone: 61 414351802
Fax: 61 8 6488 1188
Email: chloe.thomson@health.wa.gov.au

Abstract

Background: The effect of pretravel health advice (PTHA) on travel-related illness rates is poorly understood, and to date there are no published randomized controlled trials evaluating the impact of PTHA outcomes.

Objective: This study aims to determine the effect of an online PTHA intervention on travel-related illness rates in Western Australians visiting Bali, Indonesia.

Methods: Western Australian travelers to Bali will be recruited online before departure and will be randomly allocated to an intervention or control group by computer algorithm. The intervention in this study is a short animated video, with accompanying text, containing PTHA relevant to Bali. An online posttravel survey will be administered to all participants within two weeks of their return from Bali. The primary outcome is the difference in self-reported travel-related illness rates between control and intervention groups. Secondary outcomes include the difference in risk prevention behaviors and health risk knowledge between the control and intervention groups. Further secondary outcomes include whether individuals in the control group who sought external PTHA differ from those who did not with respect to risk prevention behaviors, health risk knowledge, and health risk perception, as well as the rate of self-reported travel-related illness.

Results: The study began recruitment in September 2016 and will conclude in September 2017. Data analysis will take place in late 2017, with results disseminated via peer-reviewed journals in early 2018.

Conclusions: This will be the first randomized controlled trial to examine the effect of a novel PTHA intervention upon travel-related illness. In addition, this study builds upon the limited existing data on the effectiveness of PTHA on travel-related illness.

ClinicalTrial: Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12615001230549; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=369567 (Archived by WebCite at http://www.webcitation.org/6m0G7xJg1)

(JMIR Res Protoc 2016;5(4):e236) doi:10.2196/resprot.6549

KEYWORDS

travel medicine; tropical medicine; travel; diarrhea; clinical trial; social media

Introduction

Australian Travel Overseas

Increasing numbers of Australians are traveling overseas. The number of short-term international departures from Australia doubled to over 9.4 million in 2015, compared to the previous 10 years [1].

Bali, Indonesia has been a popular holiday destination for Australians since the 1970s. Western Australian (WA) travelers now account for nearly half of the total Australian visitors to Indonesia, increasing more than six-fold between 2006 and 2015 [1]. There were over 454,000 departures from Perth to Bali in 2015, with nine flights, on average, every day [2]. Travelers from Perth to Bali are the focus of our study.

Rates of Travel-Related Disease in Returning Travelers

Reported rates of travel-related illness vary, with studies estimating that 22-64% of travelers experience some form of health impairment while traveling, depending on the destination and season of travel [3]. In Western Australia, almost 8% of communicable disease notifications are for illnesses acquired overseas. From 2006 to 2015, the proportion of overseas-acquired infections in Western Australia attributed to travel to Indonesia rose from 10% to 42% (personal communication from Paul Saunders, Data Custodian for the Western Australian Notifiable Infectious Diseases Database at the Western Australian Department of Health, April 7, 2016) [4]. The most common notifiable diseases acquired in Indonesia are dengue fever and gastroenteritis caused by *Campylobacter* and *Salmonella* species [4].

Establishing an accurate picture of travel-related infections is difficult due to underdiagnosis and under-reporting, the highly transient nature of international travel, and the emergence of new disease risks in travel destinations. In particular, while notifiable disease data are available, there are no comparable data available for non-notifiable illnesses, such as traveler's diarrhea, among residents returning to Western Australia.

Pretravel Health Advice in Travelers

Delivering appropriate and effective pretravel health advice (PTHA) to travelers may be important to reduce the risk of illness to travelers and to prevent the importation of travel-related diseases [5]. The average proportion of travelers seeking professional PTHA globally, as reported in airport surveys, is approximately 48% [5]. Travelers from the United States, Australia, and Asia are reported to consistently fall below this average [6-9], with Canadian and European travelers reporting PTHA more frequently [10-12].

Outcomes of Pretravel Health Advice: Rate of Illness

There are limited and conflicting data on the impact of PTHA in reducing travel-related illnesses. A retrospective cohort study in Scotland found that people who consulted a travel doctor prior to traveling overseas were less likely to become ill than those who had seen a general practitioner [13]. However, of the 1668 participants, only 100 had attended a travel clinic. An Italian retrospective study of 300 travelers to malaria-endemic countries showed that visiting a travel clinic pretravel was protective against travelers' diarrhea, but not against fever [14]. In an analysis of European surveillance data, travelers falling ill abroad were less likely to present with malaria, acute hepatitis, HIV, or animal bites requiring postexposure prophylaxis if they had received PTHA [15].

Conversely, some researchers have concluded that PTHA does not protect against illness in travelers [16-19]. It is proposed that people who take advice prior to travel may already be more aware of travel illnesses, possibly due to previous exposure or personal susceptibility [16,17]. In a recent prospective cohort study of 1277 patients at a Swedish travel clinic, illness after travel was compared between those who complied with the advice and those reporting noncompliance or inattention to PTHA provided [19]. Self-reported compliance with PTHA was not found to be protective against illness while travelling.

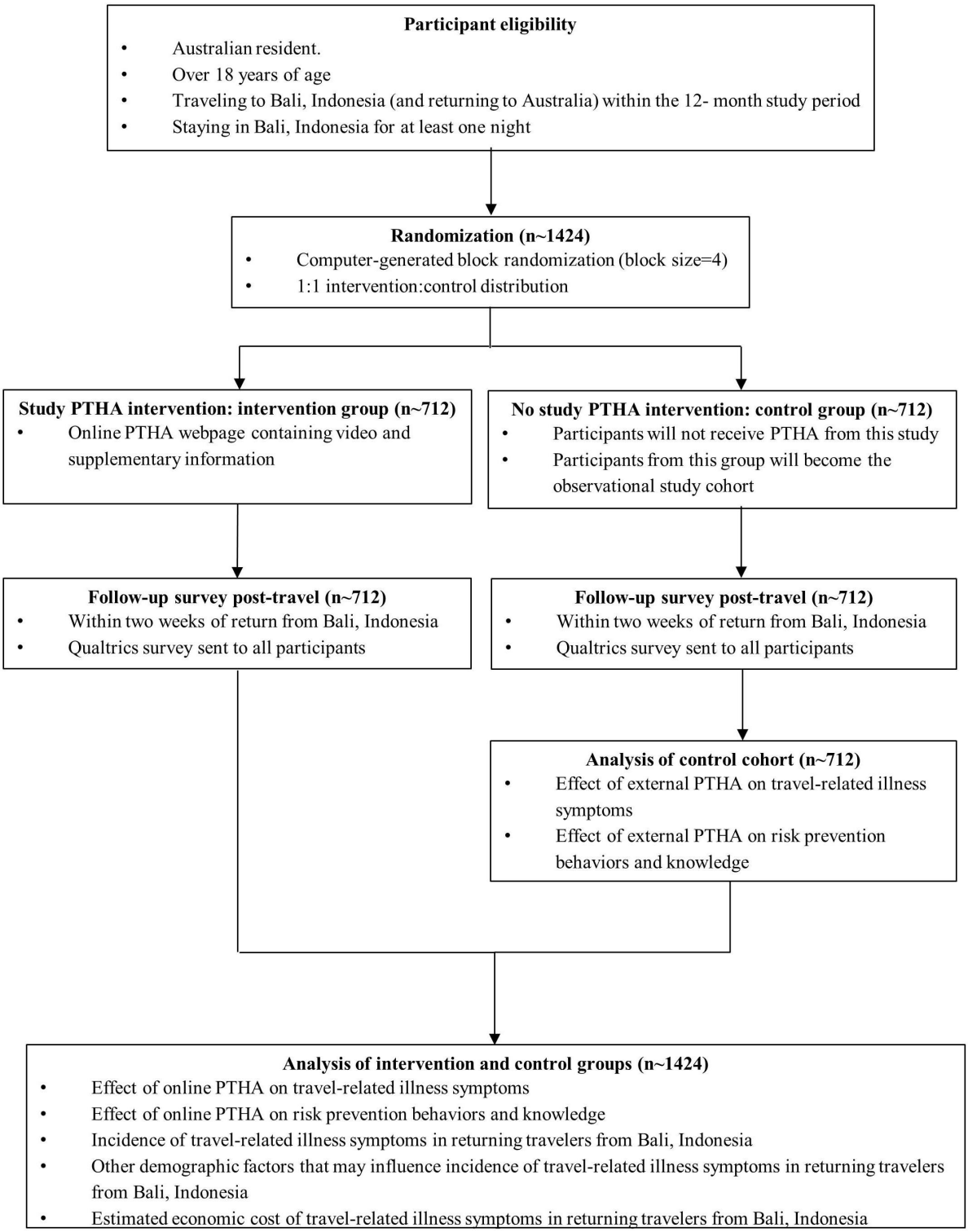
The observational studies cited above demonstrate discordant results regarding the effect of PTHA on reducing travel-related illness. However, methodological issues such as selection bias and sample size limit the inferences that can be drawn from these studies. To address these issues, our proposed study incorporates a randomized controlled trial design on a large cohort to evaluate the effect PTHA has on reported illness. Specifically, the aim of the study is to determine the effect of an online PTHA intervention on travel-related illness rates and behaviors in WA travelers visiting Bali, Indonesia.

Methods

Study Design

To evaluate the impact of PTHA on travel-related illness, rates of self-reported illness in travelers with and without PTHA will be compared (see Figure 1).

Figure 1. Pretravel health advice (PTHA) among Australians returning from Bali, Indonesia: study design and flow.



Study Population

WA residents planning to travel to Bali within a 12-month study period commencing in September 2016 will be eligible for inclusion in this study. Participants must be Australian residents, over the age of 18, traveling to Bali and staying for at least one night, and be willing and able to give consent and agree to complete the survey.

Recruitment

Recruitment will take place online, via advertisements promoting the Bali travel survey, strategically located on Facebook and Google pages. The advertisements will run for a 12-month study period to incorporate variation in travel across the year related to seasonal travel or university and school holidays. The advertisements will target people who have searched for Bali flights and/or accommodation online; this information is gathered by Facebook and Google through their single sign-on utility, as well as cookie data to track Internet activity. The main avenue for recruitment is the Internet because a previous study demonstrated that 87% of travelers to Bali make pretravel purchases—flights or accommodation—online [20]. Clicking on the advertisement will take people to a webpage, which briefly describes the study. People interested in enrolling in the study will be asked to enter their departure date, return date, sex, age range, and email address in an online form. This information will allow researchers to determine the age range and sex of those participants who later may be lost to follow-up. Participants will be asked to check a box to indicate that they consent to participate in the study. Travelers can only participate once in the study; multiple enrollments from the same email address will be blocked.

To assist with recruitment, participants will be offered an incentive of entering a lottery to win one AUD $1000 gift voucher or one of 10 AUD $100 gift vouchers. The winning names will be drawn upon study completion. Participants will be informed of the incentive via the online advertisement, consent page, and initial welcome email they receive.

Randomization

Randomization will be performed using a custom-built computer algorithm. Participants will be randomly allocated into control or intervention groups after completion of the online enrollment form, and the allocation will be sent to the email management program (MailChimp) used in the study. A block randomization (block size=4) with a uniform 1:1 allocation will be used.

Intervention

All participants will receive an email following enrollment containing a welcome message and a reminder to look for an email within two weeks of their return date. For participants allocated to the intervention group, this email will contain the link to the PTHA intervention.

The intervention in this study is a short, approximately 3-minute, online animated video containing PTHA specific to Bali and Southeast Asia. Topics covered include foodborne illness (eg, Bali belly), mosquito-borne illness (eg, dengue, chikungunya, and Zika), avoiding monkey and canine contact (eg, rabies), and checking measles vaccination status. This video is complemented by PTHA in text below the video and the webpage is optimized for mobile devices. This intervention was developed in consultation with a video producer who has previously created videos for the WA Department of Health. The information in the video and text was developed from a review of the travel-related illness literature, as well as reputable websites such as the Australian government smartraveller.org website [21]. This website was the only PTHA source that showed higher levels of health knowledge among travelers to Bali participating in an airport survey in 2014 [20]. The video producers will provide a *video heat map* that graphs each viewing session (ie, where and when the video was watched, which portions were skipped or watched again, and the percentage of the video that each participant watched). The participant may view the video multiple times, accessing it through the email link. The control group will not receive access to this PTHA video, but they may access PTHA on their own accord.

Posttravel Follow-Up

Within two weeks of the participants' nominated return dates, they will receive an email containing a link to the posttravel survey, which will be optimized for mobile devices. The control and intervention groups will receive links to surveys that are almost identical, apart from the wording of one question on PTHA. For the intervention group, this question will be phrased to make it clear they are being asked about PTHA received external to this study (ie, PTHA from their general practitioner or from their own Internet search). If the participant does not complete the survey within a week, a second email will be sent to the participant.

The survey will contain questions in six general themes: (1) information about their trip to Bali, (2) PTHA behaviors, (3) risk prevention behaviors (sample question presented in Textbox 1), (4) knowledge about disease risk (sample question presented in Textbox 2), (5) illness and symptoms during and/or posttravel, and (6) basic demographic information. The survey was adapted from a 2014 WA traveler survey [20] and will take participants, on average, between 5 and 10 minutes to complete, depending on whether or not illness is reported. The final survey and intervention were developed in consultation with WA Department of Health staff and pilot-tested, with the intervention, by a focus group in late 2015.

Textbox 1. Posttravel survey sample questions. Participants will be asked to report the health risk-prevention behaviors they engaged in during travel. Participants may choose from the following responses: Daily, Every 2-3 days, Once a week, and Never.

Please answer the following questions about your behavior during your recent trip to Bali.

- How often did you use insect repellent on this trip?
- How often did you use alcohol-based hand sanitizer on this trip?
- How often did you use a mosquito net on this trip?
- How often did you use mosquito protective clothing on this trip? (eg, long sleeves)
- How often did you eat eggs with a runny yolk on this trip? (eg, fried egg on top of fried rice)
- How often did you eat fresh fruit you did not peel yourself on this trip?

Textbox 2. Posttravel survey sample questions. Participants will be asked to report their health risk knowledge posttravel. Participants may choose from the following responses: Agree, Disagree, and Unsure.

The following questions concern your opinions on health risks while traveling.

Please indicate whether you agree or disagree with each of the statements by ticking the appropriate box.

- The risk of someone catching measles in Bali is about the same as catching measles in Australia.
- Mosquitoes that bite during the daytime are a nuisance, but they do not transmit serious diseases.
- The ice from hotels in Bali is safe to serve in drinks.
- It is safe to feed monkeys at tourist venues in Bali.
- Salads (ie, uncooked fruits and vegetables) are safe to eat in Bali.
- You should seek urgent medical attention if you are bitten by a dog or other mammal in Bali.
- It is important to always use insect repellent when outdoors in Bali.
- If you are scratched or bitten by a monkey in Bali, you should receive treatment to prevent rabies.
- You should not eat eggs with runny yolks in Bali.

Participants who report seeking medical attention for a travel-related infection will be asked for permission to obtain specified health information relating to their illness from their health care provider. If consent is given, the participant will be asked to provide some identifying information including name, date of birth, name of medical practice or hospital visited, and the date of medical visit. Participants are advised that the information to be collected from the health care provider will include details regarding relevant diagnosis, laboratory tests, prescriptions, and, if admitted, length of stay. Letters will be sent to health care providers informing them that the participant has consented to participate in the study and that a WA Department of Health employee will contact them within the week by telephone. The WA Department of Health employee will conduct a phone interview with the health care provider using a uniform script. The self-reported data on diagnoses, health services accessed, and treatment will be validated against the health records.

Study Outcomes and Data Analysis

Overview

The primary outcome of the study is a difference in self-reported overall travel-related illness between the intervention and control groups. Secondary outcomes are differences in risk prevention behaviors (Textbox 1) and health risk perceptions (Textbox 2) between the intervention and control groups. The economic cost of travel-related illness symptoms in returning travelers from Bali will also be estimated.

Data Analysis: Primary Outcome

Data analysis will be carried out using Epi Info version 7 (Centers for Disease Control and Prevention) and Stata version 12 (StataCorp LP).

The proportion of travelers in the control and intervention groups who self-report illness during their travels, or within two weeks of returning home, will be compared. A univariate analysis will be carried out using Pearson's chi-square test for comparison of proportions and a *t* test for comparison of mean risk prevention behaviors and knowledge. Logistic regression analyses will be undertaken to estimate the impact of the intervention, while adjusting for other variables such as age, sex, and use of external PTHA, if differences between intervention and control groups are observed at the baseline. Intention-to-treat analysis will be undertaken.

Data Analysis: Secondary Outcomes

Data from all participants will also be used to determine the cumulative incidence of illness symptoms in travelers returning from Bali. The impact of demographic factors, risk prevention behaviors, and knowledge on the risk of travel-related illness symptoms in the study population will be analyzed using logistic regression.

Data from the control group will be used to assess further secondary outcomes. A difference in self-reported illness, risk prevention behaviors, and health risk knowledge between those that sourced PTHA independently—external to the study—and those who did not receive any PTHA will be assessed. In addition, self-reported illness symptom rates in travelers returning from Bali will be determined.

The proportion of travelers in the control group that received PTHA from an alternative source, the source of this travel advice, and differences in demographic groups will be compared between travelers who reported illness and those who did not.

Cost-of-Illness Analysis

Data from all participants in this study will be used to estimate the cost of travel-related illness in Western Australian travelers to Bali. The cost-of-illness analysis will be carried out using the framework described by Abelson et al [22] to determine the cost of foodborne illness in Australia and New Zealand [23,24]. Costs measured in this analysis will be direct health care costs—including doctor visits, hospitalizations, medical evacuations, and laboratory tests, both in Bali and Australia—and indirect health care costs—including indirect non-health care costs (eg, workdays lost).

Sample Size Calculation

The sample size calculation was based upon the online PTHA intervention lowering the rate of self-reported illness in Western Australians returning from Bali by 10%. Existing literature

suggests that reduction in illness as a result of visiting a travel doctor before departure is approximately 20% [13,14]. The sample size calculation assumed an illness rate of 40% in the control group [3], with a reduction of 10% in the intervention group, detected at 80% power with a *P* value of .05. A sample size of 712 participants completing the study—356 control and 356 intervention participants—was determined using PS: Power and Sample Size Calculation statistical software [25]. Assuming approximately 50% of participants are lost at follow-up, which is the average for Internet-based trials [26], and although we expect less loss because of the incentive, at least 1424 participants—712 exposed and 712 unexposed participants—would need to be enrolled in the study.

Data Management

The Qualtrics survey tool will be used to create and conduct the online survey [27]. All information to and from the Qualtrics server is encrypted using the Transport Layer Security protocol. The Qualtrics servers are protected by Web application firewalls and Qualtrics employs an intrusion detection system to monitor system access for unauthorized uses. Qualtrics data collected in Australia are stored in Sydney, Australia.

Strengths and Limitations

There are multiple benefits to using our proposed study design for this project. It will be possible to simultaneously determine base rates of illness and compare existing PTHA practices (ie, PTHA sourced by the participants independently) and a novel intervention.

Limitations include the potential exclusion of those travelers without access to, or unfamiliarity with, a computer or mobile phone; however, 87% of WA travelers to Bali used the Internet to purchase flights and/or accommodation [20]. Also, 2015 social media statistics report that 82% of Australian Internet users use Google and 60% use Facebook each month for around three and eight hours, respectively [28]. In addition, the PTHA intervention is targeted to, and intended for use by, Internet-savvy consumers.

It is possible that participants with an interest in health will be more likely to enroll in this study. This may lead to an over-reporting of PTHA-seeking and risk-prevention behaviors. To minimize this effect, the online advertising and study enrollment webpage will have an emphasis on the Bali travel experience more generally and will not highlight the health risks associated with travel to this destination. In addition, the results from this study will be compared to the results from the 2014 airport survey previously undertaken by our group, which used different methodology. The demographics of the two study cohorts will be compared to determine how the online cohort compares to the cohort recruited at the airport. Participants may also claim more "favorable" health-seeking behaviors when providing health information to a health authority. To reduce this effect, the surveys have been designed to be self-administered.

The cost-of-illness analysis has several limitations. While every effort will be made to follow up with participants who report visiting a health care professional about their illness, this may not always be possible. The participant may decline to provide their information, this information may be incorrect, and some health care professionals may decline to provide the required information. In addition, if the participant has reported illness with ongoing treatment, it may be difficult to determine an accurate cost.

Ethics

Ethical approval has been obtained from the Western Australian Department of Health Human Research Ethics Committee (RA/4/1/8110) and the University of Western Australia Health Human Research Ethics Committee (Project #2015/58). This study has been registered with the ANZCTR (trial ID: ACTRN12615001230549).

Results

The study began recruitment in September 2016 and will conclude in September 2017. Data analysis will take place in late 2017, with results disseminated via peer-reviewed journals in early 2018.

Discussion

Approximately 10-20% of Western Australians visit Bali each year [1] and are exposed to the increased risk of illness associated with traveling to a developing nation. There are limited data regarding the travel-related illness burden, as infections may be non-notifiable, or notifiable but underdiagnosed and under-reported. Still, existing notifiable disease data suggest Bali travel contributes a significant burden of disease to Western Australia. Internet-based preventative measures present an opportunity for health departments to learn how to better protect the health of their residents abroad. As the number of notifiable disease cases attributed to Indonesia has risen in Western Australia [4], it is clear that current strategies are not adequate.

There have been very few studies, and no randomized controlled trials, determining the impact of PTHA on travel-related illnesses [13,14,19]. It is hoped that the results of this study may have broad applications locally and internationally. If a strategy of delivering PTHA online can prove effective, this intervention could be implemented more broadly.

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Authors' Contributions

Miss Thomson was responsible for the initial conception and design of the study and drafted the first draft of the manuscript. Dr Effler and Dr Gibbs contributed to the conception and design of the study and provided critical review of the manuscript. Prof Heyworth and Ms Giele contributed to the design of the study and provided critical review of the manuscript. Mr Firth contributed to the data analysis considerations.

Conflicts of Interest

None declared.

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Abbreviations

PTHA: pretravel health advice
WA: Western Australian

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Protocol

Examining Incentives to Promote Physical Activity Maintenance Among Hospital Employees Not Achieving 10,000 Daily Steps: A Web-Based Randomized Controlled Trial Protocol

Marc Mitchell[1], PhD; Lauren White[2], MSc; Paul Oh[1], MSc, MD; Matthew Kwan[3], PhD; Peter Gove[4], MSW; Tricia Leahey[5], PhD; Guy Faulkner[6], PhD

[1]Toronto Rehabilitation Institute, University Health Network, Toronto, ON, Canada
[2]Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, ON, Canada
[3]Department of Family Medicine, McMaster University, Hamilton, ON, Canada
[4]Green Shield Canada Inc, Toronto, ON, Canada
[5]University of Connecticut, Storrs, CT, United States
[6]School of Kinesiology, University of British Columbia, Vancouver, BC, Canada

Corresponding Author:
Marc Mitchell, PhD
Toronto Rehabilitation Institute
University Health Network
347 Rumsey Rd
Toronto, ON
Canada
Phone: 1 416 660 7781
Fax: 1 416 425 0301
Email: marc.mitchell@uhn.ca

Abstract

Background: The economic burden of physical inactivity in Canada is estimated at Can $6.8 billion (US $5 billion) per year. Employers bear a substantial proportion of the economic costs, as they pay more for inactive workers in health care and other organizational costs. In response, many Canadian employers offer wellness programs, though these are often underutilized. While financial health incentives have been proposed as one way of increasing participation, their longer term effects (ie postintervention effects) are not clear.

Objective: The objective of this paper is to outline the methodology for a randomized control trial (RCT) examining the longer term impact of an existing physical activity promotion program that is enhanced by adding guaranteed rewards (Can $1 [US $0.74] per day step goal met) in a lower active hospital employee population (less than 10,000 steps per day).

Methods: A 12-week, parallel-arm RCT (with a 12-week postintervention follow-up) will be employed. Employees using Change4Life (a fully automated, incentive-based wellness program) and accumulating fewer than 10,000 steps per day at baseline (weeks 1 to 2) will be randomly allocated (1:1) to standard care (wellness program, accelerometer) or an intervention group (standard care plus guaranteed incentives). All study participants will be asked to wear the accelerometer and synchronize it to Change4Life daily, although only intervention group participants will receive guaranteed incentives for reaching tailored daily step count goals (Can $1 [US $0.74] per day; weeks 3 to 12). The primary study outcome will be mean proportion of participant-days step goal reached during the postintervention follow-up period (week 24). Mean proportion of participant-days step goal reached during the intervention period (week 12) will be a secondary outcome.

Results: Enrollment for the study will be completed in February 2017. Data analysis will commence in September 2017. Study results are to be published in the winter of 2018.

Conclusions: This protocol was designed to examine the impact of guaranteed rewards on physical activity maintenance in lower active hospital employees.

ClinicalTrial: ClinicalTrials.gov NCT02638675; https://clinicaltrials.gov/ct2/show/NCT0 2638675 (Archived by WebCite at http://www.webcitation.org/6g4pvZvhW)

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KEYWORDS

financial health incentives; physical activity; behavioral economics; randomized controlled trial; workplace health

Introduction

There is a substantial economic burden associated with physical inactivity in Canada [1,2]. According to Janssen [1], the cost of inactivity is Can $6.8 billion (US $5.0 billion) per year, posing a significant threat to the sustainability of the Canadian health care system. On the other hand, the projected cost savings of increasing the proportion of Canadians who meet physical activity guidelines (ie, 150 minutes of moderate-vigorous physical activity [MVPA] per week, or roughly 10,000 steps per day) by just 1% is Can $2.1 billion (US $1.6 billion) per year [3]. Notably, significant reductions in health risk and associated costs and improvements in quality of life are seen when inactive (<5000 steps per day) and low active (5000 to 7499 steps per day) adults become a little more active (eg, 1000 more steps per day) [3,4]. The workplace is an ideal setting for physical activity promotion since Canadian jobs are increasingly desk-based and sedentary [5].

Not surprisingly, Canadian employers bear a significant proportion of the inactivity burden because they pay more for lower active (<10,000 steps per day) workers in health care expenses [6]. For instance, while Canadian provincial and territorial governments cover hospital- and physician-related medical costs, employers in Canada often subsidize other medical expenses, one of the costliest being chronic disease–related medications [6]. A study by Wang and colleagues [7] helps to illustrate the economic benefit of a more physically active employee population. This study found that moderately active (1 to 2 times per week) and very active (3 or more times per week) employees had Can $250 (US $185) less paid health care costs annually when compared to their sedentary counterparts (0 times per week). In addition, wellness initiatives that increase employees' physical activity have been shown to reduce absenteeism, presenteeism, and turnover [8-11]. Finally, according to health care surveys by Towers Watson [12] and Sanofi [6], Canadian employers have a vested interest in employees' physical activity levels given the positive effects on organizational costs (eg, health care expenses) and performance (eg, presenteeism).

As a result, the majority (72%) of large Canadian companies now offer wellness programs to help reduce overall health care spending and increase productivity [6]. For participating employees, such programs have been associated with a reduced risk of chronic illness and lower medical claim costs [13,14]. However, these programs are chronically underutilized. In Canada, wellness program participation rates are extremely low, less than 10% [6]. This means that more than 90% of eligible Canadian workers are not reaping the benefits of company-sponsored wellness programming. Behavioral economics, a new branch of economics that is complemented by insights from psychology, has stimulated renewed interest in financial health incentives as a means to increase wellness program participation [5,15-17].

Behavioral economics recognizes that human decisions are biased in systematic ways and that that these "decision biases" can be leveraged to facilitate healthy decision making [18]. For example, according to behavioral economics, increasing the immediately rewarding aspects of a healthy behavior (eg, with a financial incentive) may offset the so-called "present bias" where people tend to overweigh the immediate costs (and discount the future benefits) of those behaviors (eg, time out of a busy schedule to exercise) [19]. Systematic reviews by Mitchell et al [20] and Strohacker et al [21] support the theory suggesting that incentives generally stimulate physical activity in the short-term (less than 3 months) and while incentives are in place. These reviews also suggest that not enough studies have examined the longer term (ie, postintervention) impact of incentives on physical activity to draw conclusions about sustained effects [20,21]—an issue of particular interest to Canadian employers looking to deliver cost-effective incentive-based wellness programs [5,6].

Of the randomized controlled trials (RCTs) that have recently examined this issue [22-26], 4 have observed a regression to baseline behaviors after incentive removal [22-24,26] and only 1 has demonstrated persisting physical activity [25]. One reason for this may have to do with the limited application of health behavior change theories in the design of incentive programs [19]. It is increasingly suggested that for incentives to both stimulate and sustain health behavior change they should be grounded in theory [19,27,28]. In the single "positive" study, behavioral maintenance (ie, 16-week follow-up) was driven entirely by the lower active subgroup (ie, university students visiting the gym fewer than once per week at baseline)—possibly because exposure to the new behavior (ie, gym attendance) led to increased confidence to perform that behavior [25]. This presumption aligns well with self-determination theory, a global theory of motivation focused on the extent to which behaviors are done volitionally, which suggests that incentive programs designed to increase a person's confidence are more likely to foster self-determined (or intrinsic) motivation [29,30]—a key driver of sustained physical activity [30].

Realizing the potential of incentives to promote sustained physical activity, therefore, will be contingent on research that improves the understanding of theoretical (eg, self-determined motivation) and contextual (eg, target group characteristics) factors that may influence incentive program effectiveness. The purpose of this protocol is to outline the design of an RCT that will examine the longer term effects of an existing physical activity promotion program that is enhanced by guaranteed incentives for lower active employees only in a real-world, ecological setting. We hypothesize that targeting lower active employees with incentives for tailored daily step goals (in addition to the generic, one-size-fits-all approach to goal setting that is typically used) may be more likely to create mastery

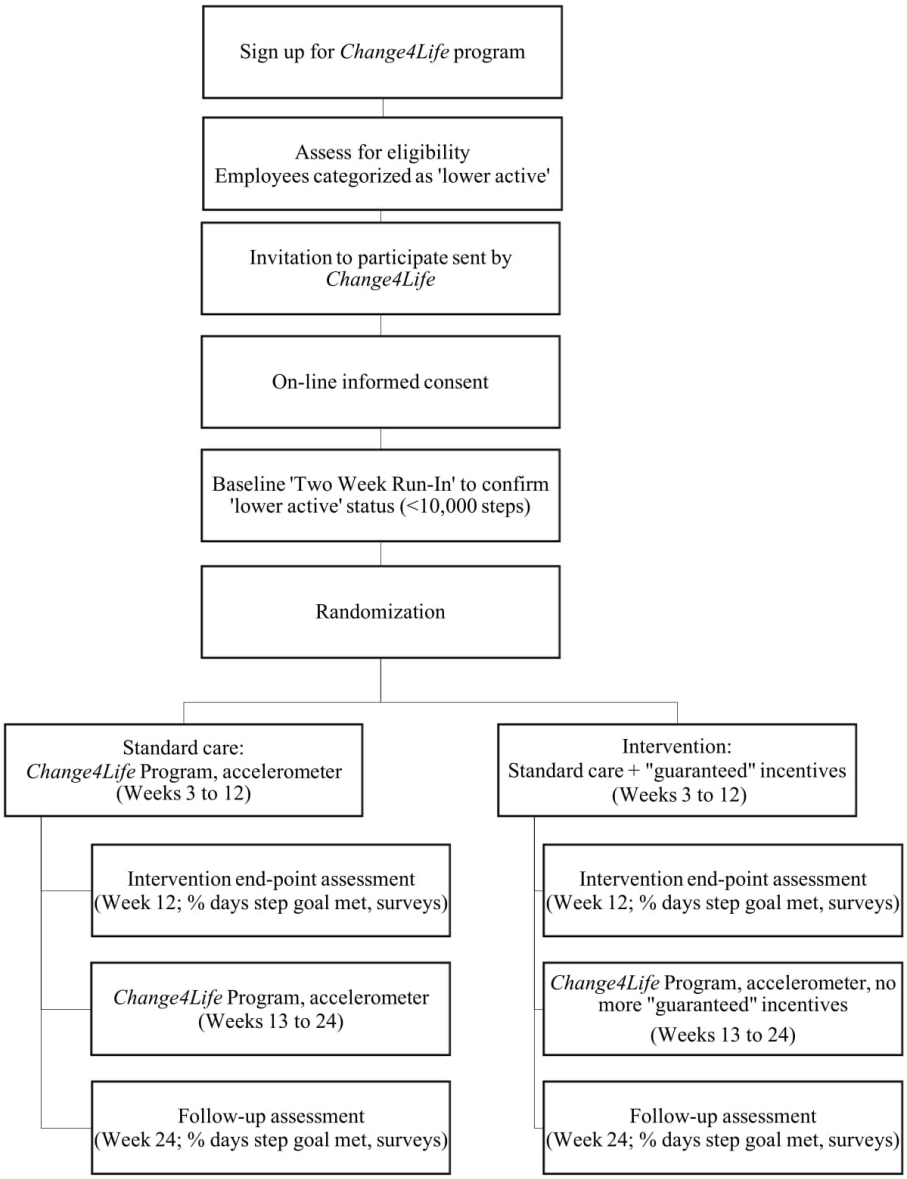
experiences, increase confidence, and promote physical activity maintenance.

Methods

Study Design

A 12-week, parallel-arm RCT with a 12-week postintervention follow-up will be employed to examine the impact of an enhanced (Can $1 [US $0.74] per day) incentive program on objectively measured physical activity among lower active employees (<10,000 steps per day) within a large Canadian hospital network. See the study flow chart in Figure 1, including an overview of the enrollment process and assessments.

Figure 1. Study flowchart.



Study Population and Recruitment

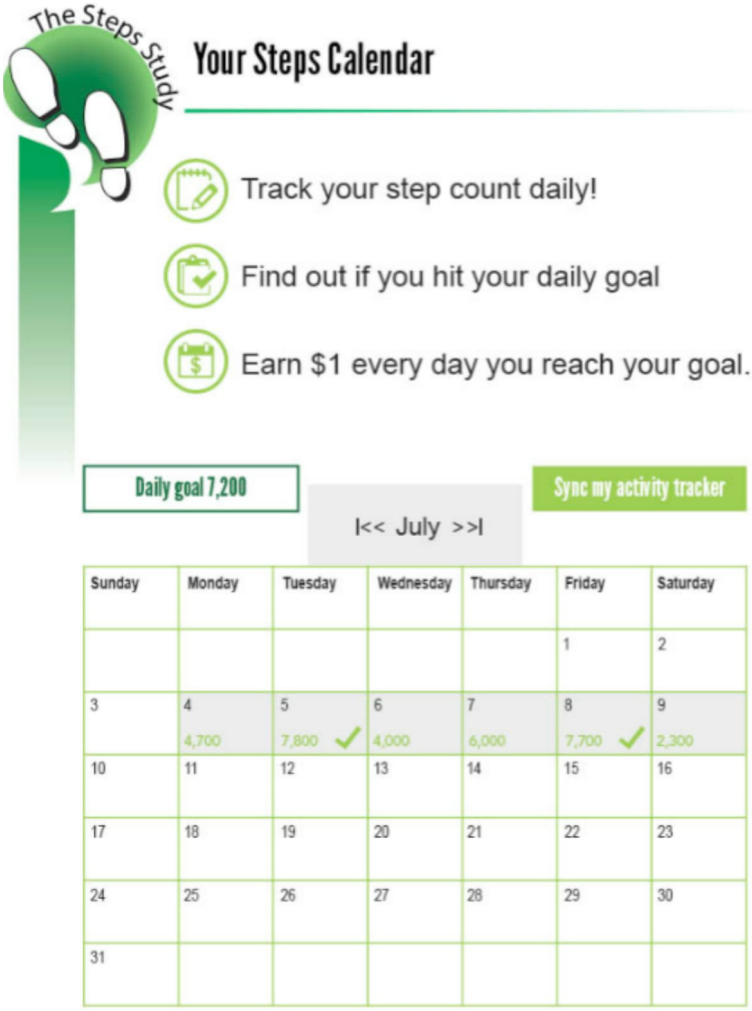
This study will specifically target lower active employees (<10,000 steps per day). Hospital employees (including health care professionals and administrative and business support personnel) enrolled in the Change4Life program will be invited to participate via website notifications and hospital newsletters. Only data from participants who accumulate less than 10,000 steps per day during the “2-Week Run-In” period will be included in the analysis. Further eligibility criteria will include: 18 years of age or older, English speaking, ready Internet access, and without medical conditions exacerbated by physical activity as assessed by the Physical Activity Readiness Questionnaire Plus. Eligible participants will be asked to provide their expressed consent using the online consent form.

Change4Life

Change4Life, a Web- and incentive-based health education and behavior change program, was launched in May 2015 at the hospital network. The hospital network is offering Change4Life to 6500 full-time employees across 8 worksites. Specifically, the Web-based wellness program offers educational information

relating to chronic disease prevention via learning modules (ie, series of short articles and quizzes). All employees who sign up for Change4Life are rewarded with points for completing these modules as well as for setting health-related goals, self-reporting health behaviors/outcomes, identifying barriers, and creating action plans—self-regulatory behaviors that have been theorized and empirically proven to promote sustained health behavior change (see the Change4Life Steps Study calendar in Figure 2) [29,30]. Using points, employees may "purchase" ballots in the Change4Life reward store and enter into drawings for health-promoting products (eg, groceries, exercise equipment). At the hospital network, Change4Life operates as a minimal chance-based incentive program (low frequency, low magnitude rewards), where participants have less than a 1 in 100 chance of winning reward drawings that generally range in value from Can $5 to $20 (US $3.70-$14.80).

Figure 2. Change4Life Steps Study calendar (ie, tracking page).



Standard Care Group

Standard care group participants will have access to Change4Life and will receive the standard minimal chance-based incentives (ie, less than 1 in 100 chance of earning Can $5 to $20 [US $3.70-$14.80] vouchers) for completing learning modules and health tasks. In addition, standard care participants will be asked to wear the accelerometer, which tracks steps and 10-minute bouts of MVPA per day, synchronize the device to the Change4Life program daily, and reach tailored daily step count goals for 10 weeks (weeks 3 to 12). Standard care participants will be instructed to increase their daily step counts by 1000 steps above their baseline average every 2 weeks until they reach the target goal of 3000 extra steps at week 7 (see Table 1). Change4Life will automatically calculate the average baseline value in the early hours of day 1, week 3 using data uploaded the previous 2 weeks (the Run-In period)—days with step counts less than 100 or greater than 50,000 will not be included in calculations [31]. This tailored and graded approach to setting step goals is more realistic than the traditional 10,000 step target (ie, the average Canadian adults accumulates only about 5000 steps per day) [32], may increase chances of intervention success (versus offering a lofty 10,000 step per day goal for everyone), and has worked well in employee populations in the past [33].

Table 1. Daily step count goals across the Change4Life program.

Study week	Step count goal
Weeks 1-2	2-Week Run-In (to confirm lower active status and calculate daily step count average)
Weeks 3-4	Increase daily steps by 1000 above baseline average
Weeks 5-6	Increase daily steps by 2000 above baseline average
Weeks 7-8	Increase daily steps by 3000 above baseline average
Weeks 9-12	Maintain steps at 3000 above baseline average

Intervention Group

The only difference between the standard care and intervention groups will be the addition of the guaranteed incentive (Can $1 [US $0.74] per day). During the intervention period (weeks 3 to 12), intervention group participants will be eligible to earn Can $1 (US $0.74) in vouchers (eg, groceries, coffee, or movies) each time tailored daily step goals are achieved. The total amount available over the intervention period will be Can $70 (US $51.82). Previous research suggests that as little as Can $6.75 (US $5) per week may be sufficient to produce favorable lifestyle health behavior changes [34], thus Can $7 (US $5.18) per week (Can $1 [US $0.74] per day) was chosen as the size of the incentive. During the study follow-up period (weeks 13 to 24), intervention participants will no longer receive the per day reward for reaching daily step goals.

Outcome Measures

The primary study outcome will be the mean proportion of participant-days that step goals are achieved during week 24 (the postintervention follow-up assessment period, T3). Mean proportion of participant-days that step goals are achieved during week 12 (intervention end point, T2) and volume of steps and 10-minute bouts of MVPA per week at T2 and T3 will be secondary outcomes. Physical activity will be objectively assessed using the StepsCount Piezo Rx accelerometer (StepsCount Inc, Deep River, ON, Canada). The Piezo Rx is a medical-grade device with a single axis piezoelectric sensor. This device has been found to be valid in calculating step counts and MVPA among adult participants [35,36]. Standard care and intervention participants will be encouraged to wear their accelerometer and synchronize it to the Change4Life program during the baseline 2-Week Run-In period (T1), as well as at the intervention end point (T2), and follow-up assessment (T3) with Can $10 (US $7.40) study retention vouchers; these vouchers for assessment completion will help minimize dropout and will not be contingent on step goal achievement.

The adherence outcome variables will be mean number of missing step count entries per week as well as mean number of Change4Life website log-ins in general. Participants' self-determined motivation to exercise will be examined using the Behavioral Regulation to Exercise Questionnaire-3 (BREQ-3) [37,38]. Participants' walking self-efficacy will be assessed using a modified version of the Self-Efficacy for Exercise Scale (SEE Scale) [39]. The BREQ-3 and the SEE Scale will be administered online at baseline (T1), intervention end point (T2), and during the follow-up assessment period (T3). The differential impact of the Can $1 (US $0.74) per day incentive on the various physical activity outcomes will be explored. For instance, we may find that while the guaranteed incentives stimulate step goal achievement at T2, they also undermine self-determined motivation and thus the prospect that people will continue to exercise after the incentive is removed.

Sample Size

Sample size calculations indicate that a final sample of 158 participants (79 per group) ensures 80% power ($P<.05$; 2-tailed) to detect a 0.20 difference in the mean proportion of participant-days step goals are reached between intervention and standard care groups for week 24 [24]. This calculation assumes that the mean proportion of participant-days step goal achieved in the intervention group in week 24 will be 0.40 (vs 0.20 in the standard care group) [24]. On the basis of data published by Patel et al [22] this difference translates into a relative effect size of 0.40. The participant enrollment target will be increased to 174 to account for a potential 10% dropout rate, a rate that has been reported by other similar studies [22,26].

Randomization and Blinding

Employees accumulating fewer than 10,000 steps per day during the baseline period (study weeks 1 and 2) will be randomized using a single, constant allocation ratio (1:1) to standard care or intervention groups. Randomization will occur using an online random number generator [40]. Participants will not be blinded to study group allocation. The research analysts will be blinded to group allocation until after the study is completed.

Statistical Analyses

For each participant on each day of the study (participant-day level) continuous step count data will be obtained and screened for outliers (less than 100 steps per day, more than 50,000 steps per day) [31]. If participants did not synchronize their accelerometer for at least 3 separate workdays at T2 and T3, the last observation will be carried forward using T1 or T2 means [33]. This procedure conservatively assumes no change in variables and allows analysis by intention-to-treat. The step count data will then be dichotomized at the participant-day level to create a binary variable where participants achieved (value = 1) or did not achieve (value = 0) their step goal. Using this binary variable, the mean proportion of participant-days where step goals were achieved at week 24 will be compared.

SPSS version 21.0 (IBM Corp) will be used to fit a generalized linear model with participant random effects, a random intercept, time-fixed effects (T1-T3), and treatment-fixed effects (by study group). A binomial distribution with logit link for models using the binary outcome will be used to estimate the adjusted

difference in the proportion of participant-days step goal achieved, and the bootstrap procedure and resampling of participants will be used to obtain 95% confidence intervals and *P* values. Comparisons across study groups will be adjusted for mean steps per day (baseline), age, gender, and income since these have moderated incentive-effects in the past [41]. The same procedures will be used to analyze T2 (ie, intervention end) binary data.

For continuous step count (ie, mean steps per day) and bout minutes (ie, total minutes of MVPA in 10-minute bouts per week) data at T2 and T3, a generalized linear model will be used, as above, except the difference in steps per day and MVPA bout minutes between groups will be obtained using least-squares means. Also, a repeated measures analysis of variance using linear mixed models with first order autoregressive covariance structures will be used to compare changes in self-determined motivation and self-efficacy between groups. Adherence will be analyzed using *t* tests comparing the mean number of missing step count entries per week and mean number of website log-ins per month between groups. This protocol is registered with ClinicalTrials.gov [NCT02638675].

Results

Enrollment for the study will be completed in February 2017. Data analysis will commence in September 2017. Study results are to be published in the winter of 2018.

Discussion

Overview

Physical activity maintenance is critical for controlling the human and economic burden of chronic disease [1,2]. While incentives have stimulated physical activity behaviors in the past [20-26], only 1 RCT to our knowledge has produced longer term, postintervention improvements [25]. The primary aim of this protocol is to outline the design of an RCT to test whether adding theoretically informed guaranteed incentives to an existing physical activity promotion program can drive physical activity for 12 weeks after guaranteed incentives are removed in a workplace context. Since one of the risks with incentives is that they damage self-determined motivation and thus people's potential for sustained change [42], the theoretical considerations in this study extend beyond behavioral economics (which merely describes how incentives may be used as a catalyst for change) [19] to include insights from self-determination theory (which describes the conditions under which incentives may produce sustained change) [29]. The literature examining the undermining effect of incentives has mostly considered simple tasks for which initial intrinsic motivation is high, although these findings should not be generalized to lifestyle health behaviors like physical activity where initial intrinsic motivation can be low [43]. In addition, incentive schemes vary greatly in their design and can differentially moderate the undermining effect [43]. While more research is needed, schemes that target less active adults for realistic behavioral outcomes are theorized to support the internalization process and promote quality behavior change [29,30].

According to self-determination theory, incentives may help to build self-determined motivation primarily through their action on self-efficacy, especially for lower active people who exhibit fewer intrinsic motives to begin with (less motivation to crowd out) [44,45]. Regarding physical activity, one hypothesis is that incentives may increase a person's self-efficacy to become more active by exposing them to a form of physical activity for the first time [29,30,44,45]. Especially if the activity is an achievable one (eg, walk 1000 more steps per day vs walk 10,000 steps per day), individuals may find their confidence to be more active increases after just a few weeks [29,30,44,45]. To align with self-determination theory, then, we decided to (1) target lower active employees only (because they have less/little self-determined motivation to crowd out) [23,24,29] and (2) offer incentives contingent on tailored/realistic step goal achievements (to maximize mastery experiences and increase self-efficacy) [45]. The main theoretical contribution of this protocol therefore is in its application of self-determination theory to the design of the incentive intervention (ie, realistic behavioral targets) and program evaluation (ie, tracking motivation throughout).

The practical implications of this research are also important given the growing popularity of incentive-based wellness programs [42]. First of all, we hope the results of this RCT encourage others to incorporate a simple but important incentive program design nuance by offering rewards contingent on tailored, rather than generic, physical activity goals. The pervasiveness of wearable physical activity monitors in general (eg, smartphones with built-in accelerometers) may make it easier for interventionists or employers to individualize physical activity goals in the context of a health rewards system (by setting goals based on an individual's own physical activity pattern). Another practical implication of this study may be in encouraging employers to consider guaranteed rewards systems for higher-risk, higher-cost employees only versus the traditional (and largely ineffective) approach of offering low-frequency, low-magnitude chance-based rewards to everyone. To manage budgets, employers often opt for the seemingly more affordable chance-based reward scheme even though there is limited evidence of its effectiveness [20]. Finally, if incentives are not amenable to employees, the intervention will almost certainly fail [46]. Employers deploying incentives should therefore consider any unintended consequences of this novel approach, including (1) perceived unfairness (eg, Why should only lower active employees be rewarded to exercise?), (2) opportunity cost concerns (eg, Should we really be spending money on this?), (3) gaming/cheating (eg, I will cheat by getting my friend to track my activity for me), and (4) low overall acceptability (eg, I don't want my employer telling me what to do) [47-49]. One way of circumventing the perceived unfairness issue may be in offering minimal chance-based rewards to all employees regardless of physical activity level as well as an enhanced incentive program to employees qualifying as lower active or higher-risk. Supporting such an approach with empirical data may alleviate concerns around unfairness, opportunity cost, and acceptability as well [47-49].

Limitations

This study protocol is not without limitations. First, given that only employees already enrolled in Change4Life (less than 10% of the eligible employee population) will be assessed for eligibility and invited to participate in the study, the results may not be generalizable. By recruiting only lower active Change4Life enrollees, we will learn more about how a higher risk employee population responds to incentives. Since the hallmark of Web-based health interventions is low engagement [49], there is potential for significant study dropout as well (ceasing daily device synchronization and not participating in assessments), especially among standard care participants. Both intervention and standard care participants will be encouraged to participate in all scheduled assessments (baseline, intervention end point, follow-up) with Can $10 (US $7.40) vouchers. Given the low participant burden and potential for lower active individuals to experience improved health, however, this voluntary incentive-based wellness program may be met with relatively high levels of engagement. Finally, participants will not be blinded to study group allocation, which could contaminate the results. Knowledge of group allocation will be assessed using a study exit survey to monitor this potential confounder.

Conclusion

The objective of this study is to improve the longer term maintenance of physical activity through a better understanding of how to structure and evaluate incentive programs. Incentives are not a panacea, of course, and may not work for all people, but as part of broader package of interventions and under certain conditions incentives may have a role to play in driving sustained health behavior change.

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Conflicts of Interest

Dr Marc Mitchell reports grant support from the Canadian Institutes of Health Research and the University Health Network as well as in-kind research support from Cookson James Loyalty Inc. Further, he is president of the financial health incentive consulting company Incentive Avenue Inc and reports consulting income from Carrot Insights Inc and stock options in Carrot Insights Inc.

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Abbreviations

BREQ-3: Behavioral Regulation to Exercize Questionnaire
MVPA: moderate-vigorous physical activity
SEE: Self-Efficacy for Exercise

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Protocol

Transdiagnostic Cognitive Behavioral Therapy Versus Treatment as Usual in Adult Patients With Emotional Disorders in the Primary Care Setting (PsicAP Study): Protocol for a Randomized Controlled Trial

Antonio Cano-Vindel[1,2], PhD; Roger Muñoz-Navarro[1,3], PhD; Cristina Mae Wood[1,2], PhD; Joaquín T Limonero[1,4], PhD; Leonardo Adrián Medrano[1,5], PhD; Paloma Ruiz-Rodríguez[1,6], MD; Irene Gracia-Gracia[1], MSc; Esperanza Dongil-Collado[1,7], PhD; Iciar Iruarrizaga[1,8], PhD; Fernando Chacón[1,2,9], PhD; Francisco Santolaya[1,9,10], PhD

[1]PsicAP Research Group, Complutense University of Madrid, Madrid, Spain
[2]Faculty of Psychology, Complutense University of Madrid, Madrid, Spain
[3]Faculty of Psychology, University of Valencia, Valencia, Spain
[4]Faculty of Psychology, Autonomous University of Barcelona, Barcelona, Spain
[5]Faculty of Psychology, Universidad Siglo 21, Córdoba, Argentina
[6]Fuenlabrada Primary Care Center, Health Service of Madrid, Madrid, Spain
[7]Faculty of Psychology, Catholic University of Valencia, Valencia, Spain
[8]Faculty of Social Work, Complutense University of Madrid, Madrid, Spain
[9]Spanish Association of Psychologists, Madrid, Spain
[10]Malva-Rosa Mental Health Service, Valencia, Spain

Corresponding Author:
Antonio Cano-Vindel, PhD
PsicAP Research Group
Complutense University of Madrid
Campus de Somosaguas
Madrid, 28223
Spain
Phone: 34 91 394 31 11
Fax: 34 91 394 31 89
Email: canovindel@psi.ucm.es

Abstract

Background: Demand for primary care (PC) services in Spain exceeds available resources. Part of this strong demand is due to the high prevalence of emotional disorders (EDs)—anxiety, depression, and somatic symptom disorders—and related comorbidities such as pain or chronic illnesses. EDs are often under- or misdiagnosed by general practitioners (GPs) and, consequently, treatment is frequently inadequate.

Objective: We aim to compare the short- and long-term effectiveness of group-delivered transdiagnostic cognitive behavioral therapy (TD-CBT) versus treatment as usual (TAU) in the treatment of EDs in the PC setting in Spain. We also aim to compare the effect of these treatments on disability, quality of life, cognitive-emotional factors, and treatment satisfaction.

Methods: Here we present the study design of a two-arm, single-blind, randomized controlled trial (N=1126) to compare TAU to TD-CBT for EDs. TAU will consist primarily of pharmacological treatment and practical advice from the GP while TD-CBT will be administered in seven 90-minute group sessions held over a period ranging from 12 to 14 weeks. Psychological assessments are carried out at baseline (ie, pretreatment); posttreatment; and at 3-, 6-, and 12-month follow-up. The study is conducted in approximately 26 PC centers from the National Health System in Spain.

Results: This study was initiated in December 2013 and will remain open to new participants until recruitment and follow-up has been completed. We expect all posttreatment evaluations to be completed by December 2017, and follow-up will end in December 2018.

Conclusions: We expect the TD-CBT group to have better results compared to TAU on all posttreatment measures and that this improvement will be maintained during follow-up. This project could serve as a model for use in other areas or services of the National Health System in Spain and even in other countries.

ClinicalTrial: International Standard Randomized Controlled Trial Number (ISRCTN): 58437086; http://www.isrctn.com/ISRCTN58437086 (Archived by WebCite at http://www.webcitation.org/6mbYjQSn3)

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KEYWORDS

anxiety; depression; somatization; treatment as usual; cognitive behavioral therapy; quality of life; primary care; emotional disorders; transdiagnostic therapy; medically unexplained symptoms; common mental health disorders

Introduction

Background and Rationale

Emotional disorders (EDs), including mood, anxiety, and somatization disorders, are a leading cause of disability and demand for primary care (PC) services [1,2]. According to Haro et al [1], 1-year prevalence rates in Spain for anxiety, depression, and somatization disorders are 6.2%, 4.4%, and 14.7%, respectively. In Spanish PC centers, the 1-year prevalence rates for depression, mood disorders, and mental disorders are 9.6%, 13.4%, and 31.2%, respectively [3]. These data indicate that approximately 1 out of 3 patients in the PC setting suffers from some type of mental disorder. In addition, comorbidity in these patients is high [4-6] and closely associated with poor quality of life [7], substance misuse, disability, and high health and social costs that rise in parallel with the increase in the number of comorbid disorders [8].

In 2001, the World Health Organization (WHO) estimated that the prevalence of mental disorders would continue to increase through the year 2020, thus imposing a significant social and economic burden on many countries around the world, especially in developed countries. For this reason, the WHO stressed the need to increase the number of specialized human resources to treat patients with EDs [9]. The most recent guidelines for depression and anxiety disorders published by the National Institute for Health and Clinical Excellence (United Kingdom) [10] recommend an evidence-based approach to identify the least intrusive but most effective interventions for the management of these disorders.

Cognitive behavioral therapy (CBT) is a highly efficacious and cost-effective approach to managing EDs; for this reason, it is currently considered the optimal therapy to treat these disorders. Although CBT is less expensive than most medical treatments, the costs can be further reduced by using a transdiagnostic group approach in which patients with different but related EDs (ie, they share certain commonalities, particularly high levels of anxiety and maladjusted thoughts) are grouped together [11]. This approach, known as transdiagnostic cognitive behavioral therapy (TD-CBT), addresses dysfunctional behaviors and thoughts with the aim of changing behavioral and thinking patterns. TD-CBT has been shown to be more effective than treatment as usual (TAU) in PC settings for the treatment of depression [12] and anxiety [13]; it has also been shown to be comparable or superior to many evidence-based psychological interventions for pain [14], especially when patients are referred by their general practitioners (GPs) [15].

Many patients with EDs are users of both PC and specialized care services. However, in many cases patients are misdiagnosed, with misdiagnosis rates of up to 78% for depression [16], 86% for panic disorder, 71% for generalized anxiety disorder (GAD), and 98% for social anxiety disorder [16,17]. Consequently, many patients may not receive appropriate treatment. Moreover, in the case of incorrect diagnoses, patients may also be subjected to costly, unnecessary, and potentially addictive and/or harmful (due to side effects) psychopharmacological treatments [16].

In Spain, the diagnosis of an ED is usually first made by the GP who must decide, in a very brief consultation (ie, less than 7 minutes), which psychoactive drugs to prescribe (if any) and whether or not the patient needs specialized care [18]. As a result of these time constraints, the most common treatments are pharmacological interventions. According to Codony et al [19], 39% of patients with anxiety disorders do not receive any treatment, one-third of patients receive medication alone, only 1% receive psychological therapy, and 27% receive combined psychological-medical therapy. These findings indicate that psychological treatment is underprescribed—often only as a last resort—in patients with an ED who seek help from their GP.

Despite the generalized underutilization of psychological treatments in the PC setting, in recent years, several countries—notably, the United Kingdom—have incorporated psychological services (including CBT) into the PC setting. In the last decade, the UK government developed and implemented a large-scale program entitled Improving Access to Psychological Therapies (IAPT) [20], designed to improve treatment of EDs among the general population. The results of that program have shown that CBT is as effective in routine PC as it is shown to be in research trials; importantly, these excellent results were achieved without any side effects, fewer relapses, and lower long-term economic and social costs than TAU [21]. The benefits of these psychological interventions include their effectiveness in reducing symptoms associated with depression and anxiety—effect size in pre-post treatment of 1.39 for anxiety problems and 1.41 for depression—and high recovery rates for those who completed treatment—74% for anxiety and 76% for depression. These benefits have helped to decrease the risk of relapse while maintaining long-term positive outcomes [22].

This efficient and novel way of providing patients with access to psychological therapies in the United Kingdom, where the most cost-effective treatment has improved the detection, diagnosis, and referral rates for these common mental health disorders, has generated intense interest in many countries as a treatment model, including in Spain. However, efforts are needed to implement this model in Spain.

Objectives

Primary Objectives

Given the strong evidence base in favor of CBT versus TAU, together with the need to improve ED treatment in the PC setting in Spain, the major aim of the *Psicología en Atención Primaria* (PsicAP) study is to verify if a group-delivered TD-CBT for EDs is more effective and efficient than TAU in Spanish PC centers. If it is so, we want to compare the short- and long-term efficacy of TD-CBT versus TAU in the treatment of these disorders.

Secondary Objectives

We also aim to compare the effect of these treatments on disability, quality of life, cognitive-emotional factors, and treatment satisfaction.

Hypothesis

Regarding the primary objectives of this study, the experimental group as compared to the control group is expected to report a greater decrease (including pre-post treatment differences and decrease at 3-, 6-, and 12-month follow-up) in dysfunctional emotional symptoms and percentage of cases with probable EDs. The total scores of anxiety, panic, depressive, and somatic symptoms will be measured by the Patient Health Questionnaire (PHQ) [23,24]. In addition, regarding the secondary objectives of this study, we hypothesize that the results will prove that TD-CBT reduces disability and that it, consequently, improves quality of life. We expect that participants allocated to the experimental group will report decreased impairment on work, family, and social domains and an increase in physical, psychological, social, and environmental quality of life at posttreatment and at 3-, 6-, and 12-month follow-up. We also expect that, relative to the control group, participants in the experimental group will have higher levels of emotional regulation and lower scores on cognitive-emotional factors such as ruminative thinking, worries, metacognitions, and cognitive biases associated with EDs. Moreover, we expect the experimental group to report higher treatment satisfaction (see detailed explanation in the Outcomes sections below).

Study Design

This is a two-arm—TAU control group and TD-CBT experimental group—single-blind randomized controlled trial (RCT); the psychologists responsible for assessing patients at the pre- and posttreatment evaluations are blinded to the treatment group. The experimental group will also include patients currently receiving TAU, which will be withdrawn if they are randomized to the TD-CBT group (see detailed explanation in the Interventions section below).

Treatment will be assessed at five time points: pretreatment (before randomization), posttreatment (at the end of the TD-CBT group session, 3-4 months after treatment initiation), and at three follow-up evaluations—3, 6, and 12 months after treatment finalization.

Methods

Study Setting

In Spain, as in many countries, PC is the first level of access to the public national health system. Following a communitarian vision of health care, PC is a level of care at which each patient's condition (and the course of disease) is monitored within the social environment. All PC centers are organized into basic structures of health—a health service concept established with the delimitation of territorial areas of health—in coordinated multidisciplinary teams (ie, GPs, nurses, pediatricians, social workers, and physiotherapists), with healing activities integrated with health promotion, disease prevention, etc. Every patient is assigned to a PC center of his or her basic structure of health and, therefore, to a team of carers at each PC center, a specialized center, and a hospital, covering all levels of possible need for health assistance. Nevertheless, clinical psychologists are not part of the PC team, but rather are located in specialized care units and hospitals.

The clinical trial is being conducted at the following 26 PC centers in Spain: Madrid (11 centers), Valencia (five centers), Biscay (one center), Albacete (one center), Mallorca (one center), Andalusia (two centers), Cantabria (one center), Navarra (two centers), and Galicia (two centers). These centers share many common characteristics, but several differences may exist between them, such as language (eg, Spanish [Castilian], Basque, Galician or Catalan) and other sociodemographic differences. As a result, this wide variety of locations makes these PC centers truly representative of Spanish society as a whole. The study may be extended to other centers in other cities around Spain given the interest in offering an alternative to TAU by PC health professionals.

Target Population

The total sample is expected to consist of 1126 adults, all of whom will have a diagnosis of anxiety, depression, and/or somatic symptom disorders. Any anxiety disorder (eg, panic with or without agoraphobia, GAD, obsessive compulsive disorder, posttraumatic stress disorder, specific phobias, and social phobia) and other conditions included under somatization (eg, medically unexplained symptoms, chronic fatigue, or pain) may be included in the trial if they are not severe. We will test severity according to specific measures of disability and severity of the emotional distress group (see detailed explanation in the Outcomes section below).

Patients with a confirmed or suspected diagnosis of any of these disorders are invited by their GP to participate in the study. In addition, all patients who visit one of the participating PC centers will have the opportunity to be screened to see if they qualify for participation. If they meet the inclusion criteria, they are asked to participate and are included in the trial if they agree.

Before inclusion, patients are informed that they will be randomly assigned to either the control (TAU) or the experimental group (TD-CBT). Written informed consent is

obtained from all patients. Participation is voluntary and confidentiality is guaranteed. The study protocol (ISRCTN58437086) has already been approved by the ethics and clinical research committee of the participating PC centers and by the Corporate Clinical Research Ethics Committee of Primary Care of Valencia (CEIC-APCV), the national research ethics committee coordinator. Participation in this trial does not involve any added risks to patients apart from the inherent risks associated with pharmacological treatment (TAU group only). The aim of this study is to maximize benefits and reduce potential harms (principle of proportionality) through TD-CBT.

Inclusion and Exclusion Criteria

Inclusion Criteria

Any adult patient between 18 and 65 years of age seeking treatment for anxiety, depression, and/or somatic symptom disorder at any of the participating Spanish PC centers may be included in the study. Participation in the study is completely voluntary. For diagnosis, patients must meet predetermined cutoff points on the relevant subscale(s) of the PHQ [23,24]. The 15-item Patient Health Questionnaire (PHQ-15) (<10 points), the 9-item Patient Health Questionnaire (PHQ-9) (<12 points or original algorithm), the 7-item Generalized Anxiety Disorder (GAD-7) scale (<10 points), and the Patient Health Questionnaire-Panic Disorder (PHQ-PD) (modified algorithm) [25] are used to detect somatization disorders, major depressive disorder (MDD), GAD, and panic disorder, respectively (see Outcome sections below for details).

Exclusion Criteria

Patients over 65 years of age are excluded from the trial to avoid distorting the outcomes due to age-related difficulties; however, once the treatment has been validated, this important part of the population will be eligible for participation in these treatment program. Other exclusion criteria include the following: severe mood disorders (eg, bipolar disorder [GP diagnosis] or severe MDD: PHQ-9<23); substance abuse or dependence; any other severe mental disorder (eg, personality disorder); a history of frequent or recent suicide attempt(s); a high level of disability (Sheehan Disability Scale [SDS]<25) [26]; difficulty understanding the Spanish language; intellectual disability; difficulties in undertaking the group therapeutic process; or participation in another clinical trial.

Interventions

Treatment-as-Usual Condition

The control group will receive TAU as provided by the GP at the Spanish PC center. This treatment has been described in previous research as nontreatment, standard treatment, pharmacological treatment, and/or practical advice by the GP delivered in routine care [27], focused on reducing negative emotional symptomatology.

The TAU is provided by the GP in their regular consultation, generally consisting of a face-to-face session (5-7 minutes) to assess the physical and/or psychological complaints of the patient. Also in this time, the GP will provide advice, medication—antidepressant, anxiolytics, or hypnotics—and/or onward referral to specialized care services. Importantly, since this is TAU, conditions are the same as in routine daily practice at the treatment center, without any modifications. If the GP recommends psychological treatment as part of the routine TAU, such patients are excluded from the final trial recruitment to avoid bias.

Experimental Condition

Rationale and Goals

The experimental group will receive TD-CBT group therapy. A well-documented and evidence-based therapeutic approach [11,22] that has been specially designed by Cano-Vindel [28] for the treatment of EDs in PC is used. This TD-CBT is focused on reducing negative emotional symptomatology in the short term using cognitive restructuring and behavioral management, which allows patients to continue without the use of medications in the long term. Any patient receiving TAU prior to study enrollment and then allocated to the TD-CBT group will be withdrawn from TAU. This means that patients in both groups may receive TAU before enrollment in the trial. Once patients are assigned randomly to the TD-CBT group, the GP is not permitted to provide or increase the TAU (ie, increasing pharmacotherapy), but may reduce or eliminate the medication if improvement is noted. It is expected that the pharmacological treatment in patients who are allocated to the TD-CBT group will be withdrawn by the GP as a result of improvement (ie, reduction) of the negative emotional symptoms due to TD-CBT.

Procedure and Schedule

Each participant will receive seven 90-minute sessions of TD-CBT group therapy—8-10 patients in each group, during approximately 12 weeks (3 months). This 12-week treatment period may be increased if necessary for scheduling purposes (ie, due to holiday periods) up to a maximum of 16 weeks (4 months). Sessions are facilitated by one clinical psychologist in a spacious and comfortable room at the PC center. The therapy is delivered with patients and therapist sitting in a circle. Space will also be needed for a relaxation session, and will include a CD player and mats. Paper material is provided for each session and patients may be required to bring a personal notebook. Table 1 shows the intervention schedule and the material provided in each treatment session.

The components of TD-CBT include the following: (1) Psychoeducation and information, designed to counteract misconceptions about emotions or EDs by providing correct information about EDs and treatment aims; (2) Relaxation, consisting of a series of techniques including training participants in progressive muscle relaxation, abdominal breathing, and visualization to reduce EDs and physical arousal; (3) Cognitive restructuring techniques to modify misconceptions about EDs; (4) Behavioral therapy to help participants learn to identify unadjusted emotions and behaviors in order to replace these with healthier ones; and (5) Relapse prevention to overcome difficulties and consolidate learning. All the components are shown in Table 2 with scheduling shown in Table 3.

Table 1. Schedule for the 7 treatment sessions.

Session	Schedule	Material provided
Session 1	First week	Presentation and group therapy rules Breathing and relaxation information sheet Breathing and relaxation self-register
Session 2	Second week	CD relaxation Cognitive restructure information sheet Activities self-register
Session 3	Third week	Down arrow exercise Cognitive biases information sheet
Session 4	Fifth week	Thought purification exercise
Session 5	Seventh week	Interpersonal solution problems sheet
Session 6	Ninth week	Reinforcement of previous activities
Session 7	Twelfth week	Relapse prevention exercise

Table 2. Components of the group TD-CBT[a] protocol.

Psychological techniques	Components of each module	Session
Psychoeducation	Information about the following: • anxiety and mood state • emotional disorders • the group therapy • treatment components and the treatment aims • cognitive biases • the relationship between thoughts and emotions • Counteraction of the following: • misconceptions of emotions • misconceptions of emotional disorders	1 and 2
Relaxation	Abdominal breathing Training progressive muscle relaxation Visualization	1 and 2
Cognitive restructuring techniques	ABC Ellis Model Information about irrational and rational thoughts Exercises for the following: • detection and refutation of irrational thoughts with rational thoughts • detection of cognitive biases • to restructure cognitive biases • to provide positive self-instructions	3, 4, 5, 6, and 7
Behavior therapy	Behavioral activation Exposure therapy Social skills and assertiveness Solutions problems	5, 6, and 7
Relapse prevention	Acceptance of relapse Restructure of relapse	7

[a]TD-CBT: transdiagnostic cognitive behavioral therapy.

Table 3. Schedule of the sessions.

Psychological techniques	Session						
	1	2	3	4	5	6	7
Psychoeducation	X	X					
Relaxation	X	X					
Cognitive restructuring			X	X	X	X	X
Behavior therapy				X	X	X	X
Relapse prevention							X

Therapist Training

All therapists are experienced clinical psychologists. To work as a clinical psychologist in the National Health System in Spain, it is necessary to be certified as a Psychologist Specialist in Clinical Psychology. To obtain this certification, the therapist must have a university degree in psychology (4-5 years) and then must undergo a residency program—Internal Resident Program (IRP)—which is a postgraduate paid training system. The IRP consists of 4 years of work and training under the supervision of a specialist in the Spanish National Health System. In addition to this training, the clinical psychologists in this trial will also undergo a standardized training course conducted by a supervisor and trainer, who would have a PhD in clinical psychology. This training consists of studying the Therapist Manual, four Internet-based lessons on the content of each session, and one face-to-face session with the trainer. This must be completed before the clinical psychologist can provide any group therapy as part of the trial. All groups are supervised by one coordinator in each province. Follow-up sessions are conducted as necessary (ie, by request) to resolve any doubts after finalization of the training course.

To reduce attrition rates after the final posttreatment assessment, a clinical psychologist will telephone patients every 6 weeks posttreatment. During the 10-15-minute telephone consultation with patients in the TD-CBT group, the clinical psychologist will reinforce the psychological techniques taught during the group sessions and will follow up on the participants' emotional state. In the control group (TAU), the clinical psychologist will assess patients' emotional state and, if appropriate, recommend that they visit their GP.

Primary Outcomes

The Patient Health Questionnaire

The PHQ [23] is a screening test derived from the Primary Care Evaluation of Mental Disorders (PRIME-MD) test, a self-reported measure of mental disorders designed for use in PC centers. We will use the Spanish version validated by Diez-Quevedo et al [24] to screen for EDs, using the sum scores of all the subscales independently, with some exceptions as explained below.

Somatization Disorder

The PHQ-15 was derived from the original PHQ studies and is commonly used to assess somatic symptom severity and the potential presence of somatization and somatoform disorders [29]. In the Spanish version, patients are asked to respond to 13 somatic symptoms, scored from 0 to 2 as follows: 0 (*not bothered*), 1 (*bothered a little*), or 2 (*bothered a lot*). Two items from the depression module (*sleep* and *tiredness*) will be added and scored as follows: 0 (*not at all*), 1 (*several days*), or 2 (*more than half the days* or *nearly every day*). The maximum score for the PHQ-15 will be 30. A probable somatization disorder is diagnosed when respondents score 2 points on at least five of the first 13 symptoms and the two items from the depression module, with a cutoff point of 10. Using this criterion, the PHQ-15 has a sensitivity of 78% and specificity of 71% for somatization disorder [30,31]. One study has shown that patients with somatization disorder (PHQ-15 diagnosis) utilize twice the amount of PC services as nonsomatizing patients, at twice the expense [30]. We used the Spanish language version of the original PHQ-15 included in the original PHQ [23].

Depression

The PHQ-9 [32] is a specific screening tool for depression in which participants use a 4-point Likert scale to respond to nine items (Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM-IV] criteria) about difficulties experienced during the prior 2 weeks. Using a cutoff of 10 points, the PHQ-9 has a sensitivity of 88% and specificity of 88% for depression. A score between 10 and 14 indicates minor depression, dysthymia, or moderate MDD; scores between 15 and 19 indicate moderately severe MDD; and scores between 20 and 27 indicate severe MDD. Participants who score between 20 and 23 will undergo a second-order assessment conducted by a clinical psychologist; in these cases, the Structured Clinical Interview for DSM Axis-I Disorders (SCID-I) scale for MDD (Spanish version) [33] is used to confirm the existence of severe MDD. Participants who score between 24 and 27 on the PHQ-9 and are confirmed by the SCID-I as having severe MDD are excluded from participation in the trial and referred again to their GP for referral to specialized care.

In a separate study [34], we studied the psychometric properties in a subsample of the larger PsicAP sample (n=178) and we found an optimal cutoff score of 12 on the PHQ-9, with a sensitivity and specificity of 84% and 78%, respectively. Nevertheless, using the original algorithm, the sensitivity and specificity values were 88% and 80%, respectively, thus recommending the use of the original algorithm due to its superior psychometric properties [34].

Panic Disorder

The PHQ-PD includes the DSM-IV-based panic disorder symptoms [23,24,35]. A diagnosis of probable panic disorder

is made when the participant responds affirmatively to the first four items on the scale and to four or more of the symptoms. Nevertheless, when we studied the psychometric properties of this module in a subsample of the large PsicAP sample [25], we obtained better sensitivity (77%) and specificity (72%) using a modified algorithm as follows: when participants respond affirmatively to the first screening item, to one of the three items on the next scale, and to four or more items of the somatic symptoms [25].

Anxiety

The GAD-7 scale is used to measure GAD and other anxiety disorders [36]. In this scale, patients rate the frequency of anxiety symptoms during the past 2 weeks. Total scores of 5, 10, and 15 indicate mild, moderate, and severe anxiety, respectively. The maximum score is 21 and the cutoff score is 8—a score of at least 2 on the first question, plus three more items. Using a cutoff of 10, the GAD-7 scale has a sensitivity of 89% and a specificity of 82% for GAD [36].

In our study, we used the validated Spanish version of the GAD-7 scale [37] instead of the PHQ items related to anxiety disorders. Factor analysis of the Spanish version of the GAD-7 scale has shown that all items in the GAD-7 scale load onto one factor and the scale uses a cutoff score of 10 to detect GAD [37]. In addition, when we evaluated the psychometric properties of this GAD-7 version in our PC subsample, an optimal cutoff score of 10 was obtained, showing a sensitivity of 87% and a specificity of 78% [34].

Eating Disorders and Alcohol Abuse

The PHQ also contains screening items to detect eating disorders such as bulimia nervosa or binge eating disorder and to check for the presence of alcohol abuse. If items 6(a)-(c) and 8 are scored as a "yes," the score is considered positive for bulimia nervosa; for binge eating disorder, the criteria is the same except for item 8 (either "no" or left blank). The Spanish version of the PHQ was used, which has a sensitivity of 92% and a specificity of 98% for any eating disorder [24]. Alcohol abuse is detected if the patient answers "yes" to any of items 10(a)-(d). The Spanish version of the PHQ [24] has a sensitivity of 76% and a specificity of 99% for probable alcohol abuse or dependence. Participants who have positive scores on these subscales are briefly interviewed by a clinical psychologist to confirm the diagnosis. If they present with an eating disorder, alcohol abuse or dependence, or probable personality disorder they are excluded from participation in the trial and referred to their GP for referral to specialized care.

Secondary Outcomes

Disability

The Sheehan Disability Scale [26] is a 5-item self-report scale that measures subjective impairment during the past month in three key areas: work, family, and social functioning. Two additional questions on the SDS are designed to assess the level of stress and perceived social support in the past week. We used the Spanish version developed by Bobes et al [38], which has shown good reliability and validity. The first four items are rated on an 11-point Likert scale from 0 (*no dysfunction*) to 10 (*maximum dysfunction*). The fifth item uses the same scale but is expressed in percentages from 0% (*no social support*) to 100% (*ideal social support*). Scores of 1-3, 4-6, and 7-9 indicate mild, moderate, or high disability, respectively. Overall scores of 25 or more indicate a high level of disability. In these cases, a psychologist will ask participants the following three questions before excluding them from the study: (1) Are you on sick leave? (2) Can you do the housework? and (3) Can you engage socially?

Quality of Life

The World Health Organization Quality of Life Instrument-Short Form [39] is a 26-item questionnaire used to measure perceived quality of life in four domains: physical, psychological, social, and environmental. This instrument is used worldwide, including in Spain [40], and shows good psychometric properties, reliability, and validity [41].

Cognitive-Emotional Factors

Several subscales or short questionnaires are used to evaluate brooding, worries, and cognitive biases. The 5-item Brooding Scale of the Ruminative Response Scale [42] has been validated in Spanish with good reliability and validity [43]. The Spanish version of the Penn State Worry Questionnaire [44,45] is used, specifically an 8-item version similar to the abbreviated version (PSWQ-A)[46]. A brief 5-item version of the Inventory of Cognitive Activity in Anxiety Disorders (IACTA) will be used to assess attentional biases.

We will use the 10-item validated Spanish version of the Emotion Regulation Questionnaire, which has been shown to have good reliability and validity [47,48] to assess emotion regulation. We will use the 6-item metacognitive beliefs subscale of the Metacognitions Questionnaire [49] to assess metacognitions. This has been validated in Spanish with good reliability and validity [50].

Note that the Spanish version of the PSWQ-A has not been validated yet and the IACTA is under review. However, the reliability and validity of these scales and subscales were recently completed in a subsample of the large PsicAP sample and results are expected to be published soon.

Treatment Satisfaction

All participants are surveyed to assess their level of satisfaction with the treatment received; participants rate their satisfaction on a scale from 0 (*high dissatisfaction*) to 10 (*high satisfaction*).

Sample Size

The minimum sample size required to obtain a significant result has been calculated with the SPSS version 21.0 Sample Power program (IBM Corp). The study will include at least 563 patients in each group for a total of 1126 patients, assuming a 20% attrition or dropout rate. With this sample size, the result will be statistically significant (85% statistical power) when comparing both groups, even if they differ by one point only on the subscales of the PHQ measures, with a standard deviation of 5. This will enable us to conclude that the result is different for each group with a 95% confidence level. As previous studies have reported [11], we expect that the rate of loss to follow-up will be considerable, despite the strong study design, which

includes telephone follow-up to reduce attrition. Consequently, this is likely to be an important limitation of our study.

Patient Recruitment

Patient recruitment is carried out in two phases, as follows.

First Phase

Patients who present with signs or symptoms of anxiety or depression, negative emotions, or physical symptoms for which there was no clear biological basis are preselected by the GP for possible participation. Patients currently being treated with antidepressants, anxiolytics, and/or hypnotics may also be invited to participate in the study. The GP will explain the clinical trial to these patients and ask if they wish to participate. Prior to study participation, patients will receive written and oral information in the patient information sheet about the content and extent of the planned study. This includes information about the potential benefits and risks for their health. All patients who agree to participate are required to sign the informed consent form.

Second Phase

All patients who consent to participate in the trial (ie, have signed informed consent forms) are contacted by a clinical psychologist, who will then schedule an appointment to complete the aforementioned screening questionnaires. Only patients who meet the study inclusion criteria on the PHQ subscales—PHQ-15, PHQ-9, PHQ-PD, and GAD-7—are enrolled, using the cutoff scores and algorithms described above. All other patients are referred back to their GP for alternative treatments.

Randomization

Participants are randomly assigned after informed consent or assent is obtained by a blinded researcher using a computer-generated allocation sequence, assuring that the groups are comparable (ie, without differences in key baseline measures). Each group will include 8-10 patients randomly allocated either to the experimental group (TD-CBT) or to the control group (TAU). They receive this allocation information via email from a graduate student trainee affiliated with the project. The email also provides login and website information for the allocated intervention. One clinical psychologist is assigned to the TD-CBT group; the clinical psychologist involved in the pre- and posttreatment assessment phases will not participate in the TD-CBT therapy. Data managers and statisticians are blinded to the treatment allocation.

Data Collection

After providing written informed consent, the participants are registered in the treating center. Pre- and posttreatment assessments are carried out using computerized self-reported screening tests. All pretreatment assessments are performed at the treating PC center after scheduling an appointment with the clinical psychologist. A computer with Internet access is used to collect data. All data are stored on a general virtual website (surveymonkey.com). At all posttreatment follow-up assessments, the same instruments will be completed in person at the treating center. However, if necessary, we will send the participant a link by email to enable the patient to complete the computerized measures at home. Patients are contacted by phone to encourage completion of the questionnaires. Moreover, those patients that discontinue or drop out of treatment will still be invited to complete the posttreatment follow-up assessments, particularly the first posttreatment assessment.

Data Analysis

Analysis will be carried out using SPSS version 21.0 (IBM Corp). Intention-to-treat (ITT) analysis will be performed. The ITT analysis will include all randomized patients in the groups to which they were randomly assigned. Analysis will take into account noncompliance, protocol deviations, dropouts, and anything else that happens after randomization. Using the ITT approach will enable us to include situations likely to occur in actual clinical practice. This “real-life” analytical approach allows us to assess the prognostic balance resulting from the original random treatment allocation, thus providing a more accurate estimation of treatment effect. Missing-data analysis will be computed using Student's *t* test and chi-square tests. Variables included in the analysis will be severity level, gender, and age; this will allow us to ascertain whether unexpected missing data due to participant dropout are related to chance or not

The two randomized groups will be compared in the treatment period; posttreatment; and at 3, 6, and 12 months after treatment finalization. In addition, within-subject comparisons will be analyzed, contrasting pretreatment and posttreatment scores. The within-group and between-group differences will be examined using mixed-effect models, since these are considered more accurate than univariate and multivariate repeated measures of variance [51]. Group differences will be analyzed after controlling for baseline levels, gender, age, and treatment center. Additionally, we will estimate the percentage of patients in each group who experience a 50% decrease in the number of clinical symptoms and scores by one standard deviation, as well as the percentage of cases with a probable ED before and after receiving treatment (according to cutoff criteria).

The TD-CBT therapy will be considered effective if average scores on ED symptoms—anxiety, depression, and somatic symptoms—of patients who receive treatment are significantly lower than average scores of the control group and if effect sizes (Cohen *d*) are low to medium. Both groups will be compared to test for differences in level of disability—work, family, and social functioning—quality of life, and treatment satisfaction.

Ethics and Dissemination

Research Ethics Approval

This is a multicenter RCT with medication (N EUDRACT: 2013-001955-11; protocol code: ISRCTN58437086) promoted by the Psicofundación (The Spanish Foundation for the Promotion of the Scientific and Professional Development of Psychology). The trial was approved by the CEIC-APCV—the national research ethics committee coordinator—and the Spanish Medicines and Health Products Agency. Approval was received by both agencies in November 2013, prior to study initiation in December 2013.

The CEIC-APCV approved the trial in three centers in the autonomous communities of Valencia (one center), the Balearic Islands (one center), and Castilla-La Mancha (one center). The study was also approved by the local ethics committees of the first three centers: the CEIC-APCV, the Clinical Research Ethics Committee of the Hospital Universitario de Albacete (CEIC-HUA), and the Clinical Ethics Committee of the Balearic Islands (CEIC-IB).

Protocol Amendments

Six protocol amendments have been presented during the course of this trial.

Amendment 1

One PC center was added to the autonomous communities of the Basque Country and was approved by the Clinical Research Ethics Committee of Euskadi (CEIC-E). In addition, a substudy—substudy 1—was approved in order to conduct the study of the psychometric properties of the PHQ subscales of the PHQ-9, PHQ-PD, and GAD-7 with 15% of the larger sample. This substudy has been conducted in four PC centers located in the autonomous communities of Valencia (one center), the Balearic Islands (one center), the Basque Country (one center), and Castilla-La Mancha (one center). The substudy was also approved by the first four local ethics committees: the CEIC-APCV, the CEIC-HUA, the CEIC-E, and the CEIC-IB.

Amendment 2

Nine centers located in the Community of Madrid were added to the study. The Clinical Research Ethics Committee of Madrid approved this amendment, as did the national ethics committee, the CEIC-APCV.

Amendment 3

One PC center was added to the group of centers in the autonomous community of Valencia. This center thus became a full participant in the trial and substudy 1, bringing the number of PC centers in substudy 1 to five. In addition, several changes to the first version of the protocol were made, including the use of the SCID-I to confirm severe MDD and questions to confirm high disability on the SDS, as described above. Also, new researchers were added to the study. The amendment was approved by the national ethics committee—the CEIC-APCV—and by the relevant local ethics committees.

Amendment 4

Three PC centers, two in Andalusia and one in Cantabria, were added to the list of participating centers. In addition, substudy 2 was presented, which is a study of the cost-efficiency measures that are conducted in the PC centers in Madrid and Valencia. Several changes to the next version of the protocol were made, including the telephone follow-up posttreatment (see Therapist Training section above). Finally, new researchers were added to the study. The amendment was approved by local ethics committees—the Clinical Research Ethics Committee of Córdoba and the Clinical Ethics Committee of Cantabria—and the national ethics committee, the CEIC-APCV.

Amendment 5

Five PC centers were added to the autonomous communities of Madrid (two centers) and Valencia (three centers) to conduct the trial. Also, new researchers were added to the study. The amendment was approved by the local ethics committee—the Clinical Research Ethics Committee of Madrid—and the local and national ethics committee, the CEIC-APCV.

Amendment 6

Six PC centers were added to the autonomous communities of Catalonia (two centers), Galicia (two centers), and Navarra (two centers) to conduct the trial. Also, new researchers were added to the study. The national legislative norms have been modified in Spain and now only one national ethics committee is required for RCTs. As a result, this amendment was approved by the national ethics committee, the CEIC-APCV. One new substudy was also presented. Substudy 3 is a modification of the protocol design (ie, stepped-wedge trial design), which will be conducted in two PC centers in Barcelona (Catalonia). In addition, a change to the next version of the protocol was made with regard to using the 4-item Patient Health Questionnaire (PHQ-4) to detect EDs in PC centers by the GP; the aim is to reduce misdiagnoses of EDs and to accelerate referral to the clinical psychologist in the second phase of the recruitment process. This will allow us to determine if the ultrashort measure of the PHQ-4 is an appropriate tool to help GPs to detect EDs and to reduce the large number of false negatives. If results are as expected, this may lead to a proposal for a new referral model in Spanish PC centers.

Consent

Regarding patient informed consent, prior to study participation, all patients receive written and oral information in the patient information sheet about the content and extent of the planned study. This includes information about the potential benefits and risks to their health. Patients who agree to participate are required to sign the informed consent form. In the case of patients who withdraw from the study, all data will be destroyed or the patient will be asked if he/she agrees to allow the use of existing data for analysis in the study.

Patient participation in the study is completely voluntary and participants can withdraw at any time with no need to provide reasons and without negative consequences for their future medical care. The protocols used in this study pose no risk whatsoever to the participants. TD-CBT is noninvasive at the cognitive level, except with regard to learning or teaching.

Confidentiality

The study is conducted in accordance with Spanish data security law. All professionals participating in the study agreed to adhere to the Helsinki Declaration and to Spanish law. All health care professionals participating in the study are required to sign a form indicating their agreement to adhere to the above-mentioned declaration and Spanish law.

The patient names and all other confidential information fall under medical confidentiality rules and are treated according to Spanish data security law. The patient questionnaires are collected by the researchers (not nurses) and mailed by secure

transport to the study center in Madrid. All study-related data and documents are stored on a protected central server and saved in an encrypted database.

The project complies with current guidelines in Spain and the European Union for patient protection in clinical trials with regard to the collection, storage, and keeping of personal data. Only direct members of the internal study team can access the data.

Access to Data

The study data are only available upon request. The name(s) of the contact person(s) to request data are available upon request to all interested researchers. Legal and ethical restrictions make data available upon request and are in accordance with the nature of the data collection.

The CEIC-APCV have some availability restrictions as part of the legal and ethical control of data from an RCT with medication.

Data are available from the promoter (Spain) for researchers who meet the criteria for access to confidential data. Interested researchers should contact Psicofundación (The Spanish Foundation for the Promotion of the Scientific and Professional Development of Psychology) at the registered office at Calle Conde de Peñalver, 45, 5o izquierda, 28006 Madrid.

Concomitant Care

No concomitant care has been registered.

Dissemination Plans

One of the major objectives of this trial is to convince public health care administrators to implement, once the efficacy has been proven, these evidence-based psychological treatments for EDs in the PC, under the guidance of clinical psychologists. Given the current situation of the National Health System in Spain, the number of clinical psychologists will need to be increased and positions will need to be created at Spanish PC centers for clinical psychologists.

Results

This study was initiated in December 2013 and will remain open to new participants until recruitment and follow-up has been completed. We expect all posttreatment evaluations to be completed by December 2017, and follow-up will end in December 2018.

Discussion

Principal Findings

Emotional disorders are common in the community, highly comorbid, and they often affect personal functioning and well-being. According to the WHO [9], mental disorders will generate a large social and economic burden in all countries in the year 2020. This organization estimates that the current number of specialized human resources to treat these disorders is insufficient [9]. Supported by international guidelines such as the UK National Institute for Health and Clinical Excellence [10], the WHO recommends implementation of evidence-based interventions to treat EDs. Psychological treatments such as CBT are considered the treatment of choice for EDs given their relative cost-effectiveness in the long term versus pharmacological treatment [52-54]. Moreover, published reports indicate that CBT may be even more effective for EDs when a transdiagnostic approach is used (TD-CBT) [11,55].

In addition to the WHO report described above, other studies have also found that human resources available for treatment of EDs, especially clinical psychologists in European countries, are inadequate [56]. Several reports have demonstrated that insufficient human resources in Spain can lead to misdiagnosis and malpractice [18,19]; moreover, this deficit of trained staff places increased demands on an already oversaturated health care system. Despite this lack of resources, several Spanish studies have found that CBT group therapy is highly efficacious in treating depression in both the short and long term [57], as well as for other EDs [58].

Given the limited availability of clinical psychologists in specialized settings, their scant presence in PC centers—the gateway of patients to the health care system—is not surprising. According to Serrano-Blanco et al [3], approximately 1 out of 3 patients in the PC setting has some type of ED. This high prevalence, together with the shortage of clinical psychologists, underscores the need to increase the availability of these specialists in PC. This is especially true given the substantial evidence supporting the effectiveness of CBT.

At present, our group is carrying out this novel project in Spain to validate the cost-efficiency implementation of psychological treatment in PC centers. Currently, patients in PC centers are primarily treated by GPs and psychiatrists. However, we advocate the use of a collaborative, stepped-care, PC-based psychological intervention to reduce anxiety, depression, somatizations, and disability while simultaneously increasing quality of life. The proposed psychological intervention—TD-CBT—is a promising intervention delivered by clinical psychologists following a rigorous scientific protocol designed to provide optimal care of patients with EDs.

If the results of this clinical trial are positive, as we expect, these outcomes will provide further support in favor of incorporating clinical psychologists into the PC setting to administer TD-CBT group therapy for EDs as the treatment of choice. Implementation of this model will likely improve treatment adherence and, consequently, lower the health care burden of treating EDs. In addition, again assuming that the results are as expected, this will provide further support to the growing body of evidence pointing to the value of TD-CBT group therapy in PC settings. We fully expect that this intervention will improve the health of patients in the experimental group and will increase the quality of life and well-being of both patients and relatives. The ability to offer TD-CBT group therapy would also help to form therapy groups consisting of patients with several comorbid disorders, thus further helping in quick group formation. It will be interesting to study what the implications could be of the cost-efficiency of this treatment modality.

One of the major interests of this project is the need to increase the number of clinical psychologists in the Spanish public health care system. The Spanish government recently acknowledged

that the public health system needs an additional 7200 clinical psychologists to reach the European average of 18 per 100,000 people. If the results of this study are similar to those achieved in studies conducted in other countries (eg, Australia [59,60], Great Britain [22], Norway [61], and the United States [62]), then this would provide further empirical evidence in support of more interventions of this type and thus more clinical psychologists. Furthermore, the experience gained in this study will enable us to easily train other clinical psychologists by applying the manualized TD-CBT program used in this trial, with no need to further train other professionals.

Study Limitations

This study has several limitations related to the functioning of Spanish PC centers. GPs are the first point of contact for patients with EDs and these physicians have only approximately 5-7 minutes to evaluate, diagnose, and offer these patients TAU or to recommend participation in this clinical trial. Logically, the recruitment process for this trial could be negatively affected by these time constraints, especially considering that the GP must make a concerted effort to motivate and recruit a large number of patients in a relatively short period of time. Another limitation is that the PC centers have not been randomly selected. Despite this limitation, it is important to highlight two of the main strengths of this study: the large sample of patients (>1000 patients) and the large number of PC centers (>20) distributed in a wide geographic range all over Spain.

Another study limitation is that the TD-CBT intervention is scheduled to last from 12 to 14 weeks and can be affected by several factors (eg, vacations and availability of participants) beyond our control. Thus, the follow-up assessments—3, 6, and 12 months posttreatment—might be performed at different time points. However, we are making every effort to ensure that the duration and timing of TD-CBT treatment and follow-up assessments are homogenous among the groups and coincide with the assessments of the TAU intervention, but we cannot rule out the possibility of variability.

Additionally, as a limitation similar to other studies of this nature, we expect a considerable rate of loss to follow-up. However, the study design includes measures—primarily telephone and email follow-up—aimed at reducing the rate of loss. Nevertheless, it seems likely that many patients in both groups will not complete all follow-up assessments. It is likely that some patients will discontinue or drop out of treatment. However, we are registering the number of sessions that patients in the TD-CBT group attend in order to determine the mean number of sessions attended; this may improve our outcome measures, particularly if it shows that some sessions are more effective than others. Nevertheless, in the TAU group, we are not registering the number of sessions, as this is an inherent condition of TAU. As said above, regarding those patients that drop out of either group, we still invite them to complete the posttreatment follow-up assessments.

An important aim of this project is to improve the current referral model, in which GPs refer patients with suspected EDs to specialist services. This new model seeks to increase interaction between GPs, clinical psychologists, and specialized centers through a new referral system based on the implementation of a stepped-care model. The use of validated instruments to achieve more accurate diagnoses, together with the use of more effective treatments, will potentially decrease the number of GP visits, thereby helping to optimize current PC resources. In this regard, the role of the clinical psychologists participating in this clinical trial is crucial.

Once recruitment is completed, patients will continue to receive care from their primary care GP, who is easily accessible, without cost to the patient. We are confident of the success of this treatment program and, if successful, it will add another tool—TD-CBT—to the available resources for treating EDs. Clinical guidelines may need to be updated to reflect the study's outcomes. We expect this study to yield valuable data about the short- and long-term efficacy of TD-CBT group therapy for EDs applied by clinical psychologists in a PC setting. Our findings could help design stronger and more effective public health strategies and treatments, leading to better care of patients with these disorders.

Finally, it is important to note that this project and its design are novel in the PC setting in Spain. If the results are as expected, this project could serve as a model for use in other areas or services of the National Health System in Spain and even in other countries.

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Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy
CEIC-APCV: Corporate Clinical Research Ethics Committee of Primary Care of Valencia
CEIC-E: Clinical Research Ethics Committee of Euskadi
CEIC-HUA: Clinical Research Ethics Committee of the Hospital Universitario de Albacete
CEIC-IB: Clinical Ethics Committee of the Balearic Islands
DSM-IV: Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders
ED: emotional disorder
GAD: generalized anxiety disorder
GAD-7: 7-item Generalized Anxiety Disorder
GP: general practitioner
IACTA: Inventory of Cognitive Activity in Anxiety Disorders
IAPT: Improving Access to Psychological Therapies
IRP: Internal Resident Program
ITT: intention to treat
MDD: major depressive disorder
PC: primary care
PHQ: Patient Health Questionnaire
PHQ-4: 4-item Patient Health Questionnaire
PHQ-9: 9-item Patient Health Questionnaire
PHQ-15: 15-item Patient Health Questionnaire
PHQ-PD: Patient Health Questionnaire-Panic Disorder
PRIME-MD: Primary Care Evaluation of Mental Disorders
PsicAP: Psicología en Atención Primaria
PSWQ-A: abbreviated version of the Penn State Worry Questionnaire
RCT: randomized controlled trial
SCID-I: Structured Clinical Interview for DSM Axis-I Disorders
SDS: Sheehan Disability Scale
TAU: treatment as usual
TD-CBT: transdiagnostic cognitive behavioral therapy
WHO: World Health Organization

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Protocol

The Effectiveness of Hand Massage on Pain in Critically Ill Patients After Cardiac Surgery: A Randomized Controlled Trial Protocol

Madalina Boitor[1], RN; Géraldine Martorella[2], RN, PhD; Andréa Maria Laizner[1], RN, PhD; Christine Maheu[1], RN, PhD; Céline Gélinas[1], RN, PhD

[1]Ingram School of Nursing, Faculty of Medicine, McGill University, Montreal, QC, Canada

[2]College of Nursing, Florida State University, Florida, FL, United States

Corresponding Author:
Madalina Boitor, RN
Ingram School of Nursing
Faculty of Medicine
McGill University
3506 University
Montreal, QC
Canada
Phone: 1 514 398 4144
Fax: 1 514 398 8455
Email: madalina.boitor@mail.mcgill.ca

Abstract

Background: Postoperative pain is common in the intensive care unit despite the administration of analgesia. Some trials suggest that massage can be effective at reducing postoperative pain in acute care units; however, its effects on pain relief in the intensive care unit and when pain severity is highest remain unknown.

Objective: The objective is to evaluate the effectiveness of hand massage on the pain intensity (primary outcome), unpleasantness and interference, muscle tension, anxiety, and vital signs of critically ill patients after cardiac surgery.

Methods: A 3-arm randomized controlled trial will be conducted. A total of 79 patients who are 18 years or older, able to speak French or English and self-report symptoms, have undergone elective cardiac surgery, and do not have a high risk of postoperative complications and contraindications to hand massage will be recruited. They will be randomly allocated (1:1:1) to standard care plus either 3 20-minute hand massages (experimental), 3 20-minute hand holdings (active control), or 3 20-minute rest periods (passive control). Pain intensity, unpleasantness, anxiety, muscle tension, and vital signs will be evaluated before, immediately after, and 30 minutes later for each intervention administered within 24 hours postoperatively. Peer-reviewed competitive funding was received from the Quebec Nursing Intervention Research Network and McGill University in December 2015, and research ethics approval was obtained February 2016.

Results: Recruitment started in April 2016, and data collection is expected to be complete by January 2017. To date, 24 patients were randomized and had data collection done.

Conclusions: This study will be one of the first randomized controlled trials to examine the effect of hand massage on the pain levels of critically ill patients after cardiac surgery and to provide empirical evidence for the use of massage among this population.

ClinicalTrial: ClinicalTrials.gov NCT02679534; https://clinicaltrials.gov/ct2/show/NCT02679534 (Archived by WebCite at http://www.webcitation.org/6l8Ly5eHS)

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KEYWORDS

massage; pain; critical care; randomized controlled trial; anxiety; muscle tension; vital signs; clinical protocol; complementary therapies; thoracic surgery

Introduction

Overview

Undergoing cardiac surgery constitutes a major event for patients that is accompanied by physical and psychological symptoms such as postoperative pain [1-5] and anxiety [6-8]. Recent studies reveal that massage could complement pharmacological treatments and have positive effects in reducing these symptoms in acute care units [9-11], yet empirical evidence is lacking to support the same effects early in the postoperative phase when patients are in the intensive care unit (ICU) and pain is at its highest.

In the ICU, postoperative pain can be compounded by routine ICU procedures such as turning, coughing, breathing, and chest tube removal, activities which are perceived to be the most painful in the immediate postoperative period [3,5]. Given the higher severity and complexity of pain in the ICU, findings from massage studies conducted on acute care wards cannot be extrapolated to the unique context of the ICU and the early recovery phase after cardiac surgery. Further evidence is needed to unravel the potential role of massage in relieving the pain of cardiac surgery in ICU patients and guide international clinical practice guidelines with regard to the use of this complementary nonpharmacological intervention in this patient population.

Background

Cardiac surgeries, such as coronary artery bypass grafting and valve replacement, rank among the most frequently performed surgical interventions worldwide [12] and necessitate the routine admission of patients to the ICU. Cardiac surgeries are commonly indicated to reduce anginal pain, but the surgical procedure itself can lead to the development of postoperative pain. Mounting evidence shows that cardiac surgery ICU patients experience moderate-to-severe pain reaching proportions as high as 74% despite the use of analgesics [2-5], with the highest pain intensity commonly experienced in the first 24 hours postsurgery [13].

Unrelieved postoperative pain can interfere with patients' ability to cough and mobilize effectively, which predisposes them to postoperative complications such as atelectasis, pneumonia, and deep vein thrombosis [2,5,14], thereby delaying recovery and ICU discharge. Moreover, the intensity of acute postoperative pain immediately after surgery is a significant predictor of the presence and severity of persistent postoperative pain up to 2 years postsurgery [15-17], a serious and often unrecognized complication after cardiac surgery that may interfere with daily activities and quality of life [18].

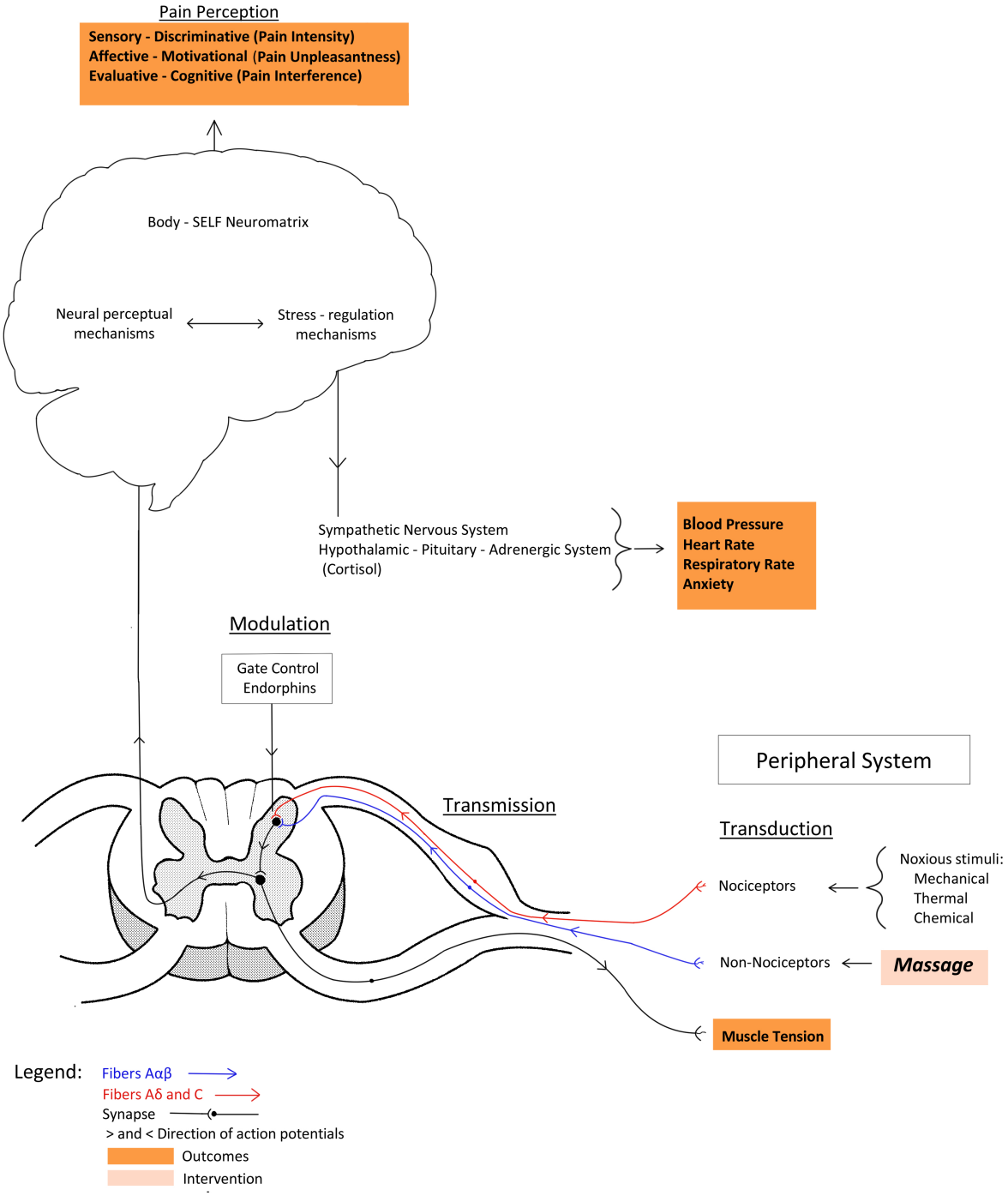
Among the pharmacological approaches to pain control, opioids constitute the mainstay of treatment in the ICU [19,20], yet pain has been shown to persist even during unrestricted use of these analgesic agents [13,21]. The use of complementary nonpharmacologic interventions such as massage has been suggested in the clinical practice guidelines of the Society of Critical Care Medicine given their opioid-sparing and analgesia-enhancing potential [20]. Massage has been defined as the manual manipulation of muscles and soft tissues of the body through the application of various systematic and rhythmic hand movements [22,23].

A recent systematic review exploring the effectiveness of massage on postoperative outcomes among patients undergoing cardiac surgery [24] indicated that out of the 7 eligible studies (N=40-252/study), 6 reported that massage therapy ranging from 20 to 30 minutes in duration improved postoperative outcomes such as pain, anxiety, and muscle tension [9,10,25-28], while only one study reported no positive results [29]. The latter study evaluated the effectiveness of a 30-minute massage therapy involving each limb for 5 minutes followed by a 10-minute back massage while patients were lying on the left side. The positioning required for the back massage might have obscured or minimized the potential benefit of massage in relieving pain, anxiety, and muscle tension given that side-lying may exert traction on the sternotomy site, causing pain [3] and increasing muscle tension and possibly anxiety as turning on one side could be perceived as a painful procedure. Of note, only one of these studies was conducted in the ICU [25], and it lacked random assignment.

One pilot randomized controlled trial (RCT) conducted with 40 ICU patients post–cardiac surgery [30] showed promising pain relief and muscle relaxant effects of up to 3 15-minute hand massages, whereas the administration of a single massage therapy did not yield any significant decrease in pain intensity or muscle tension, suggesting that repeated administration of hand massage is necessary in this patient population.

Overall, there is a paucity of high-level evidence on which to base massage therapy decisions in the management of pain in post–cardiac surgery ICU patients. Extrapolations of evidence from other patient populations and clinical settings are flawed by the differing health status and symptom severity of this specific subgroup of ICU patients. Future rigorous RCTs conducted in the context of the ICU and with cardiac surgery adults in their immediate postoperative period are essential to make recommendations for the use of massage in clinical practice including the minimal effective dose, body area massaged, and techniques employed.

Figure 1. Adapted diagram of the neuromatrix theory of pain.



Textbox 1. Eligibility criteria.

Inclusion criteria:

18 years of age and older

- Able to speak French or English
- Elective cardiac surgery
- Able to answer questions and self-report symptoms

Exclusion criteria:

- Previous cardiac surgery
- Diagnosis of cognitive or psychiatric disorder
- Pulmonary artery pressure >50 mm Hg
- Right ventricular failure
- Systolic left ventricular dysfunction (ejection fraction 35% or less)
- Body mass index >30 kg/m^2
- Prolonged bleeding from the chest drainage tubes (>200 mL/h)
- Having mechanical blood pressure support (eg, intra-aortic balloon pump)
- Receiving cardiac pacing with complete control of heart rate
- Peripheral intravenous line in the hands
- Suppurating/infective/inflammatory skin condition of the hands
- Hypersensitivity to touch

Theoretical Framework

The protocol is based on the neuromatrix theory of pain [31] where the brain's neural network, the body-self neuromatrix, integrates multiple inputs such as sensory (eg, cutaneous) and opioid systems (ie, endogenous opioids) to influence the sensory (intensity, localization, and quality), affective (unpleasantness), and cognitive dimensions (interference with daily functioning) of pain (Figure 1). The sensory stimulation of nonnociceptive fibers in the skin and muscles involved in massage could block the transmission of nociceptive impulses in the dorsal horns and may increase the release of beta-endorphins in the bloodstream [32,33], which block the release of neurotransmitters from the nociceptive fibers (especially substance P) [34], thereby blocking the transmission of nociceptive impulses from reaching the body-self neuromatrix where pain perception occurs. Similarly, by blocking the transmission of nociceptive signals, the stimulation of the stress-regulation system responsible for the activation of the noradrenergic and sympathetic nervous system could be inhibited. The resultant lack of up-regulation of adrenaline and noradrenaline could explain the potential effects of massage in decreasing blood pressure, heart and respiratory rates, and the subjective sensations of anxiety [35-37].

Aim

The primary aim of this research study is to compare the effect of 3 20-minute hand massage administrations by a trained nurse within 24 hours after cardiac surgery versus hand-holding (ie, simple touch) and standard care on the postoperative pain intensity of adult ICU patients.

Methods

Trial Design

This research study is designed as a randomized, controlled, patient-blinded, single-center superiority trial with 3 parallel groups and a 1:1:1 allocation ratio. A modified Consolidated Standards of Reporting Trials flow diagram for individual RCTs of nonpharmacologic treatments will be used to document recruitment and retention of participants (see Multimedia Appendix 1) [43].

Participants

This RCT targets adults admitted to the ICU after undergoing cardiac surgery in a university-affiliated hospital in Canada. A single setting was selected for this study because of standardized pain management practices and surgical techniques and single patient rooms. Patients will be screened for inclusion using the eligibility criteria seen in Textbox 1. Patients at higher risk of postoperative complications and those with contradictions to having their hands massaged will be excluded.

Sample Size and Sampling Procedure

A power analysis was conducted using the G*Power 3 program [38] to estimate the sample size required to capture the potential effects of massage to decrease the primary outcome (pain intensity) and to strengthen the statistical conclusion validity. The mean treatment difference was observed to be greater than 1.5 in several RCTs [11,26,39,40] and approximates the clinically significant difference of 2 points on the 0 to 10 Numeric Rating Scale (NRS) [41]. This trial is powered to be able to detect a difference in the pain intensity score of 1.5

between the hand massage and standard care group. The standard deviation of pain intensity scores is approximately a 2.0 value, which was selected for the sample size calculation. To detect a mean difference in pain intensity scores of 1.5 points (SD 2.0) immediately after the third massage with a 2-sided significance level of .05 and power of .80 with equal allocation to 3 arms and a repeated measures between factors context with 3 measurements would require a minimum of 72 patients.

Given the low attrition rates observed with this patient population (0% [9,10,30] and 35/287 (12.2%) [29]), a 10% drop-out rate is considered in the calculation of the total sample size. Therefore, the final size required for this RCT is 79, and it will be reached using convenience sampling.

Randomization

Before the study begins, permuted-block randomization will be generated for 85 patients by a statistician using SAS computer software (SAS Institute) and block sizes of 3, an allocation ratio of 1:1:1, and one strata to minimize the imbalance in the number allocated to each group. Then, the randomization schedule will be transcribed in sequentially numbered and opaque sealed envelopes by a research coordinator not involved in assignment allocation to ensure allocation concealment. The allocation list will be stored in a locked filing cabinet of the principal investigator and will not made accessible to the interventionist involved in enrollment and treatment allocation.

Recruitment of Participants

Patient recruitment will begin preoperatively when eligibility criteria such as age and language spoken will be verified (Table 1).

The remaining eligibility criteria (eg, blood loss, peripheral intravenous lines) will be evaluated post–cardiac surgery and ICU admission. After the collection of baseline data, patients meeting all the inclusion criteria will be randomly assigned to either hand massage, hand-holding, or standard care. As each participant enters the study, he or she receives the next envelope in the sequence, thereby concealing the interventionist's and trial participants' knowledge of the upcoming group assignment.

The interventionist will then administer the assigned intervention (hand massage, hand-holding) without informing participants of their group assignment until the end of data collection. Nurses and other ICU clinicians will also be masked to patients' group assignment. The similarity of the hand massage and hand-holding therapy characteristics serves to mask study participants and clinicians with regard to the specific intervention received as observed in a feasibility and acceptability study where patients receiving hand-holding referred to the intervention as massage [42]. Conversely, patients in the rest group are less likely to be masked to the group assigned.

A modified Consolidated Standards of Reporting Trials flow diagram for individual RCTs of nonpharmacologic treatments will be used to document recruitment and retention of participants [43].

Choice of Comparators

The majority of massage studies include standard care control groups to examine the absolute efficacy of massage in improving outcome variables. While this is important in attributing benefits to the massage therapy itself, studies that involve the administration of massage by a trained therapist, as recommended in Cochrane Systematic Reviews [44], should equally include a touch control group to verify if the additional manipulation included in massage is superior to touch only. Some studies suggest that touch, a free and easily administered intervention not requiring training, can have potential pain relief effects [45] and should, thus, be included as an active control group in future RCT designs to additionally examine the relative efficacy of massage. Furthermore, the touch control group can help mask patients with regard to the group assigned through its resemblance with actual massage, thereby controlling for placebo effects [44].

Interventions

Training of Interventionist and Timing of Interventions

Eligible patients will be randomized in equal proportions between hand massage, hand-holding, and standard care. One interventionist will deliver the hand massage and hand-holding interventions, which will be standardized across participants. The interventionist is a registered nurse with no previous experience in massage therapy who will be trained by a professional massage therapist through an accredited workshop of 6 hours including practical exercises and verification of competency, as was done in the pilot RCT [30].

The first intervention (hand massage or hand-holding) will be delivered in the evening of the day of surgery and the remaining two interventions the day after when patients are still in the ICU. Overall, three interventions will be administered within 24 hours postoperatively over the course of two days.

Experimental Group

Patients assigned to the experimental group will receive a 20-minute hand massage by the interventionist in addition to the standard ICU care. Before administering the massage, a favorable environment will be created that promotes calmness such as dampening the light, reducing the alarm intensity, closing the curtains and door, and posting a "do not disturb" notice, and a comfortable positioning of the patient will be ensured [9,30,46]. After performing hand hygiene and explaining the procedure to the patient, the interventionist will hold each hand for 5-10 seconds and apply 5-10 mL of unscented hypoallergenic cream to both hands and wrists. The cream will be supplied by the interventionist and reserved for use within the research context only. The interventionist will then perform massage using moderate pressure and stroking and kneading techniques during 10 minutes on the palm and back of each hand as inspired by the procedure by Kolcaba et al [47] and developed with the support of an experienced massage therapist (Textbox 2).

Table 1. Study timeline.

Procedures	Preop	POD[a] 0 evening	POD 1 early evening	POD 1 late evening	POD 2
Recruitment					
First eligibility screen	x				
Informed consent	x				
Second eligibility screen		x			
Randomization		x			
Interventions					
Hand massage		x	x	x	
Hand-holding		x	x	x	
Rest period		x	x	x	
Standard care	x	x	x	x	x
Data collection					
Demographics questionnaire	x	x			
Pain intensity		x	x	x	
Pain unpleasantness		x	x	x	
Pain interference					x
Pain location and quality		x	x	x	
Anxiety		x	x	x	
Muscle tension		x	x	x	
Vital signs		x	x	x	

[a]POD: postoperative day.

Active Control Group

The active control group will receive hand-holding by the same interventionist in addition to standard ICU care. The same hand hygiene and environmental adjustments will be made as for those receiving massage. Patients will have their hands held for 5-10 seconds and unscented hypoallergenic cream applied to both hands. Then, the interventionist will hold each of the patients' hand in her hand for ten minutes with occasional stroking for a total of 20 minutes.

Passive Control Group

The passive control group will receive the standard care administered in the ICU including a 20-minute rest period including the environmental adjustments of the experimental and active control groups. The interventionist will be outside of the patient room and have no contact with the patient throughout the 20 minutes. The standard care includes the pharmacological and nonpharmacological treatments (eg, repositioning) used to promote recovery and pain relief. In the study ICU, cardiac surgery patients are automatically prescribed a pain management protocol that includes the regular administration of morphine and breakthrough doses of analgesia as needed.

Criteria for Modifying Interventions

The allocated interventions will be discontinued upon the participant's withdrawal of consent or if skin irritation is suspected or patient comfort is disrupted due to the intervention itself, both of which will be reported as adverse events. Consenting participants will be retained in the trial whenever possible in spite of the discontinuation of the assigned intervention to allow remaining data collection and limit missing data.

Concomitant Care

Concomitant interventions may be received by patients while participating in this trial. Consenting patients will be permitted to receive any of the pharmacological treatments prescribed by their treating physician and any of the nonpharmacological interventions offered in the ICU (eg, back rub), and such data will be recorded. It is not prohibited that patients participate concomitantly in other research studies unless it involves any form of complementary therapy.

Outcomes

Primary Outcome

Pain intensity is the primary outcome and will be captured using the 0 to 10 NRS score. The analysis metric will be the change in pain intensity from baseline (preintervention) to immediately after each intervention and 30 minutes later.

Textbox 2. Hand massage routine protocol.

1. Hygiene: Wash hands with warm water.
2. Hold/connect/breathe: Make initial contact with patient, embrace hand, take a deep breath, and place feet on floor.
3. Apply cream to entire hand, dorsal and palmer aspects, including phalanges.
4. Spread (5 times) dorsal aspect of hand, using thumbs like opening a book. Repeat 5 times on palmer aspect, using the other 4 fingers to grip and glide. Spread again 5 times dorsal aspect of hand and 5 times palmer aspect.
5. Gently shake bottom hand; vibration will help the patient relax and let go of any tension.
6. Rotate wrists 3 times in each direction. Hold wrist with one hand while the other holds the patient's hand and facilitates the passive rotation.
7. Stretch the carpal ridge 3 times along wrist crease.
8. Caterpillar walk on the dorsal aspect of the hand, between the bones (ie, zoning).
9. Pinch (dorsal/palmer) aspect of the hand in between the metacarpals.
10. Gently pull the webs of fingers.
11. Knead (rock and roll) by making a fist on the palmer aspect of patient's hand, gently rotate using the knuckles to apply pressure 5 times.
12. Caterpillar walk on all areas of the palm, working proximally (towards the body) (if patient is less comfortable with palm upwards continue with hand in a neutral position, palm down).
13. Make small circles along the 5 zones of the palmer surface of the hand (proximal to distal).
14. Targeting key reflex areas, PRESS AND RELEASE 2 times in each area:
    a. Shoulder-neck ridge (base of fingers)
    b. Solar plexus (center of palm, just below the knuckle), PRESS and SPREAD (diaphragm line—moving outwards in both directions) 5 times
    c. Lateral aspect of palm
    d. Medial aspect of palm
    e. Pad of thumb
14. Pinch lateral aspect of hand 3 times.
15. Caterpillar walk on the medial border of thumb 3 times.
16. Caterpillar walk on the fingers:
    a. Caterpillar walk proximal making sure to cover all surface areas.
    b. Rotate knuckles gently 3 times in each direction (proximal to distal).
    c. Gently pull fingers.
17. Finishing touches: SWEEP entire hand, HOLD, and switch to other side.
18. Hygiene: Once both hands have been massaged, wash hands with cold water.

Secondary Outcomes

Pain unpleasantness, pain interference, muscle tension, anxiety, and vital signs will also be assessed in relation to each intervention, and means and standard deviations will be reported and used for data analysis.

Instrumentation

Pain Intensity

The NRS will be used to assess pain intensity. The NRS is an 11-point unidimensional self-report scale recommended for the assessment of pain intensity where 0 is no pain and 10 the worst possible pain. Details about the NRS and other assessment tools are summarized in Table 2.

Table 2. Description and psychometrics of the instruments used for outcome data collection.

Outcome	Instrument	Scoring	Psychometrics	
			Reliability	Validity
Pain intensity	NRS[a] (0-10)	0: no pain, 10: worst possible pain	High test-retest reliability observed in cancer patients when measuring pain exacerbations (kappa=.86) and background pain (kappa=.80) [48].	High concurrent validation with the Visual Analog Scale (r=.84 to .94, P<.001) [2,49]). Good discriminatory capability between background and peak intensity pain in the oncology population with only 14% of the 240 patients giving inconsistent evaluations [48].
Pain unpleasantness	NRS (0-10)	0: not at all unpleasant, 10: most unpleasant feeling possible		Good convergent validation with the Facial Affective Scale (r=.71, P<.01). Discriminant validation: correlated with the Functional Disability Inventory (r=.28, P<.05). Good sensitivity to change over a 2-week period (mean change 1.89, t_{68}=5.30, P<.001) in children and adolescents after surgery [50].
Pain interference	Adapted BPI[b]: pain intensity index (4 NRS 0-10 subscales), pain interference index (7 NRS 0-10 subscales)	Pain intensity: 0: no pain, 10: pain as bad as you can imagine Pain interference: 0: no interference, 10: interferes completely	Internal consistency was also supported for this patient population with Cronbach alpha coefficients .84-.89 for the severity scale and .91-.94 for the interference scale.	Factor analysis revealed two distinct factors (ie, pain intensity and interference) accounting for 66% and 75% of total variance, respectively [51]. Scores on both scales declined significantly from baseline to follow-up, thus testifying to the responsiveness of the BPI for detecting changes [51].
Muscle tension	CPOT[c] muscle tension subscale (0-2)	0: no resistance, 1: resistance, 2: strong resistance	Moderate to high interrater reliability of CPOT scores between trained raters with intraclass correlation of 0.30-0.86 [52] and kappa of 0.52-0.88 [53,54].	Discriminant validation: significant increases in CPOT scores during painful compared to nonpainful procedures [52-55]. Criterion validation: moderate correlation with patient self-report of pain intensity (r=.40-.69, P<.05) [52,53]. Convergent validation: moderate correlation with pain unpleasantness (r=.31, P<.01) [52]. Sensitivity of 86% and a specificity of 78% for the presence of pain during turning procedures were shown for a CPOT cut-off score >2 [56].
Anxiety	NRS (0-10)	0: no anxiety, 10: worst possible anxiety	Individual validity and reliability tests were not conducted to date with the NRS for anxiety, but it has been included in the Edmonton Symptom Assessment System, whose validity and reliability have received support over the past two decades [57].	

[a]NRS: Numeric Rating Scale

[b]BPI: Brief Pain inventory

[c]CPOT: Critical-Care Pain Observation Tool

Pain Unpleasantness

The NRS will be used to assess the pain unpleasantness of patients. The unpleasantness dimension of symptom experience refers to the degree to which the person is bothered by the unpleasant symptom [58]. The pain unpleasantness NRS is scored on a scale from 0 to 10 with the anchors “not at all unpleasant” for 0 and “most unpleasant feeling possible” for 10.

Pain Interference

An adapted version of the Brief Pain Inventory (BPI) will be used. The BPI is a short pain assessment scale developed to measure the intensity of pain during the last 24 hours (sensory dimension) and the interference of the pain in the patient’s life (cognitive dimension) [59,60]. The pain severity items are rated individually on an NRS with 0 assigned to “no pain” and 10 to “worst possible pain.” Patients are asked to rate their pain severity at the time of interview (pain now) and the worst pain, the least pain, and average pain during the last 24 hours. The 7

items of pain interference evaluate the impact of pain on general activity, mood, walking/mobilization, work, relationships, sleep, and enjoyment of life. The item work is not considered relevant in the context of cardiac surgery patients who are hospitalized in the ICU or acute care units and will not be administered. Instead, additional items about coughing, deep breathing, appetite, and concentration will be included; these have been observed to have moderate-to-severe pain interference in postoperative cardiac surgery patients [4,15,61].

Muscle Tension

The assessment of muscle tension will be based on an ordinal scale derived from the behavioral pain scale Critical-Care Pain Observation Tool (CPOT), which was developed and tested for the assessment of pain in critically ill patients after cardiac surgery [53]. Evaluation of muscle tension is done by performing passive flexion and extension of the upper limbs of patients at rest with a score of 0 being assigned for "no resistance to passive movements," 1 for "resistance to passive movements," and 2 for "strong resistance to passive movements or incapacity to complete them."

Anxiety

For consistency and because intensity of anxiety is of interest in this study, the NRS will also be used to assess patients' anxiety levels.

Vital Signs

Means of blood pressure (ie, systolic, diastolic, mean arterial pressure) and heart and respiratory rates will be collected from the ICU bedside monitors for 1 minute at each assessment point.

Data Collection

Sociodemographic (eg, age, gender) and medical-surgical data (eg, type of cardiac surgery, analgesia) will be collected using standardized data collection sheets. Prior to the delivery of each intervention (hand massage or hand-holding) and before the first data collection for the standard care group, patients will complete a self-administered data collection sheet with 5 short questions using the NRS for the self-report of pain intensity, pain unpleasantness, and anxiety, a body map for identifying the site of pain, and an open-ended question for a description of the quality of pain. The interventionist will be masked to patients' self-reports, which will be accessed only at the end of data collection to verify for missing data. The form will be completed before, immediately after the intervention (hand massage or hand-holding), and 30 minutes later, for a total of 3 data collection points per intervention. Those assigned to standard care will complete the form at similar times. This bundle of assessments will be repeated for each of the 3 interventions. Muscle tension and vital signs will also be evaluated at the same assessment points.

Finally, pain interference will be evaluated using a structured interview using the BPI on the second postoperative day to examine any carry-over effects.

Data Analysis

The data will be entered in the SPSS software version 22.0 (IBM Corp), and a random subset of data will be used to identify missing or erroneous values. This study aims to use intention-to-treat analysis by including every participant who has been randomized, regardless of group assignment, study withdrawal, or protocol deviations.

Descriptive statistics will be calculated for sociodemographic and medical-surgical data and the baseline scores on all the outcome variables. Group differentiation in sociodemographic and medical-surgical characteristics for participant patients will be investigated using chi-square tests of independence for nominal level variables and one-way analyses of variance (ANOVA) for interval and ratio level variables. If group differences exist, the respective variable will be included as a covariate in the subsequent analyses. Frequencies and percentages of the location and descriptors of pain (ie, sensory dimension of pain) will be calculated for each group and assessment point and used to describe the pain characteristics of participants. Data on pain location and quality will be compared over time.

Repeated measures between ANOVA factors will be used to test for treatment (hand massage, hand-holding, rest), time (before, immediately after, and 30 minutes later), and interaction effect for pain intensity, pain unpleasantness, muscle tension, anxiety, and means of vital signs. This will be run for each intervention and each of these outcome variables. One ANOVA test will be performed for pain interference with the independent variable being group assignment (hand massage, hand-holding, standard care). The main comparison of interest is between the hand massage and standard care group and the difference in means pre- and immediately posttreatment.

Ethical Considerations

Ethical approval has been granted by the Research Ethics Committee of the study setting in February 2016. This protocol has been independently peer reviewed by McGill University and the Quebec Nursing Intervention Research Network, who funded the study (F242710).

Informed and written consent will be obtained from participants. The study's aim and procedure, risks and benefits, right to refuse participation and withdraw at any time without any repercussions on the care provided, confidentiality of data, randomization process, and lack of financial incentives for participation in the study will be explained to patients. They will be equally informed that there is no guarantee that they will benefit from this study. While there are no known risks associated with hand massage and hand-holding, any harmful effects during these interventions will be noted and reported to the Research Ethics Committee.

Validity and Reliability

This study follows the most recent Consolidated Standards of Reporting Trials guidelines for nonpharmacological treatments and randomized controlled trials [62] and the Standard Protocol Items: Recommendations for Interventional Trials statement for clinical trial protocols [63].

The tools to be used for the assessment of the study outcomes have established validity and reliability in the population of interest in this study (Table 2). Data collection errors in vital

signs will be minimized by extracting their means from the bedside ICU monitors, which offer a continuous recording of vital signs. Additionally, the interventionist will be trained on the assessment of muscle tension. To enhance rigor, standardized hand massage and hand-holding will be ensured by training the interventionist on the administration of these therapies and by using a camera to monitor the consistency and fidelity with which each of these interventions is delivered [42].

Results

Recruitment started the end of April 2016, and to date 34 patients have already been recruited. Of these, 24 patients were randomized and had data collection done as several were medically unstable postoperatively or had their surgery cancelled/postponed. Data collection is expected to be complete by January 2017.

Discussion

Interpretation

Pain is one of the most common and severe symptoms cardiac surgery patients experience during their ICU stay. The adverse effects of unrelieved acute postoperative pain are numerous and can be taxing to cardiac surgery patients during their recovery but worryingly also on the long term. There is a general agreement in practice guidelines that multimodal approaches to pain management should be implemented in the ICU [20]. Massage, a complementary nonpharmacological intervention, could play an important role in enhancing pharmacological analgesia and maximizing pain relief in the cardiac surgery patients, and providing rigorous empirical evidence for its use in the ICU is strongly awaited to inform practice guidelines.

In the proposed RCT, eligible and consenting patients will be randomly assigned to either the massage (ie, experimental), hand-holding (ie, active control) or standard care group (ie, passive control). While the administration of pleasant and potentially beneficial interventions [42] can help minimize attrition rates in the experimental and active control groups, the use of standard care with rest only could cause higher withdrawals in this group and subsequently increase the risk of attrition bias. In order to counter such bias and as an incentive to make participation in the study more attractive, patients will be informed that hand massage can be offered to those assigned to the active or passive control groups at the end of data collection, if desired.

A strength of this RCT is the administration of massage in the actual ICU environment and the clinical context of the first 24 hours post–cardiac surgery when monitoring is accrued, thus enabling an evaluation of the effectiveness of this intervention on the patient's pain and related signs and symptoms. However, the same ICU environment could interfere with the delivery of some of the planned hand massages and hand-holding in the selected mode (eg, quiet environment) and dose (ie, 3 times for 20 minutes). In order to monitor these interferences and consider them in the interpretation of study findings, a camera will be used to videorecord the interventions. Nonetheless, even if these interventions can no longer be administered (eg, use of invasive equipment on hands postrandomization), attempts to continue collecting patients' self-reports of symptoms will be prioritized over imputation for missing data.

Limitations

One of the anticipated limitations of this RCT is the lack of blinding of patients in the standard care group and the respective clinical personnel responsible for their care. Although environmental adjustments will be made, these patients will have already been informed of the 3 trial arms and their implications and could easily recognize their group assignment. Equally, it is expected that the ICU personnel will notice the absence of an active intervention and assume patient assignment to standard care. Given the unlikelihood of blinding related to the standard care group, patients could modify their self-report while the personnel could practice differently compared to when they see hand massage/hand-holding administrations, thereby increasing the risk of performance bias.

Only the cardiac surgery ICU patient population will be included in this RCT, which will limit the generalizability of the findings to other ICU patients. Even so, this study will reveal the effectiveness of massage in this group of ICU patients suffering from intense pain and should be a trigger for further research internationally on the use of this intervention in the ICU in addition to the locally established standard care.

Conclusion

This funded RCT will unravel the potential benefits to reduce ICU postsurgery pain by the use of massage therapy in cardiac surgery ICU patients compared to hand-holding and standard care. The results of this study will serve to inform clinical practice guidelines with regard to the dose, timing, and technique of massage administration for the relief of acute postoperative pain in the ICU in addition to analgesia. If effective, massage could be easily implemented in ICU practice with little resources to maximize pain relief in the acute postoperative period and prevent the serious adverse consequences of unrelieved pain.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Modified Consolidated Standards of Reporting Trials flow diagram. CONSORT E-HEALTH (V1.6).

[PDF File (Adobe PDF File), 975KB - resprot_v5i4e203_app1.pdf]

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Abbreviations

ANOVA: analysis of variance
BPI: Brief Pain Inventory
CPOT: Critical-Care Pain Observation Tool
ICU: intensive care unit
NRS: Numeric Rating Scale
RCT: randomized controlled trial

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Protocol

A Prospective, Multicenter, Randomized Phase II Study to Evaluate the Efficacy and Safety of Eculizumab in Patients with Guillain-Barré Syndrome (GBS): Protocol of Japanese Eculizumab Trial for GBS (JET-GBS)

Nobuko Yamaguchi[1], BSc; Sonoko Misawa[2], PhD, MD; Yasunori Sato[3], PhD; Kengo Nagashima[3], PhD; Kanako Katayama[1], MSc; Yukari Sekiguchi[2], PhD, MD; Yuta Iwai[2], PhD, MD; Hiroshi Amino[2], MD; Tomoki Suichi[2], MD; Takanori Yokota[4], PhD, MD; Yoichiro Nishida[4], PhD, MD; Nobuo Kohara[5], PhD, MD; Koichi Hirata[6], PhD, MD; Kazutoshi Nishiyama[7], PhD, MD; Ichiro Yabe[8], PhD, MD; Ken-Ichi Kaida[9], PhD, MD; Norihiro Suzuki[10], PhD, MD; Hiroyuki Nodera[11], MD; Shoji Tsuji[12], PhD, MD; Haruki Koike[13], PhD, MD; Jun-Ichi Kira[14], PhD, MD; Hideki Hanaoka[1], PhD, MD; Susumu Kusunoki[15], PhD, MD; Satoshi Kuwabara[2], PhD, MD; JET-GBS Group[4,5,6,7,8,9,10,11,12,14,15]

[1]Clinical Research Center, Chiba University Hospital, Chiba, Japan
[2]Department of Neurology, Chiba University Graduate School of Medicine, Chiba, Japan
[3]Department of Global Clinical Research, Chiba University Graduate School of Medicine, Chiba, Japan
[4]Department of Neurology and Neurological Science, Tokyo Medical and Dental University, Tokyo, Japan
[5]Department of Neurology, Kobe City Medical Centre General Hospital, Kobe, Japan
[6]Department of Neurology, Dokkyo Medical University, Tochigi, Japan
[7]Department of Neurology, Kitasato University School of Medicine, Kanagawa, Japan
[8]Department of Neurology, Hokkaido University Graduate School of Medicine, Sapporo, Japan
[9]Division of Neurology, Department of Internal Medicine, National Defense Medical College, Saitama, Japan
[10]Department of Neurology, Keio University School of Medicine, Tokyo, Japan
[11]Department of Clinical Neuroscience, Graduate School of Medical Sciences, Tokushima University, Tokushima, Japan
[12]Department of Neurology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan
[13]Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[14]Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[15]Department of Neurology, Faculty of Medicine, Kindai University, Osaka-Sayama, Japan

Corresponding Author:
Sonoko Misawa, PhD, MD
Department of Neurology
Chiba University Graduate School of Medicine
Inohana 1-8-1
Chuo-ku
Chiba
Japan
Phone: 81 43 222 7171 ext 5414
Fax: 81 43 226 2160
Email: sonoko.m@mb.infoweb.ne.jp

Abstract

Background: Guillain-Barré syndrome (GBS) is an immune-mediated neuropathy that causes acute flaccid paralysis. Immunoglobulin and plasma exchange are established treatments for GBS; however, a substantial number of patients, particularly those with severe disease, have poor recovery and residual deficits. Recent studies suggest that complement activation plays a pivotal role in GBS-associated axonal degeneration, and eculizumab is a humanized monoclonal antibody that specifically binds to complement component 5 and potently inhibits complement activation.

Objective: This clinical trial aims to evaluate the efficacy and safety of eculizumab, a humanized monoclonal antibody directed against complement component 5, for treatment of GBS.

Methods: The Japanese Eculizumab Trial for GBS (JET-GBS) is a prospective, multicenter, placebo-controlled, double-blind, randomized phase II study conducted at 13 tertiary neurology centers and is funded by the Japan Agency for Medical Research and Development. A total of 33 GBS patients unable to walk independently within 2 weeks from symptom onset (Hughes functional grade 3-5) were randomized at a 2:1 ratio to receive either intravenous eculizumab (900 mg/day) or placebo once weekly for 4 weeks, followed by 20 weeks of follow-up. The primary endpoint for efficacy is the proportion of patients who regain their ability to walk without aid at 4 weeks after the first dose of the study treatment, while primary safety outcomes are the incidence of adverse events and serious adverse events during the trial.

Results: Enrollment for the trial began in August 2015. This trial is still ongoing. All participants have been enrolled, and follow-up will be completed in October 2016.

Conclusions: This study is the first to investigate the efficacy and safety of eculizumab for GBS. In case of a positive result, we will plan a phase III trial to investigate this issue in a larger number of patients.

ClinicalTrial: UMIN Clinical Trials Registry UMIN 000018171; https:/upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&language=J&recptno=R000020978 (Archived by WebCite at http://www.webcitation.org/6lTiG8ltG). Clinical Trials.gov NCT02493725; https://clinicaltrials.gov/ct2/show/NCT02493725 (Archived by WebCite at http://www.webcitation.org/6lVJZXKSL)

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KEYWORDS

Guillain-Barré syndrome; eculizumab; complement activation; clinical trial; antiganglioside antibody

Introduction

Guillain-Barré syndrome (GBS) is the most common cause of acute tetraparalysis in developed countries [1,2]. GBS occurs in all age groups, and the annual incidence is reported to range from 0.81 to 1.89 per 100,000 persons [3]. Although the efficacies of intravenous immunoglobulin (IVIg) and plasma exchange have been demonstrated in randomized controlled studies [4,5], GBS still carries nonnegligible mortality and morbidity [6]. Mortality within the first year is approximately 4% [6]. Recovery takes several months or years, and approximately 14% of GBS patients show severe persistent disability at one year after onset [6].

GBS is classified into two major subtypes: acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN). Over the past two decades, major advances have been made in understanding the pathophysiology of AMAN [7]. It is now established that AMAN is caused by molecular mimicry of human gangliosides by an antecedent pathogen and ensuing antiganglioside antibody-mediated attack on the axolemma. In an animal model induced by antiganglioside antibodies, complement activation contributed to disruption of the nodal and paranodal molecular architectures, leading to acute paralysis and residual deficits [7-9]. Furthermore, nafamostat mesilate, a synthetic serine protease inhibitor with anticomplement action, prevented nerve damage in a GBS rabbit model [10].

Eculizumab is a humanized monoclonal antibody that specifically binds to complement component 5 (C5) and suppresses its cleavage into active chemotaxis mediator C5a and attacks complex component C5b, thereby inhibiting membrane attack complex (MAC) formation [11,12]. Eculizumab has been approved for treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome [13,14], disorders wherein intravascular hemolysis is induced by complement activation. The efficacy of eculizumab for GBS has been shown in a mouse model mediated by antiganglioside antibody [15]. Eculizumab blocks the formation of MAC associated with terminal axonal and glial injury at the neuromuscular junction and prevents respiratory paralysis [15]. We, therefore, designed the Japanese Eculizumab Trial for Guillain-Barré syndrome (JET-GBS) study to investigate the efficacy and safety of eculizumab in GBS patients.

Methods

Trial Design Overview

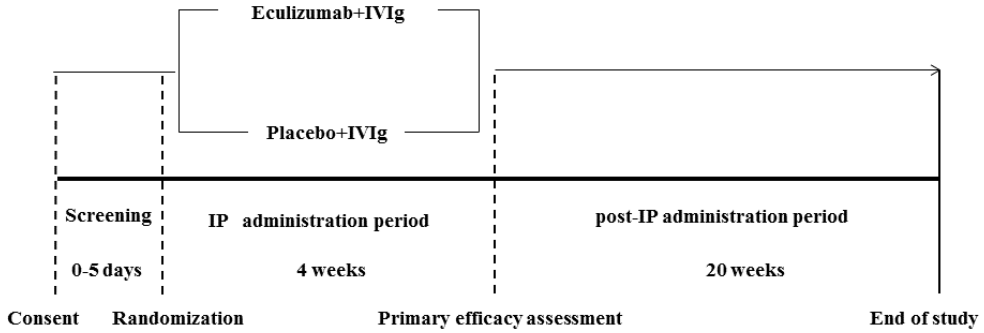
This is a prospective, multicenter, placebo-controlled, double-blind, randomized phase II trial in patients with GBS. A schematic depiction of the trial design is presented in Figure 1. The trial is composed of 3 periods: the screening period, investigation product (IP) administration period, and post-IP period. Screening is conducted within 5 days of randomization to assess eligibility and collect baseline data. Eligible patients were defined as those unable to walk independently (Hughes functional grade [FG] 3-5) within 2 weeks from the onset of weakness, because such patients have a higher risk of progression. They are randomized to receive either eculizumab or placebo at a 2:1 ratio. Eculizumab (900 mg/day) or matching placebo is administered intravenously once a week for a total of 4 doses (day 1, day 8, day 15, day 22) in conjunction with IVIg, the standard treatment for GBS (400 mg/kg daily for 5 consecutive days). IVIg can be readministered if patients show deterioration after initial improvement or stabilization (treatment-related fluctuation) following day 15. Patients are monitored periodically up to week 24. The primary endpoint for efficacy is the proportion of patients who reach FG 2 or lower (able to walk without aid) at day 29 (week 4). The primary

endpoints for safety are the proportion and severity of adverse events (AEs) and serious adverse events (SAEs).

Eligibility Criteria

GBS patients who meet all of the following inclusion criteria and none of the listed exclusion criteria are enrolled (see Textbox 1). Diagnosis of GBS is made with reference to the National Institute of Neurological Disorders and Stroke criteria [16].

Figure 1. Schematic depiction of the trial design. The study is composed of 3 periods: the screening period, investigational product (IP) administration period (4 weeks), and post-IP period follow-up (20 weeks).



Textbox 1. Selection criteria.

Inclusion criteria:

- Patients 18 years or older at time of informed consent
- Presenting within 2 weeks from onset of weakness due to GBS
- Unable to walk unaided for 5 or more meters (Hughes FG 4-5; if symptoms are progressive, patients with FG 3 can be enrolled)
- Undergoing or being considered for and will start IVIg treatment (400 mg/kg daily for 5 days)
- The first dose of eculizumab administered within 2 weeks from onset of symptoms and before the last dose of IVIg
- If female, not pregnant. All patients must use effective contraception during the study and for up to 5 months following discontinuation of IP administration
- Hospitalization during the IP administration period
- Signed informed consent

Exclusion criteria:

- Patients who are or will be treated by plasmapheresis
- Pregnant or lactating woman
- Evident neuropathy other than GBS
- Patients who have received immunosuppressive treatment (eg, azathioprine, cyclosporine, tacrolimus, or more than 20 mg prednisolone daily) within 4 weeks prior to informed consent
- Patients with a severe concurrent disease such as malignancy, severe cardiovascular disease, severe chronic obstructive pulmonary disease, or tuberculosis
- Inability to comply with study procedures and the treatment regimen
- Patients who have received rituximab within 24 weeks prior to informed consent
- Unresolved *Neisseria meningitidis* infection or a history of meningococcal infection
- Active infection that is not treated appropriately
- Patients who cannot take antibiotics as *N meningitidis* prophylaxis due to allergies
- Known allergy to eculizumab
- Known hereditary complement deficiencies
- Use of other investigational products within 12 weeks prior to informed consent, or participation in any other clinical trial
- Any condition that in the opinion of the investigator or subinvestigator could increase the patient's risk by participating in the study or confound the outcome of the study
- Patients with a history of eculizumab treatment for GBS

Interventions

Investigational Product (Eculizumab or Placebo)

Eculizumab (900 mg/day) or placebo is administered intravenously once a week for 4 weeks in patients who are being considered for, or already on IVIg treatment. The first dose of the IP is to be started before the last dose of IVIg. The patients are to be monitored by the medical staff for at least 1 hour following eculizumab/placebo infusion, because administration of eculizumab may result in infusion reactions. Administration is interrupted if severe infusion reactions occur.

Prophylactic Antibiotics

Inhibition of the terminal complement complexes predisposes patients to infections by encapsulated bacteria, especially *N meningitidis*. Therefore, all enrolled patients must receive antibiotic prophylaxis against *N meningitidis* for 8 weeks from the last dose of the IP.

Outcomes

The efficacy and safety of eculizumab will be assessed by the following endpoints. The primary efficacy endpoint is the proportion of patients who reach FG 2 or lower (able to walk without aid) at week 4, and the safety endpoints are the proportion and severity of AEs/SAEs during the trial.

The secondary endpoints include the proportion of patients with improvement of 1 or more Hughes functional grades from baseline at each visit, proportion of patients who are able to walk unaided at each visit, duration required for improvement by at least 1 Hughes functional grade, proportion of FG 1 or 0 at week 24, change from peak FG at each visit, clinically relevant improvement in the Rasch-built Overall Disability Scale (R-ODS) score and the Overall Neuropathy Limitations Scale (ONLS) score at each visit, proportion of ventilatory support, duration of ventilatory support, occurrence of relapse, overall survival, changes in grip strength, manual muscle testing score, median and ulnar nerve conduction parameters, vital capacity respectively from baseline at each visit, and proportion of IVIg readministration.

This study is also investigating antiganglioside antibodies, concentration of serum eculizumab, and serum hemolytic activity as exploratory endpoints. The data of antiganglioside antibodies assay will be used to determine the subtype of GBS, and the results of eculizumab concentration and hemolytic activity will be used to obtain exploratory data on the efficacy of eculizumab.

Study Visits and Assessments

The schedule for the study visits and assessments are summarized in Tables 1 and 2. Patients are assessed weekly for efficacy and safety during the 4-week IP administration period and on week 6, 8, 12, 16, and 24 during the 20-week post-IP period. Patients are requested to record their FG score independently using a diary until they show an improvement by one grade. If all 4 administrations of the IP cannot be completed due to AEs or other contingencies, patients remain in the trial and tests/assessments will be performed on the patients according to the trial schedule unless they meet the withdrawal criteria.

Table 1. Study visit and assessments during the screening and investigational product administration period.

Period	Screening	IP[a] administration				
Trial visit	1	2	3	4	5	6
Trial weeks		W0	W1	W2	W3	W4
Trial days	D0	D1	D8	D15	D22	D29
Time window (days)	−5		±2	±2	±2	±7
Informed consent	X					
Randomization	X					
Demography and medical history	X					
IP administration		X	X	X	X	
Chemoprophylaxis[b]		X	X	X	X	X
Clinical assessment						
FG[c]	X	X	X	X	X	X
ONLS[d]		X	X	X	X	X
MMT[e] score		X	X	X	X	X
Grip strength		X	X	X	X	X
R-ODS[f]		X				X
Physiological test						
Vital capacity	X					X
Nerve conduction study	X					X
12-lead ECG[g]	X		X			
Clinical lab test (blood test/urine test)	X		X	X	X	X
Antiganglioside antibody	X					
Eculizumab concentration/hemolytic activity		X	X			X
Pregnancy test (urine test)[h]	X					
Vital signs[i]	X	X	X	X	X	X
Concomitant drug/therapy review	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X

[a]IP: investigational product.

[b]Chemoprophylaxis will begin at the start of eculizumab infusion on day1 and be continued till 8 weeks from the last dose of eculizumab.

[c]FG: Hughes functional grade.

[d]ONLS: overall neuropathy limitations score.

[e]MMT: manual muscle testing.

[f]R-ODS: Rasch-built overall disability scale.

[g]ECG: electrocardiography.

[h]Pregnancy tests must be performed on all women of child bearing potential at the specified time points and verified to have a negative result. Pregnancy test may also be performed at any visit at the investigator's discretion.

[i]Vital signs: blood pressure, heart rate, body temperature.

Table 2. Study visit and assessments during the post–investigational product administration period.

Period	Post-IP[a] administration (outpatient)					Early termination	Follow-up visit[b]
Trial visit	7	8	9	10	11		
Trial weeks	W6	W8	W12	W16	W24		
Trial days	D43	D57	D85	D113	D169		
Time window (days)	±7	±7	±7	±7	±7	+7	+7
Informed consent							
Randomization							
Demography and medical history							
IP administration							
Chemoprophylaxis[c]	X	X					
Clinical assessment							
FG[d]	X	X	X	X	X	X	
ONLS[e]	X	X	X	X	X	X	
MMT[f] score	X	X	X	X	X	X	
Grip strength	X	X	X	X	X	X	
R-ODS[g]		X	X	X	X	X	
Physiological test							
Vital capacity					X	X	
Nerve conduction study			X		X	X	
12-lead ECG[h]					X	X	
Clinical lab test (blood test/urine test)	X	X	X	X	X	X	X
Antiganglioside antibody							
Eculizumab concentration/hemolytic activity	X						
Pregnancy test (urine test)[i]					X	X	X
Vital signs[j]	X	X	X	X	X	X	X
Concomitant drug/therapy review	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X

[a]IP: investigational product.

[b]If a patient withdraws from the trial within 8 weeks after the last IP administration, a final follow-up visit will be performed at 8 weeks after the last IP administration for safety assessment.

[c]Chemoprophylaxis will begin at the start of eculizumab infusion on day1 and be continued till 8 weeks from the last dose of eculizumab.

[d]FG: Hughes functional grade.

[e]ONLS: overall neuropathy limitations score.

[f]MMT: manual muscle testing.

[g]R-ODS: Rasch-built overall disability scale.

[h]ECG: electrocardiography.

[i]Pregnancy tests must be performed on all women of child bearing potential at the specified time points and verified to have a negative result. Pregnancy test may also be performed at any visit at the investigator's discretion.

[j]Vital signs: blood pressure, heart rate, body temperature.

Data Management, Monitoring and Auditing

Study data is recorded in the electronic case report form (eCRF) of Medidata Rave, which was configured for this study by the data management division at Chiba University Hospital Clinical Research Centre. The eCRF data maintain anonymity and identify participating patients by their assigned identification codes. Independent monitors ensure that the study is properly conducted at each site in accordance with the protocol and good clinical practice and verify that the contents of case reports and

other reports are current and accurate. The monitors and data managers assure the quality of the data at each stage of handling. Auditors who are independent from all divisions conducting the trial perform audits of the clinical trial sites and verify appropriate quality assurance.

Reporting for Adverse Events and Serious Adverse Events

All AEs are recorded on the AE page of the eCRF. The investigator at each site endeavors to obtain the outcome and severity of all AEs. AEs are reported from the time of informed consent to the last trial visit (week 24); however, SAEs with a causal relationship to the IP are monitored until resolution if possible. All SAEs are reported to all investigators and assessed through a Web-based AE reporting system that has been developed by the Japan Medical Association, Centre for Clinical Trials. SAEs that have not been reported previously are reported to the Pharmaceuticals and Medical Devices Agency.

Sample Size Calculation

The sample size was based on the results from our previous study [17] and our historical database of GBS patients. For the primary endpoint of efficacy, we estimated that the threshold value for Hughes FG 2 or lower at week 4 would be 50% and the expected value 80%. A sample size of 20 patients in the eculizumab group is required to achieve statistical significance level of 5% (1-sided) at 80% power. To allow for a 10% dropout rate, total sample size in the eculizumab group is 22. Additionally, 11 patients will be randomly assigned to the placebo control to collect efficacy and safety data. The total sample size was set at 33.

Allocation

Eligible patients who provided informed consent are registered for study enrollment and are randomized to the eculizumab or placebo arm at a 2:1 ratio via a Web-based system developed by ADJUST Co Ltd. Allocation is performed using the minimization method with biased coin assignment [18,19] balancing for FG score (FG=3 or FG≥4) and age (younger than 60 years or 60 years and older).

Blinding

Each vial of IP contains 300 mg of eculizumab or placebo. The placebo has an identical external appearance to that of eculizumab. All participating patients, investigators, study coordinators, data managers, and outcome assessors remain blinded to group assignment during the trial. In order to maintain blinding, measurements of serum 50% hemolytic complement activity are prohibited during the trial. The levels of antiganglioside antibodies, eculizumab concentrations, and hemolytic activities in serum are measured at a central laboratory and the results are masked to all patients and study personnel during the trial.

Statistical Methods

Statistical analyses and reporting of this trial will be conducted in accordance with the Consolidated Standards of Reporting Trials statement guidelines with the primary analyses based on the intent-to-treat principle without imputing any missing observations. All efficacy analyses will be primarily based on the full analysis set, which includes all patients who have received at least one dose of the study treatment.

The primary endpoint for efficacy is the proportion of patients with FG≤2 at week 4. We hypothesized that response threshold at week 4 would 50% as H_0 (null hypothesis), whereas the expected response rate would be 80% as H_1 (alternative hypothesis). The exact 90% confidence interval will be calculated by the binominal distribution for the response rate of each treatment group. The confidence limits of the confidence interval will be assessed against the response threshold; however, in primary analysis, we will not perform a statistical testing for comparison of treatment groups.

For the patient characteristics, summary statistics were constructed using frequencies and proportions for categorical data and means and SDs for continuous variables. Patient characteristics were compared using a Fisher exact test for categorical outcomes and a Student *t* test or the Wilcoxon rank sum test for continuous variables, as appropriate. All comparisons were planned, and all *P* values are 2-sided. A value of $P<.05$ is considered statistically significant. Subgroup analysis will be performed for safety and efficacy depending on GBS subtype, baseline FG, and electrodiagnosis.

All statistical analyses are performed using SAS software version 9.4 (SAS Institute) and the R statistical program version 2.13 (The R Foundation). All statistical analyses are described in the statistical analysis plan, which will be fixed prior to database lock.

Ethics and Dissemination

Research Ethics Approval and Protocol Amendments

The study protocol was approved by the institutional review board (IRB) at each site before the start of the trial. Substantial amendments of the study protocol must be approved by each IRB. The trial was registered at the University Hospital Medical Information Network clinical trials registry [20] and ClinicalTrials.gov [NCT02493725].

Informed Consent

All participants are fully informed about the nature, purpose, possible risks, and benefits of the study with both oral and written information approved by all IRBs. Participants are notified that they are free to withdraw from the study at any time. The participants are given the opportunity to ask questions and allowed time to consider the information provided before consent. The participant's signed and dated informed consent is obtained before conducting any study procedures. A copy of the consent document and explanation document is given to the participant and the original copy of the consent document is retained at the clinical trial site.

Results

The trial started enrollment in August 2015. All 34 participants have been enrolled according to plan. This trial is still ongoing. Follow-up will be completed in October 2016.

Discussion

The JET-GBS is the first phase II trial to investigate the efficacy and safety of a monoclonal antibody specifically binding C5 for the treatment of GBS. Given that complement activation and MAC deposition is known to play a pivotal role in GBS-associated nerve degeneration [7,8,9], we speculate that eculizumab can effectively prevent nerve injury, thereby accelerating recovery from GBS.

The efficacies of plasma exchange and IVIg for GBS treatment were first established in the 1980s and 1990s [4,5], but subsequent clinical trials have failed to demonstrate beneficial effects of alternative therapeutic approaches such as interferon-β1a [21], brain-derived neurotrophic factor [22], and mycophenolate mofetil [22]. Thus, IVIg and plasma exchange are still the mainstays of GBS treatment, with IVIg preferred because of its greater convenience and availability. However, new treatment options are necessary because the prognosis is still far from satisfactory for many patients [6].

There are several limitations to this study. First, the number of enrolled patients is small as this trial was designed to provide proof of concept rather than to assess the superiority of different treatments. If this study demonstrates efficacy and safety for GBS, we will plan a phase III trial to confirm its effectiveness and safety in a larger number of patients. Second, the pathogenic mechanism targeted by eculizumab (complement activation) appears active only in conjunction with antiganglioside antibody related to AMAN [8,9], as no study has clearly demonstrated a contribution of complement activation to demyelination or axonal degeneration in AIDP. However, the finding of C3d and C5b-9 deposits along the outer surface of Schwann cells in an autopsy study of AIDP suggests that eculizumab may also be effective for AIDP [23]. In the current study, we are also planning to investigate whether GBS subtype (AMAN or AIDP) or the presence of antiganglioside antibodies can influence the efficacy of eculizumab. Third, 3% of Japanese have a mutation in C5 that renders them resistant to eculizumab therapy. It might substantially affect results of this study.

There has been no substantial progress in GBS treatment over the last two decades. However, recent progress in understanding GBS pathophysiology and the development of novel biological agents targeting these pathogenic pathways could enable alternative approaches to mitigate nerve injury in GBS. The present clinical trial based on a specific pathogenic mechanism of GBS may pave the way for improved GBS therapies.

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Conflicts of Interest

The investigational product is provided by US-based Alexion Pharmaceuticals Inc under the Global Investigator-Sponsored Research Program. The interest profile of this trial is to be reviewed and approved by the conflict of interest committees of the participating sites, all in accordance with the applicable regulatory requirements and guidelines, and potential conflicts addressed through conflict of interest management and integrity assurance efforts.

Authors' Contributions

SaK and SuK conceived the study and are responsible for managing the study as co-chief investigators. NY and SM wrote the protocol and manuscript. YaS and KN contributed to statistical input, outlining of statistical methods, and analysis. KK contributed to protocol design and conduct of the study. YuS, YI, HA, and TS contributed to an intensive survey on GBS demography for enhancing patient recruitment. HH provided guidance on overall direction of the study.

The JET-GBS group consists of Dr Tadashi Kanouchi (Tokyo Medical and Dental University, Tokyo), Dr Michi Kawamoto and Dr Junko Ishii (Kobe City Medical Centre General Hospital, Kobe), Dr Norito Kokubun (Dokkyo Medical University, Tochigi), Dr Ray Masuda and Dr Takahiro Shimizu (Kitasato University School of Medicine, Kanagawa), Dr Motoi Kuwahara (Faculty of Medicine, Kindai University, Osaka-Sayama), Dr Hidenao Sasaki and Dr Makoto Hirotani (Hokkaido University Graduate School of Medicine, Sapporo), Dr Hiroshi Takazaki (National Defense Medical College, Saitama), Dr Shigeaki Suzuki (Keio University School of Medicine, Tokyo), Dr Naoko Matsui (Graduate School of Medical Sciences, Tokushima University, Tokushima), Dr Jun Shimizu (The University of Tokyo Graduate School of Medicine, Tokyo), and Dr Ryo Yamasaki and Dr Hidenori Ogata (Graduate School of Medical Sciences, Kyushu University, Fukuoka). All members of the JET-GBS group made significant contributions to trial implementation. All authors critically reviewed the study protocol and the manuscript and gave approval for this publication.

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Abbreviations

AIDP: acute inflammatory demyelinating polyneuropathy
AE: adverse event
AMAN: acute motor axonal neuropathy

C5: complement component 5
eCRF: electronic case report form
FG: Hughes functional grade
GBS: Guillain-Barré syndrome
IP: investigational product
IRB: institutional review board
IVIg: intravenous immunoglobulin
JET-GBS: Japanese Eculizumab Trial for Guillain-Barré syndrome
MAC: membrane attack complex
ONLS: Overall Neuropathy Limitations Scale
R-ODS: Rasch-built Overall Disability Scale
SAE: serious adverse event

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Protocol

Effect on Nitrogen Balance, Thermogenesis, Body Composition, Satiety, and Circulating Branched Chain Amino Acid Levels up to One Year after Surgery: Protocol of a Randomized Controlled Trial on Dietary Protein During Surgical Weight Loss

Violeta Moizé[1], RD, MSc; Xavier Pi-Sunyer[2], MD, PhD; Josep Vidal[1], MD, PhD; Patricia Miner[3], RD, PhD; Yves Boirie[4], MD, PhD; Blandine Laferrère[2], MD, PhD

[1]Institut Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

[2]Obesity Research Center, Department of Medicine, Columbia University, New York, NY, United States

[3]Queens College, City University of New York, New York, NY, United States

[4]Unité de Nutrition Humaine, Clermont Universite, Université d'Auvergne, Clermont-Ferrand, France

Corresponding Author:
Violeta Moizé, RD, MSc
Institut Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)
Rosellon 149
Barcelona, 08036
Spain
Phone: 34 932275707
Fax: 34 933129403
Email: vmoize@clinic.ub.es

Abstract

Background: Bariatric surgery (BS), the most effective treatment for severe obesity, typically results in 40-50 kg weight loss in the year following the surgery. Beyond its action on protein metabolism, dietary protein intake (PI) affects satiety, thermogenesis, energy efficiency, and body composition (BC). However, the required amount of PI after surgical weight loss is not known. The current daily PI recommendation for diet-induced weight loss is 0.8 g/kg ideal body weight (IBW) per day, but whether this amount is sufficient to preserve fat-free mass during active surgical weight loss is unknown.

Objective: To evaluate the effect of a 3-month dietary protein supplementation (PS) on nitrogen balance (NB), BC, energy expenditure, and satiety in women undergoing either gastric bypass or vertical sleeve gastrectomy.

Methods: In this randomized prospective study, participants will be randomized to a high protein supplementation group (1.2 g/kg IBW per day) or standard protein supplementation group (0.8 g/kg IBW per day) based on current guidelines. Outcome measures including NB, BC, circulating branched chain amino acids, and satiety, which will be assessed presurgery, and at 3-months and 12-months postsurgery.

Results: To date, no studies have examined the effect of dietary PS after BS. Current guidelines for PI after surgery are based on weak evidence.

Conclusions: The results of this study will contribute to the development of evidence-based data regarding the safe and optimal dietary PI and supplementation after BS.

Trial Registration: Clinicaltrials.gov NCT02269410; http://clinicaltrials.gov/ct2/show/NCT02269410 (Archived by WebCite at http://www.webcitation.org/6m2f2QLeg).

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KEYWORDS

bariatric surgery; protein intake; nitrogen balance; body composition; satiety; BCAA

Introduction

Bariatric surgery (BS) is the most effective long-term therapy for the treatment of severe obesity. BS is associated with a favorable impact on overall and cardiovascular mortality, incidence of first occurrence of fatal or nonfatal cardiovascular events, prevention and remission of type 2 diabetes mellitus (T2DM), and quality of life [1]. Short-term studies showed no apparent difference between gastric bypass (GBP) and vertical sleeve gastrectomy (SG) on T2DM remission and weight loss [2]. GBP and SG are the most accepted procedures currently being performed, with SG increasing in prevalence since its inception in 2003 [3]. Although the surgeries differ widely (GBP is considered a malabsorptive and restrictive procedure while SG is solely restrictive), the prevalence of nutrient deficiencies seems to be comparable [4]. However, the metabolic impact of dietary protein intake (PI) in the early phase of active weight loss has not been studied.

PI during diet-induced weight loss and weight maintenance has been associated with retention of fat-free mass (FFM) [5,6], better satiety [7], and, if insufficient, with malnutrition [8]. Surgical weight loss is associated with decreased circulating levels of branched chain amino acids (BCAAs) [9].

Caloric intake decreases significantly during the first 3-6 months after surgery and may be frequently associated with vitamin, mineral [4,10], and protein deficiencies [4,8-11]. Prospective studies observed that low albumin levels, a clinical marker of protein deficiency [12], can occur up to 2 years after GBP [8,13] with a prevalence ranging from 3 to 18% [9,13-15]. Protein deficiency is more commonly observed after malabsorptive procedures, such as the biliopancreatic diversion [16]. Changes in taste and food preferences, and some degree of stomach discomfort during meals (with or without dumping syndrome), contribute to a poor dietary protein tolerance, thereby affecting the net PI [17]. The potential macronutrient maldigestion and/or malabsorption observed after BS [18] may also contribute to a compromised protein status.

It is generally accepted that diets containing all indispensable amino acids (AAs) are required for optimal protein synthesis and balance [19,20], and optimal intake of dietary protein should even be increased in vulnerable populations [21]. Nitrogen balance (NB), the difference between nitrogen intake and loss, is often compromised with trauma or infection, even with attempted nutritional interventions [22,23]. BS compromises NB via lower PI and an early maintained (or generally higher) protein demand following surgery, so high protein diets are recommended by various guidelines [24-26]. The most updated American Association of Clinical Endocrinologists guidelines suggest that a minimal PI of 60 g/day (and up to 1.5 g/kg ideal body weight [IBW] per day) after BS should be *adequate*, although these recommendations are only supported by a low level of scientific evidence (grade C or D). However, as the clinical tolerance of protein-containing foods is low after BS, recommendations are rarely followed and patients often do not reach their PI goal [17]. Our group and others have shown that daily consumption of 60 g of protein can be challenging during the first 4 months after surgery, even when protein supplements are recommended and supplied at no cost [27]. PI of 1.5 g/kg IBW per day would represent (when considering IBW for a body mass index [BMI] of 25 kg/m^2) 105 g/day for a woman with an IBW of 70 kg. The low protein tolerance mentioned above makes this recommendation difficult to follow, even with the most motivated patients. Therefore, finding an acceptable amount of PI would ensure optimal FFM retention, limit muscle breakdown, maintain resting energy expenditure (REE), and contribute to the development of a healthier diet that supports weight loss maintenance without interfering with glucose homeostasis.

Background

Risk of Decreased Lean Body Mass and Resting Energy Expenditure With Surgical Weight Loss: Effect of Dietary Protein

The consequences of negative energy and protein balance on visceral mass and skeletal muscle mass are well established [28]. Surgical weight loss results in both fat mass (FM) and lean body mass (LBM) loss: 75.2% and 24.8%, respectively [29]. LBM is the main determinant of REE, and explains 70% of the REE variance [30], with REE being the largest component of 24-hour energy expenditure (EE). Thus, reduced EE after weight loss is a factor of resistance for weight loss, and it may trigger the regaining of weight in the BS population [31]. The impact of daily PI on REE after BS has not been previously addressed, while PI is known to impact postprandial thermogenesis. Although the reduction of FM in obese individuals during weight loss is beneficial, the decrease in LBM may down-regulate the metabolic process, including protein turnover and basal metabolic rate, thus compromising long-term healthy weight management [32]. Studies on the impact of PI on body composition (BC) after BS are scarce and inconclusive. While some studies failed to find a significant correlation between absolute PI and FFM loss relative to total weight loss after BS [5,33-35], others found that higher levels of PI improved BC changes by enhancing the loss of FM and reducing FFM loss after BS [36]. High protein diets may increase EE while preventing LBM loss [30] during weight loss. Increased EE from dietary protein is attributed to an enhanced thermic effect of food (15%, standard deviation [SD] 4) compared to carbohydrates (6%, SD 2) or lipids (7%, SD 3) [37]. Studies related to the effect of high protein versus standard protein diets on the prevention of LBM loss, which in turn lead to a lesser reduction in REE, are often inconclusive [8,34,38]. In addition, comparisons between GBP and SG have not been completed.

Nitrogen Balance Study in the Bariatric Surgery Setting

NB is classically used to determine adequate PI with regards to daily nitrogen loss, and to estimate whole body protein balance in response to nutritional interventions [39]. Sustained negative NB can be associated with loss of lean and fat tissue [40]. Thus, ideally the goal of PI after BS should aim at preventing and/or limiting negative NB, even under energy restriction.

Occurrence of malabsorption should be considered when assessing NB in BS subjects [11]. In a malabsorptive state, fecal losses of nitrogen may be as high as 3.5 g/day [12]. Thus, in addition to the other components of the NB equation, fecal

nitrogen losses should be measured after BS, and not simply estimated at 0.4 g/day, as recommended by the Joint Food and Agriculture Organization/World Health Organization expert committee, under nonmalabsorptive conditions [41,42]. Of note, Odstrcil et al [18] studied the contribution of malabsorption on the reduction in net energy absorption 5 and 14 months after long-limb GBP. Net absorption of protein was significantly reduced after BS, and malabsorption accounted for 13% of the total reduction in protein absorption at both study time points [18]. However, a protein kinetic study using stable isotopes demonstrated that protein digestion and absorption were not impaired, and even accelerated, 3 months after GBP [43].

Roles of Protein Supplementation on Circulating Levels of Amino Acids

It has long been recognized that circulating levels of AAs, including BCAAs, are elevated in persons with obesity, insulin resistance (IR), or T2DM, compared to healthy controls [44,45]. BS is associated with reduced concentrations of plasma BCAAs [46] and decreased IR [8,46]. To date, the protein sparing effect of long-term protein supplementation (PS) has not been studied.

Dietary Protein Intake and Satiety

High PI has been shown to increase satiety in the context of energy restriction [47,48]. Proposed factors that may enhance satiety include: a ketogenic state; relatively elevated plasma AA levels [49]; an increase of the satiety peptide YY (PYY), glucagon-like peptide 1 (GLP-1) and cholecystokinin (CCK) [50]; and/or a decrease of the orexigenic hormone ghrelin [13,51]. We aim to further explore the relationship between PI and satiety after BS procedures.

Study Aims

Considering the complexity of metabolic and behavioral changes after BS, the overall aim of our research study will be to establish adequate PI after BS. To achieve this goal, we will compare the effect of 2 levels of PI (high protein supplementation group, HPS-G; and standard protein supplementation group, SPS-G) after BS (GBP and SG) on (1) NB, (2) BC, (3) REE and diet-induced thermogenesis (DIT), (4) satiety, (5) the release of gut hormones, (6) circulating levels of BCAAs in relation to insulin sensitivity, and (7) adherence to protein supplements. Five specific objectives will address our aims.

Objective 1: Nitrogen Balance

Total body NB will be measured to assess the levels of PI and protein absorption. The measure of NB will be performed during an inpatient stay before surgery, after 3 months of controlled PS, and 12 months after BS. PI will be established at 1.2 g protein/IBW per day for all participants in the month before surgery. After surgery, participants will be randomized to either 1.2 g protein/IBW per day (HPS-G) or 0.8 g protein/IBW per day (SPS-G). Participants will receive PS for 3 months after BS, up to the second inpatient study time point. During the inpatient stay, all foods and drinks will be strictly controlled, and 24-hour urine and stool samples will be collected. Nitrogen content of food from aliquots, urine, and stool will be measured, as explained in the *Methods* section.

Objective 2: Effect of Protein Supplementation on Body Composition

We will compare the effect of HPS and SPS on LBM. Changes in BC will be assessed before surgery, at 3 months, and 12 months after surgery in the 2 PS study groups using anthropometry, total body water (TBW), and plethysmography (BOD POD).

Objective 3: Effect of Protein Supplementation on Resting Energy Expenditure and Diet-Induced Thermogenesis

We will compare the effect of HPS and SPS on EE, measured by indirect calorimetry at rest (REE) and 4 hours after a high protein liquid test meal (DIT), before surgery, at 3 months, and 12 months after BS.

Objective 4: Branched Chain Amino Acid Levels

We will characterize changes in circulating BCAA levels in relation to insulin sensitivity and PI adequacy after GBP and SG. Circulating BCAA levels will be measured by targeted metabolomics and compared to insulin sensitivity (calculated by the homeostatic model assessment-insulin resistance or Matsuda index) before surgery, at 3 months, and 12 months postsurgery.

Objective 5: Effect of Surgical Procedures on Nitrogen Balance and Satiety

We will compare the effect of HPS and SPS, the hormonal response after a meal, and NB between GBP and SG. Satiety and hunger will be measured by visual analog scales (VASs) while fasting and in response to a high protein meal, before surgery, at 3 months, and 12 months after BS. Blood samples will be obtained before and after the meal test to measure the satiety-related gut hormones CCK, PYY, GLP-1, ghrelin, along with insulin and glucose levels. NB will also be compared between the surgical procedures.

Methods

Subjects

All subjects will be recruited from the Bariatric Surgery Institute at Mount Sinai St Luke's Hospital (New York, NY), and will be required to sign an institutional review board -approved consent form prior to enrollment.

Number of Subjects

A total of 112 volunteers scheduled to undergo either GBP or SG will be recruited. Based on our experience, we anticipate a conservative 30% attrition rate. Therefore, approximately 80 patients are expected to remain in the study at completion.

Inclusion and Exclusion Criteria

BC differences exist between women and men, and the BS patient population is 75% women, so only premenopausal women (18-40 years of age, BMI <50 kg/m^2) will be included in this study. Other inclusion criteria include: any race/ethnicity; patients scheduled to undergo either GBP or SG; treated or untreated resting systolic/diastolic blood pressure less than 160/100 mmHg; fasting triglyceride concentration less than 600

mg/dl, without regard for diagnosis or prescription for other dyslipidemias; absence of diabetes, or diet-controlled diabetes (taking no medications).

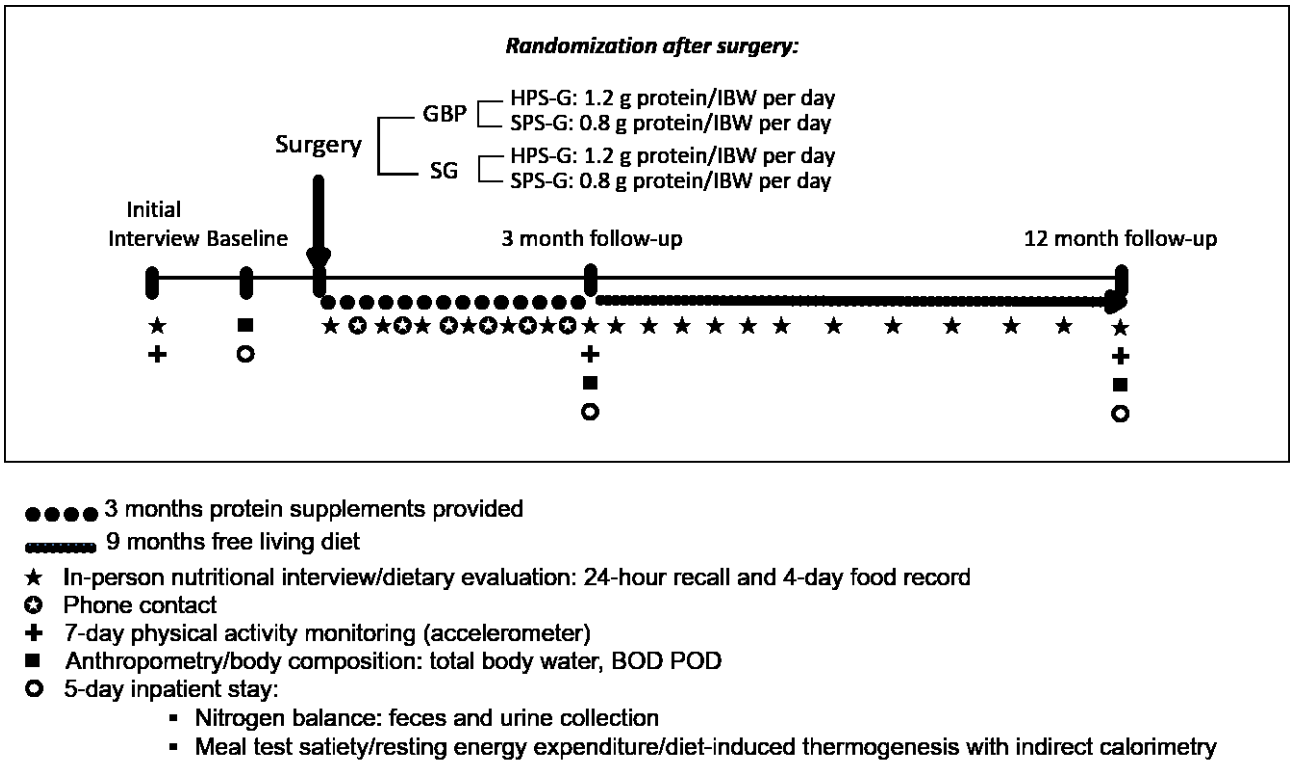
Exclusion criteria include: presence of nitrogen retention disease (eg, renal or hepatic disease); abnormal thyroid function; known malabsorption syndrome; cardiovascular disease; current mucosal (gastrointestinal, respiratory, urogenital) or skin (cellulitis) infection; any psychiatric disorder; and any other condition which, in the opinion of the investigators, may make the candidate unsuitable for participation in this study.

Study Design

Design and Setting

This study is a prospective randomized controlled trial (RCT), in which 112 obese participants (with no major comorbidities) scheduled to undergo GBP or SG will be randomly allocated to SPS-G or HPS-G cohorts. Participants will undergo three 5-day inpatient stays: presurgery, 3 months postsurgery, and 12 months postsurgery. The inpatient stays will be in the Clinical Research Resource (CRR) in the Irving Institute of Clinical and Translational Research at Columbia University Medical Center. The overall study design is displayed in Figure 1.

Figure 1. Overall study design of protein supplementation after bariatric surgery. GBP: gastric bypass; SG: sleeve gastrectomy; HPS-G: high protein supplementation group; SPS-G: standard protein supplementation group; IBW: ideal body weight.



Protein Supplementation Protocol

PS regimens will be supplied during the 3 months immediately following surgery. The HPS-G group will receive 1.2 g protein/kg IBW per day, and the SPS-G group will receive 0.8 g protein/IBW per day, with IBW established as a BMI of 25 kg/m^2 [4]. PS goals will be achieved partly by providing subjects with an instant high quality protein-isolate whey protein powder-supplement (Unjury; ProSynthesis Laboratories, Sterling, VA) [52]. Whey protein is the richest source of BCAAs and leucine, which has been demonstrated to stimulate muscle protein synthesis in elderly populations [53,54]. The SPS-G group will require approximately 1.5 servings per day (21 g protein/serving) while the HPS-G group will require 3 servings per day to meet their individually prescribed protein requirement.

Preceding Diet at Baseline

The NB study will be preceded by an outpatient diet stabilization period lasting 7 days. During this time, a meal plan will be tailored to each participant and PS will be provided, based on the individual's preferences, to promote adherence. Participants will be asked to complete a 7-day food record during this outpatient period, and will be contacted by phone one time during this period in order to evaluate adherence to, and tolerance of, the prescribed diet. This diet stabilization period is designed to allow each participant to adapt to the required level of PS [55]. Energy and protein requirements will be based on 35 kilocalorie (kcal)/IBW per day and 1.2 g protein/IBW per day, respectively [56], and will be calculated using the Nutrition Data System for Research (NDSR), 2011 [57]. Energy intake will be adjusted to minimize weight changes (within 0.75 kg of body weight) during the period of controlled diet, prior to admission, and during the inpatient stay [58].

Inpatient Study Period Before Surgery

During the initial 5-day inpatient study period all foods and drinks will be provided, and carefully monitored and controlled, under the supervision of the research dietician (VM) and the staff of the Bionutrition Unit in the CRR. All foods, drinks, and

protein supplements will be aliquoted and weighed on a 0.1-gram precision scale before consumption. To minimize variability and accurately control the intake of nitrogen, participants will eat the same diet every day. Participants will not be allowed to eat or drink any other food except for tap-filtered water. Diets will be based on regular/natural foods that require minimum manipulation. To meet the dietary PI goals, Unjury isolate whey protein products will be included in the diet as the main source of protein during the entire 5-day period. Vitamin and mineral supplementation, if any, will be continued during the inpatient study. Participants will be asked to eat the entire food portion that is served. Supervision will be ensured during each meal, and after each serving the trays will be examined by staff members, and the volume of any unconsumed beverage/soup will be measured in a graduated cylinder. All existing uneaten food will be weighed and recorded for day-to-day dietary adjustments. Meals for 1 complete day during the stay will be prepared and cooked in duplicate, and will be homogenized in a heavy duty commercial blender to obtain 24-hour diet aliquots. Two aliquots will be frozen at –70° Celsius for later analysis of total nitrogen and energy content.

Post-Bariatric Surgery Dietary Protein Supplementation Intervention

After BS, participants will be randomized using the technique of permuted block randomization to ensure that equal numbers of patients are assigned to each treatment arm (HPS-G or SPS-G). In accordance with post-BS practice guidelines, the meal plan will consist of 6 small meals per day (breakfast, morning snack, lunch, afternoon snack, dinner, and late snack), plus powdered PS that will be distributed during either 3 (SPS-G) or 6 (HPS-G) meals. Phone and in-person contacts will be provided on alternating weeks during the 12-week PS intervention. At each contact time point, dietary and PS adherence, food tolerance, and hydration will be evaluated by reviewing the food records specifically designed to quantify the number of scoops of the PS used in each meal. Urinary nitrogen excretion will be used as a biomarker for PI, and to measure compliance. Subjects will be asked to collect their 24-hour urine at 5 different time points during the 12-week period. PS containers will be supplied during the in-person participant-dietitian biweekly interviews. Participants will be asked to bring the empty PS containers for review and quantification at each appointment.

Preceding Diet and 5-Day Inpatient Stays at 3 Months and 12 Months After Bariatric Surgery

Daily energy intake during the preceding diet period, and during the inpatient stays, will be significantly reduced to a 10-15 kcal/IBW per day at 3 months post-BS. This value will increase up to 20 kcal/day at 12 months [4].

Laboratory Analyses and Outcome Measurements

Nitrogen Balance Study

Participants will be admitted for 5 days in the CRR for complete feces and urine collections during the last 3 days of the inpatient period. These collections will take place at the 3 different study time points: (1) presurgery; (2) 3 months after BS, during the active weight loss phase; and (3) 12 months after BS to evaluate the long-term carry over effect of PS on BC changes and REE.

24-Hour Complete Specimens Collection

Four 24-hour urine collections will be undertaken; 1 per day during the inpatient stay. Collection will start after the first void of the second day. Labeled urine containers will be refrigerated at 4° Celsius. Starting on the third day, and until the end of the inpatient study period, all stools will be collected with a specimen container kit placed in the toilet. Samples will be processed every day and aliquots will be obtained and stored at –70° Celsius for later analysis of 24-hour nitrogen content. To ensure a complete collection of feces and compliance with the inpatient diet, 1.5 g of polyethylene glycol (PEG) will be ingested along with other food items during the first inpatient day. PEG has been used as a fecal marker to follow time and completeness of collections, to determine when experimental diets have been eliminated, and to correct for differences in the day-to-day variation of fecal transit time [59,60]. Stool samples will be analyzed for PEG, and combustible energy from PEG will be subtracted from fecal combustible energy measured by bomb calorimetry.

Miscellaneous losses of nitrogen in sweat, sloughed skin, nails, hair, and various bodily secretions will be estimated at 8 mg/kg of body weight per day [42]. Body weight will be measured daily during the inpatient stays to estimate the daily miscellaneous nitrogen losses defined above.

NB will be calculated using the difference between daily nitrogen intake and total nitrogen losses as follows: nitrogen balance = dietary nitrogen intake–(daily urinary nitrogen excretion + daily fecal nitrogen excretion + daily miscellaneous nitrogen losses).

Anthropometry and Body Composition

Anthropometry

Anthropometry will be assessed during admission at the CRR before BS, at 3 months, and 12 months after surgery. Participants will be weighed while wearing a hospital gown, and without shoes, to the nearest 0.1 kg. Height will be determined using a fixed wall stadiometer to the nearest 0.1 cm. BMI will be calculated as weight (kg) divided by the square of the height (meters).

Body Composition

BC will be estimated based on a 3-compartment model, using 3 independent measures: body weight, TBW, and body density. To determine changes in BC after BS-induced weight loss, the 3-compartment model will be used [61].

Total Body Water

TBW will be measured using the stable isotope deuterium oxide (D_2O) as the reference method. A baseline venous blood sample (approximately 7 mL) from an antecubital vein will be taken while fasting. Immediately afterwards, a known dose of deuterated water D_2O (1 g/kg) will be taken orally. Three hours following the dose, when the D_2O has equilibrated with the body water deuterium-to-hydrogen, a second fasting blood specimen will be taken (approximately 7 mL). The TBW will

then be derived from the increase in plasma deuterium content in relation to the volume of D_2 O ingested [62].

Air Displacement Plethysmography

Body density will be measured using the BOD POD (Cosmed, Chicago, IL; software version 2.3) [63,64]. Subjects will be clothed in a Lycra-style swim cap and tight fitting underwear. Body weight will be measured to the nearest 1 g on the BOD POD electronic weight scale. Following standard calibration procedures, the subject's body volume will be measured, with correction made for thoracic gas volume, which will be estimated using the BOD POD breathing circuit system. The final thoracic gas volume and the average of 2 body volume measurements within 0.2% will be used to calculate body density [64].

Three-Compartment Calculations

FFM and FM will be measured using a modified 3-compartment model that was developed for obese subjects in the New York Obesity Research Center Body Composition laboratory, as follows: fat (kg) = 2.122 × (body weight/density) – 0.779 × TBW – 1.356 × body weight [65]. Body weight is measured in kg (measured by the Weight Tronix scale), density is derived from BOD POD, and TBW is measured in kg. FFM will be calculated as body weight minus FM.

Energy Expenditure

EE will be measured during the last day of the 3 inpatient stays (presurgery, 3 months, and 12 months postsurgery). Height, weight, blood pressure, pulse, and temperature measurements will be taken, and an intravenous catheter will be inserted. At 8:00 a.m., subjects will be placed under the hood of the metabolic cart (Parvo Medics System, True Max 2400) [66] and rest for 30 minutes. Following the resting period, REE will be measured for 30 minutes and baseline blood samples will be taken. Subsequently, all subjects will consume an isocaloric liquid meal (Boost High Protein) over 10 minutes. Subjects will receive acetaminophen with the meal to measure gastric emptying. Following meal administration, DIT (amount of EE above the REE rate due to the cost of processing food for use and storage) will be measured for 4 hours. Blood samples and questionnaire measurements will be collected at –15, 0, 15, 30, 60, 90, 120, and 180 minutes to measure hormonal and perceived satiety. REE will be calculated as an average of the last 15-20 minutes of each measurement period if values have reached steady state, defined as <10% fluctuation in minute ventilation and oxygen consumption and <5% fluctuation in respiratory quotient. DIT will be calculated by measuring the area under the curve of postprandial metabolic rate, above extrapolated baseline REE, for each time period [67]. Baseline and postprandial CCK, GLP-1, ghrelin, and PYY gut peptide concentrations will also be measured during the meal test.

Satiety

Subjective and objective assessments of satiety will be collected before the surgery, at 3 months, and at 12 months postsurgery, during the meal test on the last day of the inpatient stay, using 2 different approaches: VASs, and measurements of hormonal signals of hunger and satiety.

Visual Analog Scales

Participants will rate their feelings on the following questions by means of a mark on 100-mm line VASs: "How hungry are you?", "How full are you?", "How much stomach discomfort do you feel?", "How thirsty are you?", and "How much anxiety and nervousness do you feel?" The scale will be anchored at the low end with the lowest intensity feelings (eg, *not at all*), and with opposing terms at the high end (eg, *most imaginable*), as previously described in the literature [68].

Measurements of Hormonal Signals of Satiety

Subjects will be instructed to consume the test meal within 15 minutes. Calorie intake and nutrient distribution of the meal (Boost High Protein) will be as follows: calories, 240; protein, 15 g; carbohydrates, 33 g; fat, 6 g; sodium, 200 mg; potassium, 400 mg, fiber 0 g. Patients will be able to choose between vanilla and chocolate flavors., An intravenous catheter will be inserted at 7:00 a.m. on the day of the experiment and blood will be drawn at before the meal, and at 15, 30, 60, 90, 120, and 180 minutes after the meal to measure hormonal signals of satiety. Blood samples will be collected in ethylenediaminetetraacetic acid tubes with added aprotinin (500 kallekrein inhibitory units per mL of blood) and dipeptidyl peptidase-4 inhibitor (10 µl/mL of blood; Millipore Research), and stored at –70° Celsius. Plasma concentrations of PYY, CCK, GLP-1, ghrelin, and insulin will be determined by radioimmune assay, and glucose concentration will be determined using the glucose oxidase method with an Analox glucose analyzer (Analox Instruments, Lunenburg, MA). Serum acetaminophen levels will be measured using an enzyme-linked immunosorbent assay (Abbot Laboratories, Chicago, IL).

Measure of Food Reward

Food reward is considered a strong eating drive that could override satiety, and will be assessed by the reward-based eating drive scale [69]. This 9-question screening tool will be completed by the participant during the inpatient stay before surgery, at 3 months, and at 12 months postsurgery.

Metabolomics—Branched Chain Amino Acids

Fasted blood samples obtained prior to the meal test will be used to measure circulating BCAAs by mass spectrometry, as previously described [70]. BCAAs will be measured during the inpatient stay before surgery, at 3 months, and at 12 months postsurgery.

Insulin Sensitivity

Insulin sensitivity will be measured by the Matsuda index during the meal test as follows: 10,000/(fasting glucose × fasting insulin × mean glucose from from 0 to 180 min) × mean insulin from from 0 to 180 min)^0.5 [71].

Physical Activity

There will be no physical activity intervention in this study. A measure of the free-living physical activity will be obtained using the ActiGraph, a wireless activity monitor that will provide 168 continuous hours (1 week) of measurement before surgery, at 3 months, and at 12 months postsurgery.

Vitamins, Minerals, Prealbumin, and Albumin Levels

Laboratory assessments will be obtained as part of the regular blood tests taken before surgery, at 3 months, and at 12 months postsurgery, following the clinical practice guidelines for the evaluation of the nutritional status in the Bariatric Clinic.

Food Record

Dietary intake evaluation during the outpatient phase of the study will be performed as part of each nutritional follow-up. Food and beverage intake will be assessed using either a 7-day (during the preceding diet and the inpatient stay) or 4-day (regular dietary evaluations) throughout the study. As described above, the PI goal will be accomplished for each group (HPS-G and SPS-G) by using the specific PS resources provided. During the screening phase of the study, all subjects will attend 2 training sessions delivered by a Registered Dietitian, in which they will be instructed on how to record their food intake and include at least 1 weekend day when recording. This information will be analyzed with NDSR.

Sample Size Calculations

Sample size was calculated based on anticipated changes in REE during weight loss using data from published literature [72] and changes in BCAAs from our previous study [45]. Baba et al [72] studied changes in REE after high protein (n=7) versus low protein (n=6) weight loss diets. Weight loss was significantly higher in the high protein group (8.3 kg, SD 0.7) compared to the low protein (6.0 kg, SD 0.6). Change in REE was –132.3 kcal/day (SD 51.0) in the high protein group and –384.3 kcal/day (SD 84.6) in the low protein group. Assuming a Cronbach alpha of 0.05 and 0.80 (80%) power we would need to recruit 16 participants to each study group. Laferrère et al [45] showed that for a matched amount of weight loss (10 kg) in GBP (n=10) versus diet-induced weight loss (n=11), BCAA changes were –176.4 (SD 96.6) and –57.6 (SD 99.3) in surgical and nonsurgical groups, respectively. Assuming a Cronbach alpha of 0.05 and 0.80 (80%) power we would need to recruit 22 participants to each study group. Therefore, accounting for an attrition rate of 30% after 1 year, we will enroll a total of 28 subjects per group.

Statistical Analyses

Data will be analyzed using the SPSS statistical program (IBM Software; Armonk, NY). For most study aims, a repeated measures design will be used to examine the trajectory of changes in subjects between HPS-G and SPS-G groups regarding BC, EE, NB, satiety, and circulating BCAAs, from presurgery to 3-month and 12-month postsurgery levels. Nonlinear mixed model regression (SAS PROC NLMIXED) will be used for the actual analyses since these outcomes are not likely to be normally distributed. In addition to overall tests for differences between groups (GBP and SG, and HPS-G vs SPS-G), differences over time (presurgery, 3 months, and 12 months postsurgery), and group per time interactions. Other factors will be explored as covariates to determine possible explanatory factors for significant differences between presurgery and 3-month and 12-month postsurgery levels. Significance levels will be adjusted based on the total number of comparisons being carried out, using a Bonferroni correction. Secondary outcomes will be analyzed using a similar repeated measures design with either mixed model regression or nonlinear mixed model regression where appropriate. No adjustment for the number of comparisons will be made in the case of the secondary outcomes (ie, Cronbach alpha will be 0.05 for all comparisons).

Ethics

This proposal has been approved by the Institutional Review Board of Mount Sinai St Luke's Hospital and Columbia University. Voluntary written informed consent will be obtained from each participant prior to enrollment.

Discussion

The proposed study will determine the effect of 2 different levels of dietary PI (HPS-G and SPS-G) after SG and GBP on the NB, BC, EE, hormonal and perceived satiety, plasma levels of BCAAs, and insulin sensitivity, and feasibility of PS up to 1 year after BS. In addition, the analysis of energy excreted in feces will aid in the understanding of how much malabsorption exists in the 2 procedures studied (GBP and SG). Satiety during a liquid test meal will be assessed and its possible mediators, gastrointestinal hormones released, and gastric emptying rate will also be determined.

Two nonrandomized studies demonstrated that higher levels of PI (>60 g/day) were related to higher excess weight loss 6 months after BS [18] and at 3, 6, and 12 months postsurgery [37]. Other studies have failed to observe a significant association between PI and excess weight loss [28,35,73]. PI was positively associated with LBM retention in 3 nonrandomized studies [5,17,28], although this association was not found in other studies up to 1 year after BS [35,37]. The same authors also failed to observe a relationship between PI and REE [35,37]. The relationship between PI levels and gastrointestinal hormones needs to be explored more thoroughly. One RCT failed to observe a relationship between PI and GLP-1 or ghrelin [38]. The relationship between BCAA circulation levels and glucose homeostasis after BS also needs further attention. Elevated circulating BCAAs are associated with obesity and T2DM. Comprehensive metabolic profiling of obese versus lean human subjects revealed a BCAA metabolic signature, marked by increased circulating levels of BCAAs as well as products of BCAA catabolism [73]. The reason that circulating BCAA levels are elevated in obesity is still unclear. The mechanisms responsible for the decrease in BCAA serum levels with weight loss [47] or BS [46,74,75] are still being studied. Supplementation of a high fat diet with BCAAs in rats [76], or infusion of AAs in humans [76], results in IR. A recent epidemiological study reported that elevated plasma levels of essential AAs, including BCAAs, phenylalanine, and tyrosine in healthy individuals predicted a 5-fold increase in the risk of developing T2DM [77]. To our knowledge, there are no intervention studies that address the impact of PI on BCAA serum levels after GBP or SG. Lower levels of PI seem to have a positive effect on glucose homeostasis, while sustained low circulating levels of BCAAs may have a negative impact on protein synthesis and the integrity of the skeletal muscle mass during weight loss [78]. Plasma leucine concentration has been

shown to correlate with skeletal muscle protein synthesis [53], so the metabolomic study of BCAAs during the high protein meal test will contribute to the study of AA kinetics after massive weight loss induced by BS. Measuring the NB during a negative energy balance will provide an important means of understanding absorption and bioavailability of nitrogen.

Dietary guidelines, including PS after BS, are still under discussion since the levels of evidence of their recommendations are C or D [24]. As previously detailed, the relationship between dietary PI and the various outcome variables that will be measured in this proposed study are not well established, and the available literature is contradictory. Dietary protein plays an important role in weight loss and obesity-related comorbidities, such as diabetes [79]. BS is highly popular, making the proposed work relevant, and the study will help to clarify the relationship between PI and BS outcomes by addressing some of the existing gaps in the scientific literature.

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Authors' Contributions

VM and PM drafted the manuscript. BL, XP, JV, and YB participated in designing the study and provided manuscript revisions. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AA: amino acid
BC: body composition
BCAA: branched chain amino acid
BS: bariatric surgery
CCK: cholecystokinin
CRR: Clinical Research Resource
D2O: deuterium oxide
DIT: diet-induced thermogenesis
EE: energy expenditure
FFM: fat-free mass
FM: fat mass
GBP: gastric bypass
GLP-1: glucagon-like peptide 1
HPS-G: high protein supplementation group
IBW: ideal body weight
IR: insulin resistance
kcal: kilocalorie
LBM: lean body mass
NB: nitrogen balance
NDSR: Nutrition Data System for Research
PEG: polyethylene glycol
PI: protein intake
PS: protein supplementation
PYY: peptide YY
RCT: randomized controlled trial
REE: resting energy expenditure
SD: standard deviation
SG: sleeve gastrectomy
SPS-G: standard protein supplementation group
T2DM: type 2 diabetes mellitus
TBW: total body water
VAS: visual analog scale

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Protocol

Deep Brain Stimulation for Tremor Tractographic Versus Traditional (DISTINCT): Study Protocol of a Randomized Controlled Feasibility Trial

Bastian Elmar Alexander Sajonz[1*], MSc, MD; Florian Amtage[2*], MD; Peter Christoph Reinacher[1], MD; Carolin Jenkner[3]; Tobias Piroth[2], MD; Jürgen Kätzler[3]; Horst Urbach[4], MD; Volker Arnd Coenen[1], MD

[1]Department of Stereotactic and Functional Neurosurgery, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[2]Department of Neurology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[3]Clinical Trials Unit Freiburg, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[4]Department of Neuroradiology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[*]these authors contributed equally

Corresponding Author:
Bastian Elmar Alexander Sajonz, MSc, MD
Department of Stereotactic and Functional Neurosurgery
Medical Center, Faculty of Medicine
University of Freiburg
Neurozentrum Universitätsklinikum Freiburg
Breisacher Str. 64
Freiburg,
Germany
Phone: 49 761 270 50010
Fax: 49 761 270 50100
Email: bastian.sajonz@uniklinik-freiburg.de

Abstract

Background: Essential tremor is a movement disorder that can result in profound disability affecting the quality of life. Medically refractory essential tremor can be successfully reduced by deep brain stimulation (DBS) traditionally targeting the thalamic ventral intermediate nucleus (Vim). Although this structure can be identified with magnetic resonance (MR) imaging nowadays, Vim-DBS electrodes are still implanted in the awake patient with intraoperative tremor testing to achieve satisfactory tremor control. This can be attributed to the fact that the more effective target of DBS seems to be the stimulation of fiber tracts rather than subcortical nuclei like the Vim. There is evidence that current coverage of the dentatorubrothalamic tract (DRT) results in good tremor control in Vim-DBS. Diffusion tensor MR imaging (DTI) tractography-assisted stereotactic surgery targeting the DRT would therefore not rely on multiple trajectories and intraoperative tremor testing in the awake patient, bearing the potential of more patient comfort and reduced operation-related risks. This is the first randomized controlled trial comparing DTI tractography-assisted stereotactic surgery targeting the DRT in general anesthesia with stereotactic surgery of thalamic/subthalamic region as conventionally used.

Objective: This clinical pilot trial aims at demonstrating safety of DTI tractography-assisted stereotactic surgery in general anesthesia and proving its equality compared to conventional stereotactic surgery with intraoperative testing in the awake patient.

Methods: The Deep Brain Stimulation for Tremor Tractographic Versus Traditional (DISTINCT) trial is a single-center investigator-initiated, randomized, controlled, observer-blinded trial. A total of 24 patients with medically refractory essential tremor will be randomized to either DTI tractography-assisted stereotactic surgery targeting the DRT in general anesthesia or stereotactic surgery of the thalamic/subthalamic region as conventionally used. The primary objective is to assess the tremor reduction, obtained by the Fahn-Tolosa-Marin Tremor Rating Scale in the 2 treatment groups. Secondary objectives include (among others) assessing the quality of life, optimal electrode contact positions, and safety of the intervention. The study protocol has been approved by the independent ethics committee of the University of Freiburg.

Results: Recruitment to the DISTINCT trial opened in September 2015 and is expected to close in June 2017. At the time of manuscript submission the trial is open to recruitment.

Conclusions: The DISTINCT trial is the first to compare DTI tractography-assisted stereotactic surgery with target point of the DRT in general anesthesia to stereotactic surgery of the thalamic/subthalamic region as conventionally used. It can serve as a cornerstone for the evolving technique of DTI tractography-assisted stereotactic surgery.

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KEYWORDS

deep brain stimulation; essential tremor; magnetic resonance tractographic-assisted implantation

Introduction

Essential tremor is a hyperkinetic movement disorder characterized by a postural and kinetic tremor commonly affecting the upper extremities, but the voice, head, and lower extremities can also be involved [1]. Symptoms can result in profound disability and social withdrawal due to embarrassment affecting the quality of life [2]. In the stage of medically refractory essential tremor, deep brain stimulation (DBS) is an approved and safe procedure to achieve tremor reduction [3]. The historical target of DBS and stereotactic lesioning in essential tremor is the thalamic ventral intermediate nucleus (Vim) [4,5]. Pre–magnetic resonance imaging (MRI)–era localization of this structure was based on anterior commissure–posterior commissure (AC-PC) coordinates, and intraoperative DBS electrode placement relied on intraoperative electrophysiological analysis and tremor testing with multiple parallel trajectories in the awake patient to achieve satisfactory tremor control. Although the Vim is precisely identifiable with custom MRI nowadays, image-assisted DBS electrode placement in the Vim is still performed with a combination of the above mentioned indirect targeting procedures [6,7]. This can be attributed to the fact that the stimulation of fiber tracts seems to be more effective than stimulation of subcortical nuclei like the Vim [8], and indeed best results in tremor suppression are achieved with stimulation in the subthalamic region rather than in the Vim [9]. Recent diffusion tensor MR imaging (DTI) tractography studies revealed that the dentatorubrothalamic tract (DRT) is a promising target structure in the subthalamic region, as the current coverage of DRT fibers in Vim-DBS results in satisfactory tremor control [10-12]. DTI tractography-assisted stereotactic surgery targeting the DRT would therefore not rely on multiple parallel trajectories and intraoperative tremor testing in the awake patient. Moreover, DBS implantation in general anesthesia would offer more patient comfort and a shorter duration of surgery, reducing associated risks (eg, infection) [13]. The abandonment of multiple parallel trajectories and successive electrode manipulation during intraoperative testing should reduce the risk of intracerebral hemorrhage [14]. In a retrospective analysis, Chen et al [15] found that DBS for essential tremor with classical AC-PC coordinate-based targeting of the Vim can be performed in general anesthesia safely and effectively.

This clinical pilot trial, Deep Brain Stimulation for Tremor Tractographic Versus Traditional (DISTINCT), in patients with medically refractory essential tremor aims at demonstrating safety of DTI tractography-assisted stereotactic surgery in general anesthesia and proving its equality compared to conventional AC-PC coordinate-based stereotactic surgery with intraoperative testing in the awake patient. Accordingly, a randomized, controlled, rater-blinded, parallel group study was set up involving 2 patient groups each assigned to 1 of the aforementioned treatments. Established assessments of tremor and quality of life are used to compare the effect of treatments, which is then related to effective electrode contact positions.

Methods

Design

This is an investigator-initiated monocentric, randomized, controlled, 2-armed, interventional, observer-blinded feasibility trial conducted at the Department of Stereotactic and Functional Neurosurgery and the Department of Neurology at the Freiburg University Medical Center.

The primary objective is to compare DBS-mediated tremor reduction for 2 different approaches—DTI tractography-assisted stereotactic surgery with target point of the DRT in general anesthesia and stereotactic surgery of the thalamic/subthalamic region as conventionally used—in patients suffering from essential tremor.

Primary outcome parameter will be the reduction of tremor as assessed with the Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS) [16] including blinded video rating.

Secondary Objectives

- To assess the effect in tremor reduction of both interventions at 6 months based on the total power in tremor analysis
- To assess the quality of life
- To assess the optimal electrode contact position
- To assess differences in duration of neurosurgery in both groups
- Psychiatric assessment
- To assess safety of intervention
- To show equality of both interventions in tremor reduction at 6 months based on the total power in tremor analysis

Participants and Recruitment

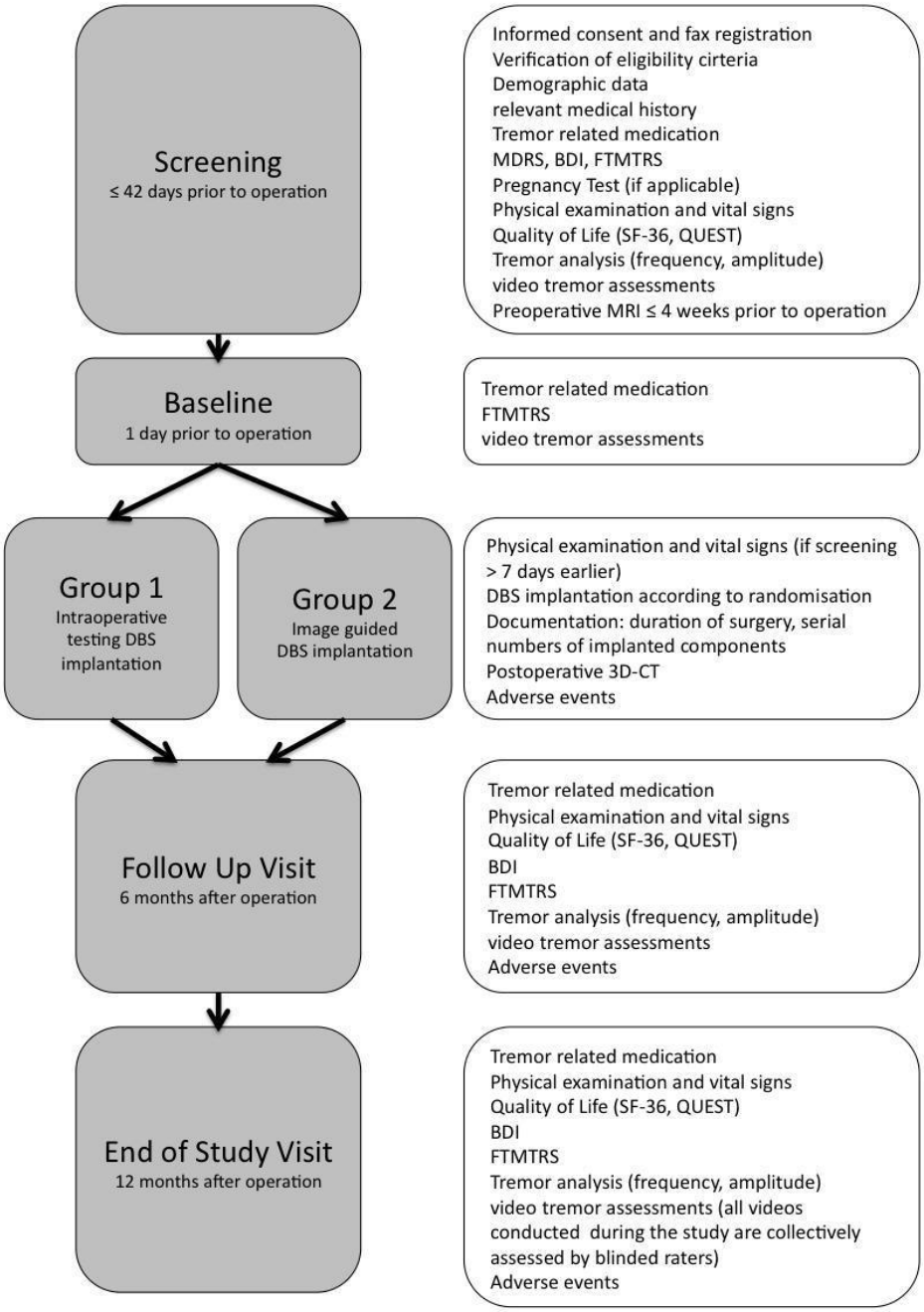
We plan to recruit 24 male or female patients (12 per treatment group). Patients who are referred to our departments due to disabling medically resistant essential tremor are informed about

this study. Patients who give their informed consent are registered in the trial and undergo the screening. Patients who gave their informed consent but do not undergo stereotactic surgery are regarded as screening failures. See Textbox 1 for eligibility criteria.

Study Events and Assessments

A schedule of study events and assessments is provided in Figure 1.

Figure 1. Schedule of study events and assessments. Study assessments on the right are conducted at the corresponding study events on the left. BDI: Beck Depression Inventory; CT: computed tomography; FTMTRS: Fahn-Tolosa-Marin Tremor Rating Scale; MDRS: Mattis Dementia Rating Scale; QUEST: Quality of Life in Essential Tremor Questionnaire.



Textbox 1. Eligibility criteria.

Inclusion criteria:

- Aged 25 to 80 years, inclusive
- Essential tremor according to the criteria of the consensus statement of the Movement Disorder Society [17] with a medical treatment–resistant and disabling postural or intentional tremor
- Stable tremor medication for at least 3 months prior to inclusion
- An FTMTRS completed within 42 days prior to surgery
- Written informed consent

Exclusion criteria:

- Major depression
- Dementia (Mattis Dementia Rating Scale [MDRS]≤130)
- Acute psychosis
- Known or persistent abuse of medication, drugs, or alcohol
- Patient incapability
- Nursing care at home
- Surgical contraindications or medications that are likely to cause interactions in the opinion of the investigator
- Persons who are in a relationship of dependence/employment with the sponsor or the investigator
- Fertile women not using adequate contraceptive methods or with current or planned pregnancy or nursing period

Screening

Screening evaluations must be performed within 42 days prior to neurosurgery. For this evaluation, inclusion and exclusion criteria are checked and validated. The complete pretherapeutic work-up includes a physical examination, medical history, demography, vital signs, body weight and height, tremor-related medications list, quality-of-life questionnaires Short Form (SF)-36 and Quality of Life in Essential Tremor Questionnaire (QUEST) [18], MDRS, Beck Depression Inventory (BDI), FTMTRS [16], and tremor analysis (amplitude, frequency). A preoperative MRI is performed within 4 weeks prior to DBS implantation.

Baseline

Baseline visit will be performed on the day prior to neurosurgery and includes assessment of tremor-related medications, FTMTRS, and tremor analysis.

Tractography of the Dentatorubrothalamic Tract

As part of the preoperative diagnostic work-up, DTI is performed on a clinical 3 Tesla MRI system (Magnetom Trio, Siemens, Erlangen, Germany) with the following specifications: single-shot, 2-dimensional; spin-echo echo-planar imaging; repetition time (TR), 10,000 ms; echo time (TE), 94 ms; diffusion values, b=0 s/mm^{2}and b=1000 s/mm^2; diffusion directions, 61; slice count, 69; voxel size, 2.0×2.0×2.0 mm^3; acquisition time, 11:40 min. Deformation correction of the EPI sequence is performed according to Zaitsev et al [19]. DTI tractography applying the fiber assignment by continuous tracking (FACT) algorithm is performed on a StealthViz workstation (Medtronic Navigation, Louisville, KY, USA) with the following parameters: fractional anisotropy level, 0.2; minimal fiber length, 10 mm; seed density, 5.0; maximal fiber cutoff angle, 50°. The seed region of interest (ROI) is placed in the ipsilateral dentate nucleus, while the target region is placed in the ipsilateral precentral gyrus.

Day of Neurosurgery

Patients will be randomized within 7 days prior to neurosurgery; the DBS system will be implanted according to the randomized treatment group.

Detailed Description of the Deep Brain Stimulation Implantation

After administration of standard antibiotic prophylaxis, a patient in a stereotactic frame (Leksell, Elekta, Stockholm, Sweden) is placed in local anesthesia in group 1 and under general anesthesia in group 2.

A computed tomography (CT) scan is performed, and the image data are transferred to the StealthViz Planning Station (Medtronic, Minneapolis, MN, USA). The previously acquired MRI sequences are coregistered to the stereotactic CT scan, and the trajectories are planned in group 1 (local anesthesia) based on AC-PC coordinates and imaging of thalamic and subthalamic region. The deepest point of the implantation will be the posterior subthalamic region or the caudal zona incerta, respectively, as visualized with a T2-weighted MRI sequence. With this technique a DBS electrode will traverse the Vim region (with the superficial contacts) while reaching the posterior subthalamic region with the most inferior contact. In group 2 (general anesthesia), based on imaging of the DRT, the subthalamic region will also be the inferior-most level of implantation.

In group 1, the bilateral DBS electrode implantation is performed under local anesthesia with the patient in a semisitting

position. Using a microtargeting drive (MicroTargeting Star Drive M/E System, FHC Inc, Bowdoin, ME, USA), a test electrode (Cosman Medical, Inc, Burlington, MA, USA) is inserted through a frontal burr hole in the cranium. Macrostimulation is performed to confirm a contralateral clinical benefit (at a low threshold) and to test for side effects (at a high threshold). The definitive DBS electrodes are then implanted under fluoroscopic control. The implantable pulse generator (ACTIVA INS, Medtronic, Minneapolis, MN, USA) in group 1 is then implanted and connected to the DBS electrodes under general anesthesia.

In group 2, the bilateral DBS electrode implantation through a frontal burr hole via the planned trajectories is performed in ongoing general anesthesia under fluoroscopic control and without any further testing followed by the implantation of an implantable pulse generator (ACTIVA INS, Medtronic, Minneapolis, MN, USA), which is then connected to the DBS electrodes.

All patients in group 1 and 2 undergo a postoperative CT scan to corroborate the final DBS electrode localization. The following items will be documented at this visit: duration of surgery (time points of mounting frame, start surgery, stop surgery (= dismounting frame) and serial numbers of implanted components.

Follow-Up

At 6 and 12 months after neurosurgery, follow-up visits will be performed. The trial for the individual patient ends at the 12-month visit. On both visits, tremor-related medication, vital signs, quality of life (SF-36, QUEST), FTMTRS, tremor analysis (amplitude, frequency), and BDI will be assessed.

Video Assessments

The rating of the FTMTRS will be digitally recorded by video at every visit. The videotapes will be rated during the study period by an external group of movement disorder specialists who are not otherwise involved in the trial. To maintain blinding for the external raters, patients should wear headgear which completely encloses the hair.

Biostatistical Planning and Analysis

Sample Size Calculation

This is a feasibility study in 24 patients with essential tremor (12 DTI tractography-assisted implantations, 12 implantations with conventional intraoperative testing). To obtain estimates for the treatment effect and its variance and, thus, to obtain a solid basis for the sample size calculation of the subsequent confirmative trial, the FTMTRS score at 6 months after intervention and its change from baseline will be subjected to exploratory descriptive analysis. Julious [20] found that a sample size of 12 per group in pilot studies seems reasonable for generation of pilot data. Given a continuous outcome, increasing the sample size beyond 12 per group did not have profound influence on the confidence interval. A dropout rate of 25% is assumed, so 30 patients will be assessed for eligibility.

Randomization

The randomization code will be generated by the clinical trials unit using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. Randomization will be performed in blocks of variable length in a ratio of 1:1. The block lengths will be documented separately and will not be disclosed to the center.

Analysis of the Primary Endpoint

The primary efficacy analysis of this clinical trial will be conducted according to the intention-to-treat principle (ITT). This means that the patients will be analyzed in the treatment arms to which they were randomized, irrespective of whether they refused or discontinued the treatment or whether other protocol violations are revealed. Confidence intervals (95%) will be calculated for means and standard deviations within groups as well as for the difference between groups in the ITT population. The effects of DTI tractography-assisted versus conventional intraoperative testing with respect to the FTMTRS score at 6 months will be estimated and tested within a linear regression model including treatment and the baseline FTMTRS score as covariates. A conservative estimate of the effect size anticipated for a subsequent confirmative trial will be derived from these analyses by a combination of clinical and statistical judgement.

Analysis of Secondary Endpoints

Effective tremor reduction (FTMTRS score reduction by 50% is regarded as “response”) at 12 months after intervention will be analyzed in an exact logistic regression model. Tremor reduction measured by tremor analysis and calculation of total power before and 6 and 12 months after intervention will be analyzed the same way as the primary endpoint.

Quality of life will be measured with the SF-36. The 8 summary scales per measurement will be evaluated based on the method implemented in the software program (SAS version 9.2 or higher, SAS Institute Inc) provided along with the questionnaire. Change from baseline will be evaluated for all summary scales after 6 and 12 months as the primary endpoint. BDI, effective contact position (with respect to DRT and AC-PC coordinates) and the volume of activated tissue will be analyzed similar to the primary endpoint using linear regression.

Rates of recruitment per month, screening failures, and drop-out from the trial will be evaluated and considered for the confirmative trial. All secondary analyses will be exploratory.

Safety analyses will be performed for all patients for whom 1 of the treatments was started. Patients will be analyzed according to treatment received. Rates of adverse events and serious adverse events will be calculated with corresponding 2-sided 95% confidence intervals.

Ethical Issues

An adequate subject insurance contract has been taken out. The study protocol has been approved by the independent ethics committee of the University of Freiburg (EK 207/15). The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and applicable regulatory requirements. The DISTINCT trial has been registered in the

German Clinical Trials Register (DRKS00008913) and at ClinicalTrials.gov (NCT02491554).

Results

Recruitment to the DISTINCT trial opened in September 2015 and is expected to close in June 2017. At the time of manuscript submission the trial is open to recruitment.

Discussion

The DISTINCT trial is an investigator-initiated, randomized, controlled, observer-blinded trial comparing DTI tractography-assisted stereotactic surgery with a target point of the DRT in general anesthesia to stereotactic surgery of the thalamic/subthalamic region as conventionally used. It is hypothesized that DTI tractography-assisted stereotactic surgery in general anesthesia is safe and is equal to conventional AC-PC coordinate-based stereotactic surgery with intraoperative testing in the awake patient.

To examine the 2 discrete treatment groups, a randomized controlled parallel group study is the appropriate design. Efforts to blind patients would annihilate favorable effects in the tractography-based treatment group (single trajectory, shorter duration of surgery), so a rater-blinded design is implemented. Reliability is enhanced by double rating of video-documented tremor assessments by 2 independent raters.

Chen et al [15] retrospectively analyzed a series of AC-PC coordinate-based Vim-DBS implantations in general anesthesia and compared it to implantations in awake patients. As clinical outcome parameter, a self-evaluation with a mailed questionnaire was used which led to a variable follow-up latency and a considerable drop-out rate. As a contrast, the focus of our study is the DTI tractography-assisted Vim-DBS implantation. Furthermore, by means of a randomized controlled trial and clinical tremor assessment more valid data can be yielded.

DTI tractography of the DRT can generally be achieved with probabilistic [21] or deterministic [10,11] fiber tracking; however, only the latter is available for stereotactic planning in CE-approved planning systems. As a result, this study employs deterministic fiber tracking.

Tractography with a seed ROI in the ipsilateral dentate nucleus and target ROI in the ipsilateral precentral gyrus reliably yields the nondecussating fibers of the DRT described by Meola et al [22]. However, as the decussating fibers cross below the level of the red nucleus and converge with the nondecussating fibers before entering the thalamus, the issue of decussation has little relevance to the stimulation target site in the subthalamic region.

Although it is generally agreed on that effects of DBS are exerted on fibers, there is only limited published evidence on DTI tractography-assisted stereotactic surgery [23]. A post hoc study of our group in 11 patients who received Vim-DBS was able to show that effective electrode positions are located inside or within proximity of the DRT [12], extending knowledge gathered by Klein et al [24] and Coenen et al [10,11]. The DISTINCT study is the first to take advantage of this recently tractographically identified target structure for treatment of medically refractory tremor. As a single-center pilot feasibility trial, the results can be limited in validity; however, it has the potential to serve as a cornerstone for the evolving technique of DTI tractography-assisted stereotactic surgery.

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Authors' Contributions

This study was designed by BS, FA, PR, and VC. The manuscript was written by BS. VC is the principal investigator of the trial and initiated the trial. CJ performed the sample size calculation and planned the statistical analyses. BS is the medical coordinator of the trial. JK made substantial contributions to the organization of this trial. PR and TP are involved in trial implementation. CJ, JK, PR, FA, TP, HU, and VC critically revised the manuscript. All authors have read and approved the manuscript.

Conflicts of Interest

Dr Sajonz reports grants from Medtronic Europe during the conduct of the study. Dr Amtage reports nonfinancial support from UCB Pharma outside the submitted work. Dr Reinacher reports grants and personal fees from Medtronic Europe during the conduct of the study; grants, personal fees, and nonfinancial support from Medtronic Europe; grants and personal fees from Boston Scientific, USA; and grants and personal fees from the German Federal Ministry for Economic Affairs and Energy outside the submitted work. Dr. Reinacher received travel support and honoraria for talks from Boston Scientific (USA). Dr Piroth reports nonfinancial support from Actelion Pharmaceuticals, Allschwil, Switzerland, outside the submitted work. Dr Coenen reports grants and personal fees from Medtronic Europe during the conduct of the study; grants, personal fees, and nonfinancial support from Medtronic Europe; grants and personal fees from Boston Scientific, USA; and grants from the German Research Foundation, BrainLinks/BrainTools Cluster of excellence outside the submitted work. Dr Coenen has been a consultant for Medtronic USA and Europe and previously received travel support and honoraria for talks and consultation. Dr Coenen has additionally received travel support and honoraria for talks and consultation from Boston Scientific (USA) and St Jude Medical (USA). C Jenkner, J Kätzler, and H Urbach have nothing to disclose.

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Abbreviations

AC-PC: anterior commissure–posterior commissure
BDI: Beck Depression Inventory
CT: computed tomography
DBS: deep brain stimulation
DISTINCT: Deep Brain Stimulation for Tremor Tractographic Versus Traditional
DRT: dentatorubrothalamic tract
DTI: diffusion tensor imaging
EPI: echo-planar imaging
FTMTRS: Fahn-Tolosa-Marin Tremor Rating Scale
ITT: intention to treat
MDRS: Mattis Dementia Rating Scale
MRI: magnetic resonance imaging
QUEST: Quality of Life in Essential Tremor Questionnaire
ROI: region of interest
SE: spin-echo
SF-36: Short Form 36
TE: echo time
TR: repetition time
Vim: thalamic ventral intermediate nucleus

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Protocol

Protocol for a Randomized Controlled Trial of Proactive Web-Based Versus Telephone-Based Information and Support: Can Electronic Platforms Deliver Effective Care for Lung Cancer Patients?

Christine L Paul[1,2,3], BA(Hons), PhD; Allison W Boyes[1,2,3], BA(Psych), MPH, PhD; Lorna O'Brien[4], RN; Amanda L Baker[5], PhD; Frans A Henskens[1,6], PhD; Ian Roos[7†], PhD; Tara Clinton-McHarg[1,2,3], PhD; Douglas Bellamy[8], RN; Glenda Colburn[9], EMBA; Shiho Rose[1,2], BFoodScHumNut; Martine E Cox[1,2,3], B Nutr & Diet; Elizabeth A Fradgley[1,2,3], PhD; Hannah Baird[4], MAppSc; Daniel Barker[10], B Math

[1]Priority Research Centre for Health Behaviour, School of Medicine and Public Health, University of Newcastle, Callaghan, Australia
[2]Hunter Medical Research Institute, New Lambton, Australia
[3]Hunter Cancer Research Alliance, Waratah, Australia
[4]Cancer Council New South Wales, Woolloomooloo, Australia
[5]School of Medicine and Public Health, University of Newcastle, Callaghan, Australia
[6]Distributed Computing Research Group, School of Electronic Engineering and Computer Science, University of Newcastle, Callaghan, Australia
[7]University of Melbourne, Parkville, Australia
[8]Cancer Network, Hunter New England Health, New Lambton, Australia
[9]Lung Cancer National Program, Lung Foundation Australia, Milton, Australia
[10]Centre for Clinical Epidemiology and Biostatistics, School of Medicine and Public Health, University of Newcastle, Callaghan, Australia
[†]deceased

Corresponding Author:
Christine L Paul, BA(Hons), PhD
Priority Research Centre for Health Behaviour
School of Medicine and Public Health
University of Newcastle
University Drive
Callaghan,
Australia
Phone: 61 2 4042 0693
Fax: 61 2 4042 0044
Email: chris.paul@newcastle.edu.au

Abstract

Background: Community-based services such as telephone support lines can provide valuable informational, emotional, and practical support for cancer patients via telephone- or Web-based (live chat or email) platforms. However, very little rigorous research has examined the efficacy of such services in improving patient outcomes.

Objective: This study will determine whether: proactive telephone or Web-delivered support produces outcomes superior to printed information; and Web-delivered support produces outcomes comparable to telephone support.

Methods: A consecutive sample of 501 lung cancer outpatients will be recruited from 50 Australian health services to participate in a patient-randomized controlled trial (RCT). Eligible individuals must: be 18 years or older; have received a lung cancer diagnosis (including mesothelioma) within the previous 4 months; have an approximate life expectancy of at least 6 months; and have Internet access. Participants will be randomly allocated to receive: (1) an information booklet, (2) proactive telephone support, or (3) proactive Web support, chat, and/or email. The primary patient outcomes will be measured by the General Health Questionnaire (GHQ-12) and Health Education and Impact Questionnaire (heiQ) at 3 and 6 months post recruitment. The acceptability of proactive recruitment strategies will also be assessed.

Results: It is hypothesized that participants receiving telephone or Web support will report reduced distress (GHQ-12 scores that are 0.3 standard deviations (SD) lower) and greater self-efficacy (heiQ scores that are 0.3 SDs higher) than participants receiving booklets. Individuals receiving Web support will report heiQ scores within 0.29 SDs of individuals receiving telephone support.

Conclusions: If proven effective, electronic approaches such as live-chat and email have the potential to increase the accessibility and continuity of supportive care delivered by community-based services. This evidence may also inform the redesigning of helpline-style services to be effective and responsive to patient needs.

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KEYWORDS

health information; lung cancer; telephone counseling; psychological distress; randomized controlled trial (RCT); telemedicine

Introduction

Background

Cancer is one of the leading causes of disease-related burden in Australia. Lung cancer is the fourth most incident cancer and approximately 10,300 cases were diagnosed in 2014 [1,2]. Lung cancer mortality rates are relatively higher than other cancer types, with only 6% of those diagnosed with small cell lung cancer surviving 5 years post diagnosis [3]. Lung cancer patients and survivors also report a wide array of physical and psychological issues and, when compared with 6 other common cancer types, report significantly higher levels of clinically significant anxiety and depression [4-6]. Despite the clear evidence-based imperative for providing supportive care to lung cancer patients to maximize their quality of life, this group is under researched in terms of supportive care [7].

Generally, cancer patients report dissatisfaction with the amount and type of information provided regarding management of their health, the failure of health care providers to attend to or offer referral for psychosocial needs, and poor coordination of services [8]. These experiences can exacerbate patients' suffering. With health care resources stretched to capacity, there is an urgent need to assess the potential benefits of alternative modes of service delivery. These modes may include services provided by community-based organizations rather than hospitals or physicians; and telephone-based or Web platforms rather than the relatively costly and less accessible face-to-face options. However, despite the evidence of their need for support, lung cancer patients are underrepresented in the overall profile of community cancer support service users [9]. Proactive strategies for engaging this vulnerable group with alternative community-based services may provide a valuable opportunity to enhance lung cancer care, particularly in providing information and support in managing the debilitating consequences of diagnoses and treatments.

There is substantial evidence that intensive psychological strategies have been associated with improved psychological health and quality of life in cancer patients [10]. A common example of an intensive strategy is cognitive behavior therapy (CBT) in which adaptive coping elements such as emotional support, positive reframing, planning, acceptance, and support seeking are incorporated into care. A Cochrane review of supportive care interventions including psychotherapeutic interventions and nurse-led counseling improved the emotional, psychological, and physical states (ie, dyspnea) of lung cancer patients [11]. In contrast, relatively little rigorous research has examined the effects of less-intensive forms of supportive care provision for cancer patients [12]. These less-intensive forms of counseling may be delivered by community-based telephone helplines, whereby, unlike hospital-based services, individuals do not receive face-to-face counseling from health professionals familiar with their current care; may have a focus on practical or informational support; and may be a singular encounter.

The Cancer Information and Support (CIS) line is a cancer-specific telephone-based service operated by each state-based Cancer Council in Australia via a national telephone number; the same model operates within the United Kingdom and United States [9,13,14]. The service is staffed by experienced health professionals and provides free, confidential support related to informational, emotional, and practical concerns based on a brief, integrative model of care. A recent review found that telephone-based follow-up care conducted by an experienced nurse was acceptable to patients, cost-effective, and at least equivalent to traditional face-to-face follow-up care in meeting patients' needs [15]. Hence, telephone delivery means that individualized services can be provided to a broad cross-section of cancer patients in a timely fashion while minimizing cost, logistic, and system barriers [16].

Although telephone-delivered supportive care services, including the CIS, have undergone evaluation of patient use, satisfaction, and acceptability, very little rigorous research has been directed toward understanding the real-world effects of low-intensity models, such as the provision of information, emotional support, and practical support in improving cancer patients' outcomes [14,17-19]. A systematic review identified only 4 randomized controlled trials (RCT) of similar services with conflicting results reported [20]. One RCT provided evidence of efficacy in that phone-based education and social support delivered by research assistants resulted in reduced mood disturbance compared with mailed education [21]. The remaining 3 trials did not find a significant effect on psychosocial outcomes including distress, anxiety, or depression [22-24]. None of these trials were conducted with lung cancer patients.

While telephone-based support is the traditional mode of delivery of these services, some services are seeking to or have recently included parallel forms of Web support [9,25]. These technology-based approaches are perceived to be accessible, safe, flexible, and anonymous by patients [26-28]. Automated

electronic platforms for the delivery of intensive psychological therapies (eg, CBT) have also been found to be effective in reducing anxiety and depression [29]. However, a review by Gustafson et al [30] identified mixed effects when information and support for breast cancer patients was delivered via automated, electronic formats. For community-based services, establishing the efficacy of Web support can provide much needed guidance for deciding if this mode of support should be included as part of the suite of services provided.

In the context of the CIS service, the most appropriate first step for testing Web approaches may be via a proactive and personalized, rather than automated, version of the service through email and live chat. Email counseling involves the patient and counselor exchanging questions and responses at the frequency of their choosing over the Internet. Live chat involves typed interactive conversations occurring in real-time over the Internet. Evidence for online peer-support forums and email is promising with a RCT of a multicomponent Web intervention reporting decreased global severity scores in a sample of 325 breast and prostate cancer patients [31]. However, there is no literature regarding Internet-delivered versions of low-intensity community-based support akin to that offered by the CIS service. For example, a Cochrane review examining the effects of email and Web-messaging between patients and health professionals was unable to establish the benefits of such Web-based platforms due to the lack of high-quality studies identified [32]; relevant to this study, none of the 9 reviewed articles included cancer samples.

This multisite, blinded, patient-RCT will be the first to conduct a robust study of the relative merits of telephone- versus Web-based methods for providing low-intensity information and support to people affected by cancer. Newly diagnosed lung cancer patients will be recruited by health professionals and randomly-allocated on a 1:1:1 ratio to 1 of 3 arms: (1) a printed information booklet, (2) proactive telephone-delivered support, or (3) proactive Web-delivered support. The Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth is used to describe this study [33].

Aims

The aims of this study are to identify among a group of newly diagnosed lung cancer patients, if: (1) information and support provided either electronically (email and live chat) or by telephone following active recruitment can produce psychosocial outcomes, which are superior to those achieved by minimal ethical care (a printed *'Understanding Lung Cancer'* information booklet), and (2) information and support provided electronically can produce psychosocial outcomes, which are comparable to those achieved by a telephone approach.

Intervention effectiveness will be measured by changes in 2 primary outcomes: General Health Questionnaire-12 (GHQ-12) and Health Education Impact Questionnaire (heiQ) scores from baseline to 3 and 6 months post recruitment. Higher GHQ-12 scores represent greater distress; once standardized, higher heiQ scores indicate better functioning as a result of improved self-efficacy and health literacy.

Hypotheses

It is hypothesized that at 6 months follow-up: (1) those in the 2 experimental conditions (proactive telephone-delivered or Web-delivered support) will have GHQ-12 scores that are 0.3 of a standard deviation (SD) lower than those for the control condition and heiQ scores that are 0.3 of a SD higher than those for the control condition, and (2) those in the proactive Web-delivered support condition will have heiQ scores within 0.29 of a SD of those in the proactive telephone-delivered support condition.

Methods

Care Coordinator, Nurse, and Clinician Recruitment

As of June 1st, 2016, care coordinators, nurses, and clinicians from 50 health services were committed to participating in the study. A variety of recruitment techniques were used. Care coordinators, nurses, and physicians also received study information with a link to a Web-based expression of interest (EOI) form via several national professional organizations such as: the Lung Foundation Australia; the Clinical Oncology Society of Australia; the Medical Oncology Group of Australia; and the Thoracic Society of Australia and New Zealand. Contacts were also identified through publicly available lists of multidisciplinary teams or through personal connections with research team members. Wherever possible, individuals received a personalized email with an embedded link to the EOI form.

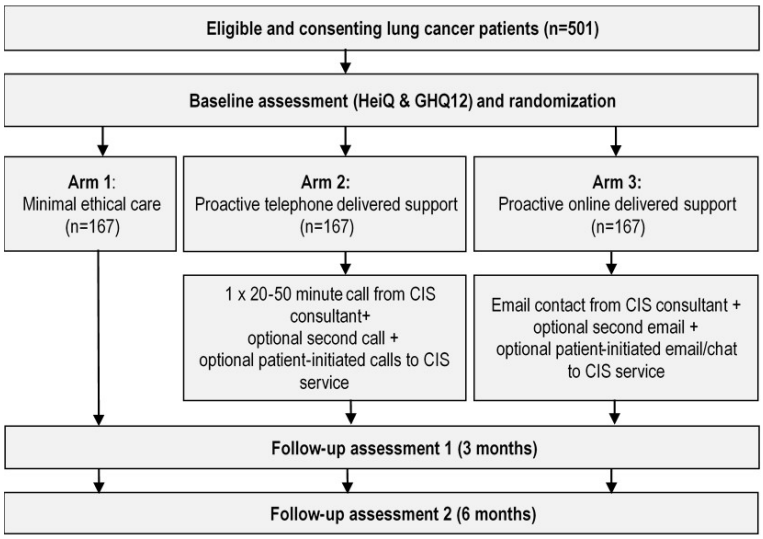
The research team contacted individuals who completed a Web-based EOI and arranged a teleconference to gauge capacity and willingness to participate in the study. No specific exclusion criteria related to the size or location of the health service were applied in order to represent the diversity of rural and urban settings in which lung cancer patients may receive care.

Study Setting

All interventions will be delivered through 1 state-based CIS service, the Cancer Council New South Wales (CCNSW). In usual practice, clients would be automatically connected to the CIS service in their state of residence. A study-specific telephone number and email address will be set up to permit isolation of study participants from other CIS clients. A directory of state-specific services will be created to ensure participants from areas outside of New South Wales can receive the information relevant to their local areas.

CIS consultants are qualified oncology and/or psychosocial health professionals (ie, nurses, social workers, counsellors). Consultants receive extensive training in supportive care principles and therapeutic communication skills. As part of their ongoing training, consultants routinely participate in clinical supervision and professional development workshops; furthermore, a sample of calls are regularly reviewed by a service manager as part of performance evaluations. A total of 6 CIS consultants will participate and are trained to deliver both the telephone- and Web-based interventions.

Figure 1. Intervention arms and data collection time-points.



Participant Eligibility Criteria

Individuals will be eligible to participate if they: are 18 years or older; have a primary diagnosis of any lung cancer type (including mesothelioma); are less than 4 months post diagnosis; have an approximate life expectancy of at least 6 months; and have current Internet access via any type of device including shared access or public access (eg, via a family member or public library).

Patient Recruitment and Consent Procedure

Eligible lung cancer outpatients will be identified and approached by health professionals (care coordinators, nurses, or clinicians) and will be recruited in 1 of 3 ways:

Full consent process completed in clinic settings immediately: during patients' appointments, clinic staff or a research assistant (depending on the clinic's preference) will ask the patient whether they have Internet access, provide study information materials to eligible patients (including a baseline survey), and invite them to participate in the study. Participants will complete a written consent form in clinic and can choose to complete the survey in-clinic or at home.

Consent for further contact completed in clinic settings immediately, with full consent process completed by a research team member: during patients' appointments, clinic staff will ask whether they have Internet access and if they would be interested in being contacted by the research team regarding the study. Interested patients will complete a consent form that allows the clinic to forward the patient's contact details to the research team. Once consent forms are forwarded to the research team, patients will be contacted via their preferred mode of contact to discuss possible study participation. Up to 2 follow-up contacts will be made to nonrespondents. Patients who would like to participate will complete a separate consent form, which will be posted along with the baseline survey.

Full consent process completed outside of the clinic setting by a health professional: health professionals, typically care coordinators, will mail information booklets and make follow-up telephone calls to patients as part of standard care procedures. As part of these standard contacts, study materials (information statement, consent form, and baseline survey) will be included in the mail-out package, and the health professional will discuss the study when making calls to patients.

Randomization Process and Blinding

Stratified block randomization will be completed by the research team using a Web-based random number generator program immediately upon receiving a completed consent form. All participants will complete the baseline survey prior to randomization. Randomization will be by patient, with analyses accounting for clustering of outcomes by CIS consultant. The randomized list of patients will then be given daily to the CIS service to contact participants using the allocated approach method (mailed booklet, telephone call, or email/live chat). Due to the nature of the interventions, patients and CIS consultants will not be blinded to the allocation arm; health professionals will not be informed of participants' allocation. Those responsible for data analysis and interpretation will be blind to group allocation. There is no foreseeable circumstance in which revealing a participant's group allocation to data analysts would be required.

Interventions

Participants will be randomized to 1 of 3 arms: (1) a booklet from the Cancer Council which contains the CCNSW CIS service details (minimal ethical care (control)), (2) phone call(s) from the CCNSW CIS service (proactive telephone-delivered support), or (3) email(s) and live chat consultation from the CCNSW CIS service (proactive Web-delivered support). See Figure 1 for brief description with data collection time-points.

Arm 1: Minimal Ethical Care (Control)

Patients will be mailed a booklet ("Understanding Lung Cancer") from the CCNSW. The booklet will contain the CIS service telephone number and email address. Although lung cancer accounts for 9% of all new cancers diagnosed, lung cancer patients account for only 1% of calls received by the CIS service. Therefore, it is not expected that a high proportion of the control group will contact the service independently. Any potential contamination via calls to the CIS service from this

group will be identified using questions in the follow-up survey and by reviewing internal CIS records.

Arm 2: Proactive Telephone-Delivered Support

The CIS model is tailored to callers' needs rather than following a manualized protocol as may be the case for delivery of some therapies such as CBT. The patient consent form will request contact details and preferred times to call. The research team will provide this information to the CCNSW CIS service and patients randomized to this intervention arm will receive a 20-50 minute outbound call from a trained consultant within a few days of the CIS service receiving their contact details. The CIS consultant will make multiple attempts (up to 5 calls made at varying times and weekdays) to establish contact with the patient. Following the initial discussion, the CIS consultant will also offer an additional, subsequent call-out. Following the completion of the 2 proactive calls from the CIS, patients in this group can initiate further contact if desired.

Call Content

Call content will reflect usual care and will follow the CIS model, in which the call is guided by patients' individual needs with 3 main types of support available: informational, emotional, and instrumental. Emotional support involves communication of caring and concern, and is argued to reduce distress by improving self-esteem and encouraging the expression of feelings [34,35]. Informational support is thought to enhance perceptions of control by reducing confusion and providing patients with strategies to cope with their difficulties [34,35]; in addition to the verbal information exchanged over the course of a call, specific examples of the informational support provided by the CIS includes: reference to Web-based videos and Web seminars; provisions of paper-based information packages; and access to a cancer service directory. Instrumental support involves the provision of tangible goods such as transportation, money, or physical assistance and leads to a decrease in feelings of loss of control [34,35]. Specific examples of instrumental support offered by the CIS service includes: linking callers with services in their local area; financial grants; transportation grants; and subsidized accommodation. CIS service manuals detailing the 3 main types of support are available upon request. Repeated contact with the same CIS consultant is preferred but not always achieved as a matter of course.

Arm 3: Proactive Web-Delivered Support.

Participants allocated to this intervention arm will be contacted within a few days of randomization via email and a hard copy letter. The letter and email will explain the available electronic options for support (email delivered or Web-based typed live chat) and provide the study-specific Web-link needed for intervention access. Participants will be able to use either or both modes of electronic contact according to their preference. If participants have not engaged with either electronic option within 2 weeks of allocation, subsequent telephone calls (up to 5 calls made at varying times and weekdays) will be conducted by the research team to confirm the participant has received the information and to provide additional instructions if needed.

Usual CIS service content (as described above) will be provided via typed rather than spoken communication, using email and Web-based chat. Equivalence of telephone- and Web-delivered content and quality will be examined via 5-10 simulated clients using standardized vignettes. These telephone and Web conversations will be transcribed. The transcriptions will BE reviewed by senior research team members with the content compared with a quality checklist developed in collaboration with CIS representatives according to their current evaluation practices. This process will occur at 3 time-points in the intervention phase and will also serve as a fidelity measure. To ensure the majority of consultants are included in this equivalence test, it may be necessary to complete up to 10 simulations.

CIS consultants will receive training and a detailed manual on the features of the Web system, including ways to convey emotional support, such as empathetic responses using typed text. This manual is available upon request. Multimedia Appendices 1 and 2 provide screenshot examples of the instructions and simulated Web-based chat conversation between a member of the research team and CCNSW consultant. Following their first electronic session, participants will be offered an additional email contact from the CIS service. Similar to the other intervention arm, participants in this group can initiate further electronic contact if desired. Continuity of care (ie, contact from the same consultant) may not always occur. Any potential contamination via calls to the CIS service from the Web-support group will be identified using questions in the follow-up survey and by reviewing internal CIS records.

Measures

The baseline and follow-up measures listed below will be collected via pen-and-paper surveys; this data will be securely stored according to approved procedures. The follow-up points for patients will be 3 and 6 months post recruitment, as approximately 60% of lung cancer patients have a life expectancy of less than 12 months [2]. Participants who do not return a survey within 2 weeks will receive a reminder letter and an additional survey package. A research team member will telephone nonresponders 2 weeks following the first reminder letter. All survey variables, including data collection time-points, are listed in Table 1.

Table 1. Study data and associated variables collected at each study time-point.

Study data	Variables	Time-point		
		Baseline	3 months	6 months
Primary outcomes				
	GHQ-12; heiQ	X	X	X
Secondary outcomes				
	SCNS-34[a] subscales (health systems and information; patient care and support)	X		X
Process measures				
	Five items exploring contact and satisfaction with CIS[b] services; perceived level of consultant skill; and use of specific CIS services (emotional; information; instrumental)			X
Demographic characteristics				
	Age at diagnosis; sex; Aboriginal or Torres Strait Islander origin; health insurance coverage; employment status; post code; marital status; highest level of education attained; primary language spoken at home; and concession card holder	X		
Emotional adjustment				
	The Mental Adjustment to Cancer Scale [36]	X		
Disease/treatment				
	Date of cancer diagnosis; cancer type; other comorbid conditions; surgery and treatments received; and history of mental health treatment prior to cancer diagnosis	X		
	Current extent of cancer; surgery and treatments received; and instances of missed prescriptions in previous week		X	X
Smoking history				
	Current smoking status; previous referral and uptake of smoking cessation assistance; and smoking quit date	X		
	Smoking status within the last 6 months			X
Social support				
	Medical Outcomes Study-Social Support Survey [37]	X		X
Illness appraisal				
	Brief Illness Perception questionnaire [38]	X		X
Health service utilization				
	Stanford Health Care Utilization tool [39]			X

[a]SCNS-34: 34-item Supportive Care Needs Survey.

[b]CIS: Cancer Information and Support.

Primary Patient Outcomes

The GHQ-12 is a widely used, self-report screening measure of general psychological distress [40]. The 12-item measure takes 2 minutes to complete and assesses an individual's perception of their health in terms of their ability to: play a useful part; make decisions; overcome difficulties; enjoy normal activities; face problems; and to feel confident, worthwhile, and happy [41]. The time-frame of the GHQ-12 covers the last 4 weeks and items are scored using a 4-point scale ("better than usual," "same as usual," "less than usual," and "much less than usual") [42]. Half of the items are worded positively, and the other half negatively. Items can be scored using either a Binary scale (0-1, maximum score = 12) or Likert scale (0-3, maximum score = 36), with a higher score indicating higher psychological distress [42]. The GHQ-12 has excellent internal consistency (Cronbach's alphas above 0.82 for cancer patients) and test-retest reliability [41]. The measure has also been validated in the general Australian community and with cancer populations, including patients with a history of lung cancer [41-44].

Participants who indicate severe levels of distress (scores > 20 on the GHQ-12) at either the baseline, 3, or 6 months survey will be mailed a letter encouraging them to discuss their feelings with their doctor. Contact details of available support services will also be provided.

The heiQ is an Australian-developed tool for assessing the efficacy and impact of health education and self-management programs for people with chronic diseases [45]. Its 42 items are closely aligned to the nature of the CIS service and map to 8 domains: (1) health-directed behavior, (2) positive and active engagement in life, (3) emotional well-being, (4) self-monitoring and insight, (5) constructive attitudes and approaches, (6) skill and technique acquisition, (7) social integration and support, and (8) health service navigation. Respondents indicate the degree to which they agree or disagree with each item on a 4-point scale. Standardized subscale scores (from 1-4) are calculated, with higher scores indicating better functioning.

The heiQ was developed using Structural Equation Modelling and Item Response Theory. It has demonstrated reliability and validity among people with a wide range of chronic diseases and demographic characteristics and sensitivity to change as a result of intervention [45,46].

Secondary Patient Outcome

Two subscales of the 34-item Supportive Care Needs Survey (SCNS-SF34) will be used to assess unmet needs [47]. The scale assesses cancer-specific perceived needs across 5, factor analytically derived domains. The 2 relevant domains for this study are: (1) health systems and information, and (2) patient care and support [47]. Respondents indicate their level of need for help over the last month on a 5-point Likert scale. Standardized domain scores ranging from 0 to 100 can be calculated. The SCNS-SF34 has Cronbach's alphaS greater than 0.86 for each subscale, and is moderately correlated with other measures of psychosocial morbidity [47].

Patient Process Measures

Process data will include: number of contacts made to and received from the CIS service; utilization of specific information and support services; acceptability of the information and support provided; and perceived skill level of the CIS consultant. All participants will provide this information at 6 months. Excepting initial telephone calls to participants who do not engage with one of the Web-delivered support options within 2 weeks of group allocation, no additional strategies will be used to increase use of the telephone or Web arms as uptake rates (with consideration of differential use by demographic characteristics) is an important indicator of the intervention acceptability.

Antecedent and Moderating Factors

Participants will complete additional survey items to account for sociodemographic, disease and treatment, and social support characteristics, which may moderate the intervention effects. Table 1 outlines these survey items, along with all study data items, and the time-point at which this information will be collected.

Sample Size

The sample size calculation is based on the post-hoc contrasts. The comparison of each intervention group with minimal ethical care is a superiority analysis, whereas the comparison of the 2 intervention arms of the study is a noninferiority analysis.

The study aims to recruit 501 subjects, and therefore complete data will be available for approximately 375 patients (125 per arm) at 6 months with an estimated 25% (125/501 participants) lost to follow-up. This sample size will provide the study with more than 80% power to detect a difference between each of the intervention groups and the control group of 0.35 SD at an alpha level of 0.01 assuming the correlation between baseline and follow-up scores is at least 0.7. This sample size will also provide the study with 90% power to claim noninferiority in the comparison between the 2 interventions if the true underlying difference between the groups is 0.29 SDs for either the heiQ or GHQ-12. A meta-analysis of Web-based emotional support reported an average effect size of approximately 0.4 across 15 studies [48]; similarly, previous research found modest effect sizes of 0.3-0.5 on the heiQ in self-management interventions in Australian and hospital-based samples [49,50]. The age group and gender of nonparticipants will be compared with that of participants to assess nonconsent bias.

Statistical Analysis

Primary analysis will compare scores on the GHQ-12 and 5 key heiQ dimensions (emotional support and well-being; monitoring and insight; constructive attitudes; skill acquisition; health service navigation) at a 6-month follow-up across the 3 groups. Differences between treatment groups on each of GHQ-12 and heiQ scores at the 6-month follow-up will be tested using analysis of covariance. The outcomes in the models will be the GHQ-12 score and heiQ score of interest at 6 months, the main predictor of interest will be treatment group and the baseline value of the GHQ-12 score and heiQ score will be included as covariates. Three post-hoc contrasts will be carried out; the first 2 of these will compare separately each of the intervention groups with the control group and the third will compare the proactive telephone-delivered support with the proactive Web-delivered support. To account for Type I error in the post-hoc analyses, Bonferroni corrections will be applied.

Results

It is hypothesized that participants receiving telephone or Web support will report reduced distress and greater self-efficacy than participants receiving booklets. Furthermore, individuals receiving Web support will report heiQ scores within 0.29 SDs of individuals receiving telephone support. Participant recruitment is underway and will conclude in September 2017.

This study has been approved by the Hunter New England Human Research Ethics Committee (NHMRC Committee Code: EC00403; Reference No. 14/05/21/4.03); the University of Newcastle Human Research Ethics Committee (NHMRC Committee Code: EC00144; Reference No. H-2014-0240); and, the Cancer Council of New South Wales (NHMRC Committee Code: EC00345; Reference No. 291). The study has also been approved by local research governance committees at each participating health service. This trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000932561) and received funding from the National Health and Medical Research Council as a Partnership Project.

Discussion

Trial Outcomes

Lung cancer patients often experience poorer prognosis, more severe physical effects, and more pronounced psychosocial distress than patients with other major cancers. A highly accessible and sustainable source of personalized community-based support would be invaluable for cancer patients and may minimize the need for more intensive and costly hospital-based services. This proposed trial aims to address 3 key issues that are largely unaddressed within the current literature: (1) how to engage patients who may benefit from, but underutilize, the service, (2) whether the model of low-intensity information, support, and referral is effective in improving relevant psychosocial outcomes in the 'real world' context, and (3) whether Web-based modes of support are acceptable to, and beneficial for, patients.

The proposed combination of active recruitment to the CCNSW CIS service, and the availability of Web-based options in the present study, has the potential to greatly increase the accessibility and continuity of supportive care for cancer patients. A positive outcome for this trial will be to produce an evidence base for redesigning the CIS service to be both effective and responsive to patient needs, in line with the national health reform's core principle of patient-centered care and increasing focus on eHealth options [51]. This evidence will also be applicable to a number of international organizations who provide community-based support services based on the CIS model.

Relevance to Other Community-Based Support Services

The findings from the rigorous examination of the efficacy of low-intensity information and support models of the CIS service are likely to be applicable to, and thus inform, other telephone services that provide similar support to many Australians. These important services, such as Lifeline, Salvo Care Line, Kids Help Line, Mensline, Beyondblue, SANE, Dementia Helpline, Hepatitis Helpline, and Stroke Helpline, are often the foremost services that are widely available to people experiencing a range of distressing and traumatic experiences, and therefore contribute significantly to the mental and social fabric of Australia.

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Authors' Contributions

All authors were involved in design of the trial and CP, LO, AWB, TCM, ALB, IR, FH, DB, and GC obtained study funding. CP, LO, AWB, DB, ALB, FH, and TCM developed the intervention and CP, SR, MC, LO, HB, and EF are responsible for implementation of the trial. CP and DB will oversee data analysis, while all authors will be involved in interpretation of results. All authors have contributed to, read, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Introduction screen and directions for proactive Web-based delivered support.

[JPG File, 154KB - resprot_v5i4e202_app1.jpg]

Multimedia Appendix 2

An example of a simulated chat conversation providing instrumental and emotional support.

[JPG File, 365KB - resprot_v5i4e202_app2.jpg]

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Abbreviations

CBT: cognitive behavior therapy
CCNSW: Cancer Council New South Wales
CIS: cancer information and support
EOI: expression of interest
GHQ-12: general health questionnaire
heiQ: health education and impact questionnaire
RCT: randomized controlled trials
SCNS-SF34: 34-item supportive care needs survey
SD: standard deviation

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Protocol

Effectiveness of a Technology-Based Injury Prevention Program for Enhancing Mothers' Knowledge of Child Safety: Protocol for a Randomized Controlled Trial

Chun Bong Chow[1], MBBS, MD; Wilfred Hing-Sang Wong[1], MMedSc; Wing Cheong Leung[2], MBBS, MD; Mary Hoi-Yin Tang[3], MBBS; Ko Ling Chan[4], PhD; Calvin KL Or[5], PhD; Tim MH Li[1], PhD; Frederick Ka Wing Ho[1], PGDE; Daniel Lo[1], BA (Hons); Patrick Ip[1], MBBS, MPH

[1]Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong, China

[2]Department of Obstetrics and Gynaecology, Kwong Wah Hospital, Hong Kong, China

[3]Department of Obstetrics and Gynaecology, The University of Hong Kong, Hong Kong, China

[4]Department of Social Work and Social Administration, The University of Hong Kong, Hong Kong, China

[5]Department of Industrial and Manufacturing Systems Engineering, The University of Hong Kong, Hong Kong, China

Corresponding Author:
Patrick Ip, MBBS, MPH
Department of Paediatrics and Adolescent Medicine
The University of Hong Kong
1/F, New Clinical Building, Queen Mary Hospital, Pokfulam
Hong Kong,
China
Phone: 852 28198501
Fax: 852 22554089
Email: patricip@hku.hk

Abstract

Background: Provision of anticipatory guidance for parents is recommended as an effective strategy to prevent injuries among young children. Technology-based anticipatory guidance has been suggested to reinforce the effectiveness of injury prevention and improve parents' knowledge of child safety.

Objective: This study aims to examine the effectiveness of a technology-based injury prevention program with parental anticipatory guidance for enhancing mothers' knowledge of child safety.

Methods: In this randomized controlled trial, 308 mothers will be recruited from the antenatal clinics and postnatal wards of two major public hospitals in Hong Kong. Participating mothers will be randomly assigned into intervention and control groups. Mothers in the intervention group will be given free access to a technology-based injury prevention program with anticipatory guidance, whereas mothers in the control group will be given a relevant booklet on parenting. The injury prevention program, available as a website or on a mobile app, includes behavioral components based on the Theory of Planned Behavior. The primary outcome measure will be the change in the mother's knowledge of child safety. The secondary outcome measures will be age-appropriate domestic safety knowledge, attitudes, intentions, perceived behavioral control, and self-reported behavior related to home safety practice. We will also determine dose-response relationships between the outcome measures and the website and mobile app usage.

Results: Enrolment of participants will begin in October 2016. Results are expected by June 2018.

Conclusions: Parents will be able to easily access the domestic injury prevention website to find information regarding child injury prevention. It is anticipated that the technology-based intervention will help parents improve their knowledge of child safety and raise their awareness about the consequences of domestic injuries and the importance of prevention.

Trial Registration: Clinicaltrials.gov Clinicaltrials.gov NCT02835768; http://clinicaltrials.gov/ct2/show/NCT02835768 (Archived by WebCite at http://www.webcitation/6lbXYM6b9)

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KEYWORDS

child safety; injury prevention; technology-based intervention; anticipatory guidance; randomized controlled trial

Introduction

Childhood injury is a major public health problem worldwide [1]. According to the World Health Organization, approximately 46 out of every 100,000 children under the age of 5 years die from unintentional injuries [2]. Childhood injury is a significant health problem in Hong Kong. Between 2010 and 2012, more than 740,000 injury cases were reported in children aged 0 to 19 attending Accident and Emergency Departments in Hong Kong [3]. Specifically, pediatric unintentional domestic injury was one of the top three injury types among children in Hong Kong, accounting for 38.67% (286,193/740,000) of injuries in the 0 to 19 age group [3]. In the 0 to 4 age group, domestic injury was the leading cause of injury, accounting for 64% of all injuries. Unlike intentional injury caused by domestic violence, pediatric unintentional domestic injury is associated with the lack of available living space and safety measures, parents' poor perception of injury risk, and children's injury risk behaviors.

Parents are the primary caregivers and role models for their children's behavior, and they should be given guidance regarding domestic injury prevention and how to modify the home to be a safe environment [4,5]. Although health care professionals are perceived as a credible provider of injury prevention information [6,7], parents will need to play an influential role in reducing their children's exposure to injury risk by adopting better childcare practices and using appropriate child safety devices in the home [8,9]. Anticipatory guidance provided to parents during pediatric medical care is an effective strategy to prevent injuries and promote child health [10]. Anticipatory guidance consists of useful information for parents and families about their children's development, and practical information on how to promote this development and adopt good practices [11]. Anticipatory guidance can be delivered in line with developmental milestones of a child [12]. Previous studies on the effectiveness of anticipatory guidance indicated that parent and child behavior outcomes were associated with reduced injuries and improved development during infancy and early childhood [7,13,14].

Technology-based interventions with anticipatory guidance information can be accessed anonymously, anytime, and anywhere. These systems can provide individualized and tailored interfaces enriched with interactive elements [15], and such interventions could be a useful approach for the prevention of domestic injury. Recent studies suggest that technology-based interventions can reinforce the effectiveness of injury prevention, and improve parents' knowledge of child safety [16-18]. A systematic review of technology-based interventions for unintentional injury prevention highlighted 10 parenting interventions for child safety; all interventions were demonstrated to improve parents' injury prevention behaviors [19]. For instance, a study by Van Beelen et al revealed that a Web-based intervention increased parents' behavior toward child safety more than a standard leaflet related to scheduled childcare counseling [20]. Only two interventions evaluated changes in safety knowledge, and both showed positive changes [19]. A study by Gielen et al reported that an online intervention had a positive effect on enhancing safety knowledge [21]. Furthermore, the systematic review found only two out of 44 technology-based interventions were available as mobile apps [19]. Mobile apps for injury prevention intervention should be developed and thoroughly evaluated.

In this study, we propose to develop a new technology-based intervention that includes parental anticipatory guidance related to child injury prevention that is accessible on the web and as a mobile app. We will examine the effectiveness of the intervention in enhancing mothers' knowledge of child safety. Using our new technology-based approach, we aim to motivate mothers to learn about pediatric unintentional domestic injury prevention to improve their knowledge of child safety, attitudes, and perceived behavioral control toward home safety practice. Website usage will be evaluated in terms of its reach and engagement statistics. User acceptance evaluations will be conducted at the end of the intervention period to collect feedback on the website interface.

Methods

Study Design

This study will be a randomized controlled trial of the effectiveness of a technology-based injury prevention program for enhancing mothers' knowledge of child safety (Figure 1). Mothers will be recruited from the antenatal clinics and postnatal wards of two major public hospitals in Hong Kong: Kwong Wah Hospital and Queen Mary Hospital. Between October, 2016 and January, 2017, nurses will identify potential participants. An experienced research assistant will provide the participants with an information sheet explaining the study, along with a consent form. The inclusion criteria will include mothers attending the antenatal clinics or staying in the postnatal wards at Kwong Wah Hospital or Queen Mary Hospital. The exclusion criteria will include subjects unable to read Chinese, and those without Internet access.

Participants will be randomly allocated into the intervention and control groups in a 1:1 ratio. All participants will be given an information pack consisting of a parenting booklet from the Maternal and Child Health Centers (MCHC). This booklet is publicly available and provides brief and general home safety tips for mothers with children under 3 years of age. The intervention group will also be given an additional leaflet containing a brief introduction to the Internet-based domestic safety platform, and instructions on how to access the website. Mothers can easily access this practical online parenting resource through the website or a mobile app. The online resource contains information on various safety topics and educational materials, including general and age-appropriate injury prevention measures suitable for mothers with infants and children between 2 and 18 months of age. Participants in the intervention group will be periodically contacted by telephone and electronic messaging to encourage them to access

and engage with the domestic safety website. The research team will provide technical support to all participants who encounter problems accessing the intervention website or mobile app. Apart from technical support, no other intervention will be provided to those accessing the website or mobile app by any therapist, nurse, care provider, or physician. The control group will receive only the MCHC parenting booklet.

All consenting participants will be asked to complete a general safety questionnaire at the antenatal clinic or postnatal ward of the two hospitals. Age-appropriate safety knowledge, attitudes, intentions, perceived behavioral control, and self-reported behavior related to home safety practice will be assessed at specific child developmental ages at 2, 6, 9, 12, and 18 months. Participants in the intervention group will be given immediate feedback on their specific injury prevention behaviors prompted by the *at-risk* (incorrect) answers obtained from their completed questionnaire. This online feedback counseling approach aims to educate mothers and enhance their awareness related to domestic injury prevention. At the end of the counseling session, each intervention participant will be provided with age-appropriate safety information. Participants' general safety knowledge will be reassessed when their children reach the age of 18 months. Intervention participants will be reminded by telephone and email to complete the age-appropriate safety questionnaires at each developmental stage, and the final general safety questionnaire. Control group participants will be contacted using the same schedule, to remind them to read the booklet and to complete the questionnaires.

This study is registered with Clinicaltrials.gov (Identifier: NCT02835768) and has been approved by the Institutional Review Board of Hong Kong University and Hospital Authority Hong Kong West Cluster (Reference number: UW 15-465). All participants will provide written informed consent.

Sample Size Calculation

With reference to a computer-based parenting intervention for child injury prevention that reported a small to medium effect (d=0.42) for knowledge change [21], 92 subjects will be needed for this intervention study to detect an effect with 80% power and a 5% significance level. Assuming a 40% attrition rate between preevaluation and postevaluation, at least 154 participants should be recruited to each of the intervention and control groups.

Randomization and Masking

Participants will be randomly assigned to the intervention group or the control group by stratified randomization within each hospital, using random numbers generated using R Statistical Software. Each participant will receive a sealed opaque envelope assigning them to either the intervention (website and mobile app access) or the control (no website or mobile app access) groups. The participant recruitment and randomization process will be independently carried out by different research assistants. Outcome assessors will be blinded to the allocation of participants in each group.

Technology-Based Anticipatory Guidance

The technology-based intervention website will be developed using the existing injury prevention website designed by the Hong Kong Childhood Injury Prevention and Research Association (CIPRA), which provides informational, educational, and motivational support to parents [22]. The existing CIPRA website contains assorted safety information (not limited to domestic safety) and online games to deliver safety messages. The CIPRA website includes two key topics on (1) types of domestic injury, and (2) preventing a range of domestic injuries. In this study, the technology-based website used by the intervention group will be based on the CIPRA website, but with limited access to only the domestic safety and domestic injury prevention topics. Topics related to domestic injury will be temporarily suspended from the main CIPRA website during the study period. A mobile app will also be developed in conjunction with the website platform to facilitate participants' acquisition of knowledge regarding child-related domestic injury prevention. The contents of the intervention website and mobile app will be the same.

The Injury Prevention Program (TIPP), an intervention website introduced by the American Academy of Pediatrics [23], will be the basis for the core strategy of our domestic injury prevention intervention. A review of the literature on childhood injury prevention demonstrated that TIPP was effective in improving safety knowledge and home safety practices [24]. Our intervention program will provide anticipatory guidance via the general domestic safety tips from the CIPRA website and TIPP. These combined resources will provide enriched domestic injury prevention information (*Home Safety Tips*) which will be divided into five stages according to the safety issues relevant to infants/young children in various age groups (Table 1). The intervention platform is intended to provide mothers with domestic injury prevention information specific to their children's age, and important injury prevention information and messages will be age-appropriate for each developmental stage. Mothers will complete a corresponding safety survey at each developmental stage that their children reach. Safety counseling topics include common injury types such as falls, drowning, burns, and poisoning, but not unintentional firearm injury. Firearms, guns, and other weapons are prohibited by law in Hong Kong, so it is unlikely that children will be injured in such a way.

Figure 1. Flow diagram of study design.

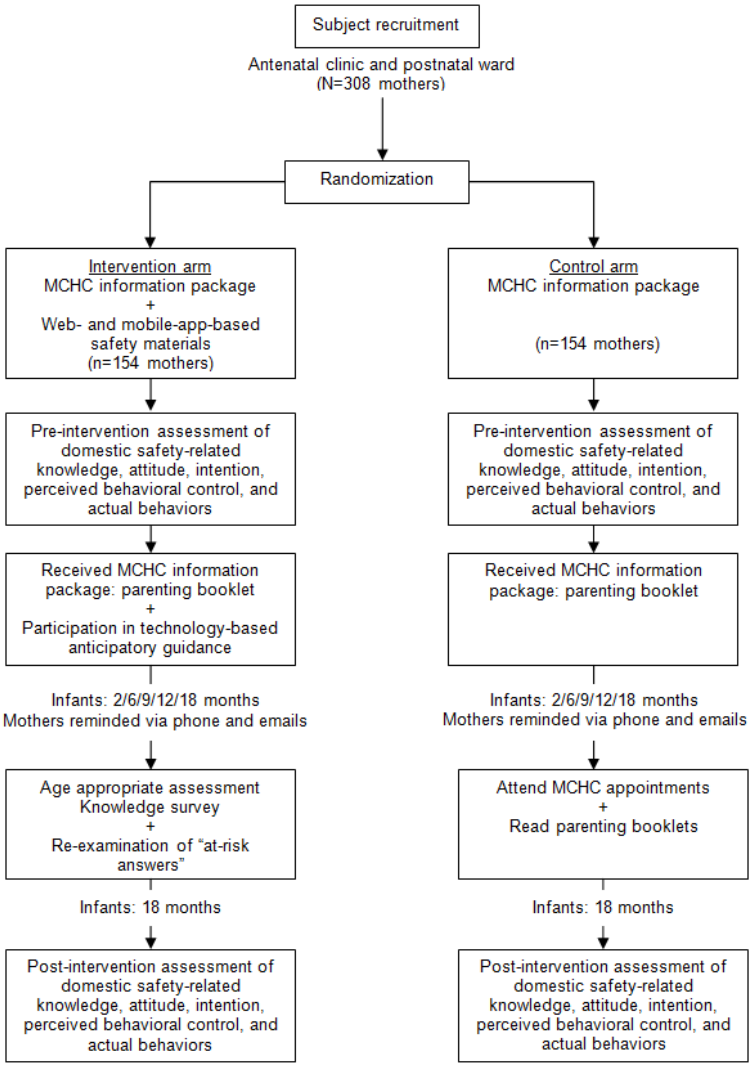

Table 1. Age-appropriate safety counseling topics adopted and modified based on The Injury Prevention Program (TIPP).

Age	Safety counseling topics
1.5 to 2 months	
	Falls
	Scalds
	Sleeping safety
	Suffocation
	Drowning
6 months	
	Falls
	Burns
	Medicine poisoning
	Drowning
	Toy hazards
9 months	
	Concussion
	Drowning
	Driving hazards
	Finger pinching
12 months	
	Poisoning
	Falls
	Sunburn
	Driving hazards
18 months	
	Poisoning
	Falls
	Sunburn
	Driving hazards

The value of using a behavioral approach to design an injury prevention program is widely recognized by researchers [24,25]. The Theory of Planned Behavior is a model that links beliefs and behavior to predict people's intention to perform actual behaviors [26]. This intention comprises three important elements: attitude, subjective norms, and perceived behavioral control. Attitudes are derived from a person's perceptions about the consequences of behavior and the importance of these consequences to the individual. Subjective norms are derived from one's perception of beliefs about significant others' preferences and the individual's motivation to comply with their wishes. Perceived behavioral control is derived from a person's perception of the difficulty to conduct the behavior. Adriaensens et al reported that an online intervention was able to deliver a positive effect on knowledge, attitudes, intentions, and actual injury-preventive behavior [27]. Therefore, besides being a knowledge hub, the intervention website and mobile app will incorporate additional feedback counseling, online consultations, a discussion forum, interactive games, and video demonstrations to improve participant's attitudes, intentions, and perceived behavioral control toward home safety practices.

Mothers can use the discussion forum to exchange opinions or ideas related to domestic safety, such as the usefulness of safety gadgets, uncommon domestic injury hazards, and home safety emergency plans. Concerned mothers can also use the forum for online consultation by asking questions about childhood injury, and can even upload photos, which will then be answered by safety experts. However, in an emergency, participants should contact emergency services and attend their nearest accident and emergency department. The forum can serve as a practical learning platform and provide parents or caregivers with additional social value through online interaction. Online discussion forums have been shown to enhance social support and the feeling of parental efficacy, and thus can improve one's attitudes and intentions to adopt safer practices [18].

Additional interactive elements such as video demonstrations, games, and quizzes will be added to the website and mobile

app. Two interactive games have been designed to deliver key information related to childhood safety and injury prevention. In the first game (named *spot the difference*), players need to identify differences in potential home hazards between two pictures. Explanations will be provided when players spot the potential home hazard, such as the type of injury (eg, scald and poisoning) that the hazard would cause. In the second game (named *cue and action*), players need to select a particular prevention tool to stop the potential hazard that may cause domestic injury. These interactive games and video demonstrations would help the participant create mnemonics for injury prevention, and enhance one's perceived behavioral control toward home safety practices. Safety practice demonstrations by health care providers who are role models and influencers have been reported to be useful in engaging mothers and reinforcing positive outcomes [6,7].

The website will contain comprehensive injury prevention information and useful links and telephone numbers. All information contained in the website and the app will be consolidated and updated regularly, taking into account the changing patterns arising from local injury profiles, caregivers' responses, and the physical environment. Reference and guidance materials such as injury-related publications of evidence-based good practices, statistical data, and frequently asked questions will be made available on the website to reinforce users' perceived behavior control toward domestic injury prevention. In addition, the injury profiles of the 18 districts in Hong Kong, with infographic summaries, will be uploaded to the website for reference [3].

Technology

The existing CIPRA website will be redesigned to accommodate the intervention program in this study, and will be cohosted by CIPRA and the authors' department. A mobile app will be made available for downloaded on Android phones and iPhones. The website will run on a Linux server located and managed under the authors' department, and will have regular backups to prevent any accidental data loss.

Measures

This study aims to increase mothers' knowledge of child domestic safety, and to improve their attitudes, intentions, perceived behavioral control, and actual behavior related to home safety practice. The following five evaluation components will be included to demonstrate the effectiveness of the technology-based intervention: general safety knowledge, age-appropriate safety questionnaire, injury prevention behavior checklist, website and mobile app usage statistics, and website and mobile app user acceptance.

General Safety Knowledge

This component aims to evaluate changes in mothers' general knowledge related to domestic injury prevention [28,29]. The items in the questionnaire are in a statement format and cover two key topics: (1) common childhood domestic injuries, and (2) safety precautions (see Multimedia Appendix 1).

Age-Appropriate Safety Questionnaire

This component examines age-appropriate domestic safety knowledge, attitudes, intentions, and perceived behavioral control toward home safety practice (Table 1) [30-32]. The multiple-choice questions in the questionnaire are categorized into two sections: (1) age-specific questions, and (2) assessment questions that were answered incorrectly in the previous stage by the participant (see Multimedia Appendix 2). This targeted component is designed to reinforce safety concepts and sustain knowledge enhancement.

Injury Prevention Behavior Checklist

This component examines different age-appropriate injury prevention behaviors. The injury prevention behavior checklist serves as a behavioral measure for: (1) identifying hazards, and (2) implementing safety measures in a home environment (see Multimedia Appendix 3).

Website and Mobile App Usage Statistics

Participants will be required to register online as a *user* to access the website and the mobile app. By logging into the system, we will be able to record all actions taken by each user, including login time, duration of website usage, and what information was accessed. The captured data can be further analyzed and used for the purpose of incentive reimbursement.

Website and Mobile App User Acceptance

Towards the end of the intervention period, subjects will be reminded to complete a user acceptance evaluation (see Multimedia Appendix 4). The practicability of the technology-based domestic injury prevention website and mobile app will be evaluated in terms of its layout, structure, usability, readability, accessibility, and ease of navigation [33].

Incentives

To enhance participation and minimize attrition in the follow-up months, incentives will be given to mothers who continue to complete evaluations. Proposed incentives include safety gadgets and cash coupons (valued at Hong Kong $50; approximately US $6.40) from companies that promote child domestic safety.

Data Analysis

Changes in participants' knowledge of child safety will be studied by comparing their knowledge before and after completing the injury prevention program, and by comparing the participants' knowledge of child safety in the intervention and control groups. Regression analysis will be used to examine the intervention effectiveness, adjusted for participant demographics (eg, gender, age, and socioeconomic status of the parent). Data will be analyzed by an intent-to-treat approach to address loss of any follow-up data. Independent sample t-tests will be used to examine the between-group differences in age-appropriate safety knowledge, attitudes, intentions, perceived behavioral control, and actual behavior related to home safety practice. Dose-response relationships between the outcome measures and the website and mobile app usage will be determined by correlation analysis. Website and mobile app usage data will be summarized based on the number of users and their time spent using these resources during the entire

intervention period. A summary of the user acceptance evaluation will be compiled to improve and develop the website and mobile app.

Results

This project was successfully funded by the Health Care and Promotion Fund (Project No. 08150345) of the Food and Health Bureau, Hong Kong government, in March, 2016 after a stringent external review process. Enrolment of participants will start in October, 2016 and results are expected by June, 2018.

It is anticipated that the technology-based injury prevention intervention will yield a small to medium effect in terms of mothers' child safety knowledge enhancement. It is estimated that intervention participants will spend more time on the mobile app than on the website. Dose-response relationships between the outcome measures and the website and mobile app usage will be examined. It is expected that intervention participants will have better age-appropriate safety knowledge, attitudes, intentions, perceived behavioral control, and actual behavior related to home safety practice compared to the control group participants.

Discussion

This study examines the effectiveness of a technology-based intervention designed to improve mothers' awareness of the severity and consequences of domestic injuries. Mothers can enhance their knowledge of child safety by accessing the online age-appropriate information related to child health, parenting, and safety. This technology-based platform can help users find available resources, services, providers, and relevant contact information.

A discussion forum will be available on the new website and mobile app as a means to facilitate communication between mothers and professionals. Mothers can also benefit from technology-mediated social support and chat rooms, and exchange lay knowledge. Safety experts and pediatricians will be invited to provide advice, professional support, and counseling through the website and the app, which will strengthen online services and promote engagement. The website will help to mobilize community stakeholders to address child safety concerns and other aspects of child health, and will allow stakeholders to raise their own concerns. The website will empower parents to take responsibility for their children's health and safety, and to adopt good health practices.

The Internet is becoming widely accepted as an effective, low-cost platform for the dissemination of health and safety information. In comparison to traditional media, information on the Internet can be updated instantly and inexpensively [34]. Electronic dissemination of information has a great deal of potential when compared to traditional media, especially when considering the speed of information propagation, because it has the ability to reach a large audience and connect with those who might otherwise be difficult to approach [35]. Technology-based interventions can also serve as platforms for viral campaigns, which involve sharing knowledge among information seekers. This easily accessible online safety platform (intervention website and mobile app) containing comprehensive up-to-date information on childhood safety will educate parents and caregivers, and encourage them to adopt safer practices. Findings from the study will contribute to good health practices, future research, and the development of user-friendly online information platforms. For example, the educational effort of CIPRA could be enhanced by combining other approaches, including legislative measures and infrastructure improvements, because a solely educational approach is limited in reach. Our main goal is to provide an effective online educational platform to be funded on an ongoing basis, which will be incorporated into the Maternal and Child Health Services under the Department of Health, and into postnatal clinics in public hospitals.

This study will be carried out in collaboration with CIPRA by sharing resources, exchanging best practices, and combining efforts towards sustainability. Furthermore, this Web-based intervention will demonstrate a sustainable health promotion strategy that mobilizes local resources with cross-sectoral collaborations to engage the community by building partnerships between private, public, and nongovernmental organizations. Upon completion of the evaluation, the information leaflet with details of the domestic safety website will be disseminated to relevant public, private, and nongovernmental organizations that promote child health, and particularly child safety. This freely accessible safety platform will allow organizations to reinforce awareness and promote domestic injury prevention among target populations.

Information on the platform can be revised regularly to ensure that users have access to high quality, up-to-date, and accurate information. All safety information contained on the website and mobile app will be shared with interested nongovernmental organizations, MCHC, and postnatal clinics. All information associated with the platform can also be linked across sectors, including the government, academic institutions, nongovernmental organizations, and private sectors in Hong Kong. The CIPRA safety information website and mobile app are expected to be easily accessible for all users, including parents, caregivers, school teachers, social workers, children, and nonacademic medical and allied health professionals. This platform will serve as an information hub for the community and a learning platform for all relevant stakeholders. When disseminating the findings from the intervention study within the community, we will also compare the intervention with other services by collecting feedback from different users, interviewing relevant stakeholders, and conducting ecological and econometric studies to assess the long-term social impact on the intervention. We will further improve the intervention platform to meet the needs of the community.

Anticipatory guidance for injury prevention should be provided to parents along with routine medical care, such as well-child visits for infants and children. An important advantage of this Internet-based intervention, apart from providing anticipatory guidance, is its potential to reach a wide audience, which can be exploited by other electronic health services that utilize community-wide interventions with intersectoral collaborations between public, private, and nongovernment organizations. The

use of technology-based interventions is increasing, and can be considered a powerful mobilization strategy for engaging various user groups. In the future, the online platform can be adapted to deliver preventive pediatric health care information in other learning areas, such as growth monitoring, nutrition, and vaccinations. All of these important child health-related areas would contribute to the establishment of a child health portal that will help to promote the well-being and optimal development of children in Hong Kong.

Conflicts of Interest

None declared.

Multimedia Appendix 1

General safety knowledge questionnaire.

[PDF File (Adobe PDF File), 150KB - resprot_v5i4e205_app1.pdf]

Multimedia Appendix 2

Age-appropriate safety questionnaire.

[PDF File (Adobe PDF File), 117KB - resprot_v5i4e205_app2.pdf]

Multimedia Appendix 3

Injury prevention behavior checklist.

[PDF File (Adobe PDF File), 32KB - resprot_v5i4e205_app3.pdf]

Multimedia Appendix 4

Website and mobile app user acceptance questionnaire.

[PDF File (Adobe PDF File), 88KB - resprot_v5i4e205_app4.pdf]

Multimedia Appendix 5

The peer-review report from the Health Care and Promotion Fund.

[PDF File (Adobe PDF File), 55KB - resprot_v5i4e205_app5.pdf]

Multimedia Appendix 6

CONSORT-EHEALTH checklist (V1.6.1) [36].

[PDF File (Adobe PDF File), 1MB - resprot_v5i4e205_app6.pdf]

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Abbreviations

CIPRA: The Hong Kong Childhood Injury Prevention and Research Association
MCHC: Maternal and Child Health Centers
TIPP: The Injury Prevention Program

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Protocol

The Effects of an E-Mental Health Program and Job Coaching on the Risk of Major Depression and Productivity in Canadian Male Workers: Protocol for a Randomized Controlled Trial

JianLi Wang[1,2,3], PhD; Scott B Patten[1,2,3], MD, PhD; Raymond W Lam[4], MD; Mark Attridge[5], PhD; Kendall Ho[6,7], MD; Norbert Schmitz[8], PhD; Alain Marchand[9], PhD; Bonnie M Lashewicz[2], PhD

[1]Department of Psychiatry, University of Calgary, Calgary, AB, Canada
[2]Department of Community Health Sciences, University of Calgary, Calgary, AB, Canada
[3]Mathison Centre for Mental Health & Education, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada
[4]Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada
[5]Attridge Consulting Inc., Minneapolis, MN, United States
[6]Department of Emergency Medicine, University of British Columbia, Vancouver, BC, Canada
[7]Digital Emergency Medicine, University of British Columbia, Vancouver, BC, Canada
[8]Department of Psychiatry, McGill University, Montreal, QC, Canada
[9]School of Industrial Relations, University of Montreal, Montreal, QC, Canada

Corresponding Author:
JianLi Wang, PhD
Department of Psychiatry
University of Calgary
Room 4D69, TRW Building
3280 Hospital Dr. NW
Calgary, AB, T2N 4Z6
Canada
Phone: 1 4032108653
Fax: 1 4032109182
Email: jlwang@ucalgary.ca

Abstract

Background: Major depression (MDE) is prevalent in men and affects men's health and productivity. Because of the stigma against depression and social/gender norms, men are less likely to seek help for emotion and stress-related issues. Therefore, innovative solutions tailored for men are needed. With rapid development of the Internet and information technologies, one promising solution that has drawn considerable attentions is electronic mental (e-mental) health programs and services.

Objective: The objective of our study is to evaluate the effectiveness of the e-mental health program BroHealth on reducing the risk of having MDE and improving productivity and return to investment.

Methods: The target population is Canadian working men who are at high risk of having MDE (N=1200). Participants will be recruited using the method of random digit dialing across the country and workplace advertisement. Eligible participants will be randomly allocated into the following groups: (1) a control group, (2) a group receiving BroHealth only, and (3) a group receiving BroHealth and telephone-based job coaching service. The groups will be assessed at 6 and 12 months after randomization. The primary outcome is the risk proportion of MDE over 12 months, which will be assessed by the World Health Organization's (WHO's) Composite International Diagnostic Interview-Short Form for Major Depression. Intention-to-treat principle will be used in the analysis. The 12-month proportions of MDE in the groups will be estimated and compared. Logistic regression modeling will be used to examine the effect of the intervention on the outcome, controlling for the effects of baseline confounders.

Results: It is anticipated that the randomized controlled trial (RCT) will be completed by 2018. This study has been approved by the Conjoint Health Research Ethics Review Board of the University of Calgary. The trial is funded by a team grant from the Movember Foundation, a global charity for men's health. BroHealth was developed at the Digital Emergency Medicine, University of British Columbia, and the usability testing has been completed.

Conclusions: BroHealth was developed based on men's needs. We hypothesized that BroHealth will be an effective, acceptable, and sustainable product for early prevention of MDE in workplaces.

ClinicalTrial: Clinicaltrials.gov NCT02777112; https://clinicaltrials.gov/ct2/show/NCT02777112 (Archived by WebCite at http://www.webcitation.org/6lbOQpiCG)

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KEYWORDS

Internet; RCT; men; workplace; major depression; prevention

Introduction

Background

Major depression (MDE) affects workers' health and productivity. In the United States, workers with depression cost an estimated US $44.01 billion per year in lost productivity [1]. One of the severe consequences of having MDE is suicide and Canadian national data showed that 76% of all suicides in 2009 were male [2]. Compounding men's risk, men are less likely than women to seek help and to disclose depressive symptoms and often delay help seeking until symptoms become severe. If they do seek help, men are often worried about anonymity and prefer flexible and timely access. Men are socialized to be emotionally stoic and exemplify traditional masculine characteristics such as independence, self-reliance, and dominance [3]. Men are concerned over the perceived negative judgments from family and friends if they access treatment for depression. These gender-specific experiences along with a limited knowledge base about effective interventions call for innovative solutions tailored for men. With rapid development of the Internet and information technologies, one promising solution that has drawn considerable attentions is electronic mental (e-mental) health programs and services.

E-mental health is "the use of information and communication technologies to support and improve mental health, including the use of online resources, social media, and smartphone applications" [4]. E-mental health programs offer information about mental health or therapeutic services remotely through the Internet or by telephone. The increasing availability of fast broadband access provide e-mental health programs several advantages including easy and flexible access to services in remote areas and low costs. To a certain extent, e-mental health programs are closely aligned with men's needs in terms of privacy protection, flexible, and timely access to help. There have been a number of e-mental health programs for therapeutic intervention. A recent review by Christensen and Petrie showed that by 2013 there had been 62 Web-based mental health interventions and 11 mobile apps [5]. Lal and Adair found 91 peer-reviewed publications on the application of e-mental health interventions between 2000 and 2010 [6]. However, the number of randomized controlled trials (RCT) has not been proportionate to the number of e-mental health programs. For example, only 30.1% of the 73 programs identified in Christensen and Petrie's review had been evaluated by one or more RCTs [5]. Many of the existing e-mental health programs for depression were developed based on the approach of cognitive behavioral therapy (CBT). The most widely disseminated e-mental health program based on CBT is MoodGYM developed in Australia [7]. Other well-known e-mental health programs for depression that have been evaluated by at least one RCT include Sadness [8], e-couch [9], BluePages [7], and myCompass [10]. Although e-mental health programs offer a non-threatening, convenient, and anonymous environment, some users reported that going through the CBT sessions and exercises were laborious, the sessions were not relevant with the users' unique personal issues, and there was a lack of personal interaction [11]. Our research project, BroMatters, intends to overcome these limitations.

BroMatters is a project aiming to develop and evaluate an e-mental health program for early prevention of major depression in Canadian male workers who do not have MDE, but are at high risk. It is a collaboration among researchers and stakeholders from five Canadian universities and six national and local non-government organizations (NGOs). To develop the e-mental health program, BroMatters conducted a national survey in male workers who did not have MDE, but were at high risk, to understand their preferences of design features of e-mental health programs [12]. Informed by the survey results, the BroMatters team developed an e-mental health program (BroHealth) to be evaluated by a RCT.

Objectives and Hypotheses

The primary objective of the proposed RCT is to evaluate the impacts of BroHealth and telephone-based job coaching on the risk of MDE among Canadian male workers who are at high risk of having MDE. We hypothesized that the 12-month risk proportion of MDE in the intervention group will be lower than that in the control group.

The secondary objectives of the proposed RCT are to (1) evaluate the impacts of BroHealth and telephone-based job coaching on changes in depression, anxiety, absenteeism and presenteeism, return on investment, and predicted MDE risk; and (2) compare participants who receive BroHealth only and those who receive both BroHealth and telephone-based job coaching services in changes in depression, anxiety, absenteeism and presenteeism, return on investment, and predicted MDE risk.

Methods

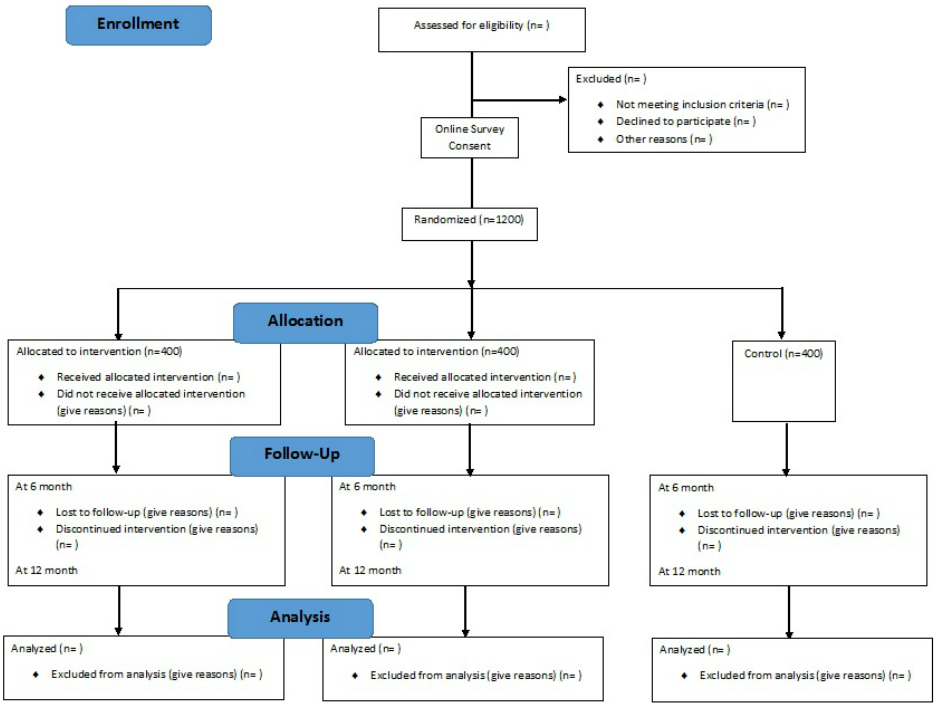
Study Design

The proposed mixed-methods study is a prospective, intention-to-treat, RCT with the following 3 arms: (1) control group (n=400) that will receive general information about men's mental health (the Movember Foundation website on men's mental health), (2) intervention arm 1 group (n=400) that will receive the e-mental health program, and (3) intervention arm

2 group (n=400) that will receive the e-mental health program, and telephone-based interactive work-life coaching.

An embedded qualitative interview component will be conducted with a sub sample of participants from the intervention groups to obtain in-depth perspectives about the effectiveness of interventions at the 12-month endpoint. A flow chart of the proposed trial based on the Consolidated Standards of Reporting Trials (CONSORT) criteria is shown in Figure 1.

Figure 1. BroMatters clinical trial flow diagram.



Study Setting and Inclusion Criteria

Eligible participants will be recruited from 10 provinces of Canada. Recruitment and fully structured baseline interviews will be conducted by Leger, a Canadian-owned polling and research firm; follow-up interviews will be conducted at the telephone interview laboratory of the Mathison Centre for Mental Health and Education, University of Calgary. The proposed trial will target Canadian male workers who are aged 18 years or older, are working for pay at the time of recruitment, and at the time of recruitment and baseline assessment, are not experiencing a MDE, but have a high risk of having MDE based on our prediction algorithm. Since it was found that 20% of Canadian adult men had a probability of 6.51% or higher in terms of the predicted MDE risk [13], for the proposed study, a personalized risk (or probability) of 6.51% or higher will be defined as high risk for men. In addition, the trial will target workers who may have had MDE in the past 12 months, but are in remission for at least 2 months prior to the study, have no language barriers to English or French, have access to the Internet for personal use, and can provide email and mailing addresses.

Intervention

BroHealth

BroHealth is an e-mental health program which was developed to reduce men's risk of having MDE and to improve productivity. The program was designed to be used by working men who don't have MDE, but are at high risk determined by a multivariable risk prediction algorithm [13]. The development of BroHealth was informed by the results of a national survey in the target population, about high risk men's preferences for the design features of e-mental health programs [12]. The product was developed at the Digital Emergency Medicine of the University of British Columbia, guided by a committee consisting of research team members with expertise in psychiatry, epidemiology, e-health, occupational psychology, addiction, information technology, and software programming. Before finalization, BroHealth was pilot tested among remaining team members, Stakeholder Advisory Committee members, and the general public recruited through personal networks and social media.

BroHealth contains the following key modules: (1) Information, (2) Self-Help, (3) Self-Check, and (4) Goal Setting and Tracking. The contents of each module are described in Textbox 1.

Textbox 1. The contents of each BroHealth module.

Module and content
1. Information: information about stress, depression, depression in the workplace, and alcohol use in the workplace.
2. Self-Help: a cognitive behavior therapy (CBT) program (Living Life to the Full) developed in the United Kingdom, a mindfulness relaxation program, and specific strategies for dealing with work related issues.
3. Self-Check: online instruments for monitoring current depressive and anxiety symptoms, occupational functioning, and future risk of major depression (MDE).
4. Goal Setting: the S.M.A.R.T goal setting and tracking system.

BroHealth is a Web-based program that is, at the current stage, opened to research participants only. Participants can log in to BroHealth with a user name and password generated at the Digital Emergency Medicine of University of British Columbia. The novelty of BroHealth is that it was designed in a modular format by which users may select any module/section, without particular sequence. Based on the preferences of the target population and feedback from stakeholders, the contents of the program are balanced with text description and video clips. Moreover, BroHealth has both English and French versions.

Telephone-Based Job Coaching

The rationale of including job coaching as part of the intervention is two-fold. First, previous research and our national survey of high-risk working men identified that a limitation of e-mental health programs is the lack of personal interaction [11,12,14]. Second, many RCTs on e-mental health programs suffered from high attrition rates [11,14,15], which is a major threat to the validity of the trials. One contributing factor that emerged from qualitative interviews is that e-mental health programs do not address issues that are relevant to the participants. Therefore, we proposed a combination of BroHealth and job coaching as an intervention arm.

The aim of coaching service is to help users set goals and discover answers to problems for themselves and to motivate users to take actions and engage their own solutions. Coaching is carried out by qualified people who work with clients to improve their effectiveness and performance. Job coaches are individuals who specialize in assisting individuals to learn and accurately carry out job duties. Job coaches provide one-on-one training tailored to the needs of the employee. The coach is well educated, skilled, and experienced in dealing with Human Resources advising, career counseling, goal setting, solution-based problem solving, and performance coaching. In the proposed trial, 5 coaches from different regions of Canada will be hired. Trial participants may access the coaching services in their region through an appointment booking system which is embedded in BroHealth. The coaches in Ontario, Quebec, and Atlantic Canada are bilingual (English and French). Participants will be eligible for one session per week. Each coaching session may last a maximum of 40 minutes.

Outcomes and Measurements

Primary Outcome

The primary outcome is the 12-month risk proportion of MDE, which is the WHO's Composite International Diagnostic Interview-Short Form (CIDI-SF) [16], will be administered to determine MDE in the past 12 months, based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria [17]. The Composite International Diagnostic Interview-Short Form for Major Depression (CIDI-SFMD) is a structured diagnostic interview for MDE, which has been repeatedly incorporated, without modification, into a series of national health surveys by Statistics Canada, starting in 1994. The CIDI-SFMD was developed from the full version of CIDI to provide a quick screen of MDE [16]. The WHO's CIDI has been widely used in population-based mental health surveys in different countries. MDE represents a purported 90% predictive cut point for the CIDI-SFMD. Using the full CIDI diagnosis as "gold standard", the sensitivity and specificity of the CIDI-SFMD was 89.6% and 93.9%, respectively [16].

Secondary Outcomes

Secondary outcome variables are changes in depression and anxiety scores, and absenteeism and presenteeism. Depression will be measured by the 9-item Patient Health Questionnaire (PHQ-9); anxiety will be measured by the 7-item Generalized Anxiety Disorder (GAD-7). The PHQ-9 is a widely used scale for assessing depressive symptoms [18], which scores each of the 9 symptoms from 0 (not at all) to 3 (nearly every day) [18]. A PHQ-9 score of greater than or equal to 10 has a sensitivity of 88% and a specificity of 88% for MDE [18]. The GAD-7 is widely used as a general screen for common symptoms of anxiety. The GAD-7 has good reliability and validity. A cut point was identified that optimizes sensitivity (89%) and specificity (82%) [19].

Absenteeism and presenteeism will be measured by the WHO's Health Performance Questionnaire (HPQ) [20,21] and the Lam Employment Absence and Productivity Scale (LEAPS) [22]. The HPQ is a brief self-report questionnaire that obtains screening information about the prevalence and treatment of commonly occurring health problems, and information about 3 types of workplace consequences (sickness absence, presenteeism, and critical incidents). LEAPS is a validated scale for measuring occupational functioning for workers with depression.

Predicted Risk and Probability of MDE

Predicted risk and/or probability of MDE will be measured using the sex-specific risk prediction algorithm [13]. This risk prediction algorithm is to be used in individuals who do not have MDE. Based on exposure to a key set of risk factors including family history, current health status, childhood trauma, and ongoing life stressors, the algorithm can generate a person's probability of having MDE in the next 4 years [13]. The

algorithm was developed using the data from over 4700 Canadian men who were followed for 4 years [13].

Return on Investment

Based on the HPQ, lost work productivity will first be calculated. The financial value of lost work productivity will be calculated as:

Value = (A x B) x C

where A is the absolute hours of combined lost work productivity (from change over time from baseline period to follow-up period in absenteeism hours and poor job performance/presenteeism hours), B is the financial value of hour of employee compensation (wages + benefits value), and C is the economic productivity multiplier (1.25). An example is shown in Textbox 2.

Textbox 2. An example of the financial value of lost work productivity equation.

Example

Per 1 month:

37 hours of lost productive time x $50 per hour = $1850

$1850 x 1.25 = $2312.50 total

This can be extrapolated to the entire year:

$2312.50 x 12 = $27,750 lost per person per year

However, this is a high estimate as normal workers are not 100% productive while at work, nor are they never absent from work. So this can also be adjusted to take into account normative employee levels of lost work time.

Other Variables

Other variables include demographic and socioeconomic characteristics, occupation, employment status, job gradient, parental and marital strain [23], self-rated physical health, alcohol use, sleep disturbance, anger, quality of life, and mental health service use. Alcohol use will be measured by the 3-item Alcohol Use Disorders Identification Test (AUDIT-C). Sleep disturbance and anger will be assessed using the measures of Patient-Reported Outcome Measurement Information System (PROMIS) of the US Department of Health and Human Services. Quality of life will be assessed by the EuroQol five dimensions questionnaire (EQ-5D) which is a widely used instrument for quality of life [24]. Questions about mental health service use are adopted from Statistics Canada's national health surveys.

Recruitment and Screening

Recruitment and screening will be contracted to Leger that has access to the numbers of household landlines and mobile phones across the country. Recruitment will be conducted using the method of Random Digit Dialing (RDD). Once a potentially eligible participant is identified, the interviewer will confirm the participant's age, working status, and access to the Internet for personal use, by asking "Do you have access to Internet for personal use, through computer or mobile device?" Then the CIDI-SFMD [16] will be administered. This is to assess MDE in the past 12 months and to ensure the participant is not experiencing a MDE at the time of interview.

If a participant has had MDE in the past 12 months, he will be asked "In the past 2 months or longer, has your mood been much improved or back to normal AND you DIDN'T have any symptom of (key phrases)?" Those who answer "no" will be excluded.

Following this, the sex-specific prediction algorithm for MDE will be administered. The algorithm for men contains 15 questions about personal and family history of MDE, current health status, childhood trauma, and recent negative life events [13]. With the input of the answers to these questions, the algorithm generates the participant's probability of having MDE in the next 4 years. The original development analysis showed that a probability of 6.51% represented the top 20% of Canadian adult men in terms of the risk of having MDE [13]. In this study, those who have a risk less than 6.51% are considered being at low risk and will be excluded from the study.

Baseline Assessment

If a person meets the eligibility criteria, the interviewer will administer demographic and occupational characteristics questions, PHQ-9 for depression, GAD-7 for anxiety, perceived risk of having MDE, the HPQ, LEAPS, self-rated physical health, alcohol use, sleep disturbance, anger, quality of life, and mental health service use.

Online Assessment

To ensure the use of the Internet, participants who complete the baseline telephone assessment will be instructed to complete a short online survey as the last step of the baseline assessment and informed consent. The online survey will include questions about Internet use with the 12-item Job Content Questionnaire [25] used in the Statistics Canada survey to measure self-reported work stress, and consent to participation.

Randomization

Participants who complete the baseline telephone and online surveys will be randomized into intervention and control groups. The randomization will be conducted and managed by the project coordinator affiliated with the project. To accomplish this, 1200 random numbers (between 0 and 1) will first be generated using Excel ("RAND()") for 1200 study identification (ID) numbers, ranging from 1 to 1200. The 1200 random numbers will then be sorted in descending order and categorized into 3 equal groups with the ID numbers in the first group (n=400) allocated to the control group, the ID numbers in the second group (n=400) allocated to BroHealth only, and the ID

numbers in the third group (n=400) allocated to BroHealth plus job coaching.

The Excel sheet with ID numbers and random numbers will be kept and printed out for randomization. For example, if a participant is the 3rd one to complete the online survey, determined by the date of completion, the project coordinator will search for ID #3 on the Excel sheet. If the random number associated with ID #3 is allocated to the second group, this participant will be assigned to the group that will receive BroHealth only.

The date of randomization will be documented. Any outcomes and/or changes that occur after the randomization will be counted to the groups, regardless of course of the BroHealth and job coaching interventions and if the interventions are used by the participants.

After randomization, the project coordinator will contact the participant by email. For those in the control group, the email will include a link to the men's mental health page of the Movember Foundation website. For those in the BroHealth only group, the email will include all information to the controls, a link to BroHealth log-in page, and the user name and password, whereas for those in the BroHealth plus job coaching group, the email will include all information to the participants in other groups, and instruction to the coaching appointment booking system in BroHealth.

Afterwards, a package including a thank you letter, the Movember Foundation website link to men's mental health, and Can $20 incentive as appreciation of their participation will be mailed to the participants.

Follow-Up Assessments

The post-randomization assessments will be conducted at 6 and 12 months. At the 6- and 12-month assessments, information regarding demographic and occupational characteristics questions, including changes in marital status and employment, alcohol use, self-rated physical health, CIDI-SFMD, PHQ-9 for depression, GAD-7 for anxiety, WHO's HPQ, sleep disturbance, anger, quality of life, and mental health service will be collected.

It is anticipated that time is needed to schedule follow-up interviews and there will be conflicts with scheduled interviews (eg, some participants may have to cancel a scheduled interview, or some do not respond to a scheduled phone call). Therefore, a 2-month interview window will be allowed for each follow-up interview.

To obtain in-depth information about how BroHealth affects men's behaviors and risk profile, qualitative interviews will be conducted via telephone with 10% of the participants in the intervention groups at the end of the RCT (ie, after the 12-month assessment). The participants will represent those with diverse outcomes (clinical and occupational trajectories, and employment status changes). Qualitative interview data will yield in-depth data about the impacts of receiving BroHealth and job coaching on the outcomes. These data will be used to support and interpret the primary quantitative data base. The multiple forms of evidence generated through mixed methods designs are particularly useful for illuminating complex health issues [26].

Data Management

The telephone interview firm will transfer password-protected baseline data to the principal investigator (PI) on a weekly basis. The 6- and 12-month follow-up assessments will be conducted at the telephone interview laboratory at the Mathison Centre for Mental Health Research & Education, University of Calgary. One month before the scheduled follow-up interviews, letters will be sent to the participants to remind them of the upcoming interview. An interview log will be developed for each participant to document interview time, schedule, call-back, contact information, and for the interviewer to make comments. All data will be kept confidential and stored on password-protected computers at the telephone interview laboratory and the PI's office, which are under 24/7 security surveillance.

Over the course of the trial, the PI and research staff will examine the data on a regular basis by running cross tabulation, frequency distribution, and estimation of means and proportions to ensure the quality of the data and identify missing values and potential outliers. If missing values and outliers are found, the records will be referred back to the interviewer for clarification or call-back.

After the 12-month interview, participants' group status will be linked with interview data by study ID numbers. Over the study period, the investigators and the interviewers who conduct the follow-up interviews in Calgary will not have access to participants' group status. The Leger interviewers, who conduct the baseline assessment and the project coordinator who manage the randomization process, will not be involved in follow-up interviews.

A sub-committee has been formed for this trial. The committee members will communicate via teleconference on a bi-monthly basis to review and discuss the progress, operational issues, final data analysis, and results interpretation.

Statistical Analysis

All data analyses will be conducted using the most recent version of STATA. An Intention-to-treat (ITT) principle will be used in the analysis (eg, initial intervention assignment rather than intervention received will be used in the analysis).

For the primary objective, the proportions of MDE over 12 months will be estimated for each group and will be compared using chi-square tests between control versus intervention #1, and control versus intervention #2. Logistic regression modeling will be used to examine the effect of the intervention on the outcome, controlling for the effects of baseline confounders. Contrast analysis will be conducted to compare different intervention groups (intervention #1 vs intervention #2) as one of the secondary objectives.

For the secondary objectives, the distributions of the changes in the depression and anxiety scores at 6 and 12 months in the intervention and control groups will be examined. The means of the changes between the intervention and control groups will be compared using *t* tests.

If the assumption of normal distribution is violated, transformation or non-parametric testing will be used. Analysis of variance (ANOVA) will be conducted to examine between group differences (separately for the 6- and 12-month assessments), controlling for the effects of baseline characteristics. Repeated-measures mixed models will be used to examine intervention effect (time x intervention), controlling for the effects of baseline characteristics. The analyses will be repeated for absenteeism and presenteeism (secondary objectives).

An economic evaluation will quantify the costs associated with work productivity loss and absence from work. Self-report measures of work performance on the HPQ can be converted into a percentage of work productivity hours and total hours of work absence. The total combined hours of work performance can then be assigned a dollar value based on consulting industry standard practices for estimating the value of an hour of work absence/productivity, typically a multiplier (eg, 1.5 or 2.0) of the employee hourly compensation rate [27,28]. The hourly compensation rate (wages and benefits combined dollar value) will be estimated for each respondent based on the mid-point of the income category level reported on the baseline assessment. The analysis will then compare the intervention versus control groups for net changes over time to determine if the intervention has a relatively more positive outcome in average work performance over the study period on a per participant basis. This dollarized outcome can then be compared to the cost of providing the intervention to yield an overall cost-benefit or return on investment test [29].

Sample Size Calculation

We propose recruiting 400 participants for each group (N=1200) at baseline. Imamura and colleagues assessed the effectiveness of integrative CBT (iCBT) in reducing the risk of MDE in a RCT [30]. Participants (N=762) were randomized into control and intervention group. Over 12 months, 0.8% and 3.9% of participants in the intervention and control group developed MDE, respectively. Based on these proportions, 374 participants in each arm are needed to detect the difference at a power of 0.80 and alpha level of.05. The sample size was calculated using statistical software STATA 14.0 (syntax: power two proportions 0.008 0.039) [31]. This is consistent with the average number of participants in the previous RCTs [32]. To offset attrition, we plan to provide a Can $20 incentive for participating in an assessment in appreciation of the participants' time and efforts.

Results

This study was approved by the Conjoint Health Research Ethics Review Board of the University of Calgary (Ethics ID: REB14-2365). The trial is funded by a team grant from the Movember Foundation, a global charity for men's health. BroHealth was developed at Digital Emergency Medicine, University of British Columbia, and the usability testing is complete. It is anticipated that the RCT will be completed by 2018.

Discussion

Principal Findings

BroHealth is novel in several ways. First, BroHealth focuses on early prevention of major depression, rather than providing treatment to those who already have MDE. The outcomes include not only reduced risk of MDE, but also improved work functioning, productivity, and return on investment. Second, BroHealth was developed through a gender lens, focusing on the working men who are at high risk of having MDE. Third, the development of BroHealth was informed by men's preferences of design features of e-mental health programs, through a national survey of the target population. To this extent, this approach enhances the acceptability of BroHealth by working men who are at high risk of MDE.

Limitations

BroHealth was designed to be used by male workers who have access to the Internet. Men who don't have Internet access for personal use will not be included. Some elements of BroHealth were based upon existing programs. For example, the CBT program of BroHealth was adapted from the abbreviated version of the UK Living Life to the Full (LLTTF), and the mindfulness relaxation program was developed by University Health Network in Ontario. However, the French materials for the mindfulness relaxation program were not available. This may affect the effectiveness of BroHealth in French speaking participants. We will examine this potential impact by conducting the proposed analyses in English and French speaking participants separately. The incidence of MDE will be measured by CIDI-SF for MDE, which is a fully structured diagnostic interview, rather than by physician diagnosis. Therefore, misclassification of diagnosis is possible.

Conclusion

MDE is a prevalent mental health condition in working men. Because of the stigma against depression and gender/social norms, men who are at high risk of MDE are reluctant to seek help and are lack of skills of self-management. BroHealth is a tool designed to overcome these gaps. The proposed RCT will provide solid evidence about the effectiveness and return on investment of this product.

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Authors' Contributions

JLW prepared the first draft of the manuscript. All authors were involved in the trial design, reviewing the manuscript, interpretation, and final approval.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy
CIDI: Composite International Diagnostic Interview-Short Form
CIDI-SFMD: Composite International Diagnostic Interview-Short Form for Major Depression
e-mental health: electronic mental health
GAD-7: Generalized Anxiety Disorder
HPQ: Health Performance Questionnaire
ID: identification
LEAPS: Lam Employment Absence and Productivity Scale
MDE: major depression
PHQ-9: Patient Health Questionnaire
PI: principal investigator
RCT: randomized controlled trial
WHO: World Health Organization

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Protocol

Engaging Moms on Teen Indoor Tanning Through Social Media: Protocol of a Randomized Controlled Trial

Sherry L Pagoto[1], PhD; Katie Baker[2], DrPH; Julia Griffith[3], MSW; Jessica L Oleski[1], MA; Ashley Palumbo[1], MS; Barbara J Walkosz[3], PhD; Joel Hillhouse[2], PhD; Kimberly L Henry[4,5], PhD; David B Buller[3], PhD

[1]Division of Preventive and Behavioral Medicine, Department of Medicine, University of Massachusetts Medical School, Worcester, MA, United States

[2]Department of Community & Behavioral Health, College of Public Health, East Tennessee State University, Johnson City, TN, United States

[3]Klein Buendel, Inc., Golden, CO, United States

[4]Department of Psychology, Colorado State University, Fort Collins, CO, United States

[5]Colorado School of Public Health, Colorado State University, Fort Collins, CO, United States

Corresponding Author:
Sherry L Pagoto, PhD
Division of Preventive and Behavioral Medicine
Department of Medicine
University of Massachusetts Medical School
55 Lake Avenue North
Worcester, MA, 01655
United States
Phone: 1 508 856 2092
Fax: 1 508 856 3840
Email: Sherry.Pagoto@umassmed.edu

Abstract

Background: Indoor tanning elevates the risk for melanoma, which is now the most common cancer in US women aged 25-29. Public policies restricting access to indoor tanning by minors to reduce melanoma morbidity and mortality in teens are emerging. In the United States, the most common policy restricting indoor tanning in minors involves parents providing either written or in person consent for the minor to purchase a tanning visit. The effectiveness of this policy relies on parents being properly educated about the harms of indoor tanning to their children.

Objective: This randomized controlled trial will test the efficacy of a Facebook-delivered health communication intervention targeting mothers of teenage girls. The intervention will use health communication and behavioral modification strategies to reduce mothers' permissiveness regarding their teenage daughters' use of indoor tanning relative to an attention-control condition with the ultimate goal of reducing indoor tanning in both daughters and mothers.

Methods: The study is a 12-month randomized controlled trial comparing 2 conditions: an attention control Facebook private group where content will be relevant to teen health with 25% focused on prescription drug abuse, a topic unrelated to tanning; and the intervention condition will enter participants into a Facebook private group where 25% of the teen health content will be focused on indoor tanning. A cohort of 2000 mother-teen daughter dyads will be recruited to participate in this study. Only mothers will participate in the Facebook groups. Both mothers and daughters will complete measures at baseline, end of intervention (1-year) and 6 months post-intervention. Primary outcomes include mothers' permissiveness regarding their teenage daughters' use of indoor tanning, teenage daughters' perception of their mothers' permissiveness, and indoor tanning by both mothers and daughters.

Results: The first dyad was enrolled on March 31, 2016, and we anticipate completing this study by October 2019.

Conclusions: This trial will deliver social media content grounded in theory and will test it in a randomized design with state-of-the-art measures. This will contribute much needed insights on how to employ social media for health behavior change and disease prevention both for indoor tanning and other health risk behaviors and inform future social media efforts by public health and health care organizations.

ClinicalTrial: Clinicaltrials.gov NCT02835807; https://clinicaltrials.gov/ct2/show/NCT02835807 (Archived by WebCite at http://www.webcitation.org/6mDMICcCE).

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KEYWORDS

skin cancer; indoor tanning; melanoma; Facebook; social media; health communication

Introduction

Indoor Tanning, Melanoma, and Public Policy

Indoor tanning elevates the risk for melanoma [1,2], which is now the most common cancer in women aged 25-29 [3,4]. Reducing indoor tanning by minors can prevent ultraviolet radiation exposure, a human carcinogen in the same class as arsenic and tobacco [2] and a primary risk factor for melanoma especially at young ages [5-11]. Indoor tanning before age 40 doubles the risk of melanoma; each tanning bed use per year increases risk for melanoma by 1.8% [12,13]. The increase in melanoma is especially evident in young, non-Hispanic, white women, paralleling the rise in their indoor tanning over the same period [14]. The Centers for Disease Control's (CDC) Healthy People 2020 and Surgeon General's Call to Action to Prevent Skin Cancer [15] have set the goal of reducing the prevalence of indoor tanning by teens. Currently, 10% to 15% of teens [16-20] (mainly girls) and 8% to 14% of caregivers [17,21-24] (mainly mothers) reported indoor tanning in the past year. Despite the substantial risk, indoor tanning remains popular among older adolescent females and mothers aged 27-45 [25].

Public policies restricting access to indoor tanning by minors to reduce melanoma morbidity and mortality in teens are emerging. Policy interventions can alter risk perceptions, preferences for risky behaviors, and barriers to change [26-28]. Currently, 29 states require parental permission for minors to indoor tan. Fewer states (n=24) have adopted indoor tanning regulations with age restrictions on access to tanning facilities, with just 13 states and 1 territory banning all minors under 18, making parental-permission regulations far more common than complete bans. Policies restricting minors' access to indoor tanning will only reduce melanoma morbidity and mortality if the tanning industry complies with them [29,30]), states enforce them, and in the case of parental permission laws, parents withhold permission from teens who want to indoor tan. Unfortunately, research suggests that parental permission policies are not currently reducing rates of indoor tanning by minors [18] due to industry noncompliance, insufficient policy enforcement [29,30], and the fact that many parents fail to recognize the dangers of indoor tanning [22,31]. Exemplifying the latter, one study found 51% of mothers exhibited very little knowledge of the health consequences of indoor tanning [22]. Most (79%) also did not know that a "base tan" from a tanning bed is not protective and many (40%) were not aware that indoor tanning is potentially more harmful to teens than adults [31]. This lack of knowledge may be due to poor dissemination of information. The Food and Drug Administration provides some guidelines for exposure limits but it has only recently required facilities to post warnings on tanning beds [32-34].

Health communication that maximizes the effectiveness of indoor tanning policy, including both parental consent and bans, might activate mothers to protect their teen daughters from the harms. The current study fills this gap in the literature by testing a social media–delivered intervention developed to educate mothers and urge them to withhold permission for daughters to indoor tan. Mothers are an important target because their permissiveness and tanning behavior are strong predictors of daughters' indoor tanning [18,22,31]. For instance, past-year indoor tanning rates are as high as 30% to 55% in teens whose mothers tan indoors [18,22,31]. Teen girls often report initiating indoor tanning with their mothers [35]. Further, girls whose first indoor tanning experience is with their mothers begin at an earlier age, become more habitual tanners, and are more resistant to change [35]. Recent research indicates that well-crafted communication can reduce maternal permissiveness about indoor tanning [36], but such communication has not been tested as a strategy specifically for maximizing indoor tanning policies. This trial leverages both health communication and behavioral strategies to improve the impact of public health policy. A social media campaign for mothers has the potential to reduce not only the prevalence of indoor tanning in adolescent girls but also the incidence of melanoma in young women. If effective, it could also easily and inexpensively be delivered by cancer-related public health organizations, many of which have social media feeds.

The present paper describes the design and methods of a randomized controlled trial of a Facebook-delivered health communication intervention to reduce mothers' permissiveness regarding their teenage daughters' use of indoor tanning, reduce their teenage daughters' perception of their mothers' permissiveness, and reduce indoor tanning by both mothers and daughters.

Hypotheses

The primary hypothesis is that the intervention will significantly reduce mothers' permissiveness regarding their daughters' indoor tanning, their daughters' perception of maternal permissiveness toward indoor tanning, and both mothers' and daughters' indoor tanning relative to the control condition. The secondary hypothesis is that a significantly greater number of mothers will support a ban on indoor tanning for minors in the intervention group compared with the control condition.

Methods

Pilot Data

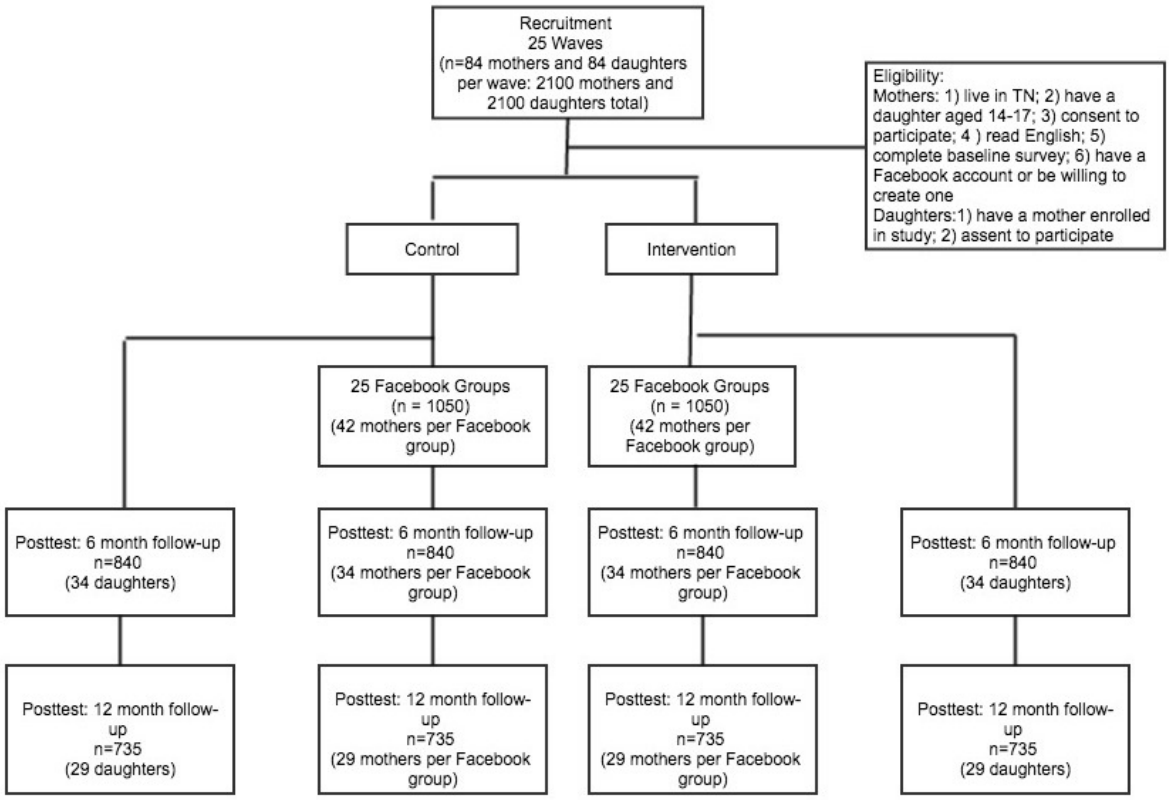
Pilot interviews were conducted with 19 mothers of teenage daughters. Interviews included opinions of indoor tanning, indoor tanning policy, and health topic concerns as they relate to their daughters. Overall, 84% (16/19) were concerned about their daughters going indoor tanning, however 32% (6/19) would allow it. Most (16/19, 84%) would sign a petition supporting an indoor tanning ban for minors. Obesity and sexual activity were the greatest health concerns for daughters (both: 5/19, 31%), followed by drug and alcohol use (4/19, 26%), exercise (3/19, 16%), nutrition (3/19, 16%), mental health (3/19, 16%), cancer (2/19, 11%), and sleep (1/19, 5%). Most (15/19, 79%)

mothers reported that they get health information from the Internet. This pilot study confirmed that many mothers would benefit from messages about the harms of allowing their daughters to indoor tan. It also helped us identify health topics of high interest to mothers.

Study Design

The study design is a randomized controlled trial comparing 2 conditions over 1 year (Figure 1). Participants will be recruited in waves of approximately 84 and then randomized into the intervention or control condition. We continue in this way until a total of 25 waves have been enrolled, producing 25 groups in the intervention condition and 25 groups in the control condition each with approximately 42 participants. Participants will be blinded to condition and assessment points will occur at baseline, end of intervention (1-year), and 6 months postintervention.

Figure 1. Study design.



Intervention Condition

In the intervention condition, participants will enter a private Facebook group that posts a feed of health messages in which 25% are focused on preventing indoor tanning and 75% are focused on other health topics (eg, nutrition, physical activity, etc). Indoor tanning increases in December, peaking in March for seasonal tanners (eg, event and regular seasonal tanners) [37,38]. During these months, indoor tanning posts will be scheduled at a higher frequency (30% of posts).

Control Condition

In the control condition, participants will enter a private Facebook group that posts a feed of health messages in which 25% are focused on preventing prescription drug abuse and 75% are focused on the same health topics as the intervention condition. We selected prescription drug abuse as our "control" content, because (1) it is completely unrelated to tanning, thus not likely to impact our primary outcomes, and (2) it is an emerging issue of great interest and relevance to young adults in east Tennessee. This 25% segment of posts is the only difference between the intervention and control conditions.

Setting

The study is being conducted in east Tennessee given that Tennessee has a parental permission law for indoor tanning and a high prevalence of indoor tanning, with 31% of adolescent girls reporting indoor tanning in a recent study [39]). Tennessee's indoor tanning policy (Tennessee Code Ann. § 68-117-104) requires that children under the age of 14 be accompanied by a parent if they use a commercial tanning facility and those ages 14 to 17 must have parents visit the tanning facility to sign a permission form in-person. The form only needs to be signed once at each facility. Communities in the region are diverse in size and rural/urban context and 84% of the public school population is white, the racial group most likely to indoor tan and at highest risk for melanoma [40].

Participants

A cohort of 2000 mother-teen daughter dyads will be recruited to participate in this study. Only mothers and daughters will be recruited because female teens are nearly 4 times more likely to indoor tan (23% in 2009-2011 Youth Risk Behavior Survey) than male teens (6% [41]) and evidence suggests maternal permissiveness is a predictor of indoor tanning. The literature

on indoor tanning by male teens is nascent with minimal data on predictors or effective intervention strategies.

Eligible mothers will meet the following criteria: (1) live in Tennessee, (2) have a daughter aged 14 to 17, (3) consent to participate, (4) read English, (5) complete the baseline survey, and (6) have a Facebook account (or be willing to create one). History of indoor tanning is not required for inclusion. Because public policy requires broad public support not just support by those most affected, ethnic minority mothers who are interested in participating (mainly African Americans; 14% are minority, 86% are non-Hispanic white) will be enrolled. The planned sample size was increased to ensure that statistical power is based on the number of non-Hispanic, white mothers. This approach will also allow for an evaluation of how the intervention affects ethnic minority mothers' support for indoor tanning bans.

Eligibility criteria for teen daughters include having a mother enrolled in the study and assenting to participate. Daughters will be enrolled regardless of their indoor tanning behavior and the sample will be inflated to insure adequate numbers of non-Hispanic whites. Daughters will be enrolled only to complete assessments. They will not have access to the Facebook group. If a mother has more than one eligible daughter, she will provide information for the one with the nearest birthday, as instructed on the enrollment website.

Sample Size and Power Calculations

Using public high school enrollment data, we estimate that approximately 20,000 eligible mothers and 25,000 eligible daughters reside in the east Tennessee region. Effect sizes for similar previous studies are in the range of moderate to large for our primary and secondary outcomes (mothers' permissiveness and indoor tanning behavior, respectively). For example, Baker et al [42] found that mothers' permissiveness and daughters' perceptions of indoor tanning declined following a 1-month intervention at an immediate posttest (mother: baseline mean 2.59 [SD 1.03], follow-up mean 2.47 [SD 0.86]; daughter: baseline mean 3.12 [SD 1.32], follow-up mean 2.74 [SD 1.1]) compared with controls (mother: baseline mean 3.02 [SD 1.08], follow-up mean 2.98 [SD 1.10]; daughter: baseline mean 3.12 [SD 1.24], follow-up mean 3.40 [SD 1.04]). Likewise, for indoor tanning behavior, Hillhouse et al [43] found the number of sessions in the past 3 months among indoor tanners was reduced in an intervention condition at 6 months (baseline mean 4.67 [SD 0.60], follow-up mean 6.80 [SD 0.93]) compared with controls (baseline mean 4.48 [SD 0.55], follow-up mean 10.90 [SD 0.93]). The frequency of indoor tanning observed in the proposed study will likely be lower, because not all mothers and daughters will indoor tan (31% of adolescent girls indoor tanned in a recent study in east Tennessee; indoor tanning is higher in rural areas [44]). Still, the effect size between conditions is expected to remain moderate to large.

We used the Optimal Design software package (version 3.0) [45] to determine sample size. Assuming a 2-tailed alpha of 0.05, a moderate effect size of d=0.50, and an intraclass correlation of 0.05 within each Facebook private group, we far exceed a power of 0.80 with 50 Facebook private groups each consisting of 25 mothers (total n=1250 mothers and 1250 daughters). We increased this sample size to account for the proportion of minority mothers and daughters (15%) we expect to recruit to achieve the needed sample size of non-Hispanic whites, the racial/ethnic group most likely to indoor tan and with the highest rates of melanoma [40]. We further inflated the sample to account for an expected loss to follow-up of 30% by 12 months (20% at 6 months). Thus, we will recruit initial samples of 2100 mothers and 2100 daughters (42/Facebook group) at baseline and expect to successfully assess 1680 in each sample (approximately 34/Facebook group) at the 6-month follow-up and 1470 in each sample (approximately 29/Facebook group) at the 12-month follow-up, with the final samples containing 1250 non-Hispanic white mothers and 1250 non-Hispanic white daughters for analysis.

Recruitment

Mother-daughter dyads will be recruited across 40 counties in east Tennessee using two primary strategies: (1) Coordinated School Health (CSH) Coordinators in each school system will provide access to mothers and daughters in high schools, and (2) study staff will recruit mothers and daughters through partnerships with community-based organizations (eg, churches, sports leagues, clubs, health clinics, etc). A local Expert Advisory Board, made up of regional CSH Coordinators, public health educators, and maternal and child health professionals is providing insight into effective community-based recruitment. CSH, which is housed in the Tennessee Department of Education, has the mission of working with schools and parents to improve children's health, making them a natural partner in this effort. CSH Coordinators are asked to send study invitations to mothers through their normal channels (eg, back-to-school packets, flyers with report cards, email, newsletters, etc). Access to families through schools can be challenging, but partnering with CSH ensures we will not interfere with time, curricular, and other constraints. Schools that assist with mother-daughter recruitment will receive a US $200 mini-grant for CSH-related program materials. At the same time, study staff will systematically canvass communities across the region, beginning in the far northeast corner of the state and working their way south and west to partner with local organizations, media outlets, and employers to advertise the study to mothers and teen daughters in the region. We chose multiple recruitment methods based on our past experience recruiting women and adolescent girls in this hard-to-reach population [46]. CSH Coordinators and community-based organizations often have direct access to mothers of high school students and can serve as credible recruiters. For eligible participants, we expect a refusal rate of 30%, based on our previous experiences in this population [46].

Mothers are the target of recruitment efforts and must enroll in the trial first and then provide permission for their daughters to participate along with their daughters' contact information. Interested mothers will sign up for the trial by visiting a study website where information is provided along with a screener that asks if they have a daughter ages 14-17 in the home, if they are a Tennessee resident, and if they have or are willing to have a Facebook account. Eligible mothers are sent to the consent and baseline survey.

When a mother completes the baseline survey, the enrollment website will send invitations to the daughter to assent and complete her own baseline survey. These invitations will be sent by email with up to 5 weekly reminders. Mothers remain eligible and enrolled in the study even if daughters do not provide assent; in such cases, daughters' missing responses will be imputed.

Intervention

Conceptual Framework

The intervention, named *Health Chat*, will be delivered in a private Facebook group. It was designed using an integrated conceptual framework combining 3 complementary theories of social and individual change to guide the intervention social media posts and attempts to generate user engagement in the Facebook groups. Content of the social media posts from the social media intervention were designed based on principles of social cognitive theory (SCT) [47,48] and transportation theory (TT) [49,50]. From SCT, the posts were written to address the social situation (increasing perceived social norms to not indoor tan or give permission for daughter to tan), behavioral capability (knowledge of the risks of indoor tanning and skills to refuse indoor tanning requests and invitations), expectations (belief that indoor tanning increases risk for melanoma), observational learning (in stories from real mom's about the dangers of letting their daughters indoor tan, including about daughters who developed melanoma as young adults), self-efficacy to avoid indoor tanning (suggestions for how to have daughter refuse indoor tanning invitations), and interest in alternatives to indoor tanning (such as using sunless tanners or going with friends for spa treatments rather than indoor tanning). A key tenet was that the intervention needs to provide parents skills for communicating with their teens (ie, active listening, self-disclosure, showing empathy, and managing conflict), not just information on the risks of indoor tanning. From TT, a number of intervention posts contained links to news stories or stories provided by public health organizations from mothers and daughters about the risks of indoor tanning and their wish they had not given permission to indoor tan or avoided indoor tanning. These stories should be very effective at influencing individuals to alter their behaviors [51] because (1) people transported into a narrative world will alter their beliefs based on information, claims, or events depicted [52], (2) individuals identify with characters in a story, and identification increases the likelihood of social influence [53,54], and (3) narratives shift normative beliefs about risks [55-62]. To test our theoretical framework, all intervention messages are classified in 3 ways: (1) narrative versus didactic, (2) social norms–based versus not, and (3) appearance- versus health risk–based. Secondary analysis will probe which type of messages drive the most engagement among participants.

TT and diffusion of innovations theory (DIT) [63] were used to explain importance of soliciting user engagement from the mothers in the social media intervention, in the form of comments, shares, and likes. These theories guided our plan to encourage user-generated content and discussion on Facebook to capitalize on the interpersonal and interpretive processes in social networks that can produce sustained changes in health beliefs and behaviors. For instance, in social media, user-generated content such as testimonials and comments from other mothers, especially those phrased as stories, may be more powerful than conventional persuasive messages in posts alone, according to TT [51]. Likewise, DIT [63] explains how comments, shares, and likes from users in the social media should increase dissemination and impact of the intervention posts. It holds that social influence occurs through a process of delivering both carefully crafted messages and diffusion of these messages by community members, especially opinion leaders. The intervention will continually invite mothers to provide comments, shares, and likes in the hopes that opinion leaders will emerge in each of the Facebook groups. These opinion leaders should stimulate collective action among the mothers because people depend on them for information, especially about issues that carry risk and produce uncertainty [64-66], which opinion leaders deliver through their central position in a social group and links to outside information sources [63]. The information shared among mothers in the Facebook groups should breed collective action, as mothers interpret and respond to it through social comparison [63,67-69]. Mothers are expected to routinely compare themselves with other social network members [70] and conform with these peers to avoid uncertainty that arises when attitudes and behavior deviate [71]. In the process, they perceive themselves in abstract social categories and roles (eg, female, friend, mother, white, healthy person), which become part of their collective identity in the group, stabilizing behavior changes [67,68]. User engagement will be assessed in the form of number of posts, comments, likes, and views in the *Health Chat* program to test its influence on intervention outcomes.

Content

All participants will be invited to private Facebook groups to participate in the *Health Chat* program. The privacy setting in these groups is set to "secret" to prevent members and content of the group being visible to the public, including other Facebook users. Members of a private group with a "secret" privacy setting can only see information in each other's profiles as indicated by their personal privacy settings. Members must also be invited to the group by the group administrator who will be a study staff member. The content of *Health Chat* is tailored to mothers and although only mothers will be in the Facebook groups, they will be encouraged to share content with their daughters. Posts will occur twice daily for 12 months for a total of 720 posts. Mothers will be encouraged to contribute their own content to the Facebook group via comments, original posts to share opinions or pose questions, and participation in group activities. Each group will be hosted by a community manager who will oversee the editorial calendar, maintain the feed, stimulate engagement, and monitor the broader media environment to discover trending topics and new research findings to post.

Our preliminary focus groups of mothers and key informant interviews of CSH coordinators revealed greater interest in a Facebook group focused broadly on health as opposed to a single topic like indoor tanning. For this reason, the *Health Chat* program will address health topics identified as of high interest by our focus group participants and CSH coordinators. These

topics include healthy lifestyle, mental health, mother-daughter communication, and substance use. An advisory board of experts on these health topics provided evidence-based protocols and resources, which were then converted to Facebook posts by our team. In the *Health Chat* feed, 80% of posts were developed in advance based on evidence-based interventions and resources while 20% of posts will be pulled from emerging research and current events (eg, news reports of new tanning legislation, public service announcements about the health topic) relevant to the health topics.

Indoor Tanning Content

Indoor tanning content was developed by the investigators and a social media marketing expert using information from published literature on risk factors, evidence-based intervention content from published trials targeting indoor tanning [43,46,72-75], public health campaigns from major nonprofit organizations (eg, CDC, Skin Cancer Foundation, etc), and investigator-developed, video-recorded interviews of local mothers and professionals about the risks of indoor tanning, experiences with skin cancer, and mother-daughter communication role modeling.

Facebook posts on indoor tanning are intended to achieve the following: (1) increase awareness of state policy on indoor tanning by minors and teen interest in indoor tanning, (2) improve knowledge of indoor tanning risks, including skin damage (wrinkling/aging) and cancer, (3) teach mothers skills and improve self-efficacy for resisting daughters' requests to indoor tan (eg, starting conversations, addressing sensitive topics, and managing conflict), (4) convey the importance of modeling tanning avoidance to daughters, (5) increase understanding of the reasons why adolescent girls indoor tan (eg, for stress reduction, self-medication of seasonal affect disorder, peer pressure, etc), (6) highlight behavioral alternatives to indoor tanning for adolescents (eg, sunless tanning, yoga, exercise, manicures/pedicures, and other spa treatments that enhance appearance, body image, and stress coping skills), (7) promote behavioral alternatives [72], and (8) give advice to avoid sun tanning and practice sun protection (ie, wear protective clothing, hat, and eyewear; seek shade; avoid midday sun; apply/reapply sunscreen with SPF 15+) grounded in SCT. Each message was designed according to our theoretical framework to ensure messages are balanced across (1) didactic versus narrative, (2) social norms based versus not, and (3) appearance- versus health risk-based messages. Once messages were developed, the entire investigative team reviewed the messages and made edits according to consensus. To evaluate the acceptability and readability of messages, focus groups were conducted with mothers of teenage daughters who viewed the messages in a private Facebook group for 1 week. Focus group participants rated each message on clarity, aesthetics, negative versus positive valence, interest, credibility, similarity to typical social media posts, and likelihood they "like," comment, or share the post. Messages were then refined based on feedback.

Control Condition

The East Tennessee State University Center for Prescription Drug Abuse/Misuse was consulted for content on opiate drug abuse. Relevant content from their website, as well as the Tennessee State Government [76], Kids Health [77], and National Institute on Drug Abuse for Teens websites [78], were converted into intervention posts.

Measures

The primary outcomes are mothers' permissiveness for daughters' indoor tanning, mother and daughter indoor tanning behavior, and mothers' support for stricter bans on indoor tannings in minors. Engagement with the *Health Chat* program and potential moderators and mediators of campaign effectiveness will also be assessed.

Primary Outcomes

Mothers' permissiveness for daughters to tan indoors will be assessed using 4 Likert-type items (1=strongly disagree, 5=strongly agree) assessing permissiveness toward their teenage daughters' indoor tanning [79]. Example items include, "I would allow my daughter to indoor tan," and "I think it's OK for my daughter to indoor tan" (Cronbach alpha=.97). Daughters will be asked the same 4 items to assess their perceptions of mothers' permissiveness (Cronbach alpha=.95) [46]. Maternal permissiveness will be assessed at baseline and both follow-ups by the combined average ratings across the 6 items.

Indoor tanning behavior will be assessed by asking mothers and daughters to report on their indoor tanning over the last year using a single open-ended item (ie, "How many times in the past year have you used a tanning bed or booth?") [80] Similar measures had strong positive correlations with diary measures of indoor tanning behavior (r=.77-.86, P<.001) in previous work [81,82]. Intention to indoor tan will also be assessed (ie, How likely is it that you will indoor tan in the next 3/6/12 months; 7-point Likert response scale), along with intention to get a sunless tan (eg, self-tanners, spray tans) in the next 12 months. We also will include an item specific to the months of December-March to capture indoor tanning during the seasonally high months of indoor tanning use. Indoor tanning behavior and intentions will be assessed at baseline and both follow-ups.

Support for strengthening bans on indoor tanning by minors will be measured via the Web server, which will record whether mothers who click on the link to "sign" the petition to strengthen the ban on indoor tanning and forward it to their legislator. At the final follow-up, mothers will be asked how much they support bans on indoor tanning by minors and about their reasons for either signing or not signing the petition.

Other Health Behaviors

Nineteen questions were included in the surveys to assess the other health behaviors addressed in the social media program. Participants rated their overall health status as excellent to poor. They described their diet by reporting the number of servings of fruits and of vegetables eaten each day and the number of times they drank regular soda or pop that contained sugar or sugar sweetened drinks (not 100% fruit juice or diet/artificially sweetened) in the past 30 days. Body mass index was calculated by asking for height (in inches) and weight (in pounds). Participants also described their regular physical activity, indicating how many times they engaged in vigorous and in light or moderate activities for at least 10 minutes per week.

Alcoholic beverage intake was assessed by both number of days consuming at least 1 alcoholic drink in the past 30 days and number of times 4 or more alcoholic drinks were consumed in a row (binging) in the past 2 weeks was reported, along with smoking behavior (ie, smoking history; smoked at least 100 cigarettes in their lifetime) and current smoking (currently smoke every day, some days, or not at all). Mental health was assessed by asking how many days in the past 30 days was their mental health not good and disability was measured as the number of days in the past 30 days when poor physical or mental health kept them from doing their usual activities. Compliance with human papillomavirus (HPV) vaccination advice was assessed by asking if the daughter had been vaccinated and if so how many shots she received. Finally, 2 items measured abuse of prescription drugs: have you ever or in the past 6 months used a drug that was not prescribed for you or that you took only for the experience or feeling it caused even once?

Engagement

Mothers' engagement (ie, number of posts, comments, likes, and views with the *Health Chat* program) will be extracted from the Facebook page using a computer program.

Maternal communication will be assessed using 8 items asking mothers if they have talked to their daughters about indoor tanning in the past year. For example, "Within the past year, I have talked with my daughter about the importance of not being pressured to go to the tanning bed to fit in." Response options will include "yes," "no," and "I prefer not to answer." Mother-daughter relationship quality will be assessed using 2 Likert-type items (1=strongly disagree, 5=strongly agree): "I let my daughter make her own decisions," and "Overall, I am satisfied with the way my daughter and I communicate." Daughters will be asked the same 2 items to assess their perceptions of relationship quality. At the end of intervention follow-up (1-year), mothers will also be asked about how they shared information from the Facebook group with their daughter (eg, showed daughter a post in the private group).

Analysis Plan

Hypotheses will be tested using a multilevel (mother-daughter dyad nested in Facebook private group) structural equation model (SEM). The following specific tests within the multilevel SEM will be used to evaluate the primary hypotheses in order to examine the effects of the social media campaign on indoor tanning outcomes. For the hypothesis regarding mothers' permissiveness for daughters to indoor tan, mothers' permissiveness (a level 1 variable) will be specified as a multiple indicator latent construct and regressed on the treatment indicator (campaign with prescription drug messages (control) vs campaign with indoor tanning messages (intervention), a level 2 variable). Similarly, for the hypothesis regarding daughters' perceptions of mothers' permissiveness, daughters' perceptions (a level 1 variable), a multiple indicator latent construct, will be regressed on the treatment indicator (a level 2 variable). Mother and daughter perceptions will be correlated. In testing the hypothesis relating to indoor tanning frequency, mothers' and daughters' tanning (level 1 variables) will be specified as a count of the number of tanning sessions (in the past 3 months) and regressed on the treatment indicators (a level 2 variable), using a zero-inflated negative binomial distribution (which simultaneously models the effect of the intervention on the prevalence and frequency (among tanners) of tanning sessions). Mother and daughter behavior will be correlated. Finally, the hypothesis relating to mothers' support for IT bans will be tested by regressing mothers' signatures on the Web-based petitions (a level 1 binary variable—signed or not signed) on the treatment indicator (a level 2 variable) in a multilevel SEM.

Moderators

Differential effects of treatment on the outcomes associated with characteristics of the mothers and daughters (ie, demographics, political ideology, skin cancer history, and skin phenotype [83]) and their relationship (maternal communication and relationship quality [84-86]) will be tested using multiple group SEM (for categorical characteristics) and a treatment by characteristic interaction term (for continuous characteristics). All moderators will be level 1 variables. Tests of moderation will be built on top of the multilevel models with latent variables described above. A Holm-Bonferroni correction will be applied to adjust for multiple exploratory tests. These effects, tested in secondary analyses, will need to be large in order for a significant effect to be detected.

Mediators

Theorized mediators (ie, indoor tanning intentions, attitudes toward indoor tanning [73,87-89], conditional perceived susceptibility to skin damage [90], self-efficacy to resistant indoor requests, and mother-daughter indoor tanning–specific communication) and campaign engagement (level 1 variables) from the 6-month follow-up will be regressed on the treatment indicator (a level 2 variable) in a multilevel SEM. If treatment effects on mediators emerge, a full multilevel SEM with direct and indirect effects on the primary outcomes of IT permissiveness and behavior will be assessed using a causal mediation framework [91,92]. A bootstrap resampling procedure will be used to construct 95% confidence intervals around each indirect effect estimate [93,94].

Seasonality Issues

In order to account for the issue of seasonality (ie, that indoor tanning is more common during certain times of the year), we will measure indoor tanning at each follow-up, asking specifically about tanning during the months of December-March. We will also include date of measurement as a covariate. We will control for month of assessment and number of months that have elapsed since baseline. In addition, the treatment and control group, randomized together, will be surveyed at precisely the same times to ensure equivalency.

Results

The first wave of the intervention began in September 2016. We anticipate on continuing recruitment through October 2018 and completing this study by October 2019. Results will be examined at that time.

Discussion

Mothers as a Key Intervention Target

The proposed research will fill 2 gaps in the existing literature by (1) decreasing mothers' permissiveness to allow their daughters to tan so as to maximize public policy on indoor tanning, and (2) using social media to deliver a health communication campaign targeting mothers. Past research on indoor tanning policy has examined industry compliance and policy impact on mothers and daughters [29,30,95-109], but has not evaluated health communication interventions to maximize the impact of indoor tanning policy. Studies of policy interventions on sun safety of youth in general are rare, limited to a few studies on policy adoption by US and Australian schools [110,111] (including a successful intervention by our team [112]) and recreation centers [113,114].

Advantages of Social Media as Intervention Modality

Social media has revolutionized communications and offers several advantages for an indoor tanning campaign. Social media can reach many across the United States, including mothers [115], because most US adults use the Internet and social media [115]. Use is especially high by women (72% are on Facebook, 25% on Pinterest, 16% on Instagram, and 15% on Twitter) [115]. Further, most US adults (80%) use the Internet to retrieve health information [116] because it is low-cost, available 24/7, private [117], can be personalized, and enhances social connections [118]. At least 20% of women aged 25-44 use social media to post about their health and share health videos/images [119-121]. Social media users create and share content that provides opportunity for information dissemination, social norm change, and broad impact [122,123]. Health is a popular topic on social media as indicated by the formation of patient communities and health-related hashtags [119-122,124]. A 2011 survey found that 34% of Internet users had read a commentary or experience about health/medical issues on a website or blog [125]. Social media can also stimulate collective action [112,126]. Social media has been at the forefront of large collective political actions, including oppositional movements in Egypt, Occupy Wall Street, the Tea Party [127], and the Obama presidential campaign (which had 32 million Facebook friends, 22 million Twitter followers [128], and 300 million YouTube views [129], and digitally raised US $525 million) [127]. Social media can also heighten awareness, frame issues, develop/expand networks, and motivate Web-based and offline collective actions (eg, writing letters, organizing meet-ups, attending hearings/events, registering to vote, and sharing information [112,126,130-132]). For example, an organ donor registration effort by Facebook in 2012, yielded 13,054 new registrations in its first day (21.1 times more than an average day) [133]. The proposed indoor tanning social media campaign is intended to change attitudes about indoor tanning and ultimately, elevate support for stricter, more effective bans on minors' access to indoor tanning facilities. Currently, very few studies have been published on social media in public health campaigns, so the proposed project will also fulfill calls by National Institutes of Health for research to identify best practices for using social media and Web 2.0 technologies in health behavior interventions. Social media interventions are not without limitations. One challenge is that frequency of social media use varies across individuals with some people logging in several times per day and others logging in once per week or less. Nonusers and infrequent users may be less likely to benefit from social media–delivered interventions, unless they are convinced to engage. In the present study, we will conduct a year-long campaign of twice daily posts to provide numerous opportunities for participants to see the content. We will also employ social media marketing strategies to encourage engagement. We will also study engagement patterns by user characteristics to inform the nascent, but much needed literature on engagement in social media interventions [134].

Many federal and state agencies, nonprofits, and health care providers already use social media extensively to disseminate information [135,136] (eg, National Institute on Drug Abuse, CDC, and Environmental Protection Agency), and also use generated video contests to reach young people on immunization [137], tobacco [138], organ donation [139], and HPV vaccine [137,140]. The indoor tanning industry also actively markets its services on social media [141]. Thus, the results of this trial will deliver social media content grounded in theory, and test it in a randomized design with state-of-the-art measures. Also, they will contribute much needed insights on how to employ social media for health behavior change and disease prevention both for indoor tanning and other health risk behaviors and inform future social media efforts by public health and health care organizations.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Summary sheets from grant review.

[PDF File (Adobe PDF File), 128KB - resprot_v5i4e228_app1.PDF]

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Abbreviations

CDC: Centers for Disease Control
FDA: Food and Drug Administration
CSH: coordinated school health
DIT: diffusion of innovations theory
HPV: human papillomavirus
SCT: social cognitive theory
SEM: structural equation model
TT: transportation theory

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Protocol

Substitution of Usual Perioperative Care by eHealth to Enhance Postoperative Recovery in Patients Undergoing General Surgical or Gynecological Procedures: Study Protocol of a Randomized Controlled Trial

Eva van der Meij[1,2], MD; Judith AF Huirne[1,2], MD, PhD; Esther VA Bouwsma[1,2,3], MD; Johanna M van Dongen[4], PhD; Caroline B Terwee[5], PhD; Peter M van de Ven[5], PhD; Chantal M den Bakker[1,6], MD; Suzan van der Meij[7], MD; W Marchien van Baal[8], MD, PhD; Wouter KG Leclercq[9], MD; Peggy MAJ Geomini[10], MD, PhD; Esther CJ Consten[11], MD, PhD; Steven E Schraffordt Koops[12], MD, PhD; Paul JM van Kesteren[3], MD, PhD; Hein BAC Stockmann[13], MD, PhD; A Dorien ten Cate[14], MD; Paul HP Davids[15], MD, PhD; Petrus C Scholten[16], MD, PhD; Baukje van den Heuvel[17], MD, PhD; Frederieke G Schaafsma[1], MD, PhD; Wilhelmus JHJ Meijerink[6], MD, PhD; H Jaap Bonjer[6], MD, PhD; Johannes R Anema[1], MD, PhD

[1]EMGO+ Institute for Health and Care Research, Department of Public and Occupational Health, VU University Medical Center, Amsterdam, Netherlands

[2]Department of Obstetrics and Gynaecology, VU University Medical Center, Amsterdam, Netherlands

[3]Department of Obstetrics and Gynaecology, Onze Lieve Vrouwe Gasthuis, Lokatie Oost, Amsterdam, Netherlands

[4]EMGO+ Institute for Health and Care Research, Department of Health Sciences, Vrije Universiteit, Faculty of Earth and Life Sciences, Amsterdam, Netherlands

[5]EMGO+ Institute for Health and Care Research, Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, Netherlands

[6]Department of Surgery, VU University Medical Center, Amsterdam, Netherlands

[7]Department of Surgery, Flevo Ziekenhuis, Almere, Netherlands

[8]Department of Obstetrics and Gynaecology, Flevo Ziekenhuis, Almere, Netherlands

[9]Department of Surgery, Maxima Medisch Centrum, Veldhoven, Netherlands

[10]Department of Obstetrics and Gynaecology, Maxima Medisch Centrum, Veldhoven, Netherlands

[11]Department of Surgery, Meander Medisch Centrum, Amersfoort, Netherlands

[12]Department of Obstetrics and Gynaecology, Meander Medisch Centrum, Amersfoort, Netherlands

[13]Department of Surgery, Spaarne Gasthuis, Haarlem, Netherlands

[14]Department of Obstetrics and Gynaecology, Spaarne Gasthuis, Haarlem, Netherlands

[15]Department of Surgery, Diakonessenhuis, Utrecht, Netherlands

[16]Department of Obstetrics and Gynaecology, Diakonessenhuis, Utrecht, Netherlands

[17]Department of Surgery, Jeroen Bosch Ziekenhuis, Den Bosch, Netherlands

Corresponding Author:
Eva van der Meij, MD
EMGO+ Institute for Health and Care Research
Department of Public and Occupational Health
VU University Medical Center
Van der Boechorststraat 7
Room B-555
Amsterdam
Netherlands
Phone: 31 20444 57 03
Fax: 31 20444 83 87
Email: ev.vandermeij@vumc.nl

Abstract

Background: Due to the strong reduction in the length of hospital stays in the last decade, the period of in-hospital postoperative care is limited. After discharge from the hospital, guidance and monitoring on recovery and resumption of (work) activities are usually not provided. As a consequence, return to normal activities and work after surgery is hampered, leading to a lower quality of life and higher costs due to productivity loss and increased health care consumption.

Objective: With this study we aim to evaluate whether an eHealth care program can improve perioperative health care in patients undergoing commonly applied abdominal surgical procedures, leading to accelerated recovery and to a reduction in costs in comparison to usual care.

Methods: This is a multicenter randomized, single-blinded, controlled trial. At least 308 patients between 18 and 75 years old who are on the waiting list for a laparoscopic cholecystectomy, inguinal hernia surgery, or laparoscopic adnexal surgery for a benign indication will be included. Patients will be randomized to an intervention or control group. The intervention group will have access to an innovative, perioperative eHealth care program. This intervention program consists of a website, mobile phone app, and activity tracker. It aims to improve patient self-management and empowerment by providing guidance to patients in the weeks before and after surgery. The control group will receive usual care and will have access to a nonintervention (standard) website consisting of the digital information brochure about the surgical procedure being performed. Patients are asked to complete questionnaires at 5 moments during the first 6 months after surgery. The primary outcome measure is time to return to normal activities based on a patient-specific set of 8 activities selected from the Patient-Reported Outcomes Measurement Information System (PROMIS) physical functioning item bank version 1.2. Secondary outcomes include social participation, self-rated health, duration of return to work, physical activity, length of recovery, pain intensity, and patient satisfaction. In addition, an economic evaluation alongside this randomized controlled trial will be performed from the societal and health care perspective. All statistical analyses will be conducted according to the intention-to-treat principle.

Results: The enrollment of patients started in September 2015. The follow-up period will be completed in February 2017. Data cleaning and analyses have not begun as of the time this article was submitted.

Conclusions: We hypothesize that patients receiving the intervention program will resume their normal activities sooner than patients in the control group and costs will be lower.

ClinicalTrial: Netherlands Trial Registry NTC4699; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4699 (Archived by WebCite at http://www.webcitation.org/6mcCBZmwy)

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KEYWORDS

eHealth; mHealth; inguinal hernia surgery; cholecystectomy; adnexal surgery; perioperative care; convalescence; return to normal activities; cost-effectiveness; economic evaluation

Introduction

Between 1993 and 2013 the number of surgical procedures per year at community hospitals in the United States increased by 16.5% to more than 26 million per year [1]. This is partly due to the growing trend in day care surgery (ambulatory surgery). This is illustrated by the fact that in 2013 the number of surgeries performed in day care (17.4 million, 65.6%) exceeded the number of surgeries performed in overnight stay (9.1 million, 34.4%) [1]. Due to the strong reduction in the length of hospital stay, perioperative in-hospital care has been reduced accordingly. Once patients have been discharged, the degree of guidance and monitoring on recovery is limited, and sometimes conflicting advice is given by the different health care providers involved in the recovery process [2-5]. In addition, patients do not always know who to contact for support in case of postoperative complaints. This poor guidance and transition of perioperative care after hospital discharge contributes to patient uncertainties and postoperative fear that may hamper their recovery [6,7]. As a consequence, return to normal activities, including work, after surgery takes much longer than expected [8,9]. The delayed recovery has a negative impact on quality of life, clinical outcomes, and medical consumption and increases the risk of work disability, leading to an increased risk of mental health problems and poor general health [10,11]. In terms of the burden on society, this increases costs: costs resulting from the increased medical consumption (direct costs) and costs in relation to the high productivity loss due to prolonged sick leave (indirect costs) [10].

Therefore, improving the quality of perioperative care may contribute to accelerated recovery and health care efficiency, which in turn may reduce health care costs. eHealth seems to be an effective tool in this process for several reasons. First, electronic devices are widely available and are increasingly popular. This means that patients can be easily reached using this medium. Second, there is an increasing demand for self-management in society; eHealth has the potential to motivate people and turn them into more active and effective managers of their own health [12,13]. Finally, eHealth is a useful tool to provide the patients with tailored information, by providing only advice based on the patient's profile. Therefore an eHealth care program has been developed to improve perioperative care after gynecological surgery [14]. The program was developed using an intervention mapping protocol, based on a systemic review of the literature, input of patients during focus groups, and consented guidelines on resumption of activities after surgery achieved after a Delphi procedure [14,15]. The effect of the eHealth care program on return to work was evaluated in a randomized controlled trial (RCT).

Patients who had access to the care program returned to work 9 days earlier than patients from the control group [16]. Because of these promising results, the care program was further developed for a broader population, according to the wishes and preferences of a sample of patients who had undergone various types of abdominal surgery. While the gynecological care program aimed to deliver additional care by providing extra support and information through eHealth, this adapted care program also aims to partly substitute perioperative care with eHealth. In addition, the care program will focus on health-behavior change techniques using an activity tracker, which has been described before as an effective strategy [17,18]. With this multicenter, single-blinded, RCT, we will evaluate whether this adapted perioperative eHealth program will be effective and cost effective as compared to usual care on the resumption of normal activities in patients undergoing commonly applied minor abdominal surgical procedures with a short duration of hospital stay.

Methods

Study Setting

Patients will be included from the surgical and gynecological departments of 7 teaching hospitals in the Netherlands. The trial was conducted in accordance with the Standard Protocol Items: Recommendations for Interventional Trials and reported in accordance with the Consolidated Standards of Reporting Trials [19-21]. The study was approved by the local medical ethics committee under registration number 2014.301 and by the institutional review boards of all participating hospitals. The study is registered at the Netherlands Trial Registry (NTR4699).

Eligibility Criteria

Eligible patients for this study are adults from 18 to 75 years old who are on the waiting list for one of the following commonly applied minor surgical procedures: laparoscopic cholecystectomy, open or laparoscopic inguinal hernia surgery, or laparoscopic adnexal surgery. Participants meeting any of the exclusion criteria will not be considered (Textbox 1).

Textbox 1. Exclusion criteria.

Exclusion criteria:

- Surgery without a curative intention or with additional radio- or chemotherapy
- Deep infiltrating endometriosis
- Ectopic pregnancy
- Adnexal surgery because of pelvic inflammatory disease or tubal ovarian abscess
- Combination of several surgical procedures
- Severe comorbidity which might complicate the postoperative course
- Patient who are unable to understand the information from the study
- Insufficient understanding or ability to complete questionnaires in Dutch

Interventions

Control Group

Patients allocated to the control group will receive usual care and access to the nonintervention part of the website (www.ikherstel.nl). On this part of the website, the patient information brochure about the surgical procedure from the hospital where the patient will have surgery is presented. This is the same brochure as the one patients often receive in various hospitals when they are scheduled for surgery. The only reason to give patients access to this website is to minimize the bias in estimation of the intervention effect. Furthermore, pre- and postoperative care will be given according to the local protocol of the hospital. In the Netherlands, patients do not receive structural and detailed instructions about the resumption of normal activities including work. Usually, after the patient is discharged from the hospital, an outpatient postoperative consultation is scheduled 4 to 8 weeks following surgery.

Intervention Group

Patients in the intervention group will receive access to the intervention part of the website, a mobile application, and an activity tracker. Table 1 provides an overview of the different components of the intervention.

Table 1. Components of the intervention.

Component	Target population	Content	Aim
Website	All patients of the intervention group	Information by text and animations[a]	Enhancing patient involvement and recovery expectations and reducing anxiety
		Making a personalized convalescence plan[a]	Creating recovery expectations and improving recovery
		Recovery monitor and recovery report[a]	Reducing uncertainties and fear related to the recovery process and improving monitoring of postoperative care
		eConsult	Increasing access to care, reducing patient uncertainties and fear related to the recovery process, and reducing costs and workload (by replacing the appointment in the outpatient clinic)
App	All patients of the intervention group with a smartphone	Information by text[a]	Enhancing patient involvement and recovery expectations and reducing anxiety
		Insight in the convalescence plan[a]	Creating recovery expectations and improving recovery
		Recovery monitor and recovery report[a]	Reducing uncertainties and fear related to the recovery process and improving monitoring and transition of postoperative care
		Creating a packing list	Helpful tool
		Section to make notes	Helpful tool
Activity tracker	All patients of the intervention group with a smartphone which can be linked to an activity tracker	Monitoring and giving feedback on recovery[a]	Reducing uncertainties and fear related to the recovery process, which may improve recovery

[a]Content is based on the intervention mapping study of Vonk Noordegraaf et al [14].

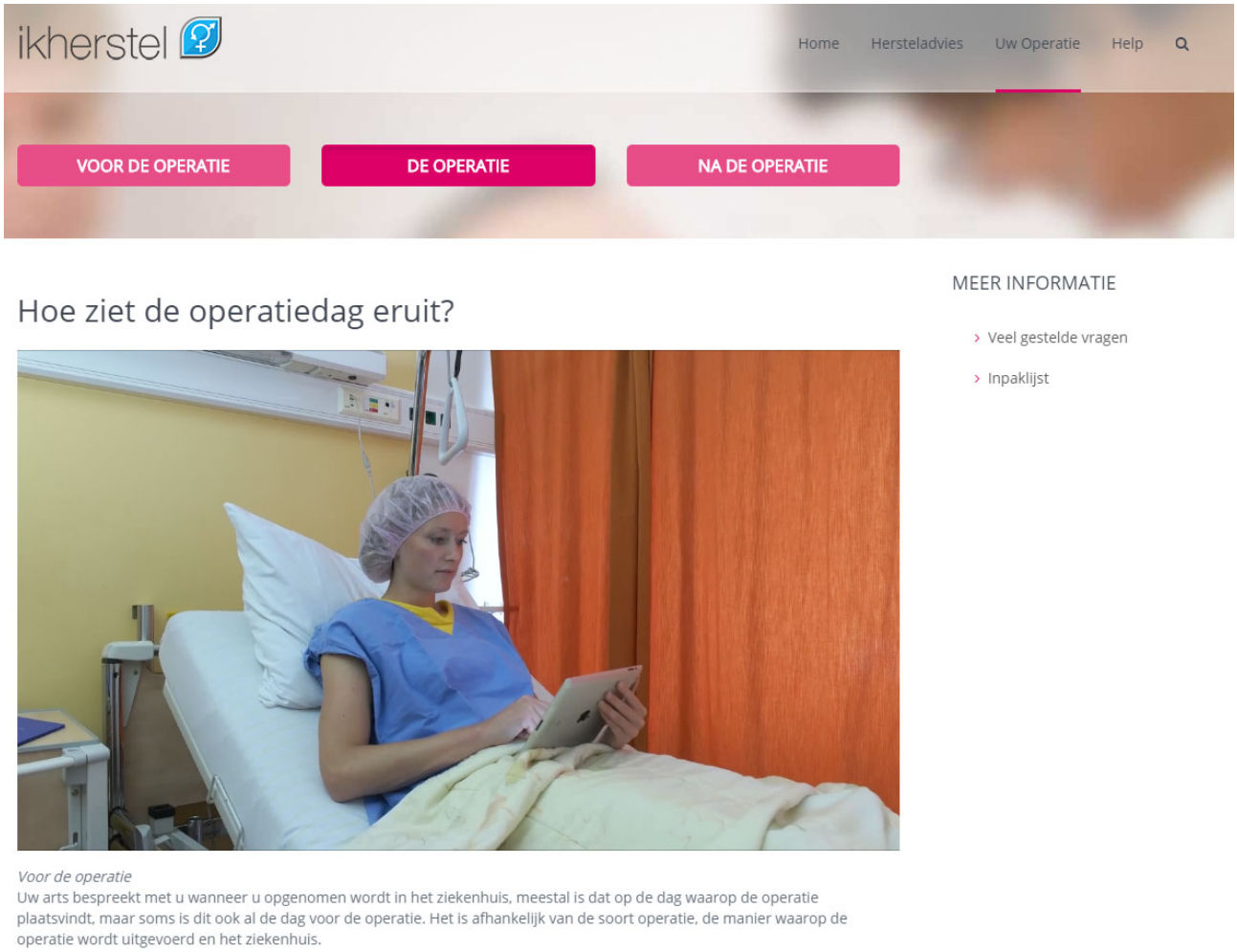
Website

The website aims to prepare patients in the best possible manner for their surgery and to offer guidance during their recovery process until full recovery and resumption of all daily activities are achieved. The following tools on the website will support this.

Providing Information About the Surgical Procedure and Recovery Process

On the website, information will be tailored to the patient, which offers the opportunity to enhance patient involvement (Figure 1) [13]. This is possible because some data are already prefilled when patients receive their website account (eg, surgical procedure, sex, hospital). The information will be offered by text as well as animations. The aim is to prepare the patient as well as possible for the day of surgery, which may contribute to the patient being more aware of what to expect and have a positive effect on anxiety and satisfaction [22]. In addition, it aims to improve recovery expectations, as expectations about the length of the recovery before surgery have proven to be an important predictor of the length of recovery [23]. After surgery, text and animations will be offered about the recovery period, which may support patients during this period and may help them with feelings of insecurity. Information about several postoperative complaints is available, including practical advice about when, how, and with whom patients should seek contact. We hypothesize that by providing this information, patients will be encouraged to resume their daily activities. In addition, this empowerment will help when deciding whether contact with a health care provider is indicated in case of complaints or complications during their recovery.

Figure 1. Text and animations on the website (see Multimedia Appendix 1 for more information).



Making a Personalized Convalescence Plan

The most important tool on the website is the option to generate a personalized and tailored convalescence plan, including advice about resumption of daily (work) activities (Figures 2 and 3). Using a modified Delphi method, specific convalescence recommendations were developed for several types of abdominal surgical procedures [24,25]. The recommendations given are tailored to the patient and are based on the input of patients' normal preoperative activities and the surgical technique (using algorithms). It aims to improve recovery, return to normal (work) activities, and quality of life. The convalescence plan will be approved electronically on the first postoperative day by the operating surgeon, resulting in a definitive convalescence plan. If complications occur during surgery, the surgeon will not approve the convalescence plan and the patient will receive a message that their initial convalescence plan is no longer applicable and that the adjusted instructions of the surgeon should be followed.

Figure 2. Personalized convalescence plan (see Multimedia Appendix 1 for more information).

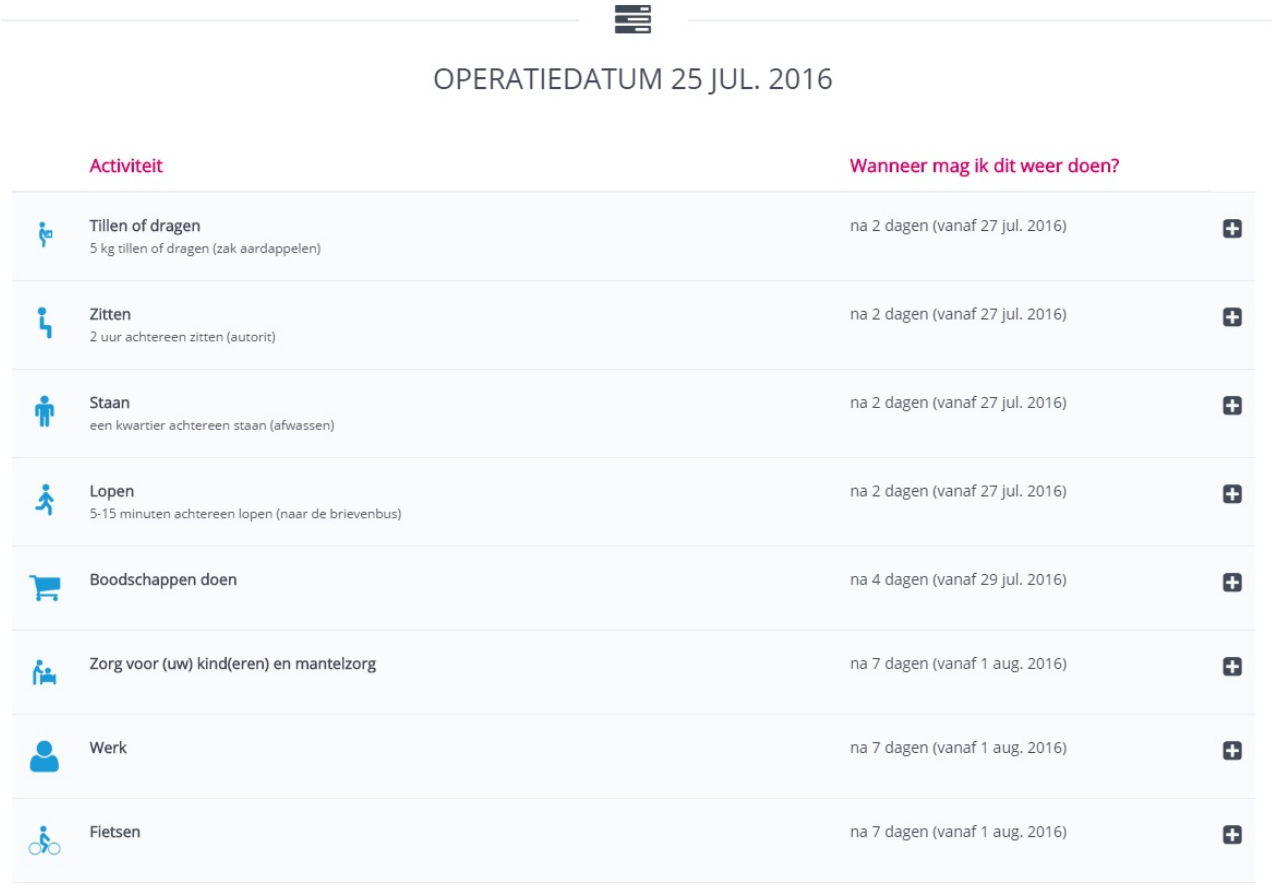
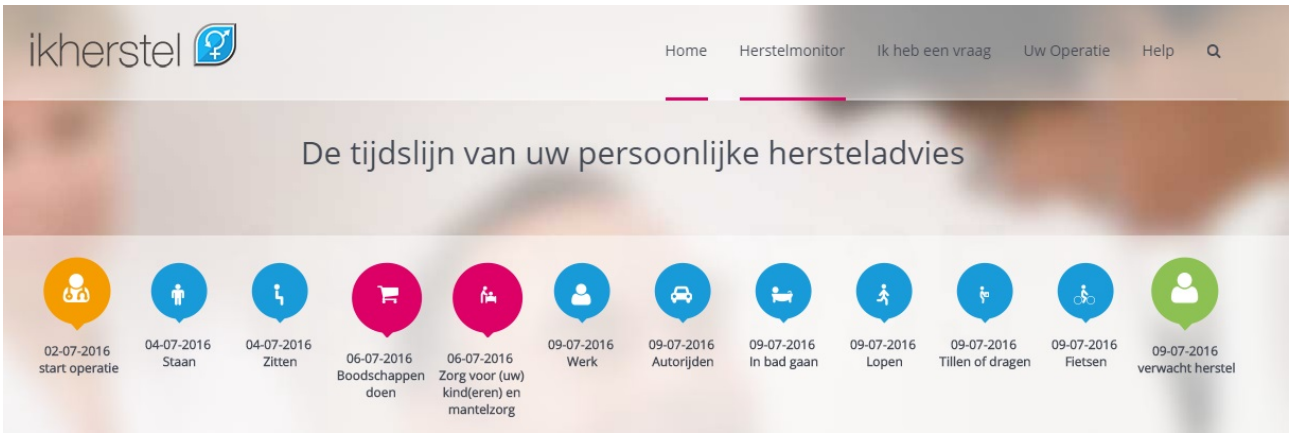


Figure 3. Personalized convalescence plan displayed on a timeline (see Multimedia Appendix 1 for more information).



Getting Feedback on Recovery by a Recovery Monitor and Recovery Report

The recovery monitor and report are tools to identify recovery problems and give patients feedback on their recovery progress. Patients are asked to indicate by a recovery monitor to what extent they have resumed their activities (Figure 4), which is subsequently graphically displayed in a recovery report allowing them to track their progress (Figure 5). If patients report a delayed recovery, an alerting system advises them to contact a specific health care professional, depending on the underlying problem. It also aims to improve monitoring and transition of postoperative care; after the patient has given consent, the Web portal can be accessed by a health care provider in secondary care to monitor the patients' recovery and thus identify recovery problems.

Figure 4. Recovery monitor (see Multimedia Appendix 1 for more information).

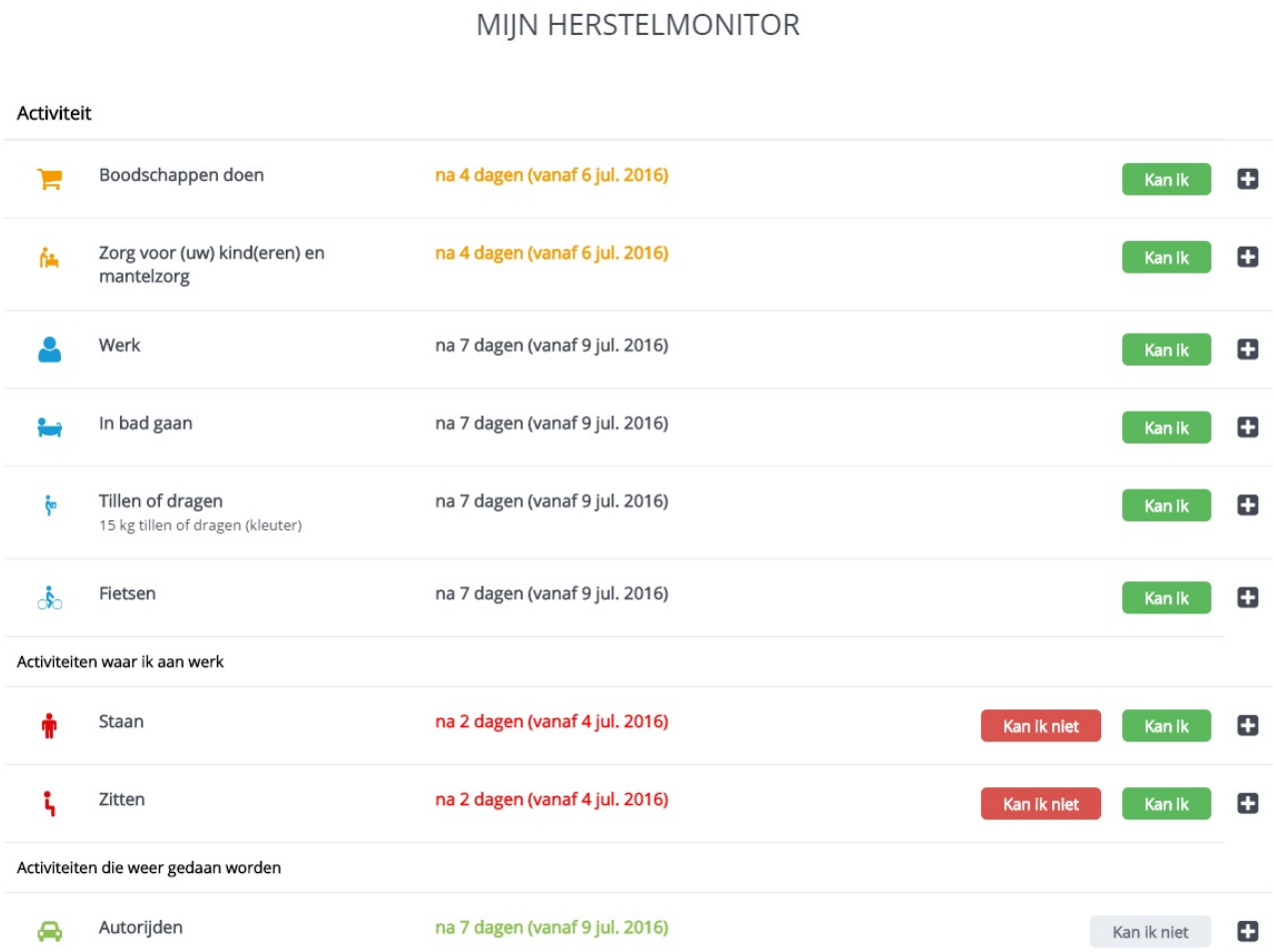


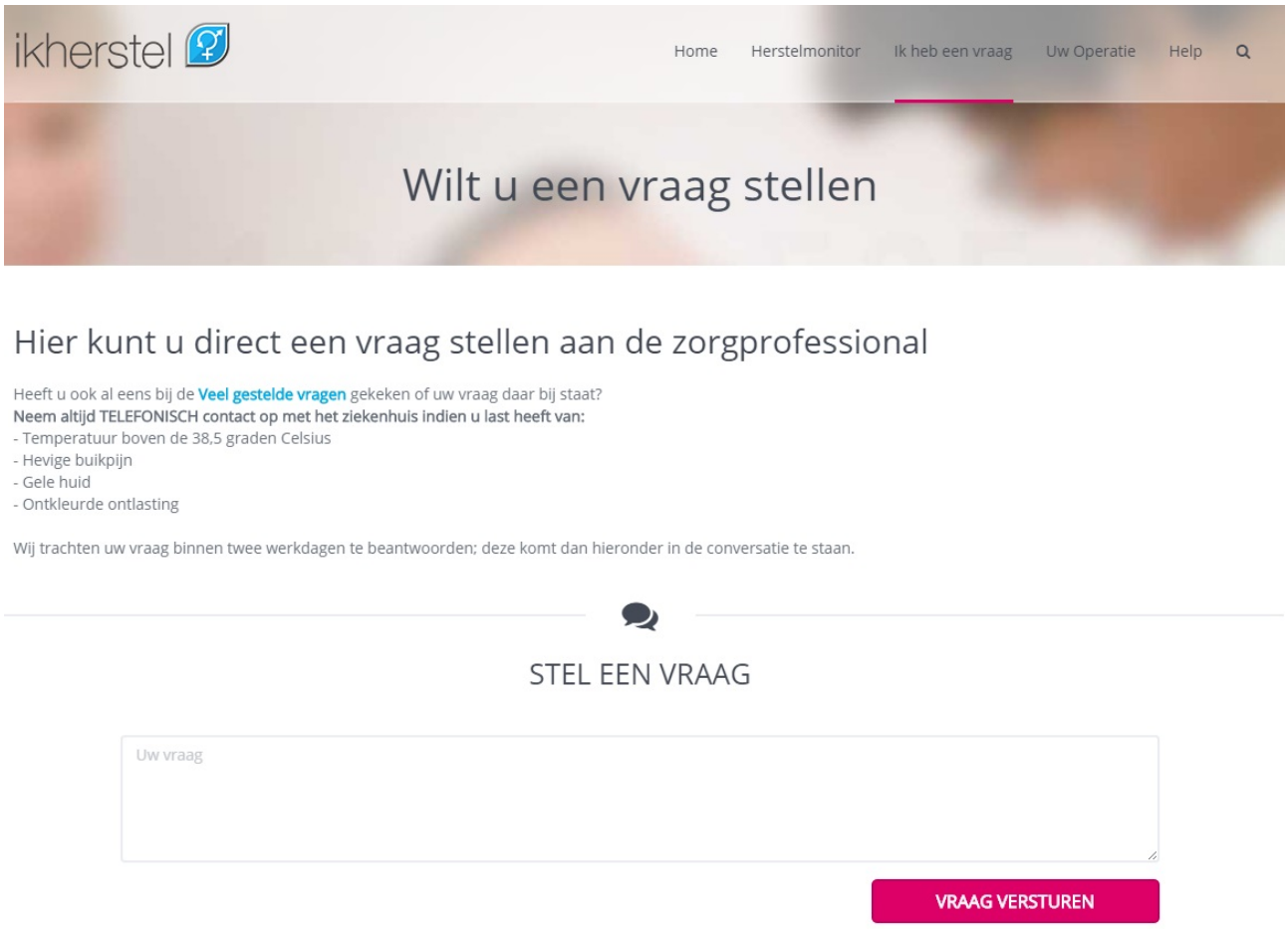
Figure 5. Recovery report (see Multimedia Appendix 1 for more information).

Postoperative Consult by eConsultation Instead of Consultation in the Outpatient Clinic

At discharge, patients from the intervention group will not receive a standard appointment at the outpatient clinic. Instead, they are offered continuous guidance via the website (information, feedback on recovery) and the possibility to ask questions on the website to a health care professional from their own hospital by means of an eConsult in case of recovery problems (Figure 6). They are informed that the question will be answered within 2 working days except for urgent matters. In that case, they receive a phone number for direct contact. In addition patients will receive a telephone call 2 weeks after

surgery to inform them about any test results. Various studies already have proven that telephone follow-up is feasible and effective after the type of surgical procedures which are included in this study [26-28]. The telehealth follow-up aims to replace the standard single postoperative consultation in the outpatient clinic to increase access to care, reduce patient uncertainties and fear related to the recovery process, reduce costs and workload, and meet patient preferences of care during out-of-office hours [29,30]. We hypothesize that patients will be more comfortable and less hampered in resuming their activities with the opportunity to ask questions whenever they prefer instead of the standard consultation several weeks after surgery.

Figure 6. eConsult (see Multimedia Appendix 1 for more information).



Mobile Phone App (mHealth) and Activity Tracker

All information which is available on the website is also available on the mobile phone app (Ikherstel app), which will be synchronized with the website. This mHealth app has been developed because of the increasing use of mobile phone apps and in order to make the intervention more accessible. This means that the convalescence plan that is created by the patient on the website will also be displayed on the app. In addition, the app will offer some extra features, such as a section to make notes and the option to compose a list of what to pack when being admitted to hospital (Figure 7). If patients do not have a smartphone they will only use the website. Patients who have a smartphone may also receive an activity tracker (UP MOVE, Jawbone). Not all kinds of smartphones can be linked to this activity tracker, so only a proportion of the patients will receive an activity tracker. This activity tracker measures daily step count. We performed a pilot study with an accelerometer in 30 patients who underwent surgery that showed that the step count had a clear correlation with activity intensity levels (data not yet published, personal communication). Patients can link the activity tracker to the app. The activity tracker will be used as an aid for patients to monitor and to give feedback on their recovery. Patients are instructed to wear the accelerometer from the seventh day before surgery until 3 weeks after surgery and during the sixth week after surgery. In the week before surgery a baseline measurement will be performed. The mean step count per day of this week will be set as their target postoperative activity level. In the app, it will be displayed on which date this target level is expected to be reached (Figure 8). This date is based on the convalesce plan which is developed by the patient. After surgery, the daily step count will be graphically displayed in the app and on the website as a percentage of their target activity level. When no baseline measurement is performed (for example, because the period between inclusion and surgery is shorter than 1 week), the target activity level will be set at 7100 steps per day (based on the mean preoperative value of the pilot study). As the pilot study also indicated that the most improvement in activity level was detected in the first 2 weeks after surgery, it was decided to ask the patients to wear the accelerometer during the first 3 weeks after surgery. The sixth

week was chosen because we hypothesize that baseline activity level will be reached in this week. Patients will be offered the opportunity to wear the activity tracker in the fourth and fifth week after surgery as well.

Figure 7. Mobile phone app (see Multimedia Appendix 1 for more information).

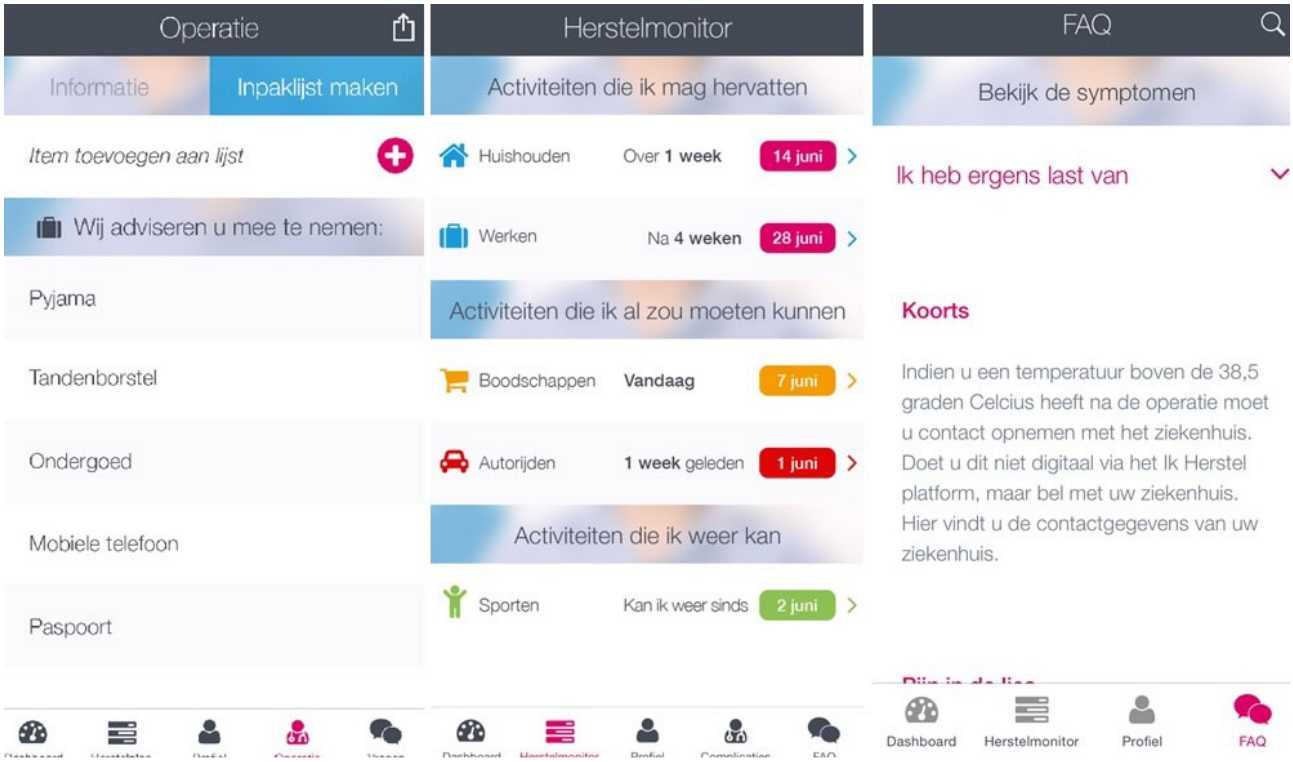


Figure 8. Activity tracker connected to the mobile phone app (see Multimedia Appendix 1 for more information).

Outcomes

Table 2 presents all outcome measures, the measurement instruments that will be used, and the time points when they will be assessed.

Primary Outcome

The primary outcome measure of the study will be time to return to normal activities (RNA). The Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Functioning item bank version 1.2 will be used to measure

limitations in daily activities. This item response theory (IRT)–based item bank has been developed and validated in the United States and translated into Dutch-Flemish [31,32]. Initial validation studies in Dutch patients confirmed the unidimensionality and underlying calibration of the IRT model (personal communication, article submitted). This item bank consists of 121 activities. We made a selection of the 29 most relevant activities for this study (Multimedia Appendix 2). We considered the 92 excluded activities as not being affected by the type of surgery (eg, "Can you brush your hair?") or as duplicate activities. The list of 29 activities will be presented to the patients at baseline (prior to surgery), and they will be asked to select 8 activities which are most relevant for them in daily life. In this way, patients will design their own personal physical functioning short form. Since items in an IRT-based item bank are calibrated onto the same continuum, one can select any subset of questions in that bank and the scores obtained from the derived short forms are comparable to that from the complete bank [33]. In the follow-up questionnaires, patients will only receive those PROMIS questions regarding the 8 activities that they selected before surgery as relevant to their personal life. Items are scored on a 5-point scale with 1 as most limited and 5 as no limitation. In addition, they will be asked postoperatively whether they can perform this activity on the same level as before surgery. If they answer "yes," they are asked to fill in since when (date), and the question will no longer be repeated in the following questionnaires. If the question is answered with a "no," the question will be asked again at the next follow-up moment. For each patient, this will result in 8 dates of resumption of their activities. These dates will be converted into time periods by calculating the number of days that have elapsed between the date of surgery and the date of the resumption of that particular activity. The moment of resumption of the last activity on the list will be defined as the RNA moment and thus the primary outcome measure will be time elapsed between surgery and resumption of the last activity. If patients have not resumed 1 or more activities at 6 months, those activities will be censored. If information about the resumption of 2 or fewer activities is missing, the RNA moment will be calculated based on 6 activities. If information about the resumption of more than 2 activities is missing, the RNA moment cannot be calculated accurately and will be considered as missing data.

Secondary Outcomes

As secondary outcomes we will use the time until the first activity can be resumed and the moment that 75% of the activities are resumed. Scores of the physical functioning short forms will also be calculated by summarizing for each patient the scores of the 8 activities and transforming them into a T-score on the PROMIS physical functioning metric, where 50 represents the average score of the US population with an SD of 10. The following outcomes will also be measured:

- Social participation: assessed with the PROMIS Ability to Participate in Social Roles and Activities version 2.0 short form 8a [34]
- Self-rated health: measured by the 3-level EuroQol-5D (EQ-5D-3L) [35]
- Durations of return to work (RTW) (only for the working population): the time until the first day on which work will be resumed and the time until full resumption of work activities will be assessed
- Physical activity: assessed by the International Physical Activity Questionnaire (IPAQ) short form [36]
- Length of recovery: measured by the recovery specific quality of life questionnaire (RI-5) short form [37].
- Pain intensity: measured by the Von Korff questionnaire visual analog scale (VAS) [38].
- Patient satisfaction: measured with a self-developed patient satisfaction questionnaire focused on satisfaction with perioperative care, the care program (both groups), the website (both groups), the app (intervention group only), and the activity tracker (intervention group only).

Table 2. Outcome measures, measurement instruments, and time points.

	Enrollment	Surgery	Post-allocation				
Time Point[a]	T_0		T_1	T_2	T_3	T_4	T_5
Enrollment							
Eligibility screen	X						
Informed consent	X						
Allocation	X						
Interventions							
Intervention group							
Intervention part of the website	XXXXXXXXXXXXXXXXXXXXXXXXXXXXX						
Mobile phone app	XXXXXXXXXXXXXXXXXXXXXXXXXXXXX						
Activity tracker	XXXXXXXXXXXXXXXXXXXXXXXXXXXXX						
Control group							
Nonintervention part of the website	XXXXXXXXXXXXXXXXXXXXXXXXXXXXX						
Assessments							
Primary outcome measure							
Return to normal activities (PROMIS[b] physical functioning item bank)	X		X	X	X	X	X
Secondary outcome measures							
Participation (PROMIS short form Social Roles)	X		X	X	X		X
Self-rated health (EuroQol-5D-3L)	X			X	X	X	X
Return to work (Return to work questionnaire)			X	X	X	X	X
Physical activity (IPAQ[c])	X			X	X	X	
Recovery (RI-5[d])	X		X	X	X		
Pain intensity (VAS[e])			X	X	X		
Patient satisfaction (Satisfaction questionnaire)						X	
Prognostic factors							
Sociodemographic data (Sociodemographic questionnaire)	X						
Potential confounding factors							
Complications during surgery (Surgical report)		X[f]					
Postoperative complications (Postoperative medical notes)					X[f]		
Process measures							
Protocol adherence (Adherence questionnaire)						X	
Cost measures							
Care program (Bottom-up approach)	X[f]						
Health care utilization (Cost questionnaire)						X	X
Informal care (Cost questionnaire)						X	X
Productivity loss							
Presenteeism: iPCQ[g] and WHO-HPQ[h]	X		X	X	X	X	X
Absenteeism: iPCQ	X		X	X	X	X	X
Unpaid productivity: Cost questionnaire						X	X

[a]T_0: 1 month before surgery; T_1: 1 week after surgery; T_2: 3 weeks after surgery; T_3: 6 weeks after surgery; T_4: 3 months after surgery; T_5: 6 months

after surgery.

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

[c]IPAQ: International Physical Activity Questionnaire.

[d]RI-5: recovery specific quality of life questionnaire short form.

[e]VAS: visual analog scale.

[f]Measured by the research team.

[g]iPCQ: Institute for Medical Technology Assessment (iMTA) Productivity Cost Questionnaire.

[h]WHO-HPQ: World Health Organization—Health and Work Performance Questionnaire.

Prognostic Factors

Before surgery (T_0), various sociodemographic data will be assessed (sex, age, level of education, living conditions, working conditions) and questions asked regarding expectations about the length of recovery. Also the T-scores of the PROMIS physical functioning short forms conducted by the patient will be calculated.

Potential Confounding Factors

Major complications during surgery (eg, conversion to an open procedure), major complications in the postoperative course (eg, leading to a prolonged hospital stay of more than 2 nights after surgery), and readmission to the hospital in the 30 days after surgery or repeated surgery in the 30 days after surgery are considered as potential confounders. The complications will be assessed by reviewing the surgical reports and postoperative notes.

Process Measures

A process evaluation of the intervention will be carried out in accordance with the Linnan and Steckler method [39]. Table 3 contains the different components of the intervention and the level at which they are measured and in what way.

Table 3. Process evaluation.

	Website	App	eConsult	Telephone consult after 2 weeks	Activity tracker
Reach: The proportion of intended target audience that participated in the study	Patients who met the inclusion criteria, signed informed consent, and are randomized to the intervention or control group[a]				
Dose delivered: The number or amount of intended units of each component delivered or provided to the intervention group	Proportion of the patients of the intervention group who received an account for the web portal and app[a]			Proportion of the patients of the intervention group who received a telephonic appointment at discharge[b]	Proportion of the patients of the intervention group who received an activity tracker[a]
Dose received: The extent to which participants from the intervention group actively engage with, interact with, are receptive to, or use materials or recommend resources	Proportion of the patients of the intervention group that made a convalescence plan[c]	Proportion of the patients of the intervention group that used the app[d]	Proportion of the patients of the intervention group that asked one or more questions on the web portal[c]	Proportion of the patients of the intervention group that received their telephonic appointment[b]	Proportion of the patients of the intervention group that connected the activity tracker to their phone[c]
Fidelty: The extent to which the intervention was delivered as planned	Proportion of the convalescence plans that are electronically approved by the specialist[c]	X	Proportion of the questions that were answered[c]	Proportion of the patients of the intervention group that came back at the outpatient office in addition to their telephonic consult[b]	Proportion of the patients of the intervention group that used the activity tracker in the first 3 weeks after surgery (minimum 3 days per week) and in the sixth week after surgery (minimum 3 days)[c]
Participant attitudes: Satisfaction and usage barriers of the intervention	Assessment of the website by the intervention group and reasons for not using the website[d]	Assessment of the app and reasons for not using the app[d]	X	X	Assessment of the activity tracker and reasons for not using the activity tracker[d]

[a]Data collection method: logistic database.

[b]Data collection method: notes in the medical record.

[c]Data collection method: web log.

[d]Data collection method: adherence and satisfaction questionnaire.

Cost Measures

Identification of Costs

Costs will be measured from a societal and a health care perspective. Societal costs will consist of costs of the intervention (ie, the substitution of perioperative care by eHealth), other health care use, informal care, absenteeism (ie, absence from work), presenteeism (ie, reduced productivity while at work), and unpaid productivity (ie, inability to perform educational activities, chores, volunteer work). When the health care perspective is applied, only costs accruing to the formal health care sector will be included (ie, costs of the intervention and other health care use).

Measurement and Valuation of Costs

Intervention costs will include all costs related to the development and implementation of the intervention and will be measured using a bottom-up microcosting approach (ie, detailed data will be collected regarding the quantity of resources consumed during the development and implementation of the intervention as well as their unit prices). All other cost categories will be measured using Web-based questionnaires administered at baseline and after 1 week, 3 weeks, 6 weeks, 3 months, and 6 months of follow-up (Table 2). Health care costs will include costs related to the use of primary care (eg, general practitioner), secondary care (eg, hospital visits), and medication. These costs will be valued using Dutch standard costs and, if unavailable, prices according to professional organizations [40]. Informal care will be valued using a recommended Dutch shadow price [40]. Absenteeism will be measured using the Institute for Medical Technology Assessment (iMTA) Productivity Cost Questionnaire (iPCQ) and valued in accordance with the friction cost approach using the estimated cost of productivity losses in the Netherlands [40,41]. Presenteeism costs will be measured using the iPCQ questionnaire and the World Health Organization Health and Work Performance Questionnaire and valued using the estimated cost of productivity losses in the Netherlands as well [42]. Unpaid productivity costs will be valued using the aforementioned recommended Dutch shadow price [40].

Sample Size Calculation

Previous studies evaluating this type of intervention on RNA are lacking. We based our sample size calculation on the outcomes on RTW after gynecological surgery of our previous study [16]. Based on this study we expected a hazard ratio (HR) of 1.4 for RNA using the optimized intervention. Considering an HR of 1.4 and using a 2-sided log-rank test at a significance level of 5%, we need to observe 285 events (patients returning to normal activities) to achieve a power of 80%. The total sample size is set at 308 (154 per arm) to account for an anticipated proportion of 2.5% of patients not returning to daily activities within the 6-month follow-up period and a dropout rate of 5%.

Recruitment and Inclusion

All patients between 18 and 75 years old who are on the waiting list for a laparoscopic cholecystectomy, inguinal hernia surgery, or adnexal surgery in one of the participating hospitals who meet the inclusion criteria will receive a letter of information about the study on behalf of their doctor. After 1 week, contact will be made by phone to evaluate their willingness to participate and to access eligibility. If the patient wants to and is eligible to participate, informed consent will be signed. Participants will not receive any financial or nonfinancial incentives.

Allocation

After inclusion, patients will be asked to complete the first online questionnaire (T_0) within the month before surgery. After patients have completed the questionnaire, randomization will take place by means of a computer-based randomization list stratified regarding hospital, sex, and surgical procedure using permuted blocks, size 2. Patients are randomized to the intervention or the control group in a 1:1 ratio. The researcher performing randomization is independent from the recruitment or data analyses.

Blinding

Patients are blinded to the intervention as they do not know which program is developed as a nonintervention or intervention care program. After allocation, patients will receive an email containing a link to the care program to which they are allocated. Both care programs can be accessed through the website, but after signing in, patients will receive access only to the part of the website to which they are randomized. The researchers involved in the analyses will be blinded to the allocation throughout the analyses. Health care providers cannot be blinded to the intervention because it is highly likely that they will be notified of the allocation either by the patient or the patient's medical file.

Data Collection

Data will be collected by means of self-reported electronic questionnaires at standard moments. Data will be collected in the month before surgery (T_0) and 1 week (T_1), 3 weeks (T_2), 6 weeks (T_3), 3 months (T_4) and 6 months (T_5) after surgery (Table 2). When data regarding RNA are missing during 2 measuring moments, an attempt will be made to collect the missing questions by telephone or email.

Data Analyses

Effect Analyses

All analyses will be performed in SPSS (IBM Corp). Baseline characteristics will be summarized using descriptive statistics and compared between the intervention and control group using *t* tests, Mann-Whitney U tests, chi-square tests, or Fisher exact tests. Survival analysis will be used to analyze time until RNA data. Both crude and adjusted analyses will be performed. Hospital, surgical procedure, and sex will be taken into account as covariates in the adjusted analyses because these are the factors for which stratification will apply. In addition, when there are clinically relevant differences between the intervention and the control group in the baseline characteristics or potential confounding factors, this will also be considered as a covariate in further analyses. To describe the distribution of the duration until RNA in both groups, the Kaplan-Meier method will be used. The Cox proportional hazard model will be applied to calculate HRs. Differences in secondary outcomes between the groups will be assessed by mixed models and multilevel logistic regression models for outcomes that are measured more than once during follow-up, and *t* tests, Mann-Whitney U tests, chi-square tests, or Fisher exact tests will be used when differences on 1 time point will be compared. Statistical analyses will be performed according to intention-to-treat principle, which will be compared to per-protocol analyses. Patients will be included in the per-protocol analyses when they used the intervention as intended, which will be defined as the generation of a convalescence plan on the website. This will be measured by a web log. Subgroup analyses will be performed regarding the surgical procedure (1. Cholecystectomy, 2. Hernia inguinal surgery and 3. Adnexal surgery) and type of surgery (gynecological vs surgical procedures). A post hoc analysis will be carried out on patients without major complications (definition described in Potential Confounding Factors).

Economic Evaluation

The economic evaluation will be performed from a societal and health care perspective. The time horizon of the economic evaluation is 6 months, thus discounting of costs and effects is not necessary. Both cost-effectiveness and cost-utility analyses will be performed. The cost-effectiveness analysis will be performed with the primary effect measure (ie, RNA). The cost-utility analysis will be performed with quality-adjusted life-years (QALYs). The patients' EQ-5D-3L health states will be converted into utilities using the Dutch tariff, and QALYs will be calculated using linear interpolation between measurement points [43]. The analyses will be done according to the intention-to-treat principle. Missing cost and effect data will be imputed using multiple imputation after which results will be pooled using Rubin's rules [44]. Cost and effect differences will be analyzed using multilevel analyses with a 2-level structure (ie, patient, hospital). The 95% CIs around the cost differences will be estimated using bias-corrected intervals with 5000 replications. The bootstrap replications will be stratified for hospital to account for the clustering of data [45]. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in mean total costs between the groups by the difference in mean effects. Uncertainty surrounding the

ICERs will be graphically presented on cost-effectiveness planes. Cost-effectiveness acceptability curves will also be estimated illustrating the probability that the optimization and substitution of perioperative care by eHealth is cost effective in comparison with usual care for a range of different ceiling ratios. Various sensitivity analyses will be performed to assess the robustness of the results.

Results

The inclusion process started in September 2015. The expected end date is August 2016. The data collection process will last until February 2017 since the follow-up duration is 6 months. The results are expected in 2018. Data cleaning or analyses have not begun as of this article's submission.

Discussion

Summary

In this RCT we will evaluate the effect of eHealth on RNA after abdominal surgery.

Strengths and Limitations

In the earlier studies performed by our research group, the effect of the eHealth intervention was evaluated in terms of duration until RTW [16,46]. The reason the primary outcome measure in this study is changed to duration until RNA is that in the earlier studies only employed patients could participate; we believe that unemployed patients can also benefit from this eHealth care program to facilitate recovery. However, one of the reasons for chosing duration until RTW in the earlier performed studies was that this outcome measure was relatively easy to measure and objectify. Duration until RNA is more difficult to measure and objectify. Most studies using this outcome measure make use of fixed measurement instruments, which may contain questions not always applicable to all patients or may not represent the most relevant problems for patients. As far as we know, this is the first study in which RNA after surgery is measured by a measurement instrument tailored to the patient. A tailored instrument increases the validity and reliability of the primary outcome measure. The ultimate form of tailoring is computer-adaptive testing (CAT), in which after the first item, the selection of items is determined by the person's responses to previous items. For example, Zanocco et al [47] used CAT to measure changes in patient-reported health before and after parathyroidectomy. PROMIS short forms and CATs are increasingly used as outcome measures across clinical studies in different fields [48]. In our study we will use individualized short forms because CAT software for use in the Netherlands is still under development [49]. Another strength of this study is that we developed a nonintervention (standard) website, which enables us to blind the patients to which group they are assigned. Blinding of the health care professionals, however, was not possible. But in our opinion this will not influence the study results, since the health care professionals do not play a substantial role in the intervention or of the data-collecting process. This study is also strengthened by the fact that state-of-the-art statistical methods, such as multiple imputation, bootstrapping, and multilevel analyses, will be used.

A limitation of the study is the heterogeneity of surgical procedures. However, the Delphi study that we performed to compose the convalescence recommendations used in this study showed more or less the same convalescence recommendations for all surgical procedures, which suggests that the recovery periods of these surgical procedures are comparable [24,25]. In addition, the heterogeneity can be considered an advantage, because the results will be applicable to a broader population. Another limitation may be that the study is carried out in 7 hospitals, which means that the usual care that the control group receives can vary between hospitals. We tried to reduce this bias by stratifying the randomization by hospital. Finally, the baseline measurement with the activity tracker will be performed in the week before surgery and therefore cannot assure that the baseline measurement will give a representative view of the normal activity pattern of the patients. However, the patients who participate in the study will undergo elective surgery. This in general will mean that the patients will not be suffering from an acute illness or bedridden at the time of surgery. Although we cannot entirely rule out that the baseline measurement will be influenced, we nevertheless believe that the risk will be minimal.

Comparison to Prior Work: What This Study Will Add

To our knowledge, there are 13 other studies which have evaluated an educational or supportive eHealth intervention in perioperative care [16,46,50-61]. Most of these studies were relatively small or did not perform a power calculation. Only 2 studies were carried out in patients undergoing abdominal surgery. In addition, almost all studies (12/13) aimed to evaluate the eHealth intervention in addition to usual care. Only 1 study aimed to evaluate eHealth as (partial) substitution of usual care; however, this study had no report of a power calculation and included patients undergoing orthopedic surgery. The most comparable study to ours is that of Bouwsma et al [46], which evaluated the cost-effectiveness of an eHealth intervention in patients undergoing gynecological surgery (results not yet published). The main differences with our study are the primary outcome measure (RNA vs RTW), the aim of the eHealth intervention (substitution of care vs additional care), and the patient population (working and nonworking men and women vs working women). A total of 9 studies found a significant positive effect of the eHealth intervention regarding an outcome measure focusing on the postoperative course. However, studies evaluating eHealth interventions in abdominal surgery to substitute usual care are lacking, which underlines the importance of this current study.

Clinical Relevance

Improving the quality of perioperative care is required because postoperative care is limited due to the reduction in the length of hospital stay. In addition, because of the increasing demand for health care due to the aging population and personnel shortages in health care, it is necessary to deliver more efficient and cost effective perioperative care. This study will evaluate whether eHealth can be used to suit this purpose. It will both give insight for health care professionals by determining the best form of perioperative care and facilitate policy makers in

deciding whether eHealth can be used to substitute usual care against lower costs. The generalizability of this study is high because the eHealth intervention will be evaluated in various types of surgical procedures and will only require minor adaptions in order to be applied to other types of procedures.

Acknowledgments

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Conflicts of Interest

EM, JH, EB, CB, and JA are the developers of the care program under study. JA and JH are setting up a spin-off company concerning the implementation of a mobile application concerning the IKHERSTEL intervention in the Netherlands.

Multimedia Appendix 1

Further information on screenshots.

[PDF File (Adobe PDF File), 29KB - resprot_v5i4e245_app1.pdf]

Multimedia Appendix 2

Selection of the Patient-Reported Outcomes Measurement Information System (PROMIS) physical functioning item bank version 1.2.

[PDF File (Adobe PDF File), 31KB - resprot_v5i4e245_app2.pdf]

Multimedia Appendix 3

Peer review report 1.

[PDF File (Adobe PDF File), 67KB - resprot_v5i4e245_app3.pdf]

Multimedia Appendix 4

Peer review report 2.

[PDF File (Adobe PDF File), 65KB - resprot_v5i4e245_app4.pdf]

Multimedia Appendix 5

Peer review report 3.

[PDF File (Adobe PDF File), 66KB - resprot_v5i4e245_app5.pdf]

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Abbreviations

CAT: computer-adaptive testing
eHealth: electronic health
EQ-5D-3L: EuroQol-5D (3 level)
HR: hazard ratio
ICER: incremental cost-effectiveness ratio
IPAQ: International Physical Activity Questionnaire
iPCQ: Institute for Medical Technology Assessment (iMTA) Productivity Cost Questionnaire
IRT: item response theory
mHealth: mobile health
PROMIS: Patient-Reported Outcomes Measurement Information System
QALY: quality-adjusted life-years
RCT: randomized controlled trial
RI-5: recovery specific quality of life questionnaire short form
RNA: return to normal activities
RTW: return to work
VAS: visual analog scale
WHO-HPQ: World Health Organization Health and Work Performance Questionnaire

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Protocol

Efficacy and Safety of High-Dose Ivermectin for Reducing Malaria Transmission (IVERMAL): Protocol for a Double-Blind, Randomized, Placebo-Controlled, Dose-Finding Trial in Western Kenya

Menno R Smit[1], MD, MPH; Eric Ochomo[2], PhD; Ghaith Aljayyoussi[1], PhD; Titus Kwambai[2,3], MSc, MD; Bernard Abong'o[2], MSc; Nabie Bayoh[4], PhD; John Gimnig[4], PhD; Aaron Samuels[4], MHS, MD; Meghna Desai[4], MPH, PhD; Penelope A Phillips-Howard[1], PhD; Simon Kariuki[2], PhD; Duolao Wang[1], PhD; Steve Ward[1], PhD; Feiko O ter Kuile[1], MD, PhD

[1]Liverpool School of Tropical Medicine (LSTM), Liverpool, United Kingdom

[2]Centre for Global Health Research, Kenya Medical Research Institute (KEMRI), Kisumu, Kenya

[3]Kisumu County, Kenya Ministry of Health (MoH), Kisumu, Kenya

[4]Division of Parasitic Diseases and Malaria, Center for Global Health, U.S. Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

Corresponding Author:
Menno R Smit, MD, MPH
Liverpool School of Tropical Medicine (LSTM)
Pembroke Place
Liverpool, L3 5QA
United Kingdom
Phone: 254 703991513
Fax: 44 1517053329
Email: menno.smit@lstmed.ac.uk

Abstract

Background: Innovative approaches are needed to complement existing tools for malaria elimination. Ivermectin is a broad spectrum antiparasitic endectocide clinically used for onchocerciasis and lymphatic filariasis control at single doses of 150 to 200 mcg/kg. It also shortens the lifespan of mosquitoes that feed on individuals recently treated with ivermectin. However, the effect after a 150 to 200 mcg/kg oral dose is short-lived (6 to 11 days). Modeling suggests higher doses, which prolong the mosquitocidal effects, are needed to make a significant contribution to malaria elimination. Ivermectin has a wide therapeutic index and previous studies have shown doses up to 2000 mcg/kg (ie, 10 times the US Food and Drug Administration approved dose) are well tolerated and safe; the highest dose used for onchocerciasis is a single dose of 800 mcg/kg.

Objective: The aim of this study is to determine the safety, tolerability, and efficacy of ivermectin doses of 0, 300, and 600 mcg/kg/day for 3 days, when provided with a standard 3-day course of the antimalarial dihydroartemisinin-piperaquine (DP), on mosquito survival.

Methods: This is a double-blind, randomized, placebo-controlled, parallel-group, 3-arm, dose-finding trial in adults with uncomplicated malaria. Monte Carlo simulations based on pharmacokinetic modeling were performed to determine the optimum dosing regimens to be tested. Modeling showed that a 3-day regimen of 600 mcg/kg/day achieved similar median (5 to 95 percentiles) maximum drug concentrations (Cmax) of ivermectin to a single of dose of 800 mcg/kg, while increasing the median time above the lethal concentration 50% (LC50, 16 ng/mL) from 1.9 days (1.0 to 5.7) to 6.8 (3.8 to 13.4) days. The 300 mcg/kg/day dose was chosen at 50% of the higher dose to allow evaluation of the dose response. Mosquito survival will be assessed daily up to 28 days in laboratory-reared *Anopheles gambiae s.s.* populations fed on patients' blood taken at days 0, 2 (Cmax), 7 (primary outcome), 10, 14, 21, and 28 after the start of treatment. Safety outcomes include QT-prolongation and mydriasis. The trial will be conducted in 6 health facilities in western Kenya and requires a sample size of 141 participants (47 per arm). Sub-studies include (1) rich pharmacokinetics and (2) direct skin versus membrane feeding assays.

Results: Recruitment started July 20, 2015. Data collection was completed July 2, 2016. Unblinding and analysis will commence once the database has been completed, cleaned, and locked.

Conclusions: High-dose ivermectin, if found to be safe and well tolerated, might offer a promising new tool for malaria elimination.

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KEYWORDS

malaria; Plasmodium falciparum; ivermectin; dihydroartemisinin-piperaquine; Anopheles gambiae s.s.; insecticide; clinical trial; pharmacokinetics; Kenya; study protocol

Introduction

Ivermectin is a potential new tool that is being considered in malaria transmission reduction strategies [1]. Ivermectin is a broad spectrum antiparasitic endectocide active against a wide range of internal and external parasites. It was originally introduced as a veterinary drug, predominantly for use in domestic livestock, but since 1987 has been widely used in human medicine [2]. Ivermectin at a dose of 150 or 200 mcg/kg is the first-line treatment for *Onchocerca volvulus* (the cause of river blindness) [3], *Wuchereria bancrofti* (the cause of lymphatic filariasis) [4], and *Strongyloides stercoralis* (roundworm, an intestinal helminth) [5]. To date more than 2.7 billion treatments have been distributed as part of mass drug administration (MDA) [6].

Ivermectin has secondary effects on ectoparasites, such as head lice, mites, bedbugs, and scabies, that feed on recently treated individuals [2,7], and it is also active against *Anopheles spp*. at concentrations present in human blood after standard doses. It reduces the re-blood feeding capacity, female fecundity, hatch rate of their eggs, the survival of progeny larvae, and importantly, it reduces the vector's lifespan [1,8-11]. It may also inhibit parasite sporogony [12]. Ivermectin has a different mode of action from other insecticides, and therefore may be effective against mosquito populations that are resistant to insecticides used on long-lasting insecticidal nets (LLINs) or indoor residual spraying (IRS). Furthermore, it is able to kill exophagic and exophillic vectors that can escape the indoor killing effects of LLINs and IRS [8].

However, several studies have shown that the effects after the standard 150 to 200 mcg/kg doses of ivermectin are generally short-lived. Three *in vivo* studies assessed the long-term effect of ivermectin on mosquito survival by conducting feedings at least 7 days after administration of ivermectin [10,13,14]. A single low dose of 200 mcg/kg showed a 1.33 fold increase in mosquito mortality when fed on blood taken from humans who had received ivermectin 1 day earlier, but there was no longer an effect when mosquitoes were fed on blood taken on day 14 post-treatment [10], while a repeated dose of 200 mcg/kg given on days 0 and 2 showed a modest effect on reduced survival 7 days post-treatment [14], and a dose of 250 mcg/kg in a single human volunteer showed a potent effect for at least 2 weeks post-treatment [13]. Population-based studies of the effect of MDA with ivermectin on malaria transmission or mosquito survival showed that MDA with a single dose of 150 mcg/kg for the control of onchocerciasis in Senegal affected survivorship of *An. gambiae s.s.* for up to 6 days, resulting in an estimated reduction of malaria transmission for at least 11 days as a result of a change in the age-structure of *An. gambiae s.s.* [15-17]. Similarly, in 3 different West African transmission settings, this same dose reduced *An. gambiae* survivorship by 33.9% for 1 week, their parity rates for more than two weeks, and sporozoite rates by more than 77% for 2 weeks [18].

Modeling has also shown that adding 3 days of ivermectin (150 mcg/kg/day) to MDA with dihydroartemisinin-piperaquine (DP) would potentially provide an important boost to the effect of MDAs with artemisinin-based combination therapy (ACT) by allowing transmission to be interrupted faster and in areas with a higher malaria prevalence than MDA with ACTs alone [19]. However, the effects are modest, and higher doses, providing a longer effect are required for ivermectin to boost malaria transmission reduction activities [19].

Ivermectin 400 mcg/kg has been suggested as an improved treatment for head lice [20], and has been found to be safe and well tolerated [21]. No studies in humans have compared the effect of ivermectin doses above 400 mcg/kg on the ability of anopheline vectors to transmit malaria (henceforth referred to as infectivity), or evaluated the effect of any dose of ivermectin higher than 400 mcg/kg on mosquito survivorship.

Ivermectin has an excellent safety profile [1], and experience with higher doses show that it is remarkably well tolerated in humans [22-27], even at doses up to 2000 mcg/kg, 10 times the 200 mcg/kg dose currently approved by the US Food and Drug Administration [24] (Table 1). In invertebrates, ivermectin causes the opening of glutamate-gated chloride channels resulting in flaccid paralysis and death [28]. Glutamate-gated chloride channels do not exist in humans. Other weakly sensitive channels are found in the human central nervous system, but the blood-brain barrier limits drug access to these channels [29].

Table 1. Studies of safety and tolerability of ivermectin incorporating dosages greater than or equal to 800 mcg/kg.

Reference	Highest single dose	Participants with single dose ≥800 mcg/kg, n	Total study population, n	Single doses in mcg/kg (n)	Adverse events: increased vs control
Awadzi 1995, 1999 [22,23]	800 mcg/kg	36	100 adult males with onchocerciasis in Ghana	150 (15), 400[a] (25), 600[a] (24), 800[a] (24), 800[b] (12)	No
Guzzo 2002 [24]	2000 mcg/kg	36	68 healthy adults, non-pregnant, in the United States	0 (17), 500[c] (15), 1000[c] (12), 1500 (12), 2000 (12)	No
Kamgno 2004 [25-27]	800 mcg/kg	330	657 adult males with onchocerciasis in Cameroon	150[d] (327), 800[d,e] (330)	Transitory mild visual side effects, without structural abnormalities upon ophthalmological exam

[a]Preceded 3 days earlier by 150 mcg/kg or placebo.

[b]Preceded 13 days earlier by 800 mcg/kg.

[c]Repeated 3 times a week (days 1, 4, and 7).

[d]Repeated 3 times monthly or once yearly.

[e]Preceded 3 or 12 months earlier by 400 mcg/kg.

The only known severe adverse events have been in individuals with *Loa loa*, possibly due to rapid lysis of parasite biomass [30]. Assessment of *Loa loa* is recommended before ivermectin administration in areas endemic for *Loa loa* filariasis [31].

DP and ivermectin have, to the best of our knowledge, never been studied under simultaneous administration. Piperaquine, the long-acting component of DP, is metabolized by, and is an inhibitor of, cytochrome-P450 3A4 (CYP3A4) [32]. There is a potential for an increase of piperaquine plasma concentrations when it is co-administered with other CYP3A4 substrates (due to competition) or CYP3A4 inhibitors [32]. Dihydroartemisinin (DHA), the short-acting component of DP, is not metabolized by cytochrome-P450, but is deactivated via glucuronidation catalyzed by UDP-glucuronosyltransferases, in particular UGT1A9 and UGT2B7 [33]. DHA has been shown to induce CYP3A activity and also up-regulate CYP2C19 and CYP2B6 [33]. DHA is a known inhibitor of CYP1A2 [32].

Ivermectin is primarily metabolized by CYP3A4 [34]. *In vitro* studies using human liver microsomes suggest that ivermectin does not significantly inhibit the metabolizing activities of CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2E1 [34]. When DP and ivermectin are administered together, however, there may be some competition for CYP3A4. The CYP3A4-inhibitory properties of piperaquine may lead to an increased availability of ivermectin. As ivermectin is not a CYP3A4-inhibitor, the potential increase in the availability of piperaquine due to competition is expected to be low.

We will conduct a placebo-controlled dose-finding study to determine the safety, tolerability, and mosquitocidal effect of 3-day courses of ivermectin when given in combination with a standard 3-day course of DP to identify safe and practical regimens to boost the arsenal of available tools to reduce or interrupt malaria transmission. Pharmacokinetic data will be collected to facilitate the construction of a pharmacokinetic/pharmacodynamic (PK/PD) model to guide future study design.

Methods

Design Overview

This is a double-blind, randomized, placebo-controlled, parallel-group, 3-arm, superiority trial to determine the safety, tolerability, and mosquitocidal effect of different doses of ivermectin (ClinicalTrials.gov: NCT02511353). The primary endpoint will be mosquito survival 14 days after a blood feed from a patient who started ivermectin 7 days earlier; 5 days after the last dose of ivermectin with a 3-day regimen administering ivermectin at 0, 24, and 48 hours (days 0, 1 and 2). Because mosquito feeding involves approximately 100 mosquitoes per feed, the study will use a clustered design with the patient as the unit of randomization and the mosquito as the unit of analysis. The study will have a nested rich pharmacokinetic component in the first 36 patients that give additional consent for rich/frequent sampling and a sparse sampling population pharmacokinetic component in the remaining patients. A second nested study will compare the effects of ivermectin when assessed by membrane feeding versus direct skin feeding in all patients who give additional consent for direct skin feeding.

Primary Objective

The primary objective of the study is to determine the safety, tolerability, and efficacy of ivermectin doses of 0, 300 and 600 mcg/kg/day for 3 days, when provided with a standard 3-day course of the antimalarial DP, on mosquito survival.

Secondary Objectives

The secondary objectives of the study are (1) to determine the effect of different doses of ivermectin on oocyst development; (2) to determine the pharmacokinetic profile of the different ivermectin regimens; (3) to determine if ivermectin interacts with the pharmacokinetics of piperaquine; (4) to determine whether the addition of ivermectin to DP affects the clinical and parasitological response to DP treatment; (5) to determine the role of genetic variants of CYP3A4 activity in metabolizing

ivermectin; and (6) to determine the effect of direct feeding versus membrane feeding on mosquito survival.

Design Considerations

Rationale for Ivermectin Doses of 300 and 600 mcg/kg/day

The goal was to design and evaluate a high-dose ivermectin regimen that could be given daily as adjunct therapy to a 3-day ACT regimen and that builds on the existing safety data available from previous studies. The highest dose of ivermectin used in studies for onchocerciasis is 800 mcg/kg given as a single dose (ie, about 48 mg in an adult male weighing 60 kg). The pharmacokinetic profile of this 800 mcg/kg dose was used to design a 3-day regimen that would achieve a similar maximum drug concentration (Cmax) after the third dose. Since the highest dose of ivermectin used in humans that was tested and found to be well tolerated and safe is 2000 mcg/kg given as a single dose, this provides a large margin of safety allowing for inter-individual variation of pharmacokinetics. The middle group was chosen at 50% of the highest dose to allow for a dose response in terms of tolerance and efficacy.

Using existing literature data [24,35] we developed a pharmacokinetic model for ivermectin in humans. Using the parameter estimates from the model, Monte Carlo simulations were performed for 1000 theoretical participants assuming a 30% variability in parameter estimates (CL/F 11.8 L/h, Vc/F 195.0 L, Q 18.9 L/h, Vp 882 L, and Ka 0.24/h). The simulations showed that the Cmax associated with a single dose of 800 mcg/kg was estimated at 108 ng/ml and the 95% percentile as 164 ng/ml (Figure 1). A regimen of 600 mcg/kg/day for 3 days would give a similar Cmax (111 ng/mL) and corresponding 95% percentile (161 ng/mL) as the single dose 800 mcg/kg regimen (Figure 2 and Table 2). A regimen of 300 mcg/kg/day for 3 days would give approximately half those values. The 3-day regimens were predicted to increase the time that ivermectin concentrations remain above the lethal concentration 50% (LC50) of 16 ng/ml [12] from 46 hours with the 800 mcg/kg single dose to 86 and 162 hours, respectively, with the 300 and 600 mcg/kg/day regimens. The 16 ng/mL threshold was chosen as this was the median of 3 LC50 concentrations reported previously [12,14,15]. The simulated data were in excellent agreement with actual data observed in a dose-finding study by Guzzo et al 2002 [24], which indicated proportional pharmacokinetics at doses ranging from 30 to 120 mg, thus giving confidence in the parameters used in the simulations.

Table 2. Summary of simulated maximum drug concentration and time above lethal concentration 50%.

Ivermectin dosing regimen	Cmax[a] (median 5th-95th percentiles)	Days above LC50[b] (median 5th-95th percentiles)
800 mcg/kg single dose	108.1 (75.3-164.4)	1.9 (1.0-5.7)
600 mcg/kg/day for 3 days	111.0 (83.2-161.2)	6.8 (3.8-13.4)
300 mcg/kg/day for 3 days	55.4 (41.6-80.6)	3.6 (2.8-7.5)

[a]Cmax: maximum drug concentration (ng/mL).

[b]LC50: lethal concentration 50% (16ng/mL).

Figure 1. Simulated plasma concentrations of ivermectin 800 mcg/kg single dose. Monte Carlo simulation of 1000 theoretical subjects of ivermectin concentration with 800 mcg/kg single dose (median: solid line, 5th and 95th percentiles: dashed lines). Cmax is 108.1 ng/mL (CI 75.3-164.4). Time above LC50 (16 ng/mL; dotted line) is 1.9 days (CI 1.0-5.7).

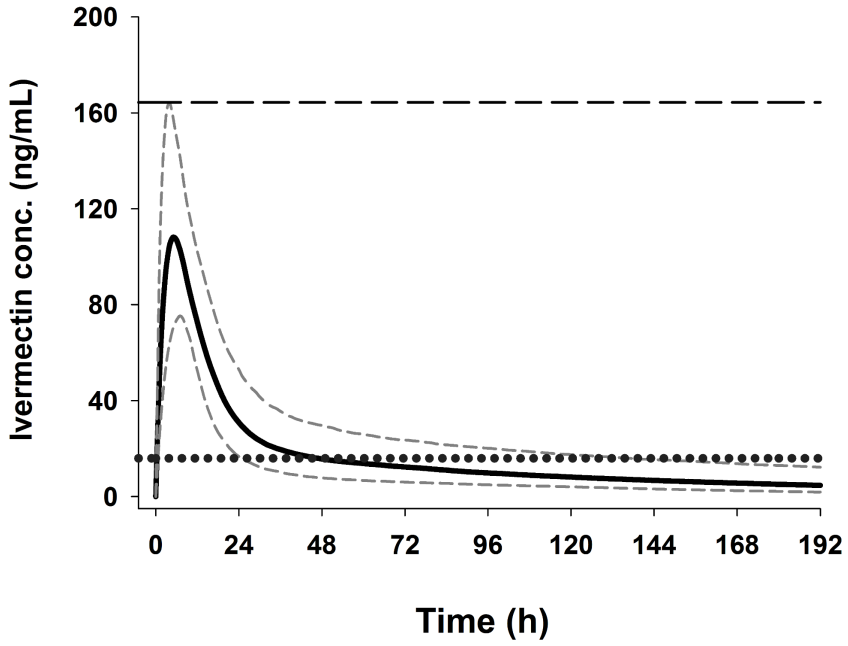
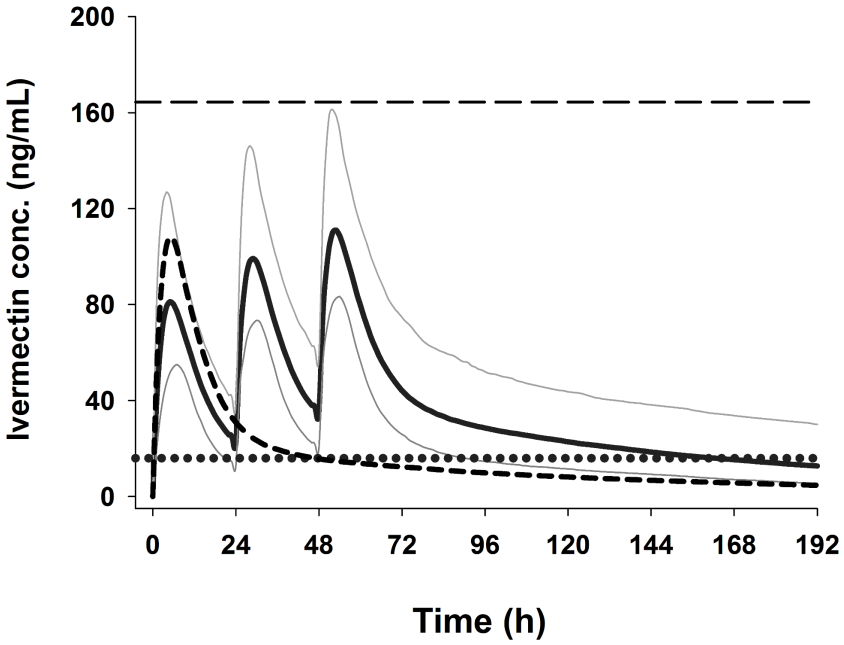


Figure 2. Simulated plasma concentrations of ivermectin 600 mcg/kg/day 3-day regimen and 800 mcg/kg/day single dose. Monte Carlo simulation of 1000 theoretical subjects of ivermectin concentrations following 600 mcg/kg/day for 3 days (median: solid line, 5th and 95th percentiles: grey lines), achieving similar Cmax concentrations compared to 800 mcg/kg single dose (median: dash curve, 95th percentile of Cmax: dashed horizontal line). The median time above LC50 (16 ng/mL; dotted horizontal line) increases from 1.9 days with 800 mcg/kg single dose to 6.8 days with 600 mcg/kg/day for 3 days.



Parallel Versus Dose-Escalation Design

The proposed study uses a standard parallel design, comparing the 2 intervention arms with the placebo arm. This parallel design, instead of a dose-escalation design (when the lower dose group would be studied first prior to enrolling patients in the higher dose group), was considered appropriate because the Cmax levels and the 95th percentile concentrations in the proposed highest dose group of 600 mcg/kg/day will be equivalent to the Cmax found with single dose 800 mcg/kg, which has been administered to at least 402 patients before as treatment for onchocerciasis or as part of regulatory studies (see Table 1). Furthermore, with 30% variation assumed, the Cmax is estimated to remain well below the Cmax value obtained with 2000 mcg/kg, the highest dose tested and which was well-tolerated in a dose escalation study.

Why Patients with Malaria?

The study will enroll patients with symptomatic uncomplicated malaria, instead of asymptomatic patients with malaria parasites (carriers) or malaria negative individuals who are the predominant target population in MDA campaigns. However, it is unlikely that the mosquitocidal effect of ivermectin will differ much amongst these groups. Preference is given to symptomatic patients based on the rationale that this study is labor intensive, requiring very frequent patient follow-up and blood sampling, and thus requires a major commitment from study participants. Symptomatic patients, aside from similarly requiring antimalarial treatment, are more likely to favor hospital admission and frequent outpatient visits than asymptomatic patients or other volunteers. The frequent follow-up is potentially also more beneficial to the patients with symptomatic malaria than asymptomatic patients.

Justification for Host Genetic Studies

The cytochrome P450s (CYPs) are the major enzymes involved in drug metabolism. To be able to interpret variations in the pharmacokinetic drug profiles of piperaquine and ivermectin, and any drug interactions, we need to determine the genotypes of the genes encoding CYP enzymes (see above).

Direct Skin Feeding Versus Membrane Feeding

The primary endpoint is based on membrane feeding of mosquitoes using blood obtained by venepuncture from patients recently treated with ivermectin. However, a nested sub-study, in all those that give additional consent, will compare mosquito mortality rates between clusters fed using standard membrane feeding versus clusters fed directly (by allowing them to feed on the arm of the study participant). Ivermectin feeding studies with direct feeding on humans [13], and cattle [36], have shown a longer mosquitocidal effect (greater than 2 weeks) in comparison with studies using membrane feeding (less than 7 days) [14].

We hypothesize that direct feeding could result in higher mosquito mortality due to potential differences between venous blood (used in membrane feeding) and blood in subdermal venuoles and arterioles (the main source of blood for mosquitoes during direct skin feeding) due to drug accumulation in subcutaneous fat, dermal, and facial tissue (2- to 3-fold higher concentrations than in venous blood [37]), or increased exposure of the mosquito to ivermectin through other means like perspiration.

There have been no studies conducted directly comparing direct feeding versus membrane feeding on mosquito mortality following ivermectin administration. However, previous studies looking at infectivity (ie, the ability of the vector to develop oocysts and sporozoites after ingesting gametocytes) showed

significant differences in terms of infectivity in favor of direct feeding (odds ratio 2.39) [38]. Although the mechanisms involved in infectivity studies may differ from studies addressing the killing effect of ivermectin, this recent infectivity study [38] indicates the importance of addressing the potential that the feeding method to expose mosquitoes to ivermectin may be an important effect modifier and that studies using membrane feeding may potentially underestimate the true effect of ivermectin.

Membrane feeding will be used as the primary outcome because direct skin feeding is labor intensive, may be unpleasant to the study participants, and result in higher refusal rates.

Study Setting

The study will be conducted in the Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) in Kisumu, western Kenya, a major tertiary care hospital. Almost 25,000 outpatients are treated for clinical malaria at JOOTRH annually, of which one-third are laboratory-confirmed. Approximately 20% of these patients are 18 to 50 years old. Malaria positive individuals will also be pre-screened at 5 nearby health facilities; those that pass pre-screening and give consent will be brought to JOOTRH for screening and all further study procedures.

Eligibility Criteria

Inclusion and exclusion criteria for the study are shown in Textbox 1.

Textbox 1. Eligibility Criteria

Inclusion Criteria:

- Symptomatic, uncomplicated *P. falciparum* infection
- Positive malaria microscopy or malaria rapid diagnostic test (RDT, pLDH)
- Age 18 to 50 years
- Provide written informed consent
- Agree to be able to travel to clinic on days 1, 2, 7, 10, 14, 21, and 28

Exclusion Criteria:

- Signs or symptoms of severe malaria
- Unable to provide written informed consent
- Women who are pregnant or breast feeding
- Hypersensitivity to ivermectin or DP
- Rate corrected QT interval (QTc) of greater than 460 ms on electrocardiogram (ECG)
- Body mass index (BMI) below 16 or above 32 kg/m2
- Hemoglobin (Hb) concentration below 9 g/dL
- Taken ivermectin in the last month
- Taken DP in the last 12 weeks
- *Loa loa* as assessed by travel history to Angola, Cameroon, Chad, Central African Republic, Congo, DR Congo, Equatorial Guinea, Ethiopia, Gabon, Nigeria and Sudan
- History and/or symptoms indicating chronic illness
- Current use of tuberculosis or anti-retroviral medication
- Previously enrolled in the same study

Trial Medications and Interventions

Participants will be randomized to one of the following 3 arms: (1) the “0 mcg/kg” (placebo) arm consisting of DP plus ivermectin-placebo 600 mcg/kg/day for 3 days, (2) the “300 mcg/kg” arm consisting of DP plus ivermectin 300 mcg/kg/day and ivermectin-placebo 300 mcg/kg/day for 3 days, or (3) the “600 mcg/kg” arm consisting of DP plus ivermectin 600 mcg/kg/day for 3 days. Patients will receive their weight-based doses of DP and ivermectin/placebo. Each dose will be given as directly observed therapy by study staff, after which participants will be monitored for 30 minutes for any vomiting and adverse reactions. If vomiting occurs within 30 minutes, then the participant will be withdrawn from the study, DP will be re-administered, and no further ivermectin will be given.

Dihydroartemisinin-Piperaquine

DP was selected as the drug of choice as it is the most likely candidate to be used in future MDA campaigns because of the longer prophylactic effect against malaria (4 to 6 weeks) compared with 2 to 3 weeks with artemether-lumefantrine (AL). Each participant will receive a weight-based dose of DP 320/40 mg (Eurartesim, Sigma Tau, Italy) as per the product insert (36 to 75 kg: 3 tablets, greater than 75 kg: 4 tablets) once a day for 3 days.

Ivermectin and Placebo

Ivermectin and/or placebo 6 mg tablets (Iver P, Laboratorio Elea, Argentina) will be administered per bodyweight. The 600 mcg/kg/day arm will receive only ivermectin tablets, the 300 mcg/kg/day arm will receive half the number of ivermectin tablets and an equal number of placebo tablets, and the 0 mcg/kg/day arm will receive only placebo tablets. All participants will receive the same total number of tablets once a day for 3 days based on their bodyweight (45 to 55 kg: 5 tablets, 55 to 65 kg: 6 tablets, 65 to 75 kg: 7 tablets, 75 to 85 kg: 8 tablets, 85 to 95 kg: 9 tablets, 95 to 105 kg: 10 tablets).

Endpoints and Outcome Measures

Primary Efficacy Outcome

The primary efficacy outcome is mosquito survival at 14 days after feeding on blood taken from study participants who started the 3-day ivermectin and DP regimen 7 days earlier (Multimedia Appendix 1).

Secondary Outcomes

Secondary outcomes include (1) mosquito survival at each day, up to day 21 or 28, after each feeding experiments performed at 0, 2 days plus 4h, 7, 10, 14, 21, and 28 days after start of treatment; (2) occurrence of oocysts from day 10 onwards after each feeding as determined by polymerase chain reaction (PCR); (3) malaria clinical and parasitological treatment response by day 28; and (4) plasma concentration profiles of piperaquine and ivermectin as described by standard pharmacokinetic metrics, for example area under the curve measurements from time zero to infinity (AUC0-∞), time zero to the time of the last measurable concentration (AUC0-tlast), Cmax, and plasma half-life, time to maximum plasma concentration, etc (Multimedia Appendix 1).

Tolerability and Safety Endpoints

Tolerability and safety endpoints are shown in Textbox 2.

Textbox 2. Tolerability and safety endpoints.

Tolerability

- Any adverse events assessed in general toxicity questionnaires asked at each study visit

Safety

- Primary

  Mydriasis quantitated by pupillometry [24]
- Secondary
  - Central nervous system (CNS) effects
  - General toxicity
  - Serious adverse events
  - Hemoglobin concentrations
  - QTc interval (see below “Electrocardiogram Monitoring”)

Participants’ Timeline

Overview Study Phases

The study plan and schedule of assessment is provided in Multimedia Appendix 1. The participant’s timeline will consist of a pre-screening visit (visit 1), consent, screening, and enrolment visit (visit 2), 2 subsequent treatment visits (3 and 4) on days 1 and 2, and 6 follow-up visits for assessment of efficacy parameters (visits 5 to 10). For those enrolled in the pharmacokinetic study additional visits for drug level sample are required as outlined in Multimedia Appendix 2.

Visits 1 and 2: Pre-Screening, Consent, Screening and Enrolment

Patients presenting to the outpatient departments of the study clinics will be pre-screened to determine if they meet readily apparent study eligibility criteria including (1) age 18 to 50 years; (2) uncomplicated malaria; (3) in Kisumu next 4 weeks; (4) hemoglobin (Hb) less than or equal to 9g/dL (if already performed); (5) not pregnant or breast feeding; (6) no known chronic illness; and (7) not previously enrolled in IVERMAL.

Patients passing pre-screening will be approached to obtain consent. For those consenting, study-specific screening procedures will take place, including demographics, full history, past medication use, travel history (*Loa* endemic countries), physical examination, electrocardiogram (ECG), pupillometry, and laboratory tests (to confirm malaria, Hb, and pregnancy). Those fulfilling all enrolment inclusion criteria and not meeting any exclusion criteria will be enrolled into the study, randomized, and treated with the appropriate tablets according to study arm (Textbox 1). Estimated duration is 1.5 to 2.0 hours.

Visits 3 and 4: Treatment Visits

Participants will return to the outpatient clinic on day 1 and 2 for the 2nd and 3rd dose of study drugs. In exceptional cases a participant will be permitted to take the study medication at home or the participant will be visited at home by study staff to administer the medication. A follow-up ECG will be taken just prior to and 4 to 6 hours after the last dose of DP plus ivermectin on day 2.

Visits 5 to 10: Scheduled Follow-Up Visits

Participants will return to the outpatient clinic for follow-up as specified (see Multimedia Appendix 1). A questionnaire will assess the presence of signs and symptoms, including any adverse effects. A brief clinical examination will be performed and a venous blood sample will be taken for malaria diagnosis, Hb, and drug levels. On visits 5 (day 2 plus 4h) and 6 (day 7), drug levels will also be determined in a finger prick sample. A final follow-up ECG will be taken on the day 28 visit. Participants will be asked to provide telephone numbers so that study staff may make every effort to follow-up participants who have missed scheduled visits (Multimedia Appendix 2, section 8.5.5, page 31).

Unscheduled Visits

At any time, participants displaying signs or symptoms of severe malaria will be admitted to the inpatient ward for further evaluation and treatment free of charge. Blood samples for malaria smears, parasite genetics (filter paper dried blood spots) and Hb will be taken if clinically indicated (e.g. documented fever greater than or equal to 37.5°C axillary, or a history of fever in the last 24 hours).

Sample Size

The study requires a total of 141 participants (47 participants in the 0, 300, and 600 mcg/kg/day groups each). This is powered at 80% to detect a relative increase of 30% (RR 1.300) in the 14-day post-feeding mortality rate (primary outcome) from 24% in the control group (0 mcg/kg ivermectin) to 31.2% in the 300 mcg/kg/day group, and a 25% (RR 1.246) increase from 31.2% with 300 mcg/kg/day to 38.9% in 600 mcg/kg/day recipients, measured from blood taken 7 days after the start of intake of ivermectin and using clusters of 100 anopheline mosquitoes allowing for 10% non-feeders (alpha=.05). The same sample size would give 90% power to detect a 35% (RR 1.348) increase from 24% (0 mcg/kg/day) to 32.4% (300 mcg/kg/day), and 27.7% increase (RR 1.285) from 32.4% (300 mcg/kg/day) to 41.3% (600 mcg/kg/day). The calculations assume an intracluster correlation coefficient (ICC) of .0622 and allow for 6.5% loss-to follow-up of participants by day 7 (ie, 44 of the 47 patients per arm contribute to the primary analysis) [14]. The 10% non-feeding rate is based on current data from the same laboratories at Kenya Medical Research Institute (KEMRI), Kisian, Kenya. The 24% mortality rate estimate by day 14 post-feeding in the control arm is average of observation at KEMRI (18.3%) and in a recent study in Burkina Faso, which showed a 21.2% mortality by day 10 [14], which when extrapolated with 4 additional days predicted a mortality of 29.7% by day 14. The ICC value of .0622 was calculated using data from the recent study in Burkina Faso (Bousema, personal communications) [14].

Assignment of Interventions

Allocation

The study will use stratified randomization (4 strata) by body mass index (BMI: high/low) and sex (male/female) as these are important determinants of the pharmacokinetics of ivermectin [14]. The high/low BMI thresholds are 23 kg/m^2 and 21 kg/m^2, for females and males respectively. Participants will be randomly assigned to 1 of the 3 study arms. The study statistician will computer-generate a randomization sequence using permuted block randomization with fixed block sizes.

Blinding

The study will be double-blinded to participants and study staff. Allocation concealment will be achieved by use of sealed opaque envelopes. All study participants in all 3 arms will receive standard dose DP, and also active (600 mcg/kg/day arm), placebo (0 mcg/kg/day arm), or a combination of active and placebo ivermectin tablets (300 mcg/kg/day arm), such that each arm receives the same number of tablets in each weight strata.

Pharmacokinetic Studies

Overview

The first 36 patients to give additional consent for rich pharmacokinetics (approximately 12 per arm), will be enrolled in a rich pharmacokinetic study using frequent sampling per individual (26 samples per patient, see Multimedia Appendix 2 [Table 2, page 15]) to determine the detailed pharmacokinetic profile of the 2 regimens and assess whether any drug interaction occurs with piperaquine that is of clinical relevance. The remaining patients (approximately 35 per arm) will contribute to a population pharmacokinetic study consisting of sparse pharmacokinetic sampling with a maximum of 13 samples per patient including baseline (1 venous sample), 6 scheduled visits as part of the main trial (6 venous and 2 finger prick samples), and 2 extra visits for population pharmacokinetic sampling (2 venous and 2 finger prick samples).

The rich and population pharmacokinetic studies combined will allow us to determine the main sources and correlates of variability in drug concentrations (for both ivermectin and piperaquine), including demographic, pathophysiological, such as BMI and gender, and other factors that might alter dose-concentration relationships. As this is a placebo controlled trial, the sampling methodology for the 47 patients in the ivermectin-placebo arm will be identical to that used for the 300 and 600 mcg/kg arms. The patients in the placebo-ivermectin arm will allow us to determine the piperaquine kinetic profile in the absence of ivermectin.

Finger prick blood draws will be performed at a maximum of 4 time points in addition to the venous blood draws. The aim is to compare the capillary and venous drug concentration levels as it has been hypothesized that these might differ for ivermectin, similar to other drugs including piperaquine. A difference between capillary and venous drug concentrations could help further explain any observed difference in mosquito mortality between membrane and direct skin feeding (see also above “Direct Skin Feeding versus Membrane Feeding”).

Standard Pharmacokinetic Study (Rich Sampling)

All of the rich pharmacokinetic participants (approximately 12 per arm) will have venous blood sampled (4 ml whole blood to obtain 2 ml plasma, or 5.2 mL of whole blood if coinciding with a scheduled follow-up visit for the main trial) at baseline and each of 21 follow-up time points listed in Multimedia Appendix

2 (Table 2, page 15). In addition, 4 finger pricks (0.5 mL whole blood) will be taken at days 2 plus 4 h, 3, 4 and 7. The total blood volume to be drawn from these patients is 98.4 mL whole blood over 28 days, 82.8 mL of which is taken during the first 10 days. If more than 2 patients withdraw from the study without giving more than 12 samples, the withdrawing patients will be replaced. Outpatients who consent to the standard pharmacokinetic study will be admitted in the hospital for the first 3 days.

Population Pharmacokinetics (Sparse Sampling)

Each of remaining patients (approximately 35 per arm), not enrolled in the rich pharmacokinetic sub-study, contribute to the population pharmacokinetic study, which consists of 13 sampling points (see Multimedia Appendix 2, page 15). Seven of the 13 time points coincide with the timing of the sample for membrane feeding (including the baseline sample), and thus do not require an extra venepuncture (ie, days 0, 2 [52 hrs; 4 hrs after last dose of ivermectin], days 7, 10, 14, 21 and 28). Six of the 13 time points are specific for the population pharmacokinetic study and will require an extra venepuncture (50, 54, 60, 72, 96 and 120 hours, ie, 2, 6, 12, 24, 48, and 120 hrs after the third and last dose of ivermectin). To ensure an equal distribution of samples across the different sampling time points for the extra 2 visits, participants will be divided into 4 extra sampling groups; each of which will contribute 2 extra time points, with the exception of group B which will contribute 1 extra time point (Table 3). In addition, a maximum of 4 finger pricks (0.5 mL whole blood) will be taken at days 2 plus 4 h, 7, and at each of the 2 population pharmacokinetic visits. Thus the total number of samples per participant will be 13 and involve a total of 46.4 mL of whole blood (including the 7 samples for the main trial). The sampling times will be noted in the case record form (CRF), and the patient given a reminder card to return to clinic at their allocated time.

Table 3. Schedule of extra sampling points for population pharmacokinetic study by 4 sampling groups.

Subject Group	Sample day[a] (plus hours after 3rd ivermectin dose)	Sample absolute time[a], hours	Number per sampling strata
A	2.08 (+2 hours)	50	9
	2.25 (+6 hours)	54	
B	2.25 (+6 hours)	54	8
C	2.50 (+12 hours)	60	9
	3 (+24 hours)	72	
D	4 (+48 hours)	96	9
	5 (+72 hours)	120	
Total			35

[a]Extra visits that need to be made specifically for the population pharmacokinetic samples. The other 7 visits contributing to the population pharmacokinetic analysis (days 0, 2, 7, 10, 14, 21, 28) coincide with the scheduled visits in the main trial. The first day is day=0; day 1 starts 24 hours after the first dose. The allocation to the sampling strata will be at random. However, if a participant indicates he/she is not able to attend a certain follow-up day, the strata can be replaced by another sampling schedule (within the same allocation strata, eg, for BMI, gender, etc) until all 15 or 16 allocations per sampling group have been used.

In anticipation of a 40% refusal rate or loss to follow-up, we estimate that the combined rich and population pharmacokinetic sub-studies will contribute 361 samples including 47 baseline samples (100%) and 314 (60%) follow-up samples out of a potential 524 follow-up samples across 22 sampling time points after baseline, 20 of which overlap, with a total of 12 to 47 observations per time point (see Multimedia Appendix 2,Table 2, page 15).

Laboratory Procedure

Mosquito Colonies

See the “Procedures for Assessing Efficacy and Safety Parameters” section above for use of mosquito colonies and procedures to assess the primary (mosquito survival) and secondary entomological endpoints (sporogony). The section below describes the maintenance of the mosquito colonies.

The mosquito colony used in this study will be *An. gambiae s.s.* Kisumu strain, originally from Kisumu, Kenya. The strain is maintained at the KEMRI/Centre for Global Health Research (CGHR) insectaries and is susceptible to all insecticides approved by the World Health Organization (WHO). When performing membrane feeds on infected human blood, mosquitoes will be kept and fed in cages or paper cups. The cages or paper cups will be kept in a temperature- and humidity-controlled insectary. The feeding and the storage of live infected mosquitoes will occur in sealed rooms with at least 2 doors and/or barriers separating the inner rooms from the outside. Mosquitoes will not be removed from their enclosures, with exception of the cage for oocyst determination. During transportation, live infected mosquitoes will be transported within paper cups that are covered with a moist towel and enclosed within locked cool-boxes to remove any chances of escape. The cool-boxes will only be opened within the confines of a double door insectary.

Ivermectin Plasma Concentration

The LC50 has been previously estimated using spiked blood (blood to which known concentrations of ivermectin are added) in membrane feeding assays [12,15]. We will test the concentration of ivermectin in human plasma in order to provide data for a pharmacokinetic/dynamic analysis to obtain estimates of the 10-day LC50 and time post-treatment that the transmission blocking effects (on mosquito survival and oocyst rates) lasts.

Hemoglobin Testing

Hb will be tested using HemoCue (Angelholm, Sweden) photometers.

Thick and Thin Blood Smears for Malaria

Thick and thin blood films for parasite counts will be obtained and examined. Malaria parasites will be counted against 200 high power fields before a slide is declared negative [39].

Processing of Pharmacokinetic Samples

Plasma will be stored locally on site at -20°C or in liquid nitrogen and shipped to a central laboratory for storage at -70°C prior to batch analysis at the Liverpool School of Tropical Medicine. Samples will be shipped in dry ice to the laboratories in Liverpool, United Kingdom where the plasma concentrations of ivermectin and piperaquine will be determined using assays validated to international Food and Drug Administration (FDA) standards. Plasma concentration-time data will be used to evaluate pharmacokinetic parameters including CL/F (oral clearance), V/F (oral volume of distribution), and Ka (absorption rate constant) using population pharmacokinetic methods. Area under the curve (AUC) and half-life will also be calculated.

Statistical Methods

A study statistical analytical plan for the final analysis, that supersedes the study protocol, has been drawn up during the course of the study before the unblinding of data at database lock (see Multimedia Appendix 3).

Procedures for Assessing Efficacy and Safety Parameters

Membrane Feeding Procedure

The following procedures will be conducted in accordance with a standard membrane feeding protocol [40]. A 1 mL sample of the participant's blood will be drawn into a sodium heparin (coated) tube pre-heated to 37.5°C. Within 2 minutes the blood will be placed in a glass bell membrane feeding system and cups of mosquitoes will commence feeding. For each feeding 3 new cups (2 cups for mosquito survival, and 1 cup for oocysts) of 50, 3 to 5 day old female, insectary-reared *An. gambiae s.s.* mosquitoes will be presented to the membrane feeder for 20 minutes. The number of mosquitoes with an engorged abdomen will be counted and those with lean abdomens discarded. Each day up to day 28 (mosquito survival cups) or day 10 (oocyst cup), the number of dead mosquitoes will be counted and removed. After the initial feeding on human blood, the mosquitoes will be kept in an incubator and maintained on sugar feeds. Insectary staff assessing mosquito survival and oocyst development will be blinded to all characteristics of the cups (ie, participant identification, study arm, duration between treatment and feeding, and feeding method).

Primary Efficacy Outcome

The primary outcome will be the survival of mosquitoes (from the 2 mosquito survival cups) at 14 days after feeding on blood taken from study participants who started the 3-day ivermectin and DP regimen 7 days earlier.

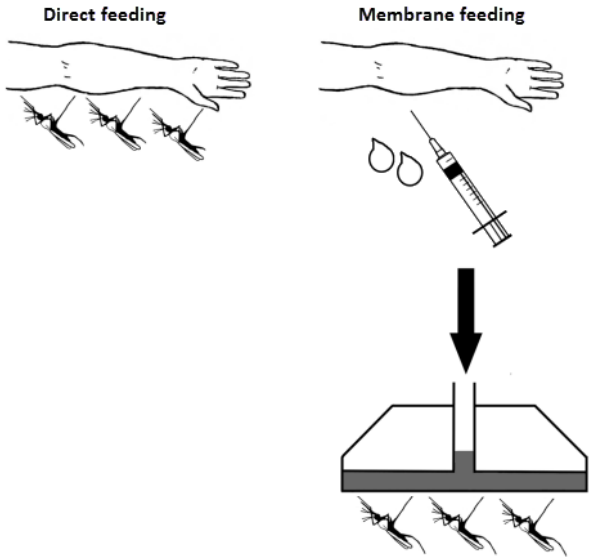
Secondary Efficacy Outcomes

Although the primary endpoint is assessed at day 14, the study will collect survival data of mosquitoes at each day up to day 21 or 28 for the mosquito survival cups and day 10 in the case of oocyst cups, after each feeding experiments performed at 0, 2 days plus 4h, 7, 10, 14, 21, 28 days after start of treatment. The methods will be identical to that described for the primary outcome where each day beyond day 14 the number of dead mosquitoes will be counted and removed until day 28 inclusive. The exact number of follow-up days (21 or 28 days) will be subject to logistical constraints of the laboratory, and mortality rates in the mosquito populations which will be further determined prior to the start of the study. The aim is to determine the median time to mortality, which requires that at least half of the mosquito population has died in each arm. It is anticipated that 21 days will be sufficient.

Direct Skin Feeding and Mosquito Survival

A sub-study will determine the effect of direct feeding versus membrane feeding on mosquito survival, after feeding experiments performed at 7 days after the start of treatment. In direct skin feeding assays, 1 cup of 50 mosquitoes is placed directly on the skin of the human host and allowed to feed for 15 minutes (Figure 3). Further procedures after direct feeding are identical to those after membrane feeding.

Figure 3. Difference between membrane feeding and direct feeding (adapted from Bousema et al 2012 [38]).



Infectivity to Mosquitoes (Oocyst Polymerase Chain Reaction)

On day 10 post membrane feeding, when residual DNA from the blood meal is highly unlikely [14,41,42], all surviving mosquitoes in the oocyst cup will be preserved to determine oocyst prevalence by PCR. Mosquitoes will be homogenized and processed, in 2 pooled batches per cup.

Asexual Treatment Response and Parasite Clearance

Standard methods will be used to assess the in vivo treatment response to DP using the microscopy and rapid diagnostic test (RDT) data collected at each scheduled follow-up visit and criteria described by World Wide Antimalarial Resistance Network (WWARN) [43].

Pupillometry

In animal studies, mydriasis has been shown to be a first sign of ivermectin toxicity. To monitor for possible toxicity, pupil diameter size will be measured at baseline and each scheduled visit using a portable, single-button activation, battery operated hand-held pupillometry device that very accurately measures pupil size requiring no calibration (NeurOptics VIP-200 Variable Pupillometer). This device measures the pupil 30 times per second over a 5-second period and provides the average pupil diameter and standard deviation (+/- 0.1 mm). The measurements will be taken in a dark room with standardized lighting conditions.

Electrocardiogram Monitoring

Piperaquine can potentially lead to prolongation of the rate corrected QT interval (QTc) on an electrocardiogram (ECG). To exclude a possible interaction between ivermectin and piperaquine leading to an increased QTc interval, 12-lead ECGs will be performed to measure the QTc interval at baseline, day 2 pre last dose, day 2 at 4 to 6h post last dose and again at day 28. The day 28 sample is included as it can be difficult to assess a true baseline in patients with acute malaria, as malaria and fever are known to increase the heart rate and decrease the QTc interval. On day 28 most, if not all, patients will be malaria free and residual piperaquine levels low enough not to affect QTc intervals. A portable ECG machine (MAC 600, General Electric, US) will be used with automated ECG interpretation. Patients with a QTc value of 480 ms or greater prior to the last dose of DP will not receive the last dose of DP, but receive a full course of artemether lumefantrine instead. Fridericia's correction will be used to calculate the QTc values for final data analysis using the following equation: $QTc = QT/RR^{0.33}$.

Adverse Events

Adverse events and serious adverse events will be monitored, managed, and recorded during the course of the study. They will be recorded and tabulated for each treatment arm, overall, and per body system (see Multimedia Appendix 2, Section 9.6, Safety Monitoring and Reporting).

Ethics Approval and Consent to Participate

This protocol, the informed consent documents, and patient information sheets have been reviewed and approved by the Research Ethics Committees at KEMRI (protocol #2775), LSTM (protocol #14.002), and JOOTRH. The Centers for Disease Control and Prevention (CDC, protocol #6720) gave approval for reliance on the KEMRI institutional review board (see Multimedia Appendix 4 Ethics Approvals KEMRI, CDC, LSTM, and JOOTRH).

Results

Recruitment started July 20, 2015. Enrolment was completed May 2016, and clinical follow-up was completed 4 weeks later in June 2016. Mosquito follow-up was completed in July 2016, 4 weeks after completion of the clinical follow-up. Unblinding and analysis will commence once the database has been completed, cleaned, and locked.

Discussion

Principal Findings

New strategies for malaria control, and eventually for elimination are critically needed. This study will seek to answer the question as to whether higher doses of ivermectin (300 and 600 mcg/kg/day for 3 days) are well tolerated, safe, and result in longer durations of mosquitocidal effects than standard 150 to 200 mcg/kg single dose treatments. This study requires major infrastructure and collaboration, as it brings together the disciplines of clinical medicine, entomology, parasitology, pharmacokinetics, and pharmacogenetics in a clinical trial. For this study, 141 patients and 150,000 mosquitoes will each be followed for 28 days. For this reason, this trial has been placed at the KEMRI, CDC, and LSTM collaboration in western Kenya, a research site, which in collaboration with its partners, has been conducting research for over 35 years and has the capacity to undertake such a trial. An important possible limitation of this study is that it will enroll participants with symptomatic malaria, whereas possible future applications of high-dose ivermectin may involve MDA with ACT's targeting asymptomatic carriers and uninfected individuals in addition to symptomatic patients. Should this study show promising results, then the next step will be to evaluate safety, tolerability, and efficacy in younger age groups with the ultimate goal of testing its effect on malaria transmission when applied at the population level through MDA.

Conclusion

High-dose ivermectin, if found to be safe and well tolerated, could potentially complement existing tools for malaria elimination.

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Authors' Contributions

FtK and MS conceived the study. MS, PPH, and FtK wrote the grant. MS, EO, and FtK drafted the protocol. DW provided statistical expertise and verified the sample size calculation. GA and SW conducted the Monte Carlo simulations to define the dosing regimen and further developed the pharmacokinetic sub studies. All investigators contributed to the refinement of the study protocol and approved the final version. MS and FtK drafted the manuscript. All authors read and approved the final manuscript prior to submission. The findings and conclusions in this paper are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Summary of study design and schedule of assessment (SPIRIT flow diagram).

[PDF File (Adobe PDF File), 288KB - resprot_v5i4e213_app1.pdf]

Multimedia Appendix 2

Full study protocol (including SPIRIT checklist): v4.1, dated 14-Jan-2016.

[PDF File (Adobe PDF File), 3MB - resprot_v5i4e213_app2.pdf]

Multimedia Appendix 3

Statistical Analytical Plan (SAP): v1.0, dated 19-Feb-2016.

[PDF File (Adobe PDF File), 347KB - resprot_v5i4e213_app3.pdf]

Multimedia Appendix 4

Ethics approvals v4.1: KEMRI, CDC, LSTM, and JOOTRH.

[PDF File (Adobe PDF File), 748KB - resprot_v5i4e213_app4.pdf]

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Abbreviations

ACT: artemisinin-based combination therapy
AUC: area under the curve
CDC: Centers for Disease Control and Prevention
Cmax: maximum drug concentration
CYP: cytochrome P450
CYP3A4: cytochrome-P450 3A4
DHA: dihydroartemisinin
DP: dihydroartemisinin-piperaquine
ECG: electrocardiogram
Hb: hemoglobin
ICC: intracluster correlation coefficient
JOOTRH: Jaramogi Oginga Odinga Teaching and Referral Hospital
KEMRI: Kenya Medical Research Institute
LC50: lethal concentration 50%
LLINS: long-lasting insecticide treated nets
LSTM: Liverpool School of Tropical Medicine
MDA: mass drug administration
PCR: polymerase chain reaction
RDT: rapid diagnostic test
QTc: rate corrected QT interval on an electrocardiogram

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Protocol

The Use of eHealth and Provider-Based Health Services by Patients with Diabetes Mellitus: Protocol for a Cross-Sectional Study

Anne Helen Hansen[1,2], BSW, MD, PhD; Meghan Bradway[3], MBA; Jan Broz[4], MD; Tor Claudi[5], MD; Øystein Henriksen[6], BSW, PhD; Silje C Wangberg[7,8], PsyD, PhD; Eirik Årsand[3,9], PhD

[1]University Hospital of North Norway, Tromsø, Norway

[2]Department of Community Medicine, Faculty of Health Sciences, UiT - The Arctic University of Norway, Tromsø, Norway

[3]Norwegian Centre for E-health Research, University Hospital of North Norway, Tromsø, Norway

[4]Department of Internal Medicine, Second Faculty of Medicine, Charles University, Prague, Czech Republic

[5]Medical Centre, Nordland Hospital, Bodø, Norway

[6]Faculty of Social Sciences, Nord University, Bodø, Norway

[7]Department of Substance Use and Mental Health, University Hospital of North Norway, Narvik, Norway

[8]Department of Health and Care Sciences, Faculty of Health Sciences, UiT - The Arctic University of Norway, Narvik, Norway

[9]Department of Clinical Medicine, UiT - The Arctic University of Norway, Tromsø, Norway

Corresponding Author:
Anne Helen Hansen, BSW, MD, PhD
University Hospital of North Norway
PO box 35
Tromsø, 9038
Norway
Phone: 47 91619655
Fax: 47 77754099
Email: anne.helen.hansen@unn.no

Abstract

Background: The prevalence of diabetes and the use of electronic health (eHealth) resources are increasing. People with diabetes need frequent monitoring and follow-up of health parameters, and eHealth services can be of great significance in this regard. However, little is known about the extent to which different kinds of eHealth tools are used, and how the use of eHealth is associated with the use of provider-based health care services among people with diabetes.

Objective: The primary objective of this study is to investigate the use of eHealth and its association with the use of provider-based health care services. The secondary objectives include investigating which eHealth services are used (apps, search engines, video services, social media), the relationship between socioeconomic status and the use of different eHealth tools, whether the use of eHealth is discussed in the clinical encounter, and whether such tools might lead to (or prevent) doctor visits and referrals.

Methods: We will conduct cross-sectional studies based on self-reported questionnaire data from the population-based seventh Tromsø Study. Participants will be diabetic patients aged 40 years and older. According to our estimates, approximately 1050 participants will be eligible for inclusion. Data will be analyzed using descriptive statistics, chi-square tests, and univariable and multivariable logistic regressions.

Results: The grant proposal for this study was approved by the Northern Norway Regional Health Authority on November 23, 2015 (HST 1306-16). Recruitment of participants for the Tromsø Study started in 2015 and will continue throughout 2016. This particular project started on July 1, 2016.

Conclusions: This project may yield benefits for patients, health care providers, hospitals, and society as a whole. Benefits are related to improved prevention services, health, experience of care services, self-management tools and services, organizational structures, efficiency of specialist care use, allocation of resources, and understanding of how to meet the challenges from the increasing prevalence of diabetes. This project has potential for generalization to other groups with chronic disease.

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KEYWORDS

use of eHealth; health care utilization; cross-sectional study; diabetes mellitus; socioeconomic status; Norway

Introduction

Solutions based on information and communication technology for health information, self-management, and novel treatment strategies have developed rapidly in recent years. These solutions have not only become an option for patient self-management, but also potential aids to health care services in their struggle to keep up with the population's increasing expectations of service. Of particular interest are patients with chronic diseases, such as diabetes mellitus (DM), who are in need of frequent monitoring and follow-up of health parameters.

Increasing Prevalence of Diabetes Mellitus

The prevalence of diabetes is increasing. In 2014 approximately 422 million adults worldwide were living with diabetes [1]. The global prevalence of DM is estimated at 8.5% [1], and 4.3% in Norway [2]. However, since many cases are undiagnosed, it is difficult to estimate the precise prevalence. The World Health Organization has declared diabetes one of the *big five* chronic diseases [3]. Patients represent a large proportion of health care contacts, and costs attributable to DM represent approximately 1.4% of total Norwegian expenditure on health care [4]. Diabetes is a considerable burden on patients in terms of morbidity and mortality, and only one out of eight patients reach the combined national treatment targets for prevention of diabetic complications [5]. Norway wants to become a leading country in the prevention, treatment, and follow-up of diabetes [6]. Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) account for approximately 20% and 80% of cases, respectively.

Increasing Use of eHealth Services

Electronic health (eHealth) refers to "the transfer of health resources and health care by electronic means" [7], and the Internet plays a major role in eHealth interventions. In the joint population of seven European counties, 44% of the total population reported using the Internet for health purposes in 2005 [8,9], increasing to 52.2% by 2007 [10]. In Poland, which is consistent with European trends, 66.7% of the population reported using the Internet for health purposes in 2012 [11]. Among Internet users in the United States and Europe, approximately three quarters conduct health-related searches [8-10,12]. Most Norwegian households (97%) had Internet access in 2015 [13], and 78% of the population 15 years and older have reported using the Internet for health purposes [14].

Relationships Between the Use of eHealth and the Use of Provider-Based Health Services

The use of eHealth is reported to be positively associated with general practitioner (GP) visits (yes/no) [9], but not associated or inversely associated with the frequency of regular provider visits [15,16]. Patients might use eHealth before the visit to seek information and/or to decide about the need to see a doctor, and after the visit for reassurance or additional information [17]. It has been stated that the use of eHealth may postpone or replace medical consultations [18], and approximately 30% of eHealth users in France (aged 15-30 years) reported that they often used the Internet instead of visiting a doctor [19]. In the same study, 88.6% of respondents reported that eHealth use did not change their consultation frequency, whereas 4.9% reported seeing a doctor more often, and 6.5% less often. This trend might differ in older populations, since eHealth use is inversely associated with age [9,10,14,20,21]. A German study found that heavy users of health services were 73% more likely to seek health information on the Internet compared to nonusers [12]. This finding conforms with the illness behavior model [22], indicating that people in poor health are more likely to seek disease-related information online and use health care services to a larger extent. Whether eHealth use in a Norwegian population with diabetes might be associated with the use of provider-based health care services has yet to be explored. Theoretically, eHealth use might enhance self-management and reduce health care visits and costs, based upon the assumption that prevention and treatment of diabetic complications (which arise due to poor disease control) represent a large burden of disease and substantial costs for health care services and society [23-25].

The use of eHealth services often takes place without doctor involvement. A study from the United States found that only 31% of users of mobile health (mHealth; mobile and wireless communication technologies that aid in health and health care) prioritized their physician's involvement [20]. The extent to which DM patients in Norway discuss the information they find on the Internet with their doctors is unknown.

Socioeconomic Status and the Use of eHealth

Health care services and communication inequalities may contribute to inequalities in health, as it is well known that new interventions and treatments reach people in higher socioeconomic groups first [26,27]. Research indicates that women, younger people, and people with middle and high socioeconomic status (SES) are more likely to seek health information and advice from the Internet [9,22,28,29]. Andreassen et al showed that both long-term illness and good health were positively associated with eHealth use in Europe [9], partly contradicting the illness behavior model [22]. In the case of DM, however, there is evidence that there is no immediate gain from implementing health technology platforms in less advantaged groups, in contrast to middle (and especially higher) educated groups, with possible consequences regarding health outcomes [28]. Regarding self-initiated use, Wangberg et al found that SES is related to differential use of eHealth, as people with higher education use eHealth tools that are more likely to influence health behaviors [30]. To our knowledge, the relationship between SES and what kinds of eHealth tools people with DM use has yet to be studied.

Planning for Future eHealth and Provider-Based Health Care Services

Teams at the Norwegian Centre for E-health Research have been developing and studying Internet-based self-management tools for chronic diseases (including DM) for more than a decade, with the understanding that communication technologies

hold great potential for making health services and diabetes care more effective and efficient. However, this potential has not been fully realized. Research on the combined use of consumer-based eHealth (as defined by the use of apps, search engines, video services, and social media) and provider-based health care, as well as the interaction between the use of these different sources of care, is scarce [24,31].

eHealth is an area of continuous and rapid development, and the use of eHealth services and their possible associations with health care utilization and socioeconomic position are likely to vary between regions, countries, diagnostic groups, health care services, and health care systems. Hence, research from different cultural and economic settings is important to achieve an overall epidemiological view and comprehensive understanding, as well as to identify vulnerable subgroups. Understanding the influence of eHealth on health care utilization in the large and growing group of patients with diabetes is important for patients, health care providers, administrators, policy makers, and society, in order to enable evidence-based planning for future eHealth and provider-based health care services, thereby providing better health outcomes.

Methods

Objectives

The primary objective is to investigate the use of eHealth in Tromsø, Norway, and its association with the use of provider-based health care services. This study will peruse the following specific objectives:

1. To investigate which eHealth services are used.

2. To investigate whether the use of eHealth is associated with the use of primary and specialist health care services.

3. To investigate whether the use of eHealth might lead to or prevent doctor visits.

4. To investigate whether patients' use of eHealth is discussed in clinical encounters.

5. To investigate whether the use of eHealth is associated with referrals to specialist care.

6. To investigate whether the use of eHealth is associated with SES.

7. To assess how knowledge gained from this study can be used to develop and implement eHealth solutions and changes in health care services, in order to increase DM patients' chances of reaching their treatment goals.

Based on previous research and the authors' experiences, the following hypotheses have been generated:

1. The use of eHealth is positively associated with one or more GP visits during a year.

2. The use of eHealth is not associated with the use of emergency departments.

3. The use of eHealth does not have any impact on the frequency of doctor visits.

4. It is more common for eHealth users not to discuss the use of eHealth in the consultation than to discuss it.

5. The use of eHealth is associated with an increase in GPs' referrals to specialist services.

6. The use of eHealth is positively associated with the use of outpatient specialist services.

7. The use of eHealth is inversely associated with hospital admissions.

8. The use of eHealth is positively associated with higher SES.

These hypotheses will be tested using data from the Tromsø Study, which will be analyzed using descriptive statistics, chi-square tests, and logistic regressions.

Study Population

Population-based health surveys have been conducted in Tromsø, Norway since 1974. We plan to retrieve questionnaire data from the seventh cross-sectional Tromsø Study (Tromsø 7), conducted in 2015-2016. Data will be available at the beginning of 2017. We have participated in the design of the survey, which for the first time includes self-reported data on the use of eHealth. Tromsø 7 also includes data on referrals, the use of primary and specialist health services, self-rated health, diseases and symptoms, use of medication, as well as demographic and socioeconomic data. The following question will be particularly important in our study: *Based on the information you have found on the Internet,have you decided (1) to consult a doctor, or (2) not to consult a doctor?* Participants were also asked if they discussed the information they gained from the Internet with their doctor.

Tromsø is the largest city in Northern Norway with 75,762 inhabitants (as of January 1, 2016). All residents aged 40 years and over (approximately 33,000 persons) were invited to participate in Tromsø 7; more details about Tromsø 7 are available at the Tromsø Study website [32]. Assuming a participation rate of 65%, 21,450 individuals will attend Tromsø 7. In the sixth Tromsø Study (Tromsø 6), conducted in 2007-2008, 4.9% of the participants (30 years and older) reported having diabetes (T1DM or T2DM). We therefore assume that approximately 1050 individuals with diabetes will constitute the study sample. The prevalence of diabetes has increased in recent years, and the Tromsø 7 participants (aged >40 years) are older than the Tromsø 6 participants (aged >30 years), making it likely that the sample will be larger.

Study Design

The study design will be cross-sectional. Data will be analyzed using descriptive statistics, chi-square tests, and univariable and multivariable logistic regressions. The following variables will be available for adjustment in the multivariable regression models: age, gender, marital status, education, income, employment status, duration of the GP-patient relationship, frequency of GP visits, patients' assessment regarding doctor visits due to the use of eHealth, if eHealth information has been discussed with the doctor, self-rated health, chronic diseases, and the Euro Quality of Life Group five dimensions scoring

scale [33]. Analyses will be performed using the newest version of Stata.

Results

The grant proposal for this protocol was approved by the Northern Norway Regional Health Authority on November 23, 2015 (HST 1306-16). Tromsø 7 has been approved by the Regional Committee for Medical and Health Research Ethics (REK; 2014/940). Recruitment of participants started in March 2015 and is currently ongoing. Written informed consent was obtained from all participants. Data will be available for analyses at the beginning of 2017. This project has been presented to the REK, which found that an application was not required according to the Norwegian Health Research Act (2015/1779/REK nord). This particular project started on July 1, 2016.

Discussion

We expect that our eight hypotheses will be confirmed during the conduct of the studies. For patients, the expected benefits of the project will be improved prevention services and prospects for improved health, improved experience of care services, and improved support for self-management tools and services. For health care providers, benefits will include improved organizational structures, tools, and services for diabetes care. Expected benefits for hospitals will be a more efficient use of specialist care, and allocation of resources for other activities. For society, benefits will include better understanding of how to meet the challenges from the increasing prevalence of diabetes, and better utilization of novel health technologies. This project has the potential to be generalized to other groups with chronic diseases.

Acknowledgments

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Authors' Contributions

All authors contributed to the design and conduct of the study. AHH drafted the protocol and the manuscript. All authors contributed with improvements and critical revisions, and approved the final version for publication.

Conflicts of Interest

None declared.

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Abbreviations

DM: diabetes mellitus

eHealth: electronic health
GP: general practitioner
mHealth: mobile health
REK: Regional Committee for Medical and Health Research Ethics
SES: socioeconomic status
T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus

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Protocol

Advancing Interprofessional Primary Health Care Services in Rural Settings for People with Chronic Low Back Disorders: Protocol of a Community-Based Randomized Controlled Trial

Brenna Bath[1,2], BScPT, MSc, PhD; Stacey Lovo Grona[1], BScPT, MSc; Stephan Milosavljevic[1], BAppScPT, MMPthy, PhD; Nazmi Sari[3], PhD; Biaka Imeah[3], BA, MA; Megan E O'Connell[4], PhD

[1]School of Physical Therapy, University of Saskatchewan, Saskatoon, SK, Canada

[2]Canadian Centre for Health and Safety in Agriculture, College of Medicine, University of Saskatchewan, Saskatoon, SK, Canada

[3]Department of Economics, University of Saskatchewan, Saskatoon, SK, Canada

[4]Department of Psychology, University of Saskatchewan, Saskatoon, SK, Canada

Corresponding Author:
Brenna Bath, BScPT, MSc, PhD
School of Physical Therapy
University of Saskatchewan
104 Clinic Place
Saskatoon, SK, S7N 2Z4
Canada
Phone: 1 306 966 6573
Fax: 1 306 966 6575
Email: brenna.bath@usask.ca

Abstract

Background: Chronic low back disorders (CLBDs) are a substantial burden on individuals and societies, and impact up to 20% of Canadians. Rural and remote residents are approximately 30% more likely to have CLBDs. Reduced access to appropriate team-based health services, including physical therapy, is a key factor that may magnify the impact of CLBD on pain, physical function, overall quality of life, health-related system costs, and individual costs.

Objective: The purpose of this project is to evaluate the validity, comparative effectiveness, costs, barriers, and facilitators of an interprofessional management approach for people with CLBDs, delivered via telehealth.

Methods: This project will examine 3 different health care delivery options: (1) in-person nurse practitioner (NP); (2) in-person physical therapist (PT); and (3) a team approach utilizing an NP (in-person) and a PT joining via telehealth. Validity of the telehealth team care model will be explored by comparing the diagnostic categorization and management recommendations arising from participants with CLBD who undergo a team telehealth, in-person NP, and in-person PT assessment. Comparative effectiveness and costs will be examined using a community-based randomized controlled trial in a rural Saskatchewan community with limited PT services. The 3 arms of the trial are: (1) usual care delivered by a local rural NP; (2) a local NP and an urban-based PT joining via telehealth; and (3) face-to-face services by a PT traveling to the community. Patient-reported outcomes of pain, physical function, quality of life, satisfaction, and CLBD care-related costs will be evaluated up to 6 months after the intervention. Patient and provider experiences with the team telehealth approach will be explored through qualitative interviews.

Results: The study was funded in July 2013 and the University of Saskatchewan Biomedical Research Ethics Board approved the study in November 2013. Participant recruitment began in September 2014 and data collection was completed in December 2015. Analysis is in progress and results are anticipated in 2017.

Conclusions: CLBD is a widespread public health problem, particularly in rural and remote areas, which requires new innovative approaches to deliver appropriate health care. The results of this project will inform the development of evidence-informed approaches and community-based implementation strategies to improve access to PT services in primary health care settings in other rural and remote underserved areas. Findings might also provide a framework for cost-effective and patient-centered models of service delivery for the management of other chronic conditions.

ClinicalTrial: ClinicalTrials.gov NCT02225535; https://clinicaltrials.gov/ct2/show/NCT02225535 (Archived by WebCite at http://www.webcitation.org/6lqLTCNF7)

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KEYWORDS

low back pain; telehealth; rural health; physical therapy

Introduction

Chronic low back disorders (CLBDs) are the leading cause of morbidity worldwide compared to 289 other diseases and conditions, when considering years lived with disability [1]. CLBDs are not only costly to individuals, but also strain health care resources due to increased primary physician care visits [2,3], specialist consultations, and diagnostic procedures [4,5]. Limited access to appropriate care at a primary care level is thought to be a contributing factor to this "medical disaster" [6]. Physical therapists (PTs), whose specialized knowledge of musculoskeletal conditions may exceed that of many physicians (with the exception of orthopedic surgeons [7]), have much to offer for improving the appropriateness and effectiveness of CLBD care.

Approximately 20% of Canadians report having CLBD, and people living in rural and remote regions are approximately 30% more likely to report having CLBD than their urban counterparts [8]. Lack of access to appropriate health care is thought to be a contributing factor to a higher proportion of rural individuals with chronic health conditions like CLBD, compared with urban dwellers [9,10]. However, recruitment and retention of a variety of health care providers to rural and remote regions represents a challenge to providing access to appropriate services that may help to reduce these health disparities [11]. Lack of access to appropriate CLBD care in primary health care is exacerbated in many rural and remote communities in Canada due to a general paucity of PTs [12]. For example, approximately 33% of residents in the Canadian province of Saskatchewan live in rural areas [13]; however, only 10% of the PT workforce is employed in rural communities [14].

Back pain is a common reason for seeking care at the primary care level. Jordan et al found that a quarter of all consultations in a United Kingdom physician-based primary care setting were for musculoskeletal problems, with the low back (14%) being the most common reason [3]. Back pain is also the fifth most common reason for all physician visits in the United States [15], and Canadians with chronic back disorders are 65% more likely to seek care from a family physician than those without chronic back disorders [16]. Although family physicians are often the first clinical contact for patents with low back disorders, they may not be the most appropriate health care providers to assess and treat these conditions, due to low levels of training and low perceived competence in the area [17,18]. Less than 3% of all curriculum hours in Canadian medical schools are devoted to training related to the entire musculoskeletal system, including low back disorders [19], and 82% of recent medical school graduates failed to demonstrate basic competency in assessment and management of musculoskeletal disorders [20]. Despite this low level of training, examination and treatment of low back disorders is rated by family physicians to be of significant importance, while remaining one of the lowest areas of their perceived professional competency [21]. Conversely, experienced PTs are highly competent in the assessment, diagnosis, and management of musculoskeletal disorders, including CLBDs [22,23]. Furthermore, the inclusion of PT services in primary care models for the management of low back disorders is potentially more cost-effective than family physician services alone. A systematic review found that the addition of activities (ie, education, exercise, behavioral counseling, and spinal manipulation) to usual general practitioner/family physician care for low back disorders was more cost-effective than usual general practitioner care alone [24].

In response to a shortage of family physicians in many rural and remote communities, nurse practitioners (NPs) have taken on an important role in the delivery of primary health care services [25]. NPs are advanced-practice registered nurses (usually with master's degrees) who are able to autonomously diagnose disorders, prescribe medications, order and interpret diagnostic tests, and perform specific clinical procedures, and have been shown to provide comparable care to family physicians [26,27]. The combination of PTs with NPs for patient-centered collaborative management is a novel approach that has the potential to improve access to appropriate health care for people with CLBDs, result in improved patient outcomes, and improve overall health system efficiency for CLBD management. However, to our knowledge, similar models have not yet been developed or evaluated in the context of rural health service delivery for people with CLBDs. Additionally, the most effective and efficient means of including physical therapy services in rural health care models has yet to be explored.

The use of secure videoconferencing/telehealth is a promising means to help improve access to physical therapy services in rural primary health care settings [28]. Although videoconferencing is effective for conducting a patient interview [29], performing an effective physical examination via this medium is perceived by many clinicians to be a primary barrier in the adoption of remotely delivered services [30]. The *crux of the issue* is that elements of a conventional face-to-face physical examination require the PT to be *hands-on* with the patient [30]. Previous research has validated some components of a PT assessment via telehealth, in comparison to in-person usual care (ie, history and subjective examination) [30]; however, remote diagnosis requires a clinician to integrate the information from a detailed history and physical examination. Based on this issue, a novel approach is required to overcome the traditional barriers associated with the need for a *hands-on* assessment. An interprofessional assessment performed by an urban-based PT (collaborating via secure videoconferencing/telehealth) with a local rural NP who can perform relevant portions of the *hands-on* assessment with a rural patient with CLBD, may be a viable solution to overcome the barriers of performing an effective remote examination and

allow for the development of appropriate management/educational strategies. Prior to widespread adoption of such a model, several issues need to be explored. First, the validity, comparative effectiveness, and relative costs of an electronic health model of interprofessional care, compared to face-to-face care by a PT or usual care by an NP, is unknown and has yet to be developed or examined. Second, the impact of videoconferencing on clinical workflow practices and interprofessional collaboration is an area that requires further study [31]. Finally, understanding readiness within rural and remote communities is an important step for the successful implementation and sustained use of videoconferencing-type services in existing systems of health care [32].

The objectives of this research study were to: (1) explore the *validity* (ie, diagnostic and management concordance) of an interprofessional assessment session with a PT and NP performed via secure videoconferencing, compared to a PT or NP in-person assessment alone; (2) examine the *impacts* and *cost-effectiveness* of an interprofessional assessment/education session with a PT and NP delivered via secure videoconferencing for people with CLBDs, compared to in-person PT only assessment/education session and usual care by an NP; and (3) explore the *perceived barriers and facilitators* of the use of secure videoconferencing for assessment and management of people with CLBDs living in rural underserved communities, from the perspectives of patients and health care providers.

Methods

Operational Definition of Chronic Low Back Disorder

Low back disorders include a large group of clinical and etiological entities and there is no *gold standard* clinical classification or diagnostic criteria for many of these conditions [33]. Furthermore, the International Classification of Diseases-10 system does not have an adequate and distinct diagnostic code(s) for chronic pain or CLBD [34]. Thus, for this study, CLBDs include self-reported pain and disability that has lasted for a minimum of 3 months that is related to low back injury (ie, sprain/strain), and/or low back pain, and/or associated hip or leg symptoms due to pain referral. CLBDs may develop from trauma or, more often, from repetitive or cumulative loading mechanisms that lead to adverse structural changes in spinal soft tissue and articular structures [35], which often have chronic, episodic, or recurrent manifestations [36].

Secure Videoconferencing Platform and Procedures

The secure videoconferencing platform used was VidyoDesktop software (Vidyo Inc., Hackensack, NJ, USA) installed on laptop computers. A detachable external web camera with remote pan, tilt, and zoom functions was attached to the laptop in the *rural* location (ie, with the NP and participant). If required, the NP could use the remote to direct the camera to provide different views of the participant during the physical examination, as directed by the PT.

Study Setting, Population, and Recruitment Strategies

The validity part of the study (Objective 1) took place in the city of Saskatoon, Saskatchewan (SK). The rural pilot trial (Objectives 2 and 3) took place in the Kelsey Trail Health Region in the communities of Arborfield and Carrot River (264 to 288 kilometers from Saskatoon, SK, respectively). These communities were identified through a combination of related research, an environmental scan, and consultation with local health care providers and managers as having reduced access to local PT services. The Kelsey Trail Health Region has an estimated population of 40,000 people and 32.2 PTs per 100,000 residents (a total of 13 PTs in 2010) compared to 83.2 PTs per 100,000 residents (a total of 262 PTs) in the Saskatoon Health Region [37]. The 2 communities are within 24 kilometers of each other and are served by 3 NPs (2 in Carrot River and 1 in Arborfield). The estimated caseload proportion of patients seeking care with CLBDs in these practices is 20% (personal communication, Kowal L, December 2012) which is consistent with published literature [3,15]. People aged 18 to 80 years with pain and discomfort localized below the costal margin and above the gluteal folds, with or without leg pain, that (1) limits usual activities or daily routine and (2) has been present for more than months [38] were invited to participate for each part of the study. Exclusion criteria included: people currently receiving third party payer funding (ie, Worker's Compensation Board, or other) for their back-related complaints; people with primarily neck (cervical spine) or mid-back (thoracic spine) complaints; and people with language, reading, or comprehension barriers that would limit adequate completion of the study paperwork. Recruitment strategies included advertisements in local newspapers, provision of study details when presenting for care at any of the participating rural providers, and posters posted at health care facilities and other community centers.

Study Design and Data Collection

Concurrent to the intervention part of the study described below, 30 people with CLBDs were recruited from the Saskatoon, SK area. Each participant underwent an interprofessional assessment with an NP (in-person) and a PT (via videoconferencing), an in-person assessment with a second PT, and an in-person assessment with a second NP. Each PT and NP completed an online clinical classification tool, adapted from one previously developed by the author [39], to allow for an interrater comparison of diagnostic and management recommendation classification (ie, PT in-person vs NP in-person vs team of NP in-person with PT joining via secure videoconferencing).

The study design for Objectives 2 and 3 included two intervention groups and a control group, with 20 participants in each group: (1) interprofessional telehealth intervention; (2) in-person PT (travelling from Saskatoon, SK to provide services); and (3) *usual care* provided by an NP (see Figure 1). Due to the interprofessional nature of the intervention, the NP involved in the telehealth-based intervention group may have altered their *usual care* practice; therefore, the control group participants were drawn from the practices of 2 NPs that were not involved in the telehealth intervention, who provided services out of Carrot River. Participants were randomly assigned to 1 of the 3 groups using simple block randomization to ensure equal group sizes [40]. Participants allocated to either of the in-person PT group or the team telehealth intervention groups were eligible to receive up to 4 in-person PT treatment sessions delivered by an urban-based PT who travelled to the

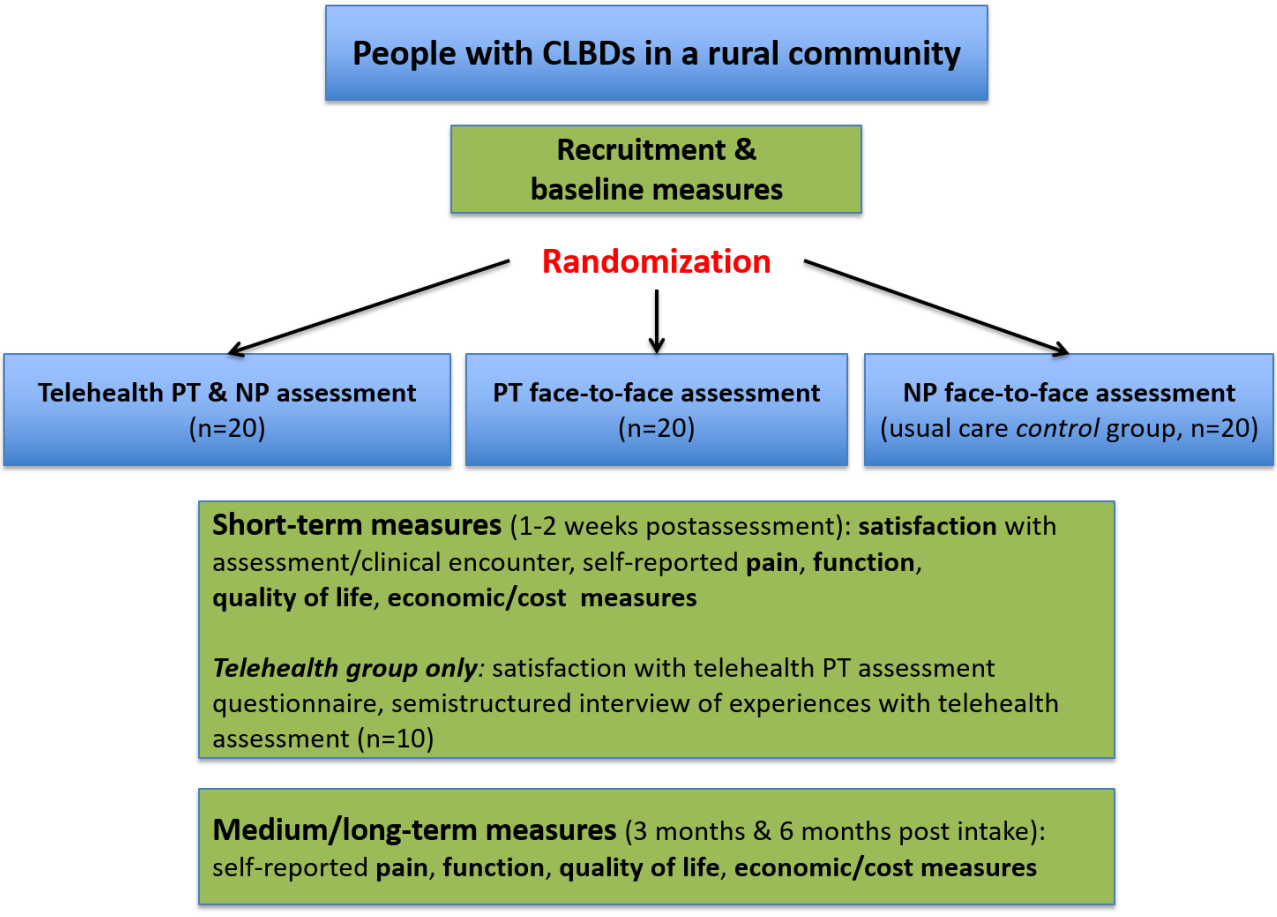
community (if recommended by the assessing health care providers).

A combination of paper-based and online questionnaires measured outcomes at 4 time points, as shown in Figure 1: (1) *baseline*, prior to the health care encounter; (2) *short term*, within 2 weeks of the initial health care encounter; (3) *medium term*, 3 months postintake; and (4) *longer term*, 6 months postintake. Baseline questionnaires covered a range of sociodemographic (eg, age, gender, education, employment and other income, work status), clinical (eg, pain location, duration) and psychological (eg, fear avoidance beliefs, depression, somatization) factors. Phone or email reminders for completion of follow-up questionnaires were performed with phone or email prompts based on the tailored design method proposed by Dillman et al [41].

The multidimensional outcome measures have demonstrated reliability, validity, and responsiveness in similar clinical populations, and will cover the domains of back-specific function, general well-being/generic health status, pain, work disability, and satisfaction with care, as recommended by international groups of back pain researchers [42,43]. The primary outcome of interest will be self-perceived function, which was assessed using the modified Oswestry Disability Index, a back-specific self-report questionnaire [44,45]. The Numeric Pain Rating Scale [46] was used to measure the intensity of current pain, pain at its best, and pain at its worst levels over the last 24 hours. Quality of life/general health status was measured with the EuroQol health survey instrument (EQ-5D-5L) [47]. Patient satisfaction was measured using a modified version of the Visit-Specific Satisfaction Instrument, as described and validated by Kennedy et al [48], as well as a space for comments regarding satisfaction with the clinical encounter, as previously published [49]. Costs were captured using self-report diaries that recorded intervention/treatment costs, work status, absenteeism and disability days related to back pain, health service use within and outside of the study (ie, both government funded and nonfunded services), and other CLBD-related costs such as medication use (ie, prescription and nonprescription drugs) and travel time and costs from the beginning of the intervention period until the end of the study period (ie, 6 months postintake).

Exploration of perceived barriers and facilitators regarding the implementation and use of secure videoconferencing was undertaken using surveys of participants of the intervention group, and the NPs and PTs involved in the videoconferencing intervention group. An adaptation of a tool developed by Russell et al [30] to measure satisfaction with PT-delivered telehealth assessments was administered to participants in this group at the short-term follow-up period. Six patient participants were invited to participate in a 30-minute semistructured interview within 2 weeks of their initial assessment date.

Figure 1. Design of rural community-based trial part of the study. CLBD: chronic low back disorder; NP: nurse practitioner; PT: physical therapist.



Analyses

Analyses are currently in process and not yet complete.

Clinical Validity of Team Telehealth Assessment

Descriptive statistics will be calculated to examine select demographic and clinical characteristics of the study sample. Differences in these variables between participants comprising the subset for the validity part of the study (n=30), and the participants in the intervention part of the study (n=60), will be evaluated with independent samples *t*-tests and chi-square tests. The level of agreement for diagnostic and management categories between each provider group will be calculated with the kappa coefficient. Weighted kappas will be calculated for categories in which more than 2 options are possible [50]. Overall observed agreement (ie, proportion of cases for which the providers agreed) will also be calculated.

Impacts and Cost-Effectiveness of Rural Trial

Descriptive analyses of all baseline measures will include frequencies and valid percent for categorical variables, and mean, standard error, median, and interquartile ranges for continuous variables. Comparisons between the baseline and outcomes at short-, medium-, and long-term time points will be completed with parametric tests (eg, paired *t*-tests) or nonparametric test equivalents (eg, Mann-Whitney *U*) where appropriate. The primary outcome will be the Oswestry Disability Index. Multivariable regression analysis (as described by Salisbury et al [51]), conducted on an intention-to treat basis, will be used to investigate between-group differences in mean Oswestry Disability Index scores at the 6-month time point, with adjustment for baseline scores. The economic evaluation will be conducted using the cost utility analysis. This analysis will involve the use of the EQ-5D-5L health survey instrument [47], for which utility weights are available for a sample of the Canadian general population [52]. Multiple linear and logistic regression analyses will be used to determine the predictive models that best explain differences and changes in both outcomes and costs related to both productivity loss and health care costs.

Perceived Barriers and Facilitators for Videoconferencing

An inductive thematic analysis will be applied to qualitatively analyze the results of the semistructured interviews with the PTs and NPs involved in the team telehealth assessment, and a sample of patient participants from the team telehealth intervention arm. A process of open and axial coding will be applied. During open coding, a constant comparative approach will be used to group the codes into categories and identify themes. Axial coding will then be completed to look at the interrelationship of categories. A coding scheme will be developed jointly, and verified independently, by 2 researchers via identifying, classifying, and labeling the primary patterns in the data.

Sample Size

A sample size of 30 for Objective 1 (validity) is adequate, based on an estimated minimum .60 kappa level between 2 PT raters and 80% power [50]. Determining the appropriate sample sizes to reach adequate power for Objectives 2 and 3 (rural community trial) is challenging, as there has been little comparable work in similar clinical populations from which to draw estimates of variance and effect sizes. Furthermore, the sample sizes suggested in the literature [46] far exceed what would was feasible given the budget, time lines, and caseload proportion of CLBDs in the rural community. A primary purpose of the intervention part of this study will be to estimate outcome variances and effect sizes, which could then be used to plan a larger, sufficiently powered, multi-site intervention.

Ethical Considerations

The largest potential burden for participants was perhaps the amount of time required to complete the baseline and follow-up questionnaires (30-60 minutes). Some participants may have felt sensitive about recording psychosocial risk factors or health history; however, assurances of study data confidentiality and anonymity should have helped to address this. All study protocols complied with Health Information Protection Act standards. The VidyoDesktop platform is a private and secure means of sharing sensitive health and personal information between patients and health care providers. Consent forms were reviewed and signed by participants prior to starting the study. Study participants' data will be confidential and identified only by study identification number; participants will not be identified in any reporting materials and only aggregate data will be presented during results dissemination. All data will be stored on a password-protected server at the University of Saskatchewan.

Knowledge Translation

The proposed project will implement the Canadian Institutes of Health Research's integrated knowledge translation approach, engage researchers and knowledge users throughout the research process, and maximize prospects for the use of findings in practice [53]. An array of clinical, community-based, and manager/decision maker knowledge users have been (and will continue to be) recruited to participate in this study, thereby shaping its design and driving health care practice implications. These partners will be consulted and engaged at key stages throughout the research process (ie, 1-2 times per year through a combination of in-person and teleconference/videoconference meetings over the course of the 3-year project).

Results

This study was funded in July 2013 and the University of Saskatchewan Biomedical Research Ethics Board approved the study in November 2013. Participant recruitment began in September 2014 and data collection was completed in December 2015. Analyses are in progress, and results are anticipated in 2017. Results of the trial component of this study will comply with the CONSORT-EHEALTH checklist [54].

Discussion

CLBDs are a widespread public health problem, particularly in rural and remote areas. New innovative models of care delivery are needed to address reduced access to PT services in many rural and remote communities worldwide. The aim of this

project is to compare *usual care* delivered by a rural health care provider (ie, NP) with 2 means of integrating a PT into a rural primary health care setting: (1) PT joining via secure videoconferencing/telehealth for a team-based approach with the in-person NP; and (2) the PT travelling from an urban center to provide face-to-face services in a rural community. This study has the potential to inform rural and primary health care reform in Saskatchewan and beyond, to improve access to needed health services in underserved rural communities, and lead to the development of important partnerships that will lay the foundation of a Saskatchewan-based program of research. The lessons learned from this project regarding barriers and facilitators will help to inform effective strategies for implementation and evaluation of similar care models in different rural and remote communities and health care contexts. This research may also help to optimize management of a range of common chronic conditions in rural and remote settings.

Despite the novel contribution of this study to the literature, and its potential to inform health services reform and access, there are notable limitations. First, given the complex and heterogeneous nature of CLBDs and variability in the biopsychosocial experiences of those with CLBDs, the characteristics of participants in this study may not be reflective of the broader population with similar conditions. Second, the assessment and management of CLBD is similarly complex and heterogeneous. Although the primary aim of this study is the comparison of a team telehealth/videoconferencing approach to in-person PT or NP care, we anticipate wide intraprofessional (as well as interprofessional) variability in approaches, which may limit the replicability of the study intervention in other contexts and with different health care providers. Countering these limitations are the use of multidimensional outcome measures using both qualitative and quantitative approaches, which will allow for a more nuanced evaluation of the different care models. Unfortunately, this study does not include an in-person *team* approach (PT and NP) as one of the comparison groups. This omission is mainly due to scope limitations imposed by funding availability. Further research should examine the validity, feasibility, and impacts of this additional health delivery model for people with CLBDs. The current research is predominantly a pilot and feasibility study, but we anticipate that the findings and lessons learned from this study will nevertheless be valuable to inform future research and health services planning.

This study is the first step of a planned multi-stage research program in which future studies will investigate how similar interventions may work in different rural and remote communities, and with other types of chronic conditions and populations. The results of this project will lead to the development of evidence-informed approaches and community-based implementation strategies to improve access to PT services in primary health care settings in other rural and remote underserved areas, and potentially provide a framework for cost-effective and patient-centered models of service delivery for management of other chronic conditions. Furthermore, the partnership approach to health services research is crucial to lay the foundation for the development and evaluation of more extensive multi-site, community-informed, team-based interventions for people with CLBDs and other chronic health conditions living in rural and remote communities.

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Abbreviations

CLBD: chronic low back disorder
EQ-5D-5L: EuroQol health survey instrument
NP: nurse practitioner
PT: physical therapist

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Protocol

High Touch and High Tech (HT2) Proposal: Transforming Patient Engagement Throughout the Continuum of Care by Engaging Patients with Portal Technology at the Bedside

Ann Scheck McAlearney[1], MS, ScD; Cynthia J Sieck[1], MPH, PhD; Jennifer L Hefner[1], MPH, PhD; Alison M Aldrich[1], MSI, MPH; Daniel M Walker[1], MPH, PhD; Milisa K Rizer[2,3,4], MD, MPH; Susan D Moffatt-Bruce[4,5,6], MBOE, MBA, MD, PhD; Timothy R Huerta[1,4], MS, PhD

[1]Research Division, Department of Family Medicine, The Ohio State University, Columbus, OH, United States

[2]Information Technology, Wexner Medical Center, Ohio State University, Columbus, OH, United States

[3]Clinical Division, Department of Family Medicine, The Ohio State University, Columbus, OH, United States

[4]Department of Biomedical Informatics, College of Medicine, The Ohio State University, Columbus, OH, United States

[5]Quality & Patient Safety, Wexner Medical Center, The Ohio State University, Columbus, OH, United States

[6]Department of Surgery, College of Medicine, The Ohio State University, Columbus, OH, United States

Corresponding Author:
Alison M Aldrich, MSI, MPH
Research Division
Department of Family Medicine
The Ohio State University
2231 N. High Street
Columbus, OH, 43201
United States
Phone: 1 614 685 4470
Fax: 1 614 293 2715
Email: alison.aldrich@osumc.edu

Abstract

Background: For patients with complex care needs, engagement in disease management activities is critical. Chronic illnesses touch almost every person in the United States. The costs are real, personal, and pervasive. In response, patients often seek tools to help them manage their health. Patient portals, personal health records tethered to an electronic health record, show promise as tools that patients value and that can improve health. Although patient portals currently focus on the outpatient experience, the Ohio State University Wexner Medical Center (OSUWMC) has deployed a portal designed specifically for the inpatient experience that is connected to the ambulatory patient portal available after discharge. While this inpatient technology is in active use at only one other hospital in the United States, health care facilities are currently investing in infrastructure necessary to support large-scale deployment. Times of acute crisis such as hospitalization may increase a patient's focus on his/her health. During this time, patients may be more engaged with their care and especially interested in using tools to manage their health after discharge. Evidence shows that enhanced patient self-management can lead to better control of chronic illness. Patient portals may serve as a mechanism to facilitate increased engagement.

Objective: The specific aims of our study are (1) to investigate the independent effects of providing both High Tech and High Touch interventions on patient-reported outcomes at discharge, including patients' self-efficacy for managing chronic conditions and satisfaction with care; and (2) to conduct a mixed-methods analysis to determine how providing patients with access to MyChart Bedside (MCB, High Tech) and training/education on patient portals, and MyChart Ambulatory (MCA, High Touch) will influence engagement with the patient portal and relate to longer-term outcomes.

Methods: Our proposed 4-year study uses a mixed-methods research (MMR) approach to evaluate a randomized controlled trial studying the effectiveness of a High Tech intervention (MCB, the inpatient portal), and an accompanying High Touch intervention (training patients to use the portal to manage their care and conditions) in a sample of hospitalized patients with two or more chronic conditions. This study measures how access to a patient portal tailored to the inpatient stay can improve patient experience and increase patient engagement by (1) improving patients' perceptions of the process of care while in the hospital; (2) increasing patients' self-efficacy for managing chronic conditions; and (3) facilitating continued use of a patient portal for

care management after discharge. In addition, we aim to enhance patients' use of the portal available to outpatients (MCA) once they are discharged.

Results: This study has been funded by the Agency for Healthcare Research and Quality (AHRQ). Research is ongoing and expected to conclude in August 2019.

Conclusions: Providing patients real-time access to health information can be a positive force for change in the way care is provided. Meaningful use policies require minimum demonstrated use of patient portal technology, most often in the ambulatory setting. However, as the technology matures to bridge the care transition, there is a greater need to understand how patient portals transform care delivery. By working in concert with patients to address and extend current technologies, our study aims to advance efforts to increase patients' engagement in their care and develop a template for how other hospitals might integrate similar technologies.

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KEYWORDS

patient portals; personal health records; patient participation; patient engagement; patient access to records; patient satisfaction; mobile computing; care transitions; chronic disease; self-efficacy; hospitalization; ambulatory care

Introduction

Background

The Burden of Chronic Illness and Multimorbidity

Chronic illnesses, including cardiovascular disease, arthritis, diabetes, asthma, cancer or chronic obstructive pulmonary disease (COPD), affect more than 145 million Americans, representing a large increase over projections made only 10 years ago [1-3]. The individual burden of chronic illness is magnified by the high rate of two or more co-occurring chronic illnesses, termed multimorbidity [1]. This population is at particularly high risk for a variety of adverse health outcomes including poor functional status, unnecessary hospitalizations, and adverse drug events [4-6]. Chronic illnesses account for 7 out of 10 deaths each year. In addition, chronic illness has resulted in huge costs to medical systems and society, accounting for 84% of the total US health care spending [1], or almost 15% of the gross domestic product (GDP). For these reasons the Agency for Health Care Research and Quality (AHRQ) has designated people with multimorbidity as a priority population [7].

Patient Self-Management Using Health Information Technologies

Individuals with chronic illness generally receive care in ambulatory settings and often look to primary care providers to direct their care. However, the rise in chronic illness is shifting the role of the physician to that of facilitator in the patient's self-management process. The increase in availability of personal disease monitoring tools such as hand-held, self-monitoring blood glucose systems [8], and a focus on patients as consumers of health care is moving expectations around management of chronic conditions away from laboratories and physicians to the patients themselves. Evidence shows that enhanced patient self-management can lead to better control of chronic illness [9-11], and health information technology (HIT) is a potentially important mechanism to facilitate patient self-management [12-15]. Large studies in outpatient settings have found that providing patients with access to their medical record, physician progress notes, personalized health information, and reminders (ie, patient-centered functionalities) leads to increases in adherence to guidelines, health status, and patient satisfaction [16,17].

Tools for Managing Health

Patient portals are a class of electronic personal health records (PHRs)—tools that patients can use to track and manage their health. The PHR is "an electronic record of an individual's health information by which the individual controls access to the information and may have the ability to manage, track, and participate in his or her own health care" [18]. PHRs can be stand-alone or tethered. Stand-alone products allow the patient full control over what data are entered and accessed and are independent of the provider, allowing the patient to input their own data from any provider regardless of the electronic health record (EHR) system (if any) the provider uses, and to carry their data with them across providers. Tethered PHRs, also called patient portals, are offered through a health care provider and are connected to the patient's EHR with that provider. These patient portals provide access to information in the patient's EHR, controlled by the provider, as well as other functions such as viewing and scheduling appointments and secure communication with the provider [19]. Both types of PHRs show promise for assisting patients in self-management of chronic conditions by allowing patients to input and track health information, facilitating communication between patients and providers, and providing access to consumer-friendly information about diseases [20-24].

Research has shown that patients with special health care needs, such as those with multiple chronic conditions, have the greatest interest in patient portals [25-27]. The first large-scale study of the use of patient portals within a large health system found that having more chronic conditions predicted both adoption and intensity of patient portal use [28]. However, there is still much to understand about why, how, and which patients use portals, and how the health care system can best support them. Currently, little is known about what motivates patients to adopt and continue to use portals, and what functionalities patients consider important for self-management of their conditions [13-15].

Patient Engagement Through Health Information Technologies

Patient engagement, defined by the Institute for Healthcare Improvement as "actions that people take for their health and to benefit from care" [29], is critical to the management of chronic diseases. A 2013 editorial in Health Affairs referred to patient engagement as the "next blockbuster drug of the century" [29]. Patient portals are positioned as a central component of patient engagement through the potential to change the physician-patient relationship and enable chronic disease self-management [30-33]. Studies of outpatient portals suggest that patients want accurate and timely information provided across the continuum of care that they can apply to their care and communicate with providers in a secure and trusted manner [14,34].

Despite the focus on patient engagement [29,35], research on patient engagement in the inpatient setting is in its infancy. A recent systematic review found only four studies testing the provision of patient-specific information in the inpatient setting [36]. The focus of these studies included providing access to the patient record and information on the care team through a mobile phone app [37], a tablet computer app to view care team profiles and hospital medication records, a tablet app with the plan of care, diet and safety information [38], and large in-room information displays in an emergency department [39]. While these small-scale qualitative case studies reported positive findings, including patient reports of enhanced engagement in the care process and satisfaction with care, none included patient-centered functionality such as the ability to send messages to the care team, allowing patients to input information or record notes—elements that have been demonstrated to further enhance patients' engagement [17,40,41].

Increasing Motivation for Patient Engagement

Information and technology are insufficient to fully engage patients in their care; patients also need motivation to engage [42-46]. A common element of health behavior change theories is the need for a trigger to action [47,48]. This is supported in studies of individual behavior change across a variety of health behaviors [49-54]. For patients with multiple chronic conditions, hospitalization is often due to exacerbations of one or more condition. We assert that hospitalization can serve as the necessary trigger that engages these patients in managing their care [47,48]. In other areas, times of acute crisis have been linked to a greater perception of risk and increased focus on health behaviors [49-52]. Therefore, hospitalization may create a window of higher engagement in which to initiate behavior change and foster interest in tools for managing health.

Addressing Barriers to Patient Portal Use

Most patient portal implementations have assumed that internal documentation is sufficient, and that the application is sufficiently intuitive for use with only a supplemental list of "frequently asked questions (FAQs)"; however, documentation and FAQs alone are not always sufficient (see Pilot Study section). In particular, individuals with low health literacy and low technological literacy may experience greater difficulty navigating these tools and may simply give up. The Institute of Medicine defines health literacy as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" [55]. Electronic health (eHealth) literacy, then, is "the ability to seek, find, understand, and appraise health information from electronic sources and apply the knowledge gained to addressing or solving a health problem" [56]. Technological literacy, including knowing how to operate computers and mobile devices, and how to make use of the information provided, are essential components of eHealth literacy.

The multimorbid tend to be older and more socioeconomically disadvantaged than the population at large [57], so people with multiple chronic illnesses may be especially challenged in developing eHealth literacy skills. However, people of all ages and status struggle with health literacy. Poor health literacy is a better predictor of poor health status than income, employment status, or education [55]. Interventions thus need to provide training specifically designed to overcome these challenges. Further, the introduction of new technology into the care process, such as tablet computers, may create barriers to participation due to the competing demands on a patient's time inherent in hospitalization. If these tools are to accomplish their intended aims of empowering patients through greater engagement, it is critical to understand the training and support materials necessary to meet diverse patient needs.

High Tech/High Touch: Our Proposed HT2 Project

We propose the first large-scale randomized controlled trial (RCT) of the impact and use of an inpatient tablet-based patient portal including a mixed methods analysis. This study examines changes in patient self-efficacy managing chronic conditions and subsequent ambulatory patient portal usage as well as associated experiences and outcomes. We will explore outcome differences across two concurrent dimensions: the provision of an inpatient patient portal for multimorbid patients and a training intervention focused on using this HIT to improve self-management. The resultant 2x2 experimental design offers the ability to measure how comfort with technology moderates the use of technology to manage chronic conditions by comparing results from differently structured Tech and Touch interventions. By addressing literacy through high and low touch intervention approaches, we will explore the value that different engagement approaches provide. Follow-up with patients post discharge will enable us to study how the inpatient experience influences ongoing usage of similar linked tools in the ambulatory setting.

Our Tech Intervention utilizes the MyChart Bedside (MCB) and MyChart Ambulatory (MCA) patient portals to assist patients in managing their chronic conditions. MCB is an inpatient portal patients can use to access their data while at an Epic-equipped hospital that has deployed the technology. MCB was developed by Epic to provide patients, and their families and caregivers, access to information customized to the inpatient setting. It includes an expected care plan for the day, health education materials, secure messaging with the care team, a place to take notes, and access to educational videos.

MCA is a Web-based ambulatory patient portal providing access to similar data, but is focused on outpatient care functions. MCA includes access to a health summary, medication listing, immunizations, patient health data entry (eg, submission of daily glucose levels), appointment tracking, secure messaging, management of preventive care, and information associated with financial management of the patient account. MCA is available from any computer with an Internet connection and a browser, and from a mobile app for iOS (Apple) and Android devices.

MCB and MCA access different elements of the medical record, and as such, are independent apps used at different times across the continuum of care. However, because the same EHR underlies both systems, there is significant overlap in the information available in each app. Patients using MCB are prompted to create an MCA account at discharge if they do not already have one. Information from a hospital stay, including all lab and test results, is available in MCA within 3 days of posting to the EHR so that patients with an MCA account will have access to their MCB information after discharge. Together, these apps have the potential to provide patients with access to the right information at the right time across the continuum of care.

Our Touch intervention provides training to patients in both the technical and application aspects of using a patient portal to manage their chronic conditions. The High Touch intervention will involve in-person guidance from a technology navigator (TN) to educate patients about the use of MCA (Low Tech) or both MCA and MCB (High Tech). The subject of this discussion will follow a predetermined script explaining various tasks, engaging patients with the portal application by allowing them to complete tasks in the presence of a TN, and addressing any issues, concerns, or questions that arise during the intervention. In contrast, patients assigned to the Low Touch intervention are presented an initial video after consent that explains the use of MCA (Low Tech) or both MCA and MCB (High Tech). In both cases, the TN will provide patients with paper-based signup and support materials on the use of MCA prior to discharge. In the High Touch case, the emphasis is on providing one-on-one training in the use of MCA (Low Tech) or both MCA and MCB (High Tech) at admission with a follow-up at discharge. While we have a preliminary design for this intervention, we expect that the tools will experience at least one iteration of improvement, and therefore our proposed project includes an initial usability study to identify timely information for the intervention.

Pilot Studies

In preparation for this project, the research team conducted extensive pilot studies, engaged in tool development, and promoted practice change and quality improvement to support the proposed study. Selected pilot projects are described in the following sections.

MyChart Bedside Use

We initiated a pilot study in 4 units within Ohio State University Wexner Medical Center (OSUWMC) that tested the specifications for implementation of MCB. This preliminary study served to formatively guide our High Tech/High Touch (HT2) proposal. For instance, the pilot identified the need for a High Touch intervention, the need to use TNs (rather than existing staff) to provision tablets, and the need for easily accessible support materials. Videos created for this pilot serve as the initial basis for our Low Touch intervention, and we will make modifications as needed for our study purposes.

MyChart Ambulatory Use

In preparation for our proposed HT2 study, we secured ongoing report data on the use of MCA. From these data we know that the mean age of MCA users is 47.6 years (SD=16); and that most are white, have managed care insurance, and have used MCA for nearly 2 years. It was found that 44.82% (31,439/70,152) of all patients created a MCA account; however, only 16.00% (5029/31,439) had logged on and used their account during the pilot study time frame. This pilot served to reinforce our need to focus on the use of functions within MCA and MCB, rather than the standard model promoting account sign up and leading to only intermittent use.

Usability Studies in Epic

Dr Huerta has been assessing usability of functions within Epic. Working with students to engage health practitioners, preliminary work was conducted to explore the usability of the system. Pilot research results have recently been made available to the health system.

Rationale for Study Design

The current state of the literature regarding patient portals is primarily based on observational or small-scale qualitative studies [13]. We propose to use a randomized controlled design to isolate the impact associated with the adoption of an inpatient patient portal (MCB), and a concomitant intervention addressing comfort with technology and health literacy. The study is of sufficient size to identify subgroup dynamics, as well as explore whether ambulatory patient portal usage (MCA) is influenced by the availability and usage of the inpatient portal. Our study will also examine how use patterns may impact health outcomes (eg, readmission rates), patient-reported outcomes (eg, perceived self-efficacy in chronic disease management), and patients' experiences (eg, satisfaction with care).

Focus on Multimorbidity Patients

By focusing specifically on engaging patients with multimorbidity in the use of patient portals across the continuum of care, HT2 addresses one of the main goals set forth in the 2010 Department of Health and Human Services report, Multiple Chronic Conditions: A Strategic Framework [4], to implement and effectively use health care technology. As multimorbidity research is not disease-specific, our study focuses on self-efficacy and satisfaction as the outcomes of interest because they have been associated in previous research with positive health outcomes [7] and are considered generic outcome measures that are responsive to change over time [6]. Current studies of patient portal use focus mainly on metrics such as number of users and email response times, but these do not necessarily reflect use in a way that impacts an individual's health. We plan to study the potential for how introducing patient portals during an inpatient stay can influence

patient-centered care and outcomes including patients' perceived self-efficacy for managing chronic conditions across the continuum of care. Further, we expect to be able to examine both readmission rates and rates of ambulatory patient portal utilization (MCA) after discharge in this priority patient population.

Potential to Increase Patient Engagement in Disease Self-Management and the Process of Care

Our study also highlights the importance of patients' engagement in their care. Patient portals offer several tools to help patients become and remain engaged. In the inpatient setting, when patients may be particularly ready to learn about managing their health, patients can learn how and why it is important to track biometric measures such as weight or blood glucose levels, receive feedback from and ask questions of their providers specific to the management of their conditions, and access disease-specific educational materials. They can also send secure messages to their hospital and family physicians. This communication opportunity has the potential to change patient engagement with their nursing team as well. In our MCB pilot study (discussed below), nursing staff considered it important to disseminate educational material throughout the hospital stay rather than simply at discharge, because this allows education to happen when the patient is ready to engage. These same materials can then be made available in MCA when the patient leaves the hospital. With this study, we seek to clarify and measure how engagement in the inpatient setting (use of MCB) facilitates continued engagement once the patient leaves the hospital (ongoing use of MCA). At issue is whether use during an inpatient stay reinforces ambulatory use.

Study Results Are Likely to Improve Health Care and Outcomes

Our study aims to improve health care and outcomes through implementation of enhanced patient-centered HIT. The integration of patient portals within EHR systems has the potential to improve the patient experience and the quality of patient care [28,58-60]. However, use of patient portals beyond creating an initial account remains limited, and is based on the technology's relevance to the patient and the ability of the technology to enhance the physician-patient relationship [34,61,62]. Our study focuses on increasing relevance and improving communication to promote patient portal use in order to improve care, outcomes, and experience for patients with multiple chronic conditions. We specifically explore the impact of education strategies as a means to compensate for differences in technology and health literacy. In doing so, we intend to explore the use of both technology and literacy training to increase self-efficacy in the use of these tools. Evidence shows that enhanced patient self-efficacy for management activities can lead to better control of chronic illness [9-11].

Widespread Reach of Epic

The patient portals to be studied at OSUWMC are available through the Epic EHR system in use at Ohio State. Epic currently touches over 50% of all Americans as they receive health care and is available to 50 million patients in the United States [20,63]. Both MCA and MCB patient portals are integrated into the Epic EHR at OSUWMC.

Methods

Approach Overview

Our study uses a mixed methods approach to examine an inpatient patient portal called MyChart Bedside (MCB) combined with patient-specific training. We use a 2x2 experimental design within an RCT to study both use and impacts of MCB. We compare levels of Tech and Touch both independently and together to improve understanding of both short- and long-term effects at the critical time for behavioral change hospitalization. The large sample size (N=6000) provides an opportunity to effectively engage in subgroup analysis.

Conceptual Framework and Study Hypotheses: The Health Belief Model

The Health Belief Model [47] provides a context for understanding why the use of a patient portal during an inpatient stay may increase engagement in managing chronic conditions in the future. This model suggests that the likelihood of a person engaging in a health-related behavior, such as managing a chronic illness, is based on (1) perceptions of factors such as risk, seriousness, and their own ability to make that change; and (2) aspects of the environment that might trigger taking action. First, the patient's assessment and understanding of the seriousness of their condition and consequences of not addressing it, combined with how susceptible they believe they are to the consequences of their condition, influence how much of a threat the person perceives from not taking action. Perceived threat, along with the person's assessment of the benefits and barriers to taking action, and their confidence that they can take that action (called self-efficacy) are then expected to influence how likely a person is to take a health-related action. In the person's environment, cues to action can provide additional motivation to take action. We posit that hospital admission can serve as one of these cues to action.

With diabetes, for example, a health-promoting action a patient can take is monitoring his blood sugar level. According to the Health Belief Model, the likelihood of taking this action would be influenced by several factors including (1) how serious the patient perceives the consequences of not monitoring their blood sugar (eg, hospitalization); (2) their perceived risk of experiencing those consequences; (3) what benefits they might experience from monitoring (eg, more even blood sugar control); (4) barriers to monitoring (eg, painful finger sticks); (5) how confident they feel in monitoring their blood sugar; and (6) reminders in their environment of the need to monitor. Training a patient to monitor their blood sugar after discharge and communicate that information to his/her physician can reduce the likelihood of readmission for uncontrolled diabetes.

While the hospital experience is often about moving a patient out of crisis, it also represents an opportunity to influence the patient's assessment of the benefits and barriers to taking action (seriousness and risk), and their confidence that they would be able to achieve the necessary behavioral change required to

achieve the desired consequence (self-efficacy). Patient portals in this setting offer tools to increase self-efficacy during a particularly receptive time that can be continued in the outpatient environment. Our intervention provides not only the tools for continued management, but patient-centered training in their use as well.

Study Hypotheses

We expect that participants in each of the experimental groups (see Figure 1) will have a fundamentally different experience as a result of the intervention arms. As such, we have generated 7 (H1 to H7) hypotheses (Textbox 1). Within these general hypotheses, we will also explore effects among different subgroups including variations based on health literacy, computer self-efficacy, health conditions, and socioeconomic status.

Textbox 1. Study hypotheses.

H1: Patients with access o MyChart Bedside (MCB) (High Tech) will report higher satisfaction with care experience, greater changes in self-efficacy, and fewer readmissions than those who did not have MCB access.

H2: Patients who receive in-person training interventions (High Touch) will report higher satisfaction with care and greater changes in comfort with technology than those who were not provided with in-person training.

H3: An interaction effect will exist between High Tech and High Touch, such that the provision of both will result in better experiences than the provision of only one intervention component.

H4: Use of patient education materials within MCB will be linked to greater perceived self-efficacy for patients' management of chronic disease.

H5: Across all patients, patients with increased use of technology (High Tech) will experience lower readmission rates.

H6: Patients with access to MCB (High Tech) will be more likely to use MyChart Ambulatory (MCA) more often and with greater intensity and have better experiences in primary care (ie, higher patient satisfaction), controlling for preadmission MCA use (available only to patients who use Ohio State University Wexner Medical Center [OSUWMC] providers as outpatients).

H7: Patients with training in both MCA and MCB (High Tech) will use MCA more often and with greater intensity, and have better experiences in primary care than those who were provided access to both but no training.

Figure 1. Study design. MCA: MyChart Ambulatory; MCB: MyChart Bedside.

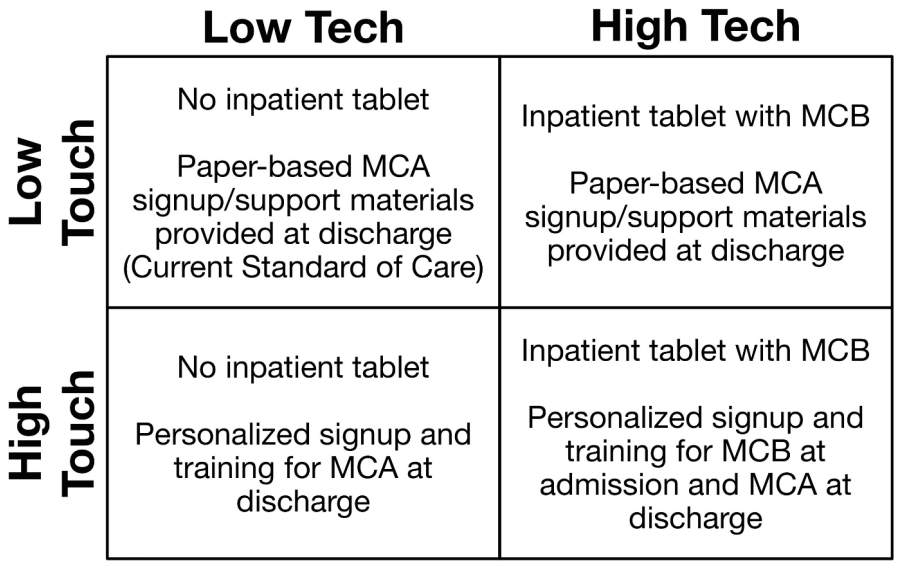
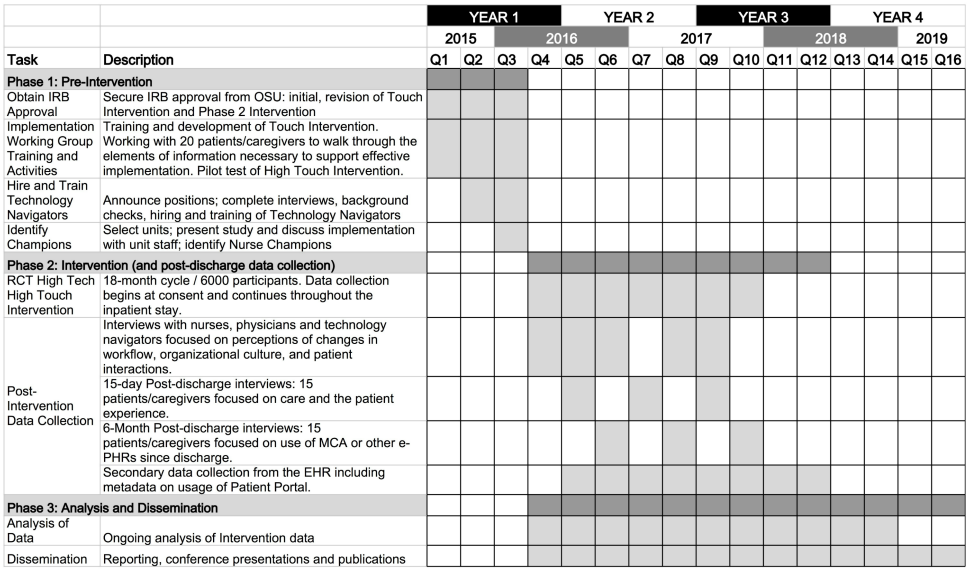


Figure 2. Project timeline. IRB: institutional review board; OSU: Ohio State University; RCT: randomized controlled trial; MCA: MyChart Ambulatory; PHR: personal health record; EHR: electronic health record.



Textbox 2. Inclusion criteria.

1. Patient admitted in the last 24 hours.
2. Expected discharge is more than 3 days away (over 72 hours); the average length stay at Ohio State University Wexner Medical Center (OSUWMC) is currently 5.4 days.
3. Two or more chronic conditions.
4. Patient is available in room.
5. Patient is capable of providing informed consent.

Study Design

We have delineated 4 study arms that vary based on the level of the Tech and Touch interventions planned (Figure 1). We have selected an experimental design that will allow us to explore the impact of providing supportive patient portal training as well as technology, but separate and apart from one another. The Touch interventions will be designed to provide approximately equivalent in-person time with a TN in order to control for bias. The Low Touch/Low Tech group was designed to allow for interaction with the TN but in a manner that should not affect the assessment model. Only patients assigned to the research study and selected for the High Tech intervention will be able to create accounts using MCB while they are hospitalized.

Study Population and Setting

The study randomizes individual patients within 1 of 6 general medicine units from OSUWMC into 1 of 4 study arms (Figure 1). While the unit of analysis and intervention is the patient, absent unit level controls, the study would suffer from endogeneity issues related to unit workflow dynamics that are changed by the presence of the tools, and as such the use of a unit-level control is justified. We will identify 6 matched pairs of general medicine units (12 total) on the basis of Case Mix Index, average length of stay, number of beds, nurse staffing levels and "nurse to bed staffing ratio," and select units for the intervention in each pair. Matched controls offer the ability to calculate a de-identified reference cohort of patients against which readmission and MCA uptake can be measured. In addition, we will conduct interviews with a purposive sample of health care professionals across the system to examine how the roll out of MCB impacts patient discussions in both the inpatient and ambulatory care settings; these interviews will include topics such as expectations of MCA usage, and perceptions of the technology and touch interventions.

Sample Size and Power Calculations

Sample size and power calculations were made using current patient satisfaction scores as a baseline for each measure using G*Power 3.1 software. We expect this design to be sensitive enough to identify changes of between 2.2% and 3.8% across the panel of patient satisfaction scores in the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) with a minimum of 968 observations per cell to accomplish this level of sensitivity. Our approach entails conservative oversampling (1500) to mitigate potential participant drop out. Inclusion criteria for the study is presented in Textbox 2.

Study Activities

Below is a description of the study activities across 3 phases. See the Timeline section for a month-by-month depiction providing additional information about the study phases and timing of data collection activities.

Phase 1: Pre-Intervention

This phase of the study will begin immediately upon funding and is expected to take 9 months. In total, 20 patients and/or caregivers will be involved in the pre-intervention phase.

Obtain Institutional Review Board Approval

While the study is minimal risk, it does involve direct patient contact and will require institutional review board (IRB) approval. The IRB process at Ohio State University is conservative in its review of patient-contact research. As such, we propose to begin work on the IRB application upon notification of funding (pre-study) to allow sufficient time for securing approval.

Implementation Working Group Training and Activities

We have established an Implementation Working Group consisting of 3 patients, 4 providers (2 physicians and 2 nurses), and 2 content experts, as well as study investigators (see Innovation section). The Implementation Working Group will participate in a multi-week training program designed to encourage all members to voice their concerns equally and to orient group members to the study. Patient members of this group will receive US $150 in remuneration annually in recognition of the time involved with participation in this process. Physician and nurse participants will conduct this work as part of their obligation to engage in research as academic practitioners and thus will not receive additional remuneration for study participation.

The Implementation Working Group will develop the High Touch intervention materials building on the current training available in our pilot studies. Our intent is to establish a triage model in which patients receive materials matched to their comfort level in managing their care using MCB and MCA. We will gather user experience data to develop support materials for MCB through "Talk Alouds," a common model for usability testing that helps to identify the elements of information necessary to support effective implementation [64]. In these sessions, users will work with tablet devices and be prompted to talk through their experiences with the technology. Participants' utterances and the associated screenshots will be recorded, managed, and coded using Morae software [65]. The "Talk Aloud" process will collect participant information including demographics, as well as information about experience with technology, and technological resources.

The MCB platform will be examined using Nielsen's heuristic principles [66] to identify aspects contrary to a user-friendly design. Usability testing will be conducted iteratively to optimize the intervention (see Timeline). We will first conduct individual sessions with 10 patient and caregiver volunteers with diverse levels of comfort with technology. These data will help to identify elements of MCB and MCA that will need particular attention in the High Touch intervention. The research team will then present the Implementation Working Group with a triage model for the High Touch and Low Touch intervention that can be aligned to individual patients' levels of comfort and understanding, and support collaborative development of the intervention. Upon finalization of the Touch intervention material, we will conduct individual sessions with an additional 10 patient volunteers to pilot test the Touch interventions, gather feedback, and conduct a final revision of the materials accordingly.

Hire and Train Technology Navigators

We will utilize TNs to enroll patients in the RCT, administer admission and discharge surveys, and to deliver the High and Low Touch interventions. TNs will complete Collaborative Institutional Training Initiative (CITI) training and infection control training as needed for research that involves contact with patients. TNs will then be trained in the effective dissemination of the Phase 1 support materials and will serve as the primary conduit through which the High Touch interventions will be delivered to patients in participating inpatient units.

Identify Unit-Level Champions

For each of the 6 general medicine units participating in the study, we will identify a staff nurse champion to support the HT2 project. These champions will help promote the HT2 project.

Phase 2: Intervention

The intervention phase of the study is expected to be completed within 18 months. The targets for recruitment are 6000 patients and/or caregivers, and 100 providers.

Initial Contact: Patient and Caregiver Recruitment

Patients will be recruited based on the inclusion criteria presented in Textbox 2. Consent and completion of the admission survey (details below) will take place on a tablet device using Research Electronic Data Capture (REDCap), a secure Web-based application for building and managing online surveys and databases. At the conclusion of the survey, the tablet screen will display a visual cue (ie, the background color of the screen will change) indicating to the TN to which treatment group the patient has been assigned; this code will be indecipherable to the study participant. Based on the cue, the TN will initiate the appropriate study group intervention.

The High Tech/High Touch Intervention

Enrolled patients admitted to one of the 6 selected hospital units over the 18-month study period will be randomly assigned to one of the 4 study groups (see Figure 1).

Intervention at Discharge

Prior to the patient's discharge, TNs will return to the patient room to activate the discharge survey on the tablet and collect the device from the High Tech groups. The TN will provide material necessary to create an MCA account if the patient does not have one or verify that the patient has access to their credentials before discharge (in case they forgot). As well, for those in the High Touch study groups, the TN will provide additional training in use of MCA as an outpatient. If a participant is re-admitted to the hospital, the TNs will again provide tablets to those patients in the High Tech group to enable continued study participation during the subsequent hospital stay.

Primary Data Collection

Both admission and discharge surveys will include questions on health literacy and experience with technology, and self-efficacy for managing chronic disease; the discharge survey will also include questions on patient satisfaction. In the discharge survey, a supplemental section for the High Tech groups assesses satisfaction with MCB and communication with staff in areas MCB may affect. When possible, question sets were used or adapted from existing sources. Table 1 lists the variables to be measured, the published source of the tool if applicable, the data collection instrument, and when the variable will be collected [67-69]. In addition, TNs will keep an ongoing weekly log of process measures, including variables such as the rate of patient refusal to participate, the number of participating patients who are discharged before the TN can return for the discharge survey, and problems encountered conducting the intervention.

Table 1. Variables to be measured.

Variable	Data collection instrument	Time of collection
Patient demographics and self-rated health status	Pre-survey and post-survey	At study assignment and at discharge
Chronic conditions and projected length of stay	EHR[a]	At study assignment
Self-efficacy to manage chronic conditions [67]	Pre-survey and post-survey	At study assignment and at discharge
Self-efficacy for using computers to access information (source: investigator)	Pre-survey and Post-survey	At study assignment and at discharge
Satisfaction with MCB[b] (adapted from [68])	Post-survey	At discharge
Patient satisfaction [69]	Post-survey	At discharge
Rate of MCA[c] use	EHR	6 months post-discharge
Information about the patients' doctors (OSU[d] versus non OSU for primary care and/or specialists)	EHR	6 months post-discharge
Readmission rate	EHR	6 months post-discharge

[a]EHR: electronic health record.

[b]MCB: MyChart Bedside.

[c]MCA: MyChart Ambulatory.

[d]OSU: Ohio State University.

Post-Intervention Data Collection

There are 4 types of post-intervention data collection: (1) 15-day post discharge patient interviews, (2) 6-month post discharge patient interviews, (3) interviews with providers and staff, and (4) and secondary data collection. All interviews will be audio recorded for transcription and to permit rigorous qualitative analysis. Patients (or caregivers) will be provided with gift cards as a token of appreciation for their participation in the interviews. In addition, we will contact patients who were discharged from the facility no less than 15 days post-discharge to request their participation in follow-up telephone interviews. Interviews will be conducted over the telephone and include a sufficiently large number of patients to ensure saturation of concepts across settings and experimental conditions. A semi-structured interview guide will be used including questions about the patient's use of MCB or other technology while admitted and during the patient's transition to the outpatient setting. We will also contact patients 6 months post discharge to request participation in phone interviews. These interviewees will be asked about their use of MCA or other patient portals since discharge, as well as asking about their experience with MCB and, if applicable, use of MCB during subsequent admissions. We will interview 20 providers (nurses and physicians) and all TNs every 4 months. Interviews will be focused on perceptions of changes in workflow, organizational culture, and patient interactions. Finally, secondary data collection will include abstraction from the EHR of participating patients and collection of de-identified metadata from university computer systems. This will provide information on frequency and type of use of both the MCB and MCA platforms. The Information Technology (IT) department, under the supervision of co-investigator Rizer, will provide these metadata. When patients are consented to join the study, the consent document will include a release of access to their EHRs for purposes of retrieving data at 6 months post-discharge on readmission rates, MCA use rates, and information on the patient's doctors (in health system versus out of network).

Phase 3: Analysis and Dissemination

Analytic Plan

We will employ a true mixed-methods research (MMR) model—one where both qualitative and quantitative data collection are employed to develop better theory. Creswell and Plano-Clark [70] define the central premise of MMR as "the use of quantitative and qualitative approaches in combination (that) provides a better understanding of research problems than either approach alone." While we have identified aims reflecting the research questions guiding this project, we must also acknowledge that these questions have not been asked in this way. As a result, the process of piloting instruments and using

accumulated knowledge to inform later components of the study is necessary in MMR. The qualitative effort is critical to achieving our specific aims because we need to understand the "why" behind what we are seeing in the data (ie, the context of variability).

Quantitative Data Analysis

As a first step, we will employ standard statistical tests (eg, analysis of variance, *t* tests) to compare patient and provider characteristics to examine whether the 4 cohorts are similar. While both multivariable regression and propensity score (PS) models are widely used to adjust for measured confounders and can be expected to yield similar findings, we plan to use a PS model.

We will construct a logistic regression model to predict use of MCA as a function of patient, provider, and covariate variables thought to be associated with the outcomes of interest. Across deciles of the PS distribution, we will compare factors associated with adoption (eg, age, comorbidities) between cohorts. To test for robustness, we will trim patients from the extremes of the PS distribution, refit the PS model, and evaluate overlap of the PS distributions (ie, common support) for the cohorts. Based on this evaluation, we will choose a strategy for matching, adjustment, or inverse weighting based on PS [71], and apply multilevel modeling (eg, hierarchical linear models). Co-investigator Huerta has published a number of studies using robust quantitative methods including significant work in the use non-parametric analytic approaches [72-75].

Qualitative Data Analysis

Qualitative analyses will be overseen by investigator McAlearney, a nationally recognized expert in qualitative methods, and will use the constant comparative method and a grounded theory approach to analysis [76]. Our iterative approach will involve reading interview transcripts, reviewing the literature, and discussing findings among investigators as the study progresses. This approach will enable us to explore emergent themes, and ensures saturation in data collection. Analysis will prioritize the elucidation of key concepts from individuals' statements made in interviews (extraction), and conceptual development based on constant comparative analysis and the classification of data through code development [77,78]. The research team will use the ATLAS.ti software package [79] to facilitate coding and data analyses.

Project Deliverables and Dissemination

Throughout the course of this project we intend to produce the following series of formal deliverables: (1) Interim Project Reports, summarizing preliminary findings at the end of each project year, (2) a Final Project Report summarizing and synthesizing findings across the project, and (3) a White Paper providing information about the HT2 interventions. We will also disseminate findings locally throughout OSUWMC, and broadly by producing a Public Webinar Presentation of Findings to be held at the conclusion of the project.

For further dissemination of research results, we will prepare and submit at least two peer-reviewed articles for publication in academic journals after concluding this research study, and we will seek to make presentations of findings at national meetings including Academy Health, and the Academy of Management, and the Healthcare Information and Management Systems Society (HIMSS). Further, we have included resources to support the submission of manuscripts to open source journals.

Beyond formal deliverables submitted to AHRQ, this project will also create products of value to a broad audience. Our Implementation Work Group training program will provide a structure that can serve as a model for any organization wishing to focus on these intervention areas, thus supporting the spread and long-term sustainability of this approach. In addition, our patient portal training materials ("High Touch") will generate topic-specific materials that can be utilized by other organizations planning to implement patient portals and include patients in the process. Each of these products will be made available online upon completion of the project.

Results

The proposed project has been funded as an Agency for Healthcare Research and Quality (AHRQ) R-01 study (#5R01HS024091-02). Data collection is underway. This research is expected to conclude in August 2019.

Discussion

Innovation

This study is groundbreaking. There are no randomized trials that have explored inpatient patient portals, in part because the technology itself has only recently emerged. However, we should expect these technologies will play a significant role in both inpatient and outpatient care in the future. While current patient portals have primarily been positioned to support the ambulatory care settings, as described earlier, the emergence of inpatient portals will open a new opportunity for engagement that may have implications across inpatient and outpatient settings.

Innovative Technology

OSUWMC is only the second health system in the nation to offer this highly innovative patient portal designed specifically for the inpatient environment. MCB provides patients with situation-specific information, such as daily schedule information, routing of questions to their care team, information about the care team, and immediate release of lab and test results. This will be the first large-scale study of an interactive tablet-based patient portal available at the inpatient bedside. This is a significant step toward using HIT to engage patients across the continuum of their care. OSUWMC has a strong relationship with Epic, and the research we propose will likely influence Epic implementations throughout the United States, thus potentially improving care delivery and outcomes nationwide.

Further, while health systems have not yet deployed such systems, the issue is more associated with an absence of tools provided by vendors as opposed to an unwillingness of health systems to implement. As the technology matures and more information comes online detailing the value proposition, these

tools will see increasing use as well as greater diversity of tool availability (eg, tablet-based, mobile PHRs, etc). Further, as patients are better able to manage their disease states, they will "bend the cost curve" [80] by moving from high-cost interventions (eg, emergency room visits) to lower cost management of their conditions. The supposition is that the better we can engage patients in self-management of their own care and be effective at that practice, the lower the cost of care. Our study thus seeks to explore and gain a greater knowledge of how one such tool an inpatient patient portal can serve to not only influence outcomes related to the inpatient setting but throughout the entire continuum of care, including transitions and the outpatient care environment.

Compelling Experimental Design

While it would have been possible to conduct a smaller study that sought to explore the implications of patient portal adoption in greater detail, the need for larger-scale quantitative studies is without question. Existing studies have been resource limited and have not explored their implications in a RCT. As HIT tools such as patient portals become more prevalent, the likelihood of being able to execute a controlled trial is diminished. Rarely is a health system willing to subject the organization to such a broad scale intervention as Ohio State University is proposing.

Innovative Education Model

In addition, our Touch intervention will train patients not only in the technical aspects of utilizing the inpatient patient portal (MCB, the *how*) but also in the general use of an ambulatory patient portal (MCA) to manage their specific health condition over time (the *why*). Because the tablet MCB app allows an assessment of the patient's comfort with technology and health literacy at the time of training, the Touch intervention can be tailored to the individual patient's needs.

New Information Provided Through Subgroup Comparisons

Finally, our study will collect quantitative and qualitative data from a sufficiently large and diverse sample of patients to enable us to make comparisons across patient subgroups. We will assess the impact of our interventions in a variety of subgroups including those identified by demographics, by health condition, and by experience and comfort with technology. The results of this study will thus help health systems and providers understand what levels of technology and training work best to engage which patients.

Limitations

Several limitations are inherent to this study, and we have explicitly tried to reduce the risks they pose. To address the possibility of missing data for the discharge survey, the TN will re-visit participating patients to activate the survey on the tablet and stay with patients during survey completion. This process should ensure that we have a high response rate. However, we do acknowledge that discharge can be unexpected and the TN will not be able to return to all participating patients before their discharge, particularly when discharge occurs sooner than planned or over a weekend. We attempt to mitigate this limitation with our recruitment protocol.

Currently, only two health systems in the United States are utilizing the Epic MCB product. While ambulatory patient portals are seeing a rise in use, inpatient portals have yet to emerge as a common engagement tool. This is due, in no small part, to requirements for meaningful use (MU) defined by the Office of the National Coordinator (ONC) as part of the Accountable Care Act. The stages that define MU have minimum participation requirements, and if a linkage between usage of MCB and MCA engagement is substantiated, we could see a rapid adoption of inpatient technology. Given that over 50% of US patients have their medical information stored within the Epic platform, the results of the present study may serve to either encourage or discourage (depending on the results) wider adoption and a proliferation of similar inpatient tools.

We have also taken steps to address platform and infrastructure changes. With such a long data collection period, there is a chance that the technology intervention may change as new functionality is brought online. Given the upgrade schedule at OSUWMC, we expect to see two updates to MCB as we await determination on the status of this proposal, and an additional update during the intervention. These pragmatic issues stand with any study, and the team is committed to addressing issues should they arise, in part by including leadership in the study, and by maintaining the Implementation Working Group throughout the data collection period.

Strengths and Future Directions

The use of technology is an important ongoing issue in the study of how care is provided. With technology playing an ever-increasing role in the provision of care, tools such as patient portals offer another avenue through which behavior change can be facilitated. The proposed study will be the first RCT to examine the role that the new technology of inpatient portals could play to transform the way care is delivered.

Achievement of our HT2 study aims will lay the groundwork for future research and provide information to various health policy groups as well as increasing understanding about HIT implementation efforts for health systems. While qualitative studies offer insight into how and why things work, a determination of magnitude requires an experimental design such as an RCT. We expect this work will serve to provide information about how to integrate patient portals into practice, as well as about their contributions to care quality and their impact on readmissions, if such effects occur. Further, there are a number of hypotheses that could be tested within the context of this study outside of its primary focus that we are unable to enumerate due to space limitations. We expect these opportunities to be leveraged by doctoral students as part of dissertation work in the College of Public Health where Drs McAlearney and Huerta hold appointments and frequently serve on dissertation committees. Thus, this research can support practice innovation, researcher training, and future opportunities for training supplements.

Conflicts of Interest

None declared.

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Abbreviations

AHRQ: Agency for Health Care Research and Quality
eHealth: electronic health
EHR: electronic health record
FAQ: frequently asked question
HIT: health information technology
HT2: High Tech/High Touch
IRB: institutional review board
MCA: MyChart Ambulatory
MCB: MyChart Bedside
MMR: mixed-methods research
MU: meaningful use
OSUWMC: Ohio State University Wexner Medical Center
PHR: personal health record
PS: propensity score
RCT: randomized controlled trial
TN: technology navigator

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Protocol

Development of a Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo): Study Protocol

Alfonso Iorio[1,2], MD, PhD; Arun Keepanasseril[1], MDS, MSc; Gary Foster[3,4], PhD; Tamara Navarro-Ruan[1], MEd, MLS; Alanna McEneny-King[5], MSc; Andrea N Edginton[5], PhD; Lehana Thabane[3,4], PhD

[1]Health Information Research Unit, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada

[2]Hamilton Niagara Hemophilia Program, Department of Medicine, McMaster University, Hamilton, ON, Canada

[3]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada

[4]Biostatistics Unit, St. Joseph's Healthcare, Hamilton, ON, Canada

[5]School of Pharmacy, University of Waterloo, Waterloo, ON, Canada

Corresponding Author:
Alfonso Iorio, MD, PhD
Health Information Research Unit
Department of Clinical Epidemiology and Biostatistics
McMaster University
CRL 140
1280 Main Street West
Hamilton, ON
Canada
Phone: 1 905 525 9140 ext 20152
Fax: 1 905 577 8478
Email: iorioa@mcmaster.ca

Abstract

Background: Individual pharmacokinetic assessment is a critical component of tailored prophylaxis for hemophilia patients. Population pharmacokinetics allows using individual sparse data, thus simplifying individual pharmacokinetic studies. Implementing population pharmacokinetics capacity for the hemophilia community is beyond individual reach and requires a system effort.

Objective: The Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo) project aims to assemble a database of patient pharmacokinetic data for all existing factor concentrates, develop and validate population pharmacokinetics models, and integrate these models within a Web-based calculator for individualized pharmacokinetic estimation in patients at participating treatment centers.

Methods: Individual pharmacokinetic studies on factor VIII and IX concentrates will be sourced from pharmaceutical companies and independent investigators. All factor concentrate manufacturers, hemophilia treatment centers (HTCs), and independent investigators (identified via a systematic review of the literature) having on file pharmacokinetic data and willing to contribute full or sparse pharmacokinetic data will be eligible for participation. Multicompartmental modeling will be performed using a mixed-model approach for derivation and Bayesian forecasting for estimation of individual sparse data. NONMEM (ICON Development Solutions) will be used as modeling software.

Results: The WAPPS-Hemo research network has been launched and is currently joined by 30 HTCs from across the world. We have gathered dense individual pharmacokinetic data on 878 subjects, including several replicates, on 21 different molecules from 17 different sources. We have collected sparse individual pharmacokinetic data on 289 subjects from the participating centers through the testing phase of the WAPPS-Hemo Web interface. We have developed prototypal population pharmacokinetics models for 11 molecules. The WAPPS-Hemo website (available at www.wapps-hemo.org, version 2.4), with core functionalities allowing hemophilia treaters to obtain individual pharmacokinetic estimates on sparse data points after 1 or more infusions of a factor concentrate, was launched for use within the research network in July 2015.

Conclusions: The WAPPS-Hemo project and research network aims to make it easier to perform individual pharmacokinetic assessments on a reduced number of plasma samples by adoption of a population pharmacokinetics approach. The project will also gather data to substantially enhance the current knowledge about factor concentrate pharmacokinetics and sources of its variability in target populations.

Trial Registration: ClinicalTrials.gov NCT02061072; https://clinicaltrials.gov/ct2/show/NCT02061072 (Archived by WebCite at http://www.webcitation.org/6mRK9bKP6)

(JMIR Res Protoc 2016;5(4):e239) doi:10.2196/resprot.6558

KEYWORDS

hemophilia; population pharmacokinetics; factor VIII; factor IX; tailored prophylaxis

Introduction

Hemophilia A and B are X chromosome–linked bleeding disorders caused by mutations in the factor VIII (FVIII) and factor IX (FIX) genes. Both factors take part in the intrinsic pathway of blood coagulation. Affected individuals have severe, moderate, or mild forms of the diseases, defined by factor plasma levels of 1% or less, 2% to 5%, and 6% to 40%, respectively. Both hemophilia A and B are rare diseases; the prevalence of hemophilia A is 1 in 5000 male live births and that of hemophilia B is 1 in 30,000 [1,2]. Factor replacement therapy with plasma-derived or recombinant concentrates at regular intervals to prevent both bleeding and the resultant joint damage (ie, primary prophylaxis) is the mainstay of treatment of hemophilia [2,3].

Tailoring prophylaxis to individual patient characteristics has been suggested as an effective way to increase the net clinical benefit of hemophilia A and B treatment [4,5]. It has been demonstrated that hemophilia patients require either higher or lower prophylactic doses of clotting factor replacement products than the standard 20 to 50 IU/kg 2 to 3 times per week, and at least one-third of the patients can be effectively treated with lower doses or less frequent infusions [6-8]. A key element needed to tailor prophylaxis is the estimation of the pharmacokinetic disposition of FVIII/FIX at the individual level. The main barriers to pharmacokinetic assessment in clinical practice are the burden of multiple blood sampling required over 24 to 72 hours (usually 11 points for the classical approach) and the inconvenience for the clinician of performing the needed calculations, which, even adopting the approximation of a single compartment model kinetic, are beyond the expertise of most hemophilia treaters [9]. Furthermore, most of the newer extended half-life products require adoption of 2- or even 3-compartment models leading to substantially more complex calculations [10-13]. Population pharmacokinetics facilitates easier but still reliable estimation of individual parameters using reduced data points from each individual patient because it is based on mathematical models derived from previous knowledge from the entire available patient population. However, there are very limited readily accessible comprehensive hemophilia population pharmacokinetics applications available to clinicians. The Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo) project aims to bridge this gap. The original study protocol was registered at ClinicalTrials.gov [NCT02061072].

The project has the following overarching objectives: (1) to empower hemophilia treatment by making it easier to perform individual pharmacokinetic assessments, (2) to allow for robust estimation of individual pharmacokinetic parameters with a reduced number of plasma samples, and (3) to enhance knowledge about the pharmacokinetics of FVIII and FIX.

The project has the following specific objectives: (1) to collect and compile published and unpublished individual classic pharmacokinetics data (individual patient data from independent investigators and factor concentrate manufacturers), (2) to create and make available population pharmacokinetic models for the concentrates derived from the data collected, (3) to develop a Web-based application intended to use the above models to calculate pharmacokinetic parameters for individual patients, (4) to test system functionality by use of fabricated test data, (5) to test the reliability of the pharmacokinetic reports provided by WAPPS-Hemo, and (6) to determine the potential value of this Web service for clinicians.

Methods

Study Design and Pharmacokinetics Repository

WAPPS-Hemo is a multicentric prospective project led by McMaster University, Hamilton, Ontario, Canada. The project is based on a population pharmacokinetics application hosted on a Web-accessible platform developed and run by the Health Information Research Unit, McMaster University. Pharmaceutical companies and independent investigators will be invited to provide already existing on-file individual pharmacokinetic data for developing the population pharmacokinetics models. All the factor concentrate manufacturers having on-file pharmacokinetic data and hemophilia treatment centers (HTCs) or independent investigators willing to contribute full or sparse pharmacokinetic data will be eligible for participation. All investigators of the pharmacokinetic studies identified via a systematic review of the literature will be contacted and invited to provide data.

Research Network

Active hemophilia treaters will be invited to participate as coinvestigators and share ownership of the prospective pharmacokinetic database, to which they will be invited to provide plasma levels on sparse samples from eligible patients. They will be invited to provide feedback on the WAPPS-Hemo performance and functionality during the development phase of the project and to propose any substudy they could be interested to run in the network. Patient participation in the project will be mediated by their participating treatment center, as WAPPS-Hemo will not be directly available to patients. Initial emails will be sent out to the clinicians/hemophilia treaters to determine interest in this project. Once initial agreement of project participation has been confirmed, research agreements will be sent to facilitate data transfer. Research agreements will be operationalized offline and kept on file. No

remuneration will be provided to either participating centers or patients.

Anticipated Outcomes

The WAPPS-Hemo project will result in the availability of a repository of published and unpublished factor concentrate concentration-time datasets for hemophilia patients. Published data will be summarized in a systematic review and submitted for publication. Further, population pharmacokinetics models for the factor concentrates for which concentration-time data are available will be established. The model development process is described in a separate scientific report [14]. The extended version of this report will be available as part of the study documentation, while a synthetic version will be submitted for publication. A major outcome will also be that a Web-based WAPPS-Hemo engine will be made available to participating clinicians that will provide tailored pharmacokinetic estimates for their patients, including estimated terminal half-life; time to 1%, 2%, and 5% plasma clotting factor level; and expected plasma level of factor concentrate at 24, 48, and 72 hours postinfusion. The engine will also report the credibility estimates. Once the system is fully developed and validated we will consider releasing a version of the service available to clinicians unable or unwilling to participate in the research network and effort. However, we envision that any users, independent of the level of participation into the project, will require an identification and authentication process as well as the authorization to reuse anonymized data for modelling purposes. Indeed, quality and reliability of the data provided to the system and potentially used to refine the models require a mechanism to contact the user to perform data quality checks.

Sample Size Considerations

We expect to be able to derive models for concentrates for which we have 20 or more preexisting densely sampled individual pharmacokinetic profiles. We expect to have data available for 4 or more different factor concentrates. We expect participation from 10 clinical centers with each center contributing data from approximately 10 patients.

Project Development Phases

In order to fulfill the aims and objectives, the project will be operationalized as distinct but closely related work components as listed below. The work components will proceed in an iterant and parallel mode.

1. A systematic review to identify all existing publications reporting pharmacokinetic data on FVIII and FIX

2. Collection of individual pharmacokinetic data on file from investigators and factor concentrate manufacturers by signing bilateral data transfer agreements

3. Establishment of population pharmacokinetics models for factor concentrates

4. Creation of a Web-accessible platform, WAPPS-Hemo, to calculate patient-specific pharmacokinetic estimates from clinician-input concentration-time data

5. Integration of the population pharmacokinetics models into the WAPPS-Hemo Web service

6. Recruitment of HTCs and hemophilia treaters from across the world to the research network

7. User testing of the Web interface by participating centers by use of the Software Usability Score [15] and think-aloud techniques [16] using standardized fabricated patient data

8. Testing the reliability of the pharmacokinetic report provided by the WAPPS-Hemo Web service

Development of the Web-Accessible Population Pharmacokinetic Service—Hemophilia Web Interface

Overview

The system will be developed by and hosted at the Health Information Research Unit, McMaster University, Ontario, Canada. A cluster of fully resilient Hewlett Packard servers (Windows Web servers in network load balancing configuration) for hosting the site, Microsoft SQL (Microsoft Corp) for the database, and a Windows server for the modelling software, located in 2 different buildings, will support the system platform. The system will incorporate fully mirrored hard disks and redundant https connection. All WAPPS-related URLs (eg, .com, .org, .ca) were blocked immediately at project funding notification. All the needed licenses will be acquired, including a single-site license for the population pharmacokinetics software, NONMEM (ICON Development Solutions). The website, database access interface, and back-end NONMEM interface will be programmed in Microsoft (Microsoft Corp) dot.Net programming language. The user interface will be device responsive.

System Development Approach and Architecture

We will use Agile software developing methods to develop the WAPPS-Hemo. Agile methodology was selected over the conventional software development life cycle method because, unlike conventional methods, it allows the team to iteratively plan and strategize the development of the system [17]. We indeed postulated that the Agile strategy of developing the system in small iterations (known as sprints) is particularly suited to a project of dynamic nature like WAPPS-Hemo because it allows the team to adapt to changing requirements based on short-term goal-setting stemming from a large collaborating network of HTCs [18]. The system architecture schema is presented in Figure 1.

Figure 1. Schematic representation of the Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo) system architecture. PK: pharmacokinetics; PPK: population pharmacokinetics; CTRL: control.

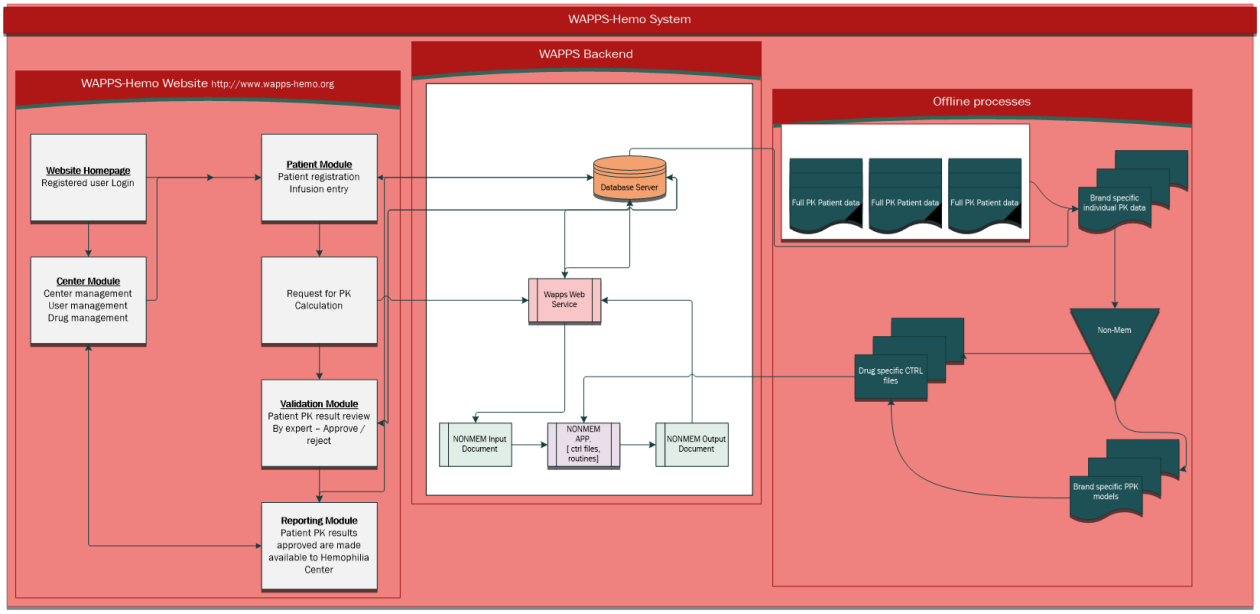
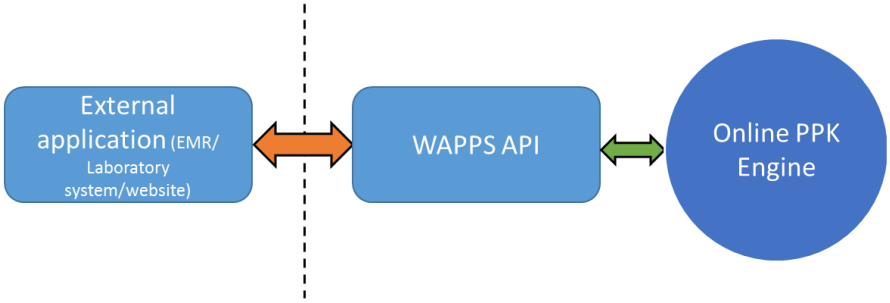


Figure 2. Schematic representation of the Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo) application programming interface implementation. EMR: electronic medical record; API -application programming interface; PPK: population pharmacokinetics.



The system will be provided with an application program interface to facilitate potential integration with electronic medical record software, database, and clinical trial case report forms at a later stage (see Figure 2).

Field testing will be performed by each participating center. Initially, fabricated patient data will be used. Following successful registration, the centers will be provided with a standardized set of data and asked to generate records for those patients. Population pharmacokinetics estimates will be requested, reports generated, and feedback on the entire process gathered; we will troubleshoot any arising issues. We will conduct a formal usability evaluation using the Software Usability Scale, think-aloud technique, and focus group feedback to modify the service accordingly.

Description of Expected Information Flow on the Website

User Registration

The home page of the website will have a section where a user can register or log in to the service. Registration will be open to participating centers/local investigators after they agree to and sign the research agreement. Registration requests will be validated before the center is activated. Data on the laboratory tests used by the center will be collected at the time of patient data input but will be stored as user characteristics for subsequent use for future patients from that center.

Patient Registration

The goal is to allow the participating center to identify their patients while still respecting privacy regulations. Patient identification is critical in allowing re-input of the same patient's data in the future and dispatching of the reports to the proper requester. The patient registration module will be activated for each participating center/investigator following ethics approval. The system will require a local patient identifier to be created for which any combination of alphanumeric codes will be accepted. Identifiable personal health information will be stored centrally, locally, or not stored at all in agreement with local privacy and ethical requirements. Patient date of birth, sex, diagnosis, and severity are the mandatory data required for patient registration. Optional fields may be collected as well, on each patient or prompted by specific characteristics (see Figure 3). We plan to include among optional fields blood group and inhibitors (actual and peak titer as Bethesda units/mL, date of peak, last measurement, and actual treatment regime). Ethnicity, race, genotype, or other information potentially associated with pharmacokinetics will or will not be added to the optional fields based on user feedback.

Infusion and Plasma Level Data Entry

After a patient record is created, an infusion record can be added (see Figure 4). This will require the input of patient body weight, the specific factor concentrate infused, the total dose infused, the infusion time and duration. Predose plasma factor level will be provided when available. Postinfusion factor levels will be input as sampling time and factor concentration in IU/mL. Samples for which the level falls below the detection threshold will be identified as below the level of quantitation.

Figure 3. Web-Accessible Population Pharmacokinetic Service–Hemophilia new patient entry page.

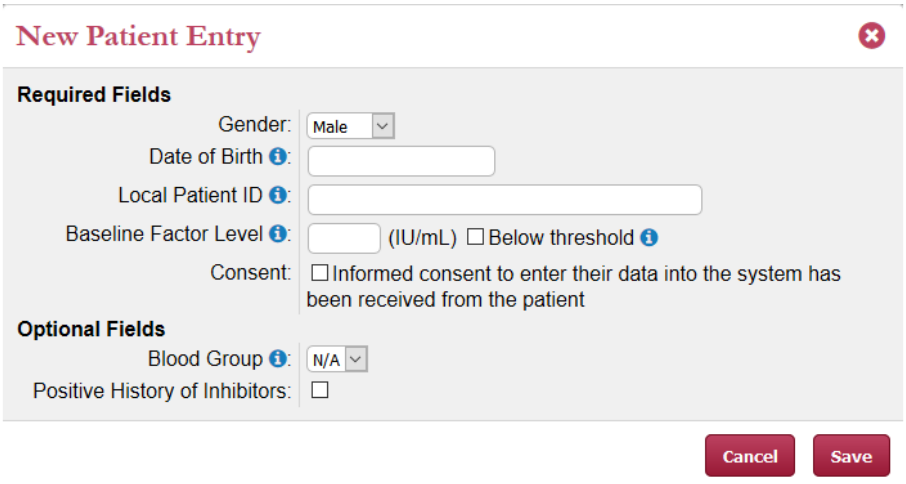
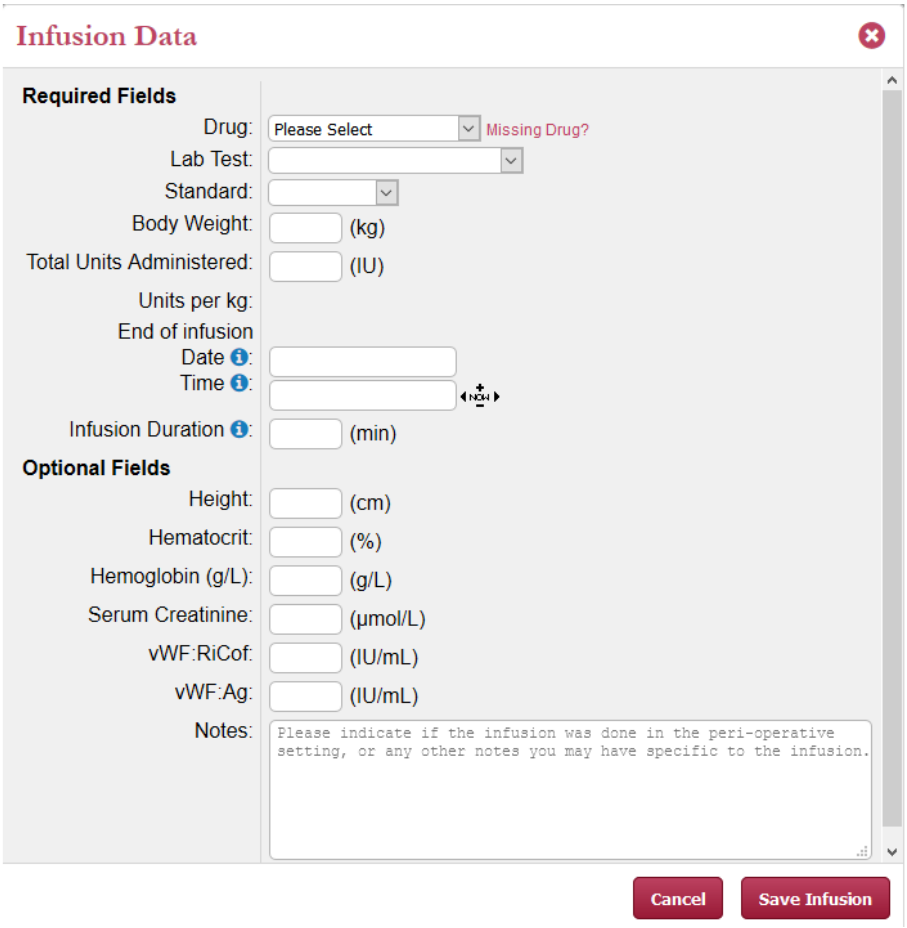


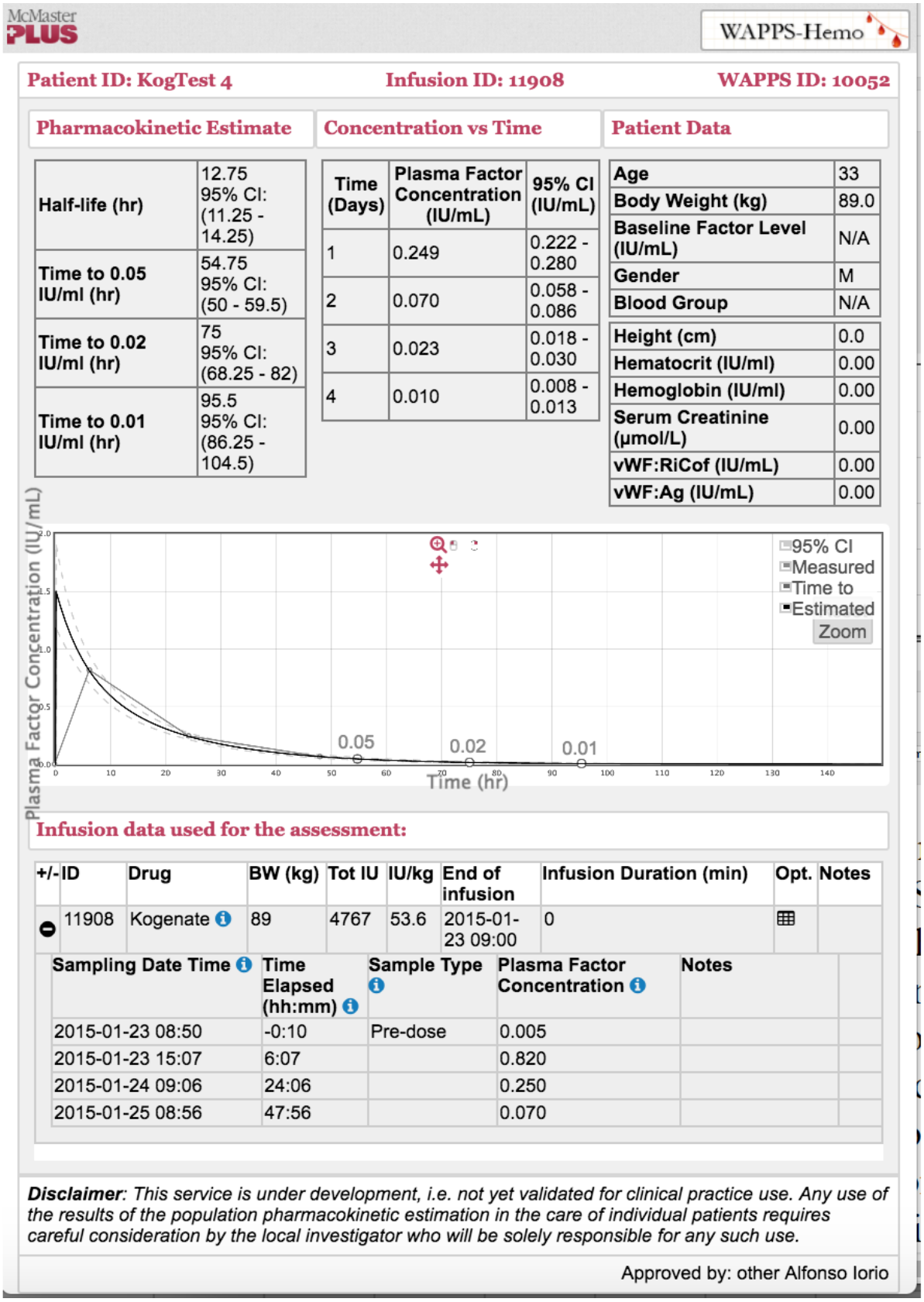
Figure 4. Web-Accessible Population Pharmacokinetic Service–Hemophilia measurement entry page.



Pharmacokinetic Estimation

After completion of the data input step, the user will request the estimation of the individual pharmacokinetic parameters. A congruency check will be performed on the submitted input data. Details about the development and evaluation of the underlying population pharmacokinetics models as well as details of the postmodelling Bayesian estimation are provided in a separate paper [14].

Figure 5. Web-Accessible Population Pharmacokinetic Service–Hemophilia result page.



Reporting

Each individual infusion will be reported. The report will contain inputted data; terminal half-life; time to 0.05, 0.02, and 0.01 IU/mL of plasma factor level with Bayesian credibility intervals; expected plasma concentrations at 24, 48, and 72 hours; and an interactive graphical representation of the predicted postinfusion concentration-time profile (see Figure 5). To ensure that the data and estimates are reliably accurate, automated and human checks will be performed to determine congruency of the data

and estimates before releasing the results. Therefore, there will be no real-time reporting of the data and pharmacokinetic estimates.

Risks

There are no additional risks to the patient beyond the risk associated with standard of care at each participating center. During the initial development of the service we will not offer the Web application beyond the boundaries of the participating centers. The website will be made available to those in the research network during the testing phase using only fabricated data. Although participating centers will have the opportunity to input real patient data and receive pharmacokinetic reports, we will clearly identify the prototypal and experimental use of the system in both the research agreements and the website page as a "Research service not yet ready for clinical practice." A clear disclaimer will indicate that "Any use of the results of the population pharmacokinetic estimates in the care of individual patients should not be considered part of the project in this phase."

Research Ethics Approval

The WAPPS-Hemo project has received ethical approval from the Hamilton Integrated Research Ethics Board. Only data already collected as part of other studies will be used for the establishment of population pharmacokinetics models and, as such, these studies have already received ethics approval. Legal approval for the use of the data will be sought from the owner of the data. Any other applicable procedures will also be followed.

The local investigator from the participating center will submit the WAPPS-Hemo study protocol, including a localized consent form, to their local ethical review board for approval. The coordinating center at McMaster will support the local investigator in the application to the local research ethics board if requested to do so. The local investigator will obtain informed consent for the input of patient data on the WAPPS-Hemo system from each participant whose data is provided. Copies of the ethical approval and informed consent letters will be stored locally. When a participating center submits patient data to WAPPS-Hemo, the investigator will need to declare that the patients have provided consent. Any important protocol modifications will be sent to the relevant parties through email.

Data Access, Security, and Confidentiality

Only anonymized patient data already collected as part of clinical studies or on file from factor concentrate manufacturers will be collected for the development of models. No personal identifying information such as name or social insurance number will be collected.

In the prospective phase, users will be allowed to access and use the system only after a moderated registration process. The head of the participating center will be required to go through a registration process, and following validation by the core McMaster team, that person will receive credentials to access the website and will subsequently be able to authorize other users from the center to access the system. Each individual user will have unique access credentials and will be authorized to manage patients from the center she or he belongs to. Only authorized users will be able to create and access patient records and input the information required for the pharmacokinetic assessment.

For the initial identification of patients, the system will require a local patient identifier to be created for which any combination of alphanumeric codes will be accepted. It will then be the responsibility of the participating center to track the local patient WAPPS-Hemo identifier in the patient case report form. Each center will be free to adopt, in respect of their local ethical and privacy regulation and by-laws, any structured or unstructured way of identifying their patients, including the use of alphanumeric strings for patient first and last names. Whenever possible, use of an existing patient identifier from the local health care system as WAPPS identifier is recommended.

All data held at McMaster will be stored on a secure server with adequate physical, technical, and administrative safeguards. Physical access to the data center is limited to the information technology manager and programmers of the unit via a swipe card system and is monitored at all times by video surveillance. The administrative website and backup database will be accessible only over a virtual private network. The system will be available around the clock with expected downtime less than 0.1%. Access to the Web service will be tightly controlled via robust passwords. We will use a secure https connection for added security. Any data used for statistical analysis and reporting will have been previously anonymized. Only the research team will have access to the data.

Participants of this project will not be identified in any reports or publications. No paper records of the data will be maintained. Patients will have the right to request complete cancellation of their personal data through the local investigator or to completely deidentify any concentration-time points (this last information will be retained in the system if already used for scientific reporting for as long as allowed by current regulation).

Results Dissemination Policy

As a part of a research project, results from all the above activities will be reported in peer-review publications. All scientific communications regarding the population pharmacokinetics models (whether abstract, scientific meeting, or peer-reviewed publication) stemming from this project will go through a formal approval step with all the entitled authors, including any factor concentrate manufacturer's publication committee.

Project Funding and Sustainability

The development and initial operation of the WAPPS-Hemo website is supported by a research grant, awarded as result of a competitive peer-reviewed grant competition by the Association of Hemophilia Center Directors of Canada Baxter Canadian Hemophilia Epidemiological Research Program. We plan to seek additional research funding and to sustain ongoing operation of the project with intramural funds from the Health Information Research Unit of McMaster University.

Results

The WAPPS-Hemo research network currently involves 47 registered active HTCs from across the world. Figure 6 illustrates the geographical distribution of the network.

An additional 26 HTCs are in various stages of the internal approval process, and 29 more HTCs have expressed interest in joining the network.

We have collected dense individual pharmacokinetic data on 878 subjects, including several replicates, on 21 different molecules from 17 different sources. We have collected sparse individual pharmacokinetic data on 289 subjects from the participating centers through the testing phase of the WAPPS-Hemo Web interface.

We have developed prototypal population pharmacokinetics models for 11 molecules. All developed models and methodological issues involved in the development and validation of models are reported in separate scientific reports [14,19]. In brief, assessment of validity of a system like WAPPS-Hemo is a complex process which will be covered in a stepwise fashion. After validation of the population models by bootstrapping and comparing population and structural estimates, we will prospectively validate the prediction by asking WAPPS-Hemo users to resample the patient after the pharmacokinetics has been estimated; the measurements will be used to assess the goodness (validity, precision) of the prediction. The final validation step will be to assess the impact of adopting WAPPS-Hemo–based forecasts to tailor treatment. This will require an ad hoc designed prospective clinical trial, currently in the planning stage.

The WAPPS-Hemo website (available at www.wapps-hemo.org, version 2.40), with core functionalities allowing hemophilia treaters to obtain individual pharmacokinetic estimates on sparse data points after 1 or more infusions of a factor concentrate, was launched for use within the research network. Asynchronous user support is currently made available via a monitored email service; we expect response time within the following working day, and a phone interaction can be started by the help desk when deemed to be necessary.

A formal usability study of the WAPPS-Hemo interface involving 13 participants (physicians, nurses, and clinical coordinators) from 2 centers in Canada, 1 in the United States, 1 in the United Kingdom, and 1 in Turkey has been performed. Two iterations resulted in new releases of the software interface. Detailed results will be reported in a separate publication. The WAPPS-Hemo interface has been translated into 11 languages: Arabic, Chinese, English, French, German, Italian, Japanese, Farsi, Portuguese, Spanish, and Turkish.

Two large prospective studies addressing the value of pharmacokinetic tailored prophylaxis, one in hemophilia A and one in hemophilia B, have been recently funded and are underway in the United States, both adopting WAPPS-Hemo as the population pharmacokinetics engine (personal communication).

Figure 6. Web-Accessible Population Pharmacokinetic Service–Hemophilia research network.

Discussion

Overview

The WAPPS-Hemo service is the first dedicated population pharmacokinetics calculator available on an institutional website, essentially simplifying and facilitating individual pharmacokinetic assessment for treatment of hemophilia A and B. We expect that the widespread adoption of the system will lead to a reduction in the need for blood samples in individual patients, with particular benefit for the assessment of pharmacokinetics in pediatric patients. The capability of assessing pharmacokinetic parameters on sparse data will bear the potential to extend the use of pharmacokinetics to different scopes, including monitoring and optimizing prophylaxis regimes, identifying individual treatment targets, and switching from product to product. This should result in better care while optimizing resource utilization.

The WAPPS-Hemo system is built for progressive refinement of its own capabilities. Patient data will be periodically merged into the reference database of the system, and models will be

periodically recalibrated. This continuous quality assurance process will enhance its capability to perform precise predictions.

The WAPPS-Hemo system is built to support research and knowledge translation. The system will progressively accrue individual pharmacokinetic data for both hemophilia A and B and different factor concentrates, which will be shared within the WAPPS-Hemo research network. The availability of a large database of pharmacokinetic data jointly with a research network of centers with a specific interest in pharmacokinetics will pave the way to a deeper understanding of the individual pharmacokinetic properties of different concentrates and will increase the evidence base used to treat hemophilia patients.

Limitations

The main limitation of the current project design is the need for users to have some basic understanding of pharmacokinetics. Indeed, the system does not have built-in functions to support simulation of different dose regimens. Other limitations are integral to the need to demonstrate the true net impact of population pharmacokinetics modelling in hemophilia care, the identification of the most efficient sparse sampling protocols, and the identification of relevant covariates to maximize the impact of using a population pharmacokinetics approach.

Conclusion

In summary, WAPPS-Hemo is well positioned and has become the largest pharmacokinetic data repository in the field. The interconnection of a Bayesian engine, population pharmacokinetic routines, and smart end-user interface constitute an innovative blend of different high-tech approaches with potential to impact the care of hemophilia.

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Conflicts of Interest

None declared.

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Abbreviations

FVIII: factor VIII
FIX: factor IX
HTC: hemophilia treatment center
WAPPS-Hemo: Web-Accessible Population Pharmacokinetic Service—Hemophilia

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Protocol

Investigation of the Association Between Alcohol Outlet Density and Alcohol-Related Hospital Admission Rates in England: Study Protocol

Ravi Maheswaran[1], MD; John Holmes[2], PhD; Mark Green[1], PhD; Mark Strong[1], MBChB, PhD; Tim Pearson[1], MSc; Petra Meier[2], PhD

[1]Public Health GIS Unit, School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom

[2]Sheffield Alcohol Research Group, School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom

Corresponding Author:
Ravi Maheswaran, MD
Public Health GIS Unit
School of Health and Related Research
University of Sheffield
Regent Court
30 Regent Street
Sheffield, S1 4DA
United Kingdom
Phone: 44 1142220681
Fax: 44 1142220749
Email: r.maheswaran@sheffield.ac.uk

Abstract

Background: Availability of alcohol is a major policy issue for governments, and one of the availability factors is the density of alcohol outlets within geographic areas.

Objective: The aim of this study is to investigate the association between alcohol outlet density and hospital admissions for alcohol-related conditions in a national (English) small area level ecological study.

Methods: This project will employ ecological correlation and cross-sectional time series study designs to examine spatial and temporal relationships between alcohol outlet density and hospital admissions. Census units to be used in the analysis will include all Lower and Middle Super-Output Areas (LSOAs and MSOAs) in England (53 million total population; 32,482 LSOAs and 6781 MSOAs). LSOAs (approximately 1500 people per LSOA) will support investigation at a fine spatial resolution. Spatio-temporal associations will be investigated using MSOAs (approximately 7500 people per MSOA). The project will use comprehensive coverage data on alcohol outlets in England (from 2003, 2007, 2010, and 2013) from a commercial source, which has estimated that the database includes 98% of all alcohol outlets in England. Alcohol outlets may be classified into two broad groups: on-trade outlets, comprising outlets from which alcohol can be purchased and consumed on the premises (eg, pubs); and off-trade outlets, in which alcohol can be purchased but not consumed on the premises (eg, off-licenses). In the 2010 dataset, there are 132,989 on-trade and 51,975 off-trade outlets. The longitudinal data series will allow us to examine associations between changes in outlet density and changes in hospital admission rates. The project will use anonymized data on alcohol-related hospital admissions in England from 2003 to 2013 and investigate associations with acute (eg, admissions for injuries) and chronic (eg, admissions for alcoholic liver disease) harms. The investigation will include the examination of conditions that are wholly and partially attributable to alcohol, using internationally standardized alcohol-attributable fractions.

Results: The project is currently in progress. Results are expected in 2017.

Conclusions: The results of this study will provide a national evidence base to inform policy decisions regarding the licensing of alcohol sales outlets.

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KEYWORDS

alcohol; outlets; hospital; admissions; geography; epidemiology

Introduction

Purpose of Study

Availability of alcohol is a major policy issue for governments and one of the availability factors is the density of alcohol outlets in a geographic area. However, whilst numerous international research studies on alcohol outlet density have examined associations with consumption and with crime and disorder [1-4], few have examined associations with alcohol-related hospital admissions [5-9].

The costs of alcohol-related health harms that are placed upon national health services are substantial. There are an estimated 800,000 alcohol-attributable hospital admissions per year in England, and the total yearly cost of alcohol-related harm to the National Health Service (NHS) has been estimated to be approximately £2.7 billion [10,11].

Patterns in alcohol outlet density have changed in recent years in England. There has been a general decline in the number of local pubs, but this has been accompanied by an increase in off-premise outlets, including supermarket outlets. There has also been an increase in the concentration of bars in city centers. These observations are based upon unpublished work carried out in our department.

A shift is occurring in alcohol licensing policies within the United Kingdom, with increasing emphasis on controlling alcohol consumption and harm by bringing public health bodies (or considerations) into licensing decision-making [12,13]. Local authorities have been given powers to control alcohol outlet density through cumulative impact policies in England and Wales, and licensing statements in Scotland, but the consideration of chronic harms in licensing policy is currently hampered by the very limited evidence base [14].

The purpose of our study is to investigate the association between alcohol outlet density and hospital admissions for alcohol-related conditions in a national (English) small area level ecological study. We aim to determine whether correlations exist between outlet density and hospital admissions at the small area level, and to examine whether changes in outlet density over time are associated with changes in alcohol-related admissions.

The key novel aspects of our proposal include the investigation of hospital admissions for a range of alcohol-related conditions, incorporation of both cross-sectional and longitudinal analyses, the use of small geographic areas, and the examination of patterns (and changes in patterns) in the density of different types of alcohol outlets.

Literature Review

Several studies have been carried out to investigate associations between alcohol outlet density, alcohol consumption, and harm, which have been summarized in systematic reviews [1-4]. The great majority of studies examined the effects of outlet density on alcohol consumption, several examined effects on crime and disorder, and a few examined links between outlet density and child abuse, sexually transmitted infections, and suicide [1-4]. Very few studies, however, have examined the effects of outlet density on chronic harms, which typically include conditions such as alcoholism and alcoholic liver disease.

Alcohol outlets may be classified into two broad groups: on-trade outlets, comprising outlets in which alcohol can be purchased and consumed on the premises (eg, pubs); and off-trade outlets, in which alcohol can be purchased but not consumed on the premises (eg, off-licenses). Early studies examining chronic effects of alcohol consumption used large geographic areas as the units of analysis, for example a state level analysis in the United States which found that on-trade outlet density was correlated with liver cirrhosis mortality [15]. More recently, Theall et al found an association between neighborhood-level off-trade alcohol outlet density and self-reported liver problems in Los Angeles and Louisiana [16]. Two recent studies in British Columbia found that increases in the density of off-trade outlets were associated with increases in alcohol-related mortality [17,18].

Few published studies to date have examined associations between outlet density and hospital admissions [5-9]. Alcohol-related hospital admissions are useful to study because they allow both acute and chronic effects of outlet density to be examined. Livingston, in a Melbourne study, found that on-trade outlets were strongly associated with assault-related hospital admissions (an acute effect) but were also associated with chronic alcohol-induced conditions to a lesser extent, whilst off-trade outlets were strongly associated with both assaults and chronic alcohol induced conditions [6]. Stockwell et al examined a broader group of conditions in British Columbia and found associations between off-trade outlets (private liquor stores) and hospital admissions for both acute and chronic conditions, but no significant associations were observed for on-trade outlets [7]. Tatlow et al found an association between outlet density and alcohol-related hospital admissions in San Diego County, but did not distinguish between acute and chronic conditions and did not present results separately for on-trade and off-trade outlets [5].

Regarding evidence on outlet density and harm in the United Kingdom, there are two recent studies of note [8,9]. Fone et al examined the association between alcohol outlet density and alcohol consumption, hospital admissions, accident and emergency attendances, and crime in Wales and found evidence of association with all four of these outcomes. However, this study did not differentiate between on-trade and off-trade outlets, and did not distinguish between admissions for acute and chronic conditions related to alcohol [8]. Richardson et al examined the association between on-trade and off-trade outlet density, and hospital admissions and mortality in the four largest cities in Scotland [9]. This study combined all conditions wholly attributable to alcohol, but also examined alcoholic liver disease separately as an indicator of chronic harm, and found associations with both on-trade and off-trade outlet density. This study did not examine subcategories of on-trade and off-trade outlets.

In addition, there are two online reports examining alcohol outlet density in the United Kingdom. Chiang found an association between alcohol outlet density and crime in Glasgow, but the study did not differentiate between on-trade

and off-trade outlets [19]. A mapping exercise of alcohol outlet density was carried out in the East Midlands, but associations with outcomes were not examined [20]. We recently completed work on a joint Medical Research Council/Economic and Social Research Council (MRC/ESRC)-funded strategic program grant (Interdisciplinary Alcohol Policy Effectiveness Research Programme), which included an element examining alcohol outlet density and alcohol consumption.

Theoretical Considerations and Hypotheses to Be Investigated

Robust theoretical models of the relationship between alcohol outlet density and alcohol-related harm are still being developed, and these often reflect empirical analyses by focusing on the relationship between on-trade density and acute harms or violence [21,22]. Models in which the proposed mechanism for the outlet density impact does not necessarily require high alcohol consumption (eg, where violence occurs due to collisions between drinkers exiting several densely situated on-trade outlets) are relevant for explaining acute harms [23].

Economic models suggest that alcohol outlet density may impact on chronic harms through increased consumption. A key proposition is that increased outlet density lowers the full cost of alcohol purchases by increasing average proximity to outlets, thereby reducing travel, energy, and time costs [22]. Competition between densely situated outlets may also exert downward pressure on prices, or lead to diversifications of the market, which stimulate consumption by better matching supply and demand [24]. The above theoretical considerations, in addition to previous empirical results, inform the hypotheses that we plan to investigate.

We hypothesize that on-trade outlets (specifically bars and pubs) will be associated with acute alcohol-related hospital admissions, based on the theoretical considerations outlined above, and on previous results [6]. We also expect that on-trade outlets will be associated with admissions for chronic alcohol-related conditions, based on results from previous studies [6,9].

We hypothesize that off-trade outlets will be associated with chronic alcohol-related conditions, and that this association will be most clearly observed for hospital admissions which are wholly attributable to alcohol (eg, chronic liver disease), based on the theoretical considerations outlined above and on results from previous studies [6,7,9]. We hypothesize that off-trade outlets will also be associated with acute harms, based on previous research and theories supporting this link, which includes violence related to high alcohol consumption (eg, domestic violence and local street violence) and *pre-loading*, especially due to the purchase of cheap alcohol from off-licenses and convenience stores [6].

We have previously found that alcohol-related mortality rates in England are much higher in men, reach a peak in the middle-aged adult population, and are substantially higher in the most socioeconomically deprived areas [25]. We therefore plan to investigate associations in deprived and nondeprived areas, in both men and women, and in young and older adults. We anticipate that associations will be stronger in more deprived areas and in men, and that stronger associations will be seen for acute harms in younger adults and for chronic harms in older adults. The geography of urban and rural areas is quite different, with more dispersed populations and alcohol outlets in rural areas. We therefore plan to investigate associations in urban and rural areas.

Methods

Study Design and Area of Study

We plan to use cross-sectional (ecological correlation) and longitudinal (cross-sectional time series) study designs. Geographic units of analysis will include all Lower and Middle Super-Output Areas (LSOAs and MSOAs) in England (53 million total population; 32,482 LSOAs; 6781 MSOAs). LSOAs (approximately 1500 people per LSOA) are the smallest spatial units at which anonymized hospital admission data are available, and will support investigation at a fine spatial resolution. Spatio-temporal associations will be investigated using MSOAs (approximately 7500 people per MSOA). Both the LSOA- and MSOA-level analyses will be at a finer spatial scale than those used in some of the previously published ecological studies on alcohol outlet density and hospital admissions. Average populations in the geographic units of analysis were approximately 17,000 and 52,000 in two studies [6,7] and >10,000 in another study (which did not provide further details) [5]. Studies in the United Kingdom used spatial scales similar to the LSOAs that we plan to use [8,9].

Ethics Approval

The study has been approved by the University of Sheffield (School of Health and Related Research) Research Ethics Committee.

Data on Alcohol Outlets

We purchased comprehensive coverage data on alcohol outlets in England from CGA Strategy for 2003, 2007, and 2010 for our MRC/ESRC-funded project, and are negotiating the purchase of 2013 data. CGA Strategy has estimated that the database includes 98% of all alcohol outlets in England. In the 2010 dataset, there were 132,989 on-trade and 51,975 off-trade outlets. The longitudinal data series will allow for the examination of associations between changes in outlet density and changes in hospital admission rates.

In our MRC/ESRC-funded program, we carried out a comprehensive investigation of the association between different outlet category groups and alcohol consumption, using data on the latter from the national General Lifestyle Survey [26]. We classified on-trade outlets into three categories: pubs, bars, and nightclubs; restaurants; and other premise types (which included hotels, casinos, social clubs, and sports venues). We classified off-trade outlets into two categories: supermarkets; and other off-trade outlets (which included off-licenses and convenience stores). We calculated densities of these different subcategories of outlets within 0.25 kilometers (kms), 1 km, 3 km, and 5 km of postcode centroids (>1 million residential postcodes in England). We also calculated distance to the nearest outlet within each subcategory. In addition, we calculated distances from postcode centroids to the nearest cluster of pubs, bars, and

nightclubs, with a cluster defined as four or more outlets within 250 meters of each other.

The key results were (1) increasing density of pubs, bars, and nightclubs within a 1 km radius of postcode centroids was associated with increasing alcohol consumption and (2) increasing density of smaller off-trade outlets (off-licenses and convenience stores) within a 5 km radius of postcode centroids was associated with increasing alcohol consumption. We therefore plan to use these two categories of outlets and their respective distance radii as the primary exposure measures. The National Travel Survey indicates that 1 km is the average walking journey length [27], while a Competition Commission report indicates that 80-90% of consumers live within 5 km of a convenience store [28].

As the units of analysis in this proposed project are LSOAs and MSOAs, we will calculate the average outlet density (mean and variance) for postcodes within each LSOA and MSOA (there are approximately 25 postcodes per LSOA and 125 per MSOA), weighting the average by the number of domestic delivery points for each postcode as a proxy for postcode population counts [29].

We will also investigate whether the density of young people's circuit bars and nightclubs (a subcategory within pubs, bars, and nightclubs defined by the data provider based on the demographic profile of the clientele and design of the venue, such as provision of a dance floor or low seats-to-patrons ratio) is associated with acute hospital admissions amongst teenagers and young adults, as these venues might be more likely to be associated with pub-crawl and binge drinking activities. We plan to analyze the other outlet categories as well, and anticipate that associations seen with on-trade outlets will be specific to pubs, bars, and nightclubs, and not restaurants or other types of premises. We also anticipate that associations with off-trade outlet density will be specific to off-licenses and convenience stores, and will be unlikely for supermarkets. Supermarkets are likely to serve large catchment areas, particularly if the use of home delivery is employed, and are used by most the population, making them unlikely to exert a strong local density-type effect.

Availability of Data and Material

The data on alcohol outlets may be obtained from CGA Strategy [30]. Data on hospital admissions in England may be obtained from NHS Digital [31].

Hospital Admissions Data

We plan to use anonymized Hospital Episode Statistics (HES) data to examine hospital admissions in England from 2003 to 2013. HES data include the primary diagnosis (International Statistical Classification of Diseases and Related Health Problems-10; ICD-10 code) for each admission. We plan to examine associations separately for acute and chronic conditions, and examine lag effects for chronic conditions. The contribution of alcohol to the etiology of numerous conditions has been investigated previously, and has resulted in internationally standardized alcohol attributable fractions (AAFs). AAFs are used by Public Health England to estimate the proportion of the burden of harm, classified by age and sex, from each condition that is attributable to alcohol [32,33]. For acute conditions, we will include conditions that are partially attributable to alcohol, as most conditions in this category have AAF<1. For chronic conditions, we will examine two categories: conditions that are wholly attributable to alcohol (ie, AAF=1), and conditions that are partially attributable to alcohol (ie, AAF<1).

The major contributors to admissions in the AAF=1 category include, "mental and behavioral disorders due to use of alcohol" (ICD-10 code F10), "alcoholic liver disease" (ICD-10 code K70), and, "chronic pancreatitis (alcohol induced)" (ICD-10 code K86.0). In 2010 and 2011 the combination of these three ICD conditions accounted for 39,869 patients being admitted to hospitals (accounting for 52,316 admissions). The HES data will allow multiple admissions for the same patient to be identified through a pseudoanonymized identifier, and this will be considered in the analysis.

Examples of acute alcohol-related conditions include admissions for assault (ICD-10 code X85-Y09) and intentional self-harm (ICD-10 codes X60-X84 and Y10-Y34). These data will be extracted using the *Cause* field in HES. These admissions are not wholly attributable to alcohol (AAF=0.27 and AAF=0.34, respectively). A total of 119,360 patients were admitted to hospitals (accounting for 142,388 admissions) due to these causes in 2010 and 2011.

Data on Confounding and Interaction

We plan to examine associations in several groups: young and older adults; men and women; areas with high, intermediate, and low levels of socioeconomic deprivation; and urban and rural areas. We will adjust for age (five-year bands) within the wider age groups. We will use the Index of Multiple Deprivation Income Domain as the indicator of socioeconomic deprivation at the small area level [34]. Population denominators will be obtained from the Office for National Statistics.

Statistical Analyses

The relationship between alcohol outlet density and alcohol-related hospital admissions is complex, and is mediated through a range of factors including *supplier side* factors (eg, price and marketing) and individual level factors (eg, attitudes about alcohol, drinking behaviors, and demand for alcohol). These largely unobserved factors in ecological analyses may induce spatial and temporal correlation in outlet density and hospital admissions, and statistical models must account for these correlations if parameters are to be properly estimated. We propose to use Bayesian hierarchical modelling methodology, including a structural equation model framework in which we represent relationships between observed and unobserved *latent* variables, and in which we allow model errors to have spatial and temporal autocorrelation. Bayesian spatial models may be computationally intensive, and we have access to grid computing facilities for this purpose.

In the ecological correlation analyses, in which spatial associations will be examined, we will use LSOAs as the units of analysis, taking into account spatial autocorrelation (ie, the statistical nonindependence of neighboring geographic areas) and using an adjacency matrix in which LSOAs with common boundaries are classified as neighbors. Nonlinear associations

will be investigated as increases in availability of alcohol outlets may have diminishing effects on alcohol-related harm as baseline availability increases [22]. This aspect is relevant, as our current MRC/ESRC work indicates that outlet density in the United Kingdom is generally much higher than that of other countries.

When examining changes over time, we plan to use the cross-sectional time series panel study methodology that has been used previously [7,17,18]. We aim to implement this methodology within a Bayesian framework, using MSOAs as the spatial units of analysis and years as time points. This methodology will allow for control of unmeasured spatial confounders and general time trends in hospital admission rates. The spatio-temporal methods will also allow for the examination of lag effects between exposure and outcome; lag time may be an important variable. For example, Stockwell et al observed that alcohol price changes exerted effects observable at zero lag for hospital admissions related to acute alcohol-related conditions, but these effects only became apparent from a two-year lag onwards for admissions related to chronic alcohol-related conditions [7].

Reverse causality hypotheses pose particular challenges in the interpretation of associations observed in analyses of outlet density and health outcomes. One hypothesis is that outlets cluster in *unhealthy* areas. To address this issue, we plan to investigate associations between outlet density and hospital admissions for conditions that would not be expected to be related to alcohol (eg, lung cancer and all emergency admissions unrelated to alcohol). Such conditions would reflect general influences on hospital admission, including the effects of area-level factors, provider units, and primary and community care, and should therefore control for these effects. A further reverse causality hypothesis is that low demand leads to a low density of alcohol outlets (as opposed to low outlet density resulting in low consumption levels, and therefore low alcohol-related hospital admissions). We will investigate whether this hypothesis can be ruled out by using cross-lagged models. These models are structural equation models in which, for example, the effects of two variables X and Y are measured at repeated time points (t1 and t2) and analyzed to investigate their effects on each other (ie, X1 on Y2 and Y1 on X2) [35].

Results

The project is currently in progress. Results are expected in 2017.

Discussion

If we do find associations, this study will provide the first contemporary England-specific evidence that changes in alcohol availability contribute to rates of alcohol-related harm. This finding would provide a useful evidence base to inform public health contributions and considerations for alcohol licensing decision-making. The results will allow local authorities to quantify the potential benefits of restricting outlet density on hospital admission rates. Alternatively, if we discover no evidence of association, this finding will be based on comprehensive national data. These data would support licensing authorities in not considering NHS costs due to hospital admissions as a priority in decision-making, in relation to outlet density. This finding would also add to the evidence base on appropriate approaches for reducing alcohol-related harm in England.

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Authors' Contributions

RM and JH conceived the original idea for the study. MG, MS, TP, and PM contributed to developing the detailed study design and methodology. All authors approved the final study protocol.

Conflicts of Interest

PM is Scientific Advisor to the Institute of Alcohol Studies. All other authors declare that they have no competing interests.

Multimedia Appendix 1

Peer review of grant application (Reviewer 1).

[PDF File (Adobe PDF File), 50KB - resprot_v5i4e243_app1.pdf]

Multimedia Appendix 2

Peer review of grant application (Reviewer 2).

[PDF File (Adobe PDF File), 41KB - resprot_v5i4e243_app2.pdf]

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Abbreviations

AAF: alcohol attributable fractions
HES: Hospital Episode Statistics
ICD-10: International Statistical Classification of Diseases and Related Health Problems-10
km: kilometer
LSOA: Lower Super-Output Area
MRC/ESRC: Medical Research Council/Economic and Social Research Council
MSOA: Middle Super-Output Area
NHS: National Health Service

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Proposal

Securing the Continuity of Medical Competence in Times of Demographic Change: A Proposal

Joachim Paul Hasebrook[1], PhD; Jürgen Hinkelmann[2], MD; Thomas Volkert[3], MD; Sibyll Rodde[4], PhD; Klaus Hahnenkamp[5], MD

[1]zeb.business school, Steinbeis University Berlin, Muenster, Germany

[2]University Hosptial Frankfurt, Frankfurt, Germany

[3]Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Muenster, Muenster, Germany

[4]zeb.health care, zeb.rolfes.schierenbeck.associates, Muenster, Germany

[5]Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine, University Medicine Greifswald, Greifswald, Germany

Corresponding Author:
Joachim Paul Hasebrook, PhD
zeb.business school
Steinbeis University Berlin
Hammer Str. 165
Muenster, 48153
Germany
Phone: 49 251 97128 ext 940
Fax: 49 251 97128 50
Email: jhasebrook@zeb-bs.de

Abstract

Background: University hospitals make up the backbone of medical and economic services of hospitals in Germany: they qualify specialist physicians, ensure medical research, and provide highly specialized maximum medical care, which other hospitals cannot undertake. In addition to this assignment, medical research and academic teaching must be managed despite a growing shortage of specialist physicians. By the year 2020, the need for the replacement of retired physicians and increased demand will total 30,000 positions. The situation will become more difficult because, on the whole, patients are becoming older and sicker and because specialist physicians are able to find more attractive working conditions in smaller hospitals, abroad, or outside of curative medicine.

Objective: In order to retain sufficient qualified employees, major improvements in quality are required in terms of working and training conditions. For this purpose, a sustainable innovation process is necessary, which incorporates solutions from outside of the health care sector in order to be able to learn from experiences and mistakes from other industries. The FacharztPlus project aims to find suitable measures in order to retain specialist physicians for more years after the completion of 5 years of professional training. This should determine the suitability of additional qualifications alongside the professional career and an expertise-related work organization oriented to different stages of life.

Methods: Structured interviews, surveys, and repertory grids are used as preparation for cross-industry expert panels to create future work scenarios for university hospitals. Industries involved are harbor logistics (container terminal), airports, and digitized industrial production (“industry 4.0”) because these industries are also facing a shortage of qualified staff and have to respond to rapidly changing demands. Based on the experts’ scenarios, consensus groups will be established in each university hospital trying to reach consensus about the implementation of relevant factors in order to improve employee retention.

Results: We expect these consensus groups to develop and introduce measures for more structured training procedures, individual and team incentives, organizational guidelines for better recruiting and retention in hospitals, models of flexible and attractive working conditions including shift work and vacation planning, and use of new learning tools (eg, tablet PCs and mobile phones).

Conclusions: All measures are implemented in the Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine at the University Hospital Muenster (UKM) with approximately 150 physicians and in the further 44 departments of the UKM and 22 teaching hospitals, which all together employ more than 5000 physicians. The measures will also be implemented at the university hospitals in Aachen, Rostock, and Greifswald. All decisions and measures will be discussed with representatives from hospital management and professional associations. Results will be presented at conferences and published in journals.

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KEYWORDS

shortages of specialist physicians; working life models; flexible working time models; additional medical qualification; promotion of women; combining work and family

Introduction

Hospitals' Economic Power and Shortage of Medical Staff

Despite the total number of doctors increasing in recent years, a shortage of well-trained doctors is predicted in at least some disciplines for at least 18 countries of the Organisation for Economic Cooperation and Development (OECD) with comprehensive workforce prediction models [1]. The Association of American Medical Colleges predicts, for example, that the United States will need 26% more physicians over the period of 2006 to 2025 [2]. However, the calculated supply of physicians will increase by only 10% to 12% [3]. The European Union sees the issue in the same way: the aging of society and the rising prevalence of diseases related to sedentary lifestyles will increase the burden of disease by 10% to 15% until 2030 (measured as disability-adjusted life years) [3]. The European region is the most affected by noncommunicable diseases and their growth is alarming. Consequently, all European countries need to increase the number of health professionals in the near future. The EU Commission estimates a shortage of 1 million health professionals by 2020, if action is not taken [4]. A lack of health professionals will result in 15% of care services not being delivered due to lack of resources [5].

The shortage of medical staff will continue to advance in coming years. According to details from the German Medical Association, by the year 2019, 18,940 physicians will enter retirement due to their age [6]. These positions need to be replaced, but there are also 5500 that are already vacant and a further 4800 extra positions needed due to increasing life expectancy and patient comorbidity; between 2015 and 2025, the morbidity rate is expected to increase from 5% to 15% [7]. This results in a combined replacement, extra and additional demand for 29,240 medical jobs by 2019. Besides this, the amount of part-time positions will increase by 10,270 during the same period and also add to the open positions. According to more recent studies. Among other reasons, this is caused by the fact that medical doctors are currently predominantly male, while the proportion of females in the workforce will grow significantly in the next few years.

University hospitals have to work under special conditions, because, besides patient care, their employees are also active in research and teaching. There are currently almost no university hospitals that are able to financially combine care, research, and training successfully [8]. In order to be able to comply with the various demands of the future, ensure medical care at a high level, and evade the ever-increasing shortage of medical staff, the staff potentials that are available need to be used more efficiently and sustainably.

Career Perspectives for Talents

The age structures in all European countries are changing, and together with contracting populations as a whole, the potential labor force will be significantly reduced in the coming decades. The German Institute for Employment Research presents a worst-case scenario in which there is an unsatisfied demand for approximately 6 million open positions in the year 2020 [9]. As stated above, the need for well-trained specialist physicians will continue to rise.

In the regular expert monitor from the German Institute for Vocational Education over 80% of the surveyed personnel managers report a considerable worsening of education levels due to errors in spelling and abilities to cope with a workload [10]. More and more industries are noticing the change from an "employer's market" to an "applicant's market," on which applicants rather than employers influence the market [11]. Bernhard Marschall, academic dean of the faculty of medicine at the University of Muenster, wrote in a major German newspaper (Frankfurter Allgemeinen Zeitung, F.A.Z.) on September 22, 2011: "While medicine used to be seen as an attractive career with good opportunities to earn well, now the focus is on job security, compatibility of work and family and the high social image." In rankings of school and university leavers, it is easy to see a further focus on fewer courses of study [12,13]. Finally, there are many other alternatives to curative work in German hospitals that compete for well-trained medical students. Curative work is often abandoned due to more attractive working conditions elsewhere, in particular in health care management, external assessments, commercial research, but also for caring for their own child [14]. Of the approximately 17,000 medical staff who were trained in Germany, working abroad caused a training investment of approximately €350,000 per graduate to be lost [15,16].

In consequence, a new focus must be on the value and performance culture and an ongoing exchange of interests of economic and performance-based demands of hospitals with the individual demands of staff [17]. This will lead to a "democratization of talent management" [18] bringing individualized job descriptions and flexible competence management to the top agenda of human resource management [19,20].

Work-Related Values: A Generational Comparison

This "democratization of talent management" can be traced to the changed values of today's working generations [21]: (1) baby boomers (born 1955-1969), who are reliable at dealing with competition and conflict due to coping with high birth rates, high awareness of loyalty and duty (live to work); (2) Generation X (born 1970-1980), resistant to stress, motivated, pragmatic, and willing to train further, the combination of private life, family, and work is especially important (work to live); and (3) Generation Y (born 1981-1995), expects a

performance orientation and a "feel-good culture," which is said to promise a consumption-oriented attitude to work and limited loyalty with a great need to achieve self-fulfillment (live, even at work).

This assessment of different generations has been detailed by a study by German studies [22] and has been confirmed by international research [23]: "youth materialism" (ie, possessing money and status objects) grew over the time and reached its peak in Generation X at the beginning of the 1990s and has remained persistently high until the generation born after the turn of the century (so-called Generation Me or Z). While these materialistic values increased, the predominant value of work (so-called work centrality) continued to decrease, which indicates a growing gulf between material demands and willingness to work for them [24]. Today, hospitals are not just faced with an applicant's market, but also a new understanding of work and new demands for leadership and participation [25]. These are characterized by a greater desire for communication, teamwork, and appreciative leadership style and a high level of pragmatism [26].

The fact that the work environment and especially communication between leaders and staff is changing fundamentally is only slowly being accepted by the medical and financial management levels in hospitals [27]. Leading doctors and managers in hospitals have noticed that dealing with young doctors and job starters is becoming much more time-consuming and complicated, and that established structures and the organization of work is being questioned. The necessity to work overtime, the quality of training, and the style of communication have all come under fire: the change from an employer's market to an applicant's market demands far-reaching changes in personnel management, which most hospitals are currently not yet ready for.

Need for Intergenerational Work in Hospitals

While baby boomers often occupy the managing positions in hospitals and members of Generation X can look back on an established career and possibly their own family life, Generation Y represents the emerging talent for highly qualified specialists and managers in hospitals [28]. This generation has high demands for the material equipment and flexibility of the work. Another aspiration is the higher importance of family and the growing wish of young men to relinquish their traditional role of "breadwinner" and to experience their fatherhood [29,30]. However, it is not men, but rather women, who represent the future majority of medical staff. The share of female medical students has continued to grow over the years and, according to recent German education report, is approximately two-thirds, the future of the medical profession is thus clearly female [31]. The working environment is currently still very far removed from the ideals of young women [32] and family life is also only moving slowly toward an equal time division and workload for men and women [33].

The measures that have been taken so far are neither enough, nor sufficiently long-term, to be able to counter the problems on the labor market resulting from demographic change, requirements of new generations, and the increasing share of female medical staff. The FacharztPlus project, therefore, shall create improvements in the following areas for flexible work, better life-long working perspectives, and continuous improvement to specialist work in hospitals:

1. The abandonment of patient care must be slowed down and reduced: this exit from curative work is often due to more attractive working conditions especially in health care management, external assessments, commercial research, and child care [14].

2. The appeal of medical employment in Germany needs to be raised in comparison to foreign employers in order to reduce physician migration abroad, and thus to reduce the loss of training investments (especially important in regions near national borders such as Muensterland): 17,000 medical staff who were trained in Germany work abroad, by the year 2019, this will have increased by 11,300; so that the training investment of approximately €350,000 per graduate is lost [34].

3. Experienced staff members and the expertise that they hold must be used more effectively for experiential learning on-the-job and optimal patient care. For example, this can mean that experienced specialists with particular knowledge can share it better in special clinical cases.

4. Medical care and career qualification must offer close interaction and longer-term perspectives in order to transform the idea of "forwarding" specialists from university hospitals to regional hospitals toward a principle of "additional qualification" at university hospitals after completion of specialist examinations.

5. The combination of work and family must be improved, especially for female specialists, by offering more flexible and individually adjustable working models (eg, in part-time work) [15].

Objectives

Life-Long Working Perspectives as an Aim

The FacharztPlus project aims to develop and test measures in order to gain specialist physicians for 5 or more years of further work after completion of their 5 to 6 years of professional training. The project aims to ensure that especially female specialists find work and career perspectives at university hospitals or other hospitals upon completion of their 5-year specialist training for at least the same time again. The core of the project is expertise-based staffing in order to join medical care and further qualifications together. While such models have already been successfully implemented in other industries, such as production management, there is currently no link between generally short-term expertise-based staffing and long-term, flexible work and career planning—neither in hospital operations, nor in any other industry. Exactly this combination makes up the specialist core of the FacharztPlus project and will be systematically investigated and tested for hospitals first. Beyond this, the concept will then be transferred to other industries.

Flexible and Individual Work for Life-Long Working Perspectives

Shift work with high pressure and often night duty, as well as changing demands at short notice displace especially older and more experienced specialist physicians from the extremely experience-dependent world of university medicine. So flexible duty rosters that can be changed at short notice are being developed to ease medical staff. For this purpose, large methodological and technical obstacles would need to be overcome in long- and short-term staffing (eg, through simulating personnel scenarios and electronic shift exchange portals) and additional services would need to be provided in order to ease the workload of specialist physicians (eg, for stress reduction). There is currently no personnel software on the market, which is tailored to the specific needs of staffing in university hospitals, and accordingly, there is no related personnel and organizational guide. The necessary information technology (IT) and technical concepts for this purpose are being developed and tested as part of the project.

Life-Long Qualification for More Attractive Careers

The university hospital in Muenster sets standards for student training, for instance with its own student hospital and the unique, live three-dimensional–simulated learning environment, which allows simulated rescue work in a German university hospital, for example. However, the expectations that this raises are not fulfilled in the subsequent training to become a specialist. There simply is no subsequent "specialist physician curriculum." The additional qualification should be made more appealing through attractive forms of self-managed learning and practical knowledge management (eg, through social software and e-learning portfolios). By involving academic experts as well as networks, the additional qualification is expanded to a sustainable qualification platform and—where feasible and meaningful—consolidated into a curriculum.

Expertise-Based Staffing to Combine Medical Care and Further Qualification

Staffing mostly occurs based on availability and presence. Certain special competencies, such as anesthetics for infants, will not follow this staffing method, as they require special training. The opportunity to learn while working in special medical cases is not used enough. Thus, the aim is to establish expertise-based staffing, based on recording competence groups (eg, application fields, process groups) and competence levels (eg, "only under supervision," "independent," "can supervise others") and oriented toward comparable models, such as those from production management. This kind of staffing allows optimal utilization of available expertise, but also more targeted planning of additional qualifications, for example, specialist physicians that can supervise others might always work with colleagues that need to gather experience in a certain situation.

Ongoing Optimization and Innovation Processes

It is difficult to initiate, implement, and sustainably establish changes. This is made more difficult in university hospitals due to fluctuations of specialists and training rotations. The FacharztPlus project aims to establish a process model for sustainable innovation processes at University of Muenster (UKM) that is based on interdisciplinary exchange and establishing fixed-communication structures in internal and external networks. Through flexible organization of work, personal flexibility should also be established so that as many physicians as possible can take part in innovation processes.

Specialist Consulting

A range of specialist consulting services that currently does not exist on the market is being developed; these will include flexible learning and working conditions in hospitals with related implementation support regarding change management and personnel and IT concepts. The specific demographic developments for medical care make a consistent legal, organizational, and IT solution for hospitals necessary, but this kind of solution does not currently exist. However, the solution does not just need to be feasible in terms of personnel, technology, and organization, but it must also be able to be financed through billable compensation. In that respect, it must be considered that the continued medical training, as provided at university hospitals, is not financed through lump compensations (German diagnosis-related groups). The project will thus involve developing a financially feasible package of measures based on IT and technical concepts. These concepts must allow innovative, IT-supported learning scenarios and their evaluation. For this purpose, a form of education management and controlling that is somewhat new for hospitals must be developed.

Methods

Learning From Other Industries

The implementation strategy and process in the FacharztPlus project are based on the basic presumption that a hospital uses solutions for flexible learning and working conditions only to a limited extent. Through a cross-sector search, more solution approaches come into view, but they have not been trialed in daily hospital work, and thus need to be exactly tested, adjusted, and checked for their day-to-day feasibility. This basic consideration results in a stepwise comparison and improvement process (Textbox 1).

Textbox 1. Stepwise cross-industry comparison and improvement process.

1. Comparison of working and career models between industries:

Solutions that are used in hospitals are professionally, methodically, and technically insufficient for effectively countering the shortage of specialist physicians. Framework conditions, planning, and implementation and successes of new working and career models are thus compared in an industry panel and selected for further assessment and testing.

2. Cross-sector transfer of strengths and selection of measures:

Measures that may be worth considering for university hospitals are identified in a meta-analysis based on quality standards. Quality standards that are relevant in hospitals form the basis (cooperation for transparency and quality in health care [35]). The result consists of measures that are checked for their quality from the point of view of a hospital.

3. Review of measures for labor law, organization, and technology:

The selected measures are subjected to a thorough review of labor law and organizational and technical factors. For this purpose, various implementation scenarios are developed and reviewed by the institute for innovative working conditions in hospitals in terms of their feasibility pertaining to labor law. An appropriately staffed academic project council that also supports the planning and evaluation of measures carries out an academic review. Subsequently, UKM carries out a personnel, organizational, and technical review. The industry panel, quality assessment, and review criteria and results are documented in an interim report.

4. Planning, implementing, and evaluating measures:

UKM supports the development of an implementation and evaluation plan that will be implemented in a pilot trial in the hospital. Every 2 months, a progress and success assessment will be made regarding personnel, technical, and financial factors. Depending on the implementation progress and success, during the pilot trial, measures can be aborted, changed, or added in order to achieve implementation successes. If initial implementation successes are achieved at UKM, then further departments will be added. This applies to the other departments at UKM, but also to implementation partners that have also been added to the project.

5. Use and development of internal and external networks:

In order to gain other hospitals for the implementation of measures, the pilot trials and their evaluation results will be presented to the UKM departments, centers, and institutions as well as teaching hospitals as part of regular UKM events. Hospital and professional associations, specialist publications, and medical congresses that take place during the project schedule will be used to spread the results and experiences. The specialist program council plays a major role both in the assessment and the spreading of project results, especially of implementation successes in the hospitals. This council is made up of representatives from the leading associations from the health care sector and medical self-government.

Accompanying Research

The accompanying research is aligned with the implementation strategy. First, it is of preeminent importance to better understand personal reasons for retention and change. Simple surveys do not help to uncover hidden motives or give an insight in the long-term development of personal reasoning. Therefore, we apply participatory assessment methods and personal construct theory to employees along the “life cycle” in a hospital: from assistant physician in early training stages to experienced supervising physicians and persons, who left the hospital. Second, we integrate a great number of experts from industries with similar challenges, that is, companies employing highly qualified staff and dealing with quickly shifting working demands. We are applying scenario technique and focus on experts from airport management, harbor management, and “Industry 4.0” (Germany’s digital industrial production) in order to achieve new insights and ideas to improve the work organization in hospitals. Third, we create a test bed for the measures inspired and created by the experts from other industries in order to ensure transferability of all measures. The test bed has three stages: (1) experimental environment in which the main project partner, University Hospital Muenster, tries out early versions of the measures (eg, a new guideline to employee interviews); (2) reality check of the measures that will introduced in some parts of the hospital (eg, new employee interviews for one specific group of physicians); and (3) roll-out to the entire hospitals as well as transfer to other hospitals, namely the project partners and University Hospitals in Aachen, Rostock, and Greifswald. The transfer is a test in itself, what measures and to what extend measures can be transferred from hospital to another.

Retention Factors and Personal Constructs

We want to apply methods that combine qualitative and quantitative aspects as well as personal views and institutional variables. In a first step, we interview a sample of approximately 30 physicians in order to extract major personal aspects of retention and change motives. In a second step, we derive a structured Web-based survey based on these factors and apply it to all more than 300 physicians employed at the 4 university hospitals involved in the project. In a third step, we try to understand “personal constructs” by using Kelly Grids (or repertory grids) to visualize personal construct spaces (Figure 1) from different target groups, including young professionals in their training phase, experienced physicians, medical management, and persons who left the hospital and work elsewhere. Repertory Grids is a computer-based survey that combines qualitative and quantitative elements: interviewees respond to predefined elements, such as “nurses,” “physicians,” and “hospital management,” and decide whether these elements are “similar” or “different.” If they are different, interviewees give a short explanation, why they are different (eg, physicians are “flexible in planning and decision making”) and the opposite (eg, “bureaucratic, inflexible decision making”). In a second step, all predefined elements are rated from 1 to 10 on all scales, which have been created in the first step (eg, on the scale from 1=flexible to 10=bureaucratic, physicians get a 3 and hospital managements is rated 9). This technique has been successfully applied to various aspects of work life in hospitals [36]. It allows

for mapping out of "mental landscapes" showing the mental distance between elements, with what terms they are described, and whether they are rated more positively or negatively [37] (Figure 2).

Expert Panels

The expert panels should bring together human resource (HR) managers from airport management, harbor management, and "Industry 4.0." We start with onsite visits and separated expert panels helping us to understand how HR is handled in the different industries and what practice may be transferred to work life in hospitals. After having identified experts and useful practices, we shall invite experts from these industries and practitioners from hospitals to attend "practice forums." These forums will apply an abbreviated form of a "scenario technique," which is frequently applied to strategy and restructuring processes [38]. More specifically, scenario technique is used for impact and risk analysis in health care processes [39]. We will apply an abbreviated form of scenario analysis, which has been developed and used by the German Ministry of Education and Research, for instance, for technical options assessment [40] (Figure 3). As a result a these workshops, we expect stimuli and best practices from other industries as well as impact and risk scenarios concerning the transfer of these practices from other industries into hospitals.

Figure 1. Project plan and milestones of FacharztPlus project.

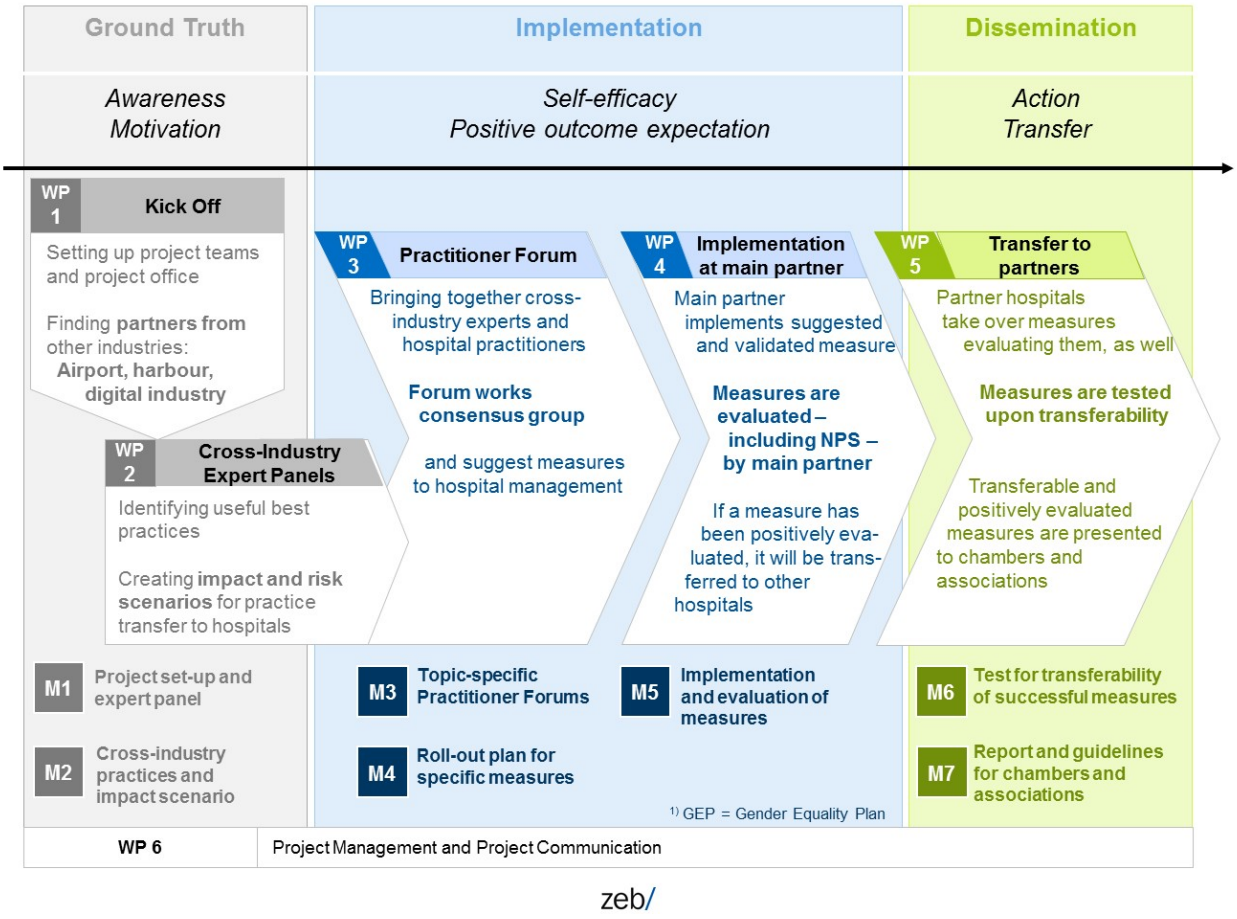


Figure 2. Visualization scheme for Kelly Grids (left) with sample result taken from FacharztPlus project (right).

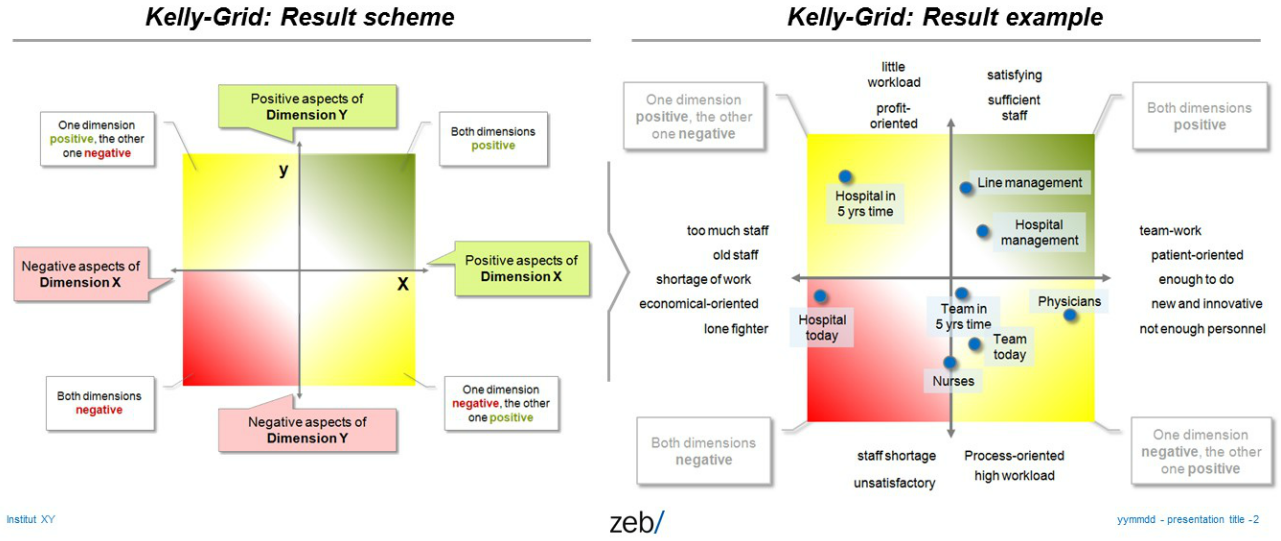
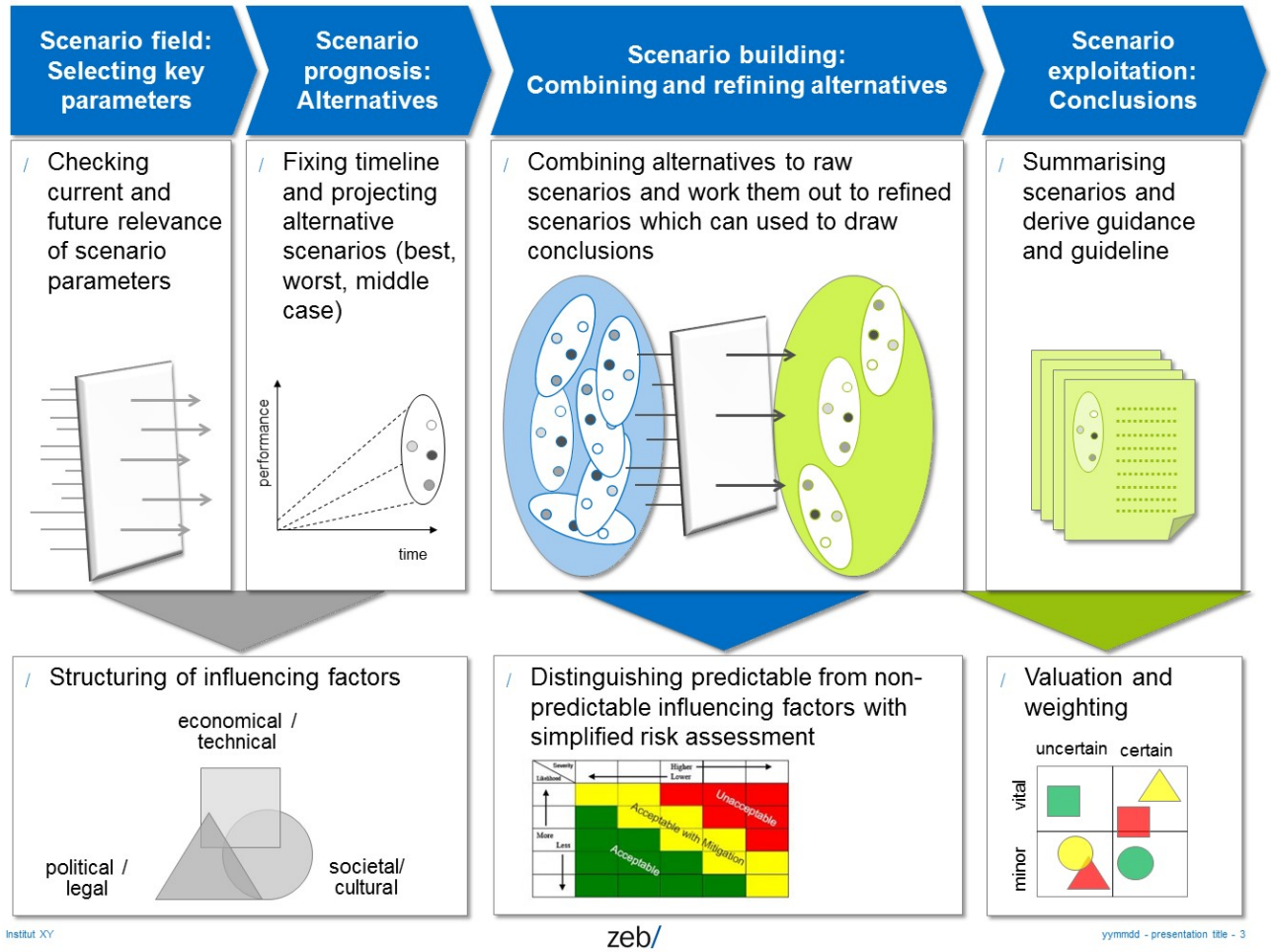


Figure 3. Full (top) and abbreviated (bottom) form of scenario analysis for workshops and expert panels. (Source: FacharztPlus project.)



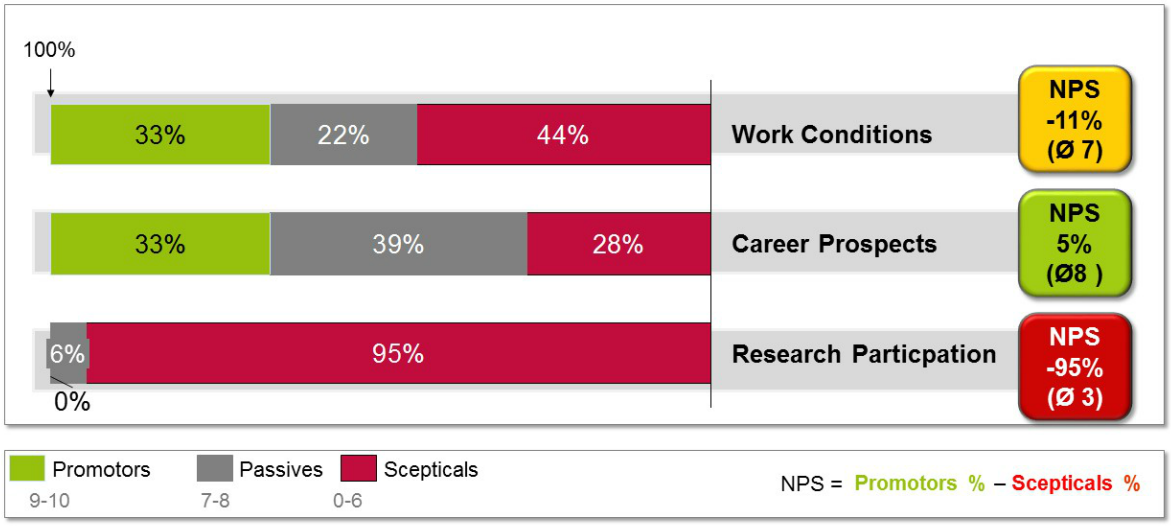
Planning, Testing, and Dissemination

Based on the scenarios, the main research partner, University Hospital Muenster, establishes different workgroups consisting of 6 to 8 participants and taking 3 to 5 meetings to come up with full consensus. The measures suggested by the groups will be presented to and confirmed by the university hospital's management. We apply the Nominal Group Technique (NGT) in order reach and document consensus about necessary organizational transformational measures. Research has shown that NGT is superior to moderated discussions in focus groups and other more structured techniques, because it regards individual differences, accounts for the strength of conviction, and documents the progress toward achievement of consensus [41]. Moreover, NGT is well-documented [42], easy to learn and apply [43], as well as largely applied in health care and

nursing [44]. Nominal grouping is a highly structured technique designed to maximize the individual contribution of each respondent. Comparative studies reveal that nominal group members produced a significantly larger amount of enhancements than respondents in focus groups and show greater levels of group member satisfaction [41]. The different steps of the NGT documents individual inputs, as a list of ideas, and group decisions in the form of ranking tables. Therefore, ideas and decisions can be easily validated, shared, and used as input for further refinement.

As soon as a measure has been implemented to the main research partner more consensus groups are initiated at the partner university hospitals in Greifswald, Rostock, and in Aachen. As soon as a new measure is being implemented, the percentage of persons promoting the new measure as compared with the percentage of skeptical people is constantly measured via the Internet. This proportion is derived from customer loyalty metrics called "Net Promoter Score" [45] and gives a clear indication to what extend gender equality is promoted within the hospital (Figure 4).

Figure 4. Net Promoter Score showing the percentage of physicians in favor of or against working, career, and research conditions in a university hospital.



Results

Preparing and Conducting the Project

During the reviewing process of the research proposal, the reviewers made several suggestions for improvements. For better academic support and spread of project results, the reviewers recommend establishing a specialist and academic council. In addition, the social partners are to be involved into the project. Therefore, an advisory council has been established and works alongside the steering committee, which itself is made up of managers from the UKM and Department and a partner from zeb. The advisory council consists of representatives from medical self-government (medical associations), professional associations (German society for anesthesiology and intensive care), the project sponsor (central federal association of health insurance funds), and hospital associations (German Hospital Federation, DKG, and special purpose associations). The council meets at least twice per year and is informed about project progress on a quarterly basis. In addition, the project management, consisting of 1 representative from UKM and 1 from zeb, is supported by an academic supervisory council, which methodically provides consultation and reviews in topics, such as work organization and development of competence and organization.

The possibility to transfer to other university hospitals is to be ensured through the selection of suitable implementation partners and potentially including further hospitals as implementation partners. Therefore, university hospitals in Greifswald, Rostock, and Aachen were gained as implementation partners. The hospitals offer all modern procedures of general and local anesthesiology and possess proven expertise in the area of anesthesiology and intensive therapy support for high-risk patients. Each year, these implementation partners conduct more than 50,000 cases of anesthetics. It remains possible that further implementation partners (eg, regional hospitals for basic medical care) be added during the course of the project.

Expected Project Results

The high pressure to act due to the growing shortage of specialist physicians, the beacon function of the UKM, and the close involvement of many medium-sized and regional hospitals and of associations in the course of the project, as well as the information offered by it encourages other hospitals to test flexible working and career models. This will prove and incrementally improve the transferability of the procedures and measures of FacharztPlus project, which are built on the following material project results: (1) industry panel–airport, sea harbor, automotive, financial services, and health care sectors–to measures for flexible working and career models for highly-qualified executives with additional need for

qualification; (2) quality review of the industry panel in terms of planning, implementation, review, and sustainability; (3) comprehensive review of hospital-relevant measures with regard to organizational, technical, and labor law-related aspects; (4) implementation consulting and support for hospitals that want to introduce flexible and more sustainable working and career models; and (5) reliable data on acceptance, performance capacity, recommendation levels, and intentions to stay (especially for female specialist physicians).

Exploitation of Project Results

Commercial Exploitation

Economically, the optimal utilization of available specialist physicians allows for optimal utilization of surgery capacities and greater patient security. A higher retention of specialist physicians through more opportunities for additional qualification and more flexible working hours reduces the costs for familiarization and unwanted fluctuation. A greater attractiveness of work reduces the costs associated with searching and recruiting. A further cost reduction is achieved through higher process efficiency and consistent data in human resources. FacharztPlus develops an organizational guide for hospitals and a criteria catalog for selecting and using personnel software at hospitals. A consulting portfolio for sustainable improvement of medical working conditions will be created together with the professional associations and medical councils.

Economic Benefits for University Hospitals

University hospitals can only offer specialist physicians an attractive life-long working perspective if flexible working conditions (even in part-time work) are associated with additional qualifications that are linked to specific experiences (eg, workforce planning and placement, which allows to work with rare clinical cases). Such a close combination of working conditions, personnel resources, and competence development is decisive for recruiting and retaining, but also for cost-carrying utilization of highly-specialist and highly qualified medical staff. Approaches for solving this core problem in hospitals, thus, have several cost effects at the same time (Textbox 2).

Academic and Technical Exploitation

When demographic factors are considered, the academic interests in concepts and measures for better recruiting, retaining, and training of specialist physicians are enormous. Already through the discussion of the FacharztPlus project, invitations arose to prepare specialist medical papers and to attend scientific conferences. Through utilization of the project, substantial contributions can be expected on several issues (Textbox 3).

Textbox 2. Expected cost effects of improved employee retention.

- The costs for recruiting fall because the employer appeal increases through the publications on the project and their long-term effects even after project completion. Currently, the recruiting costs amount to €20,000 to €80,000 per position. With total recruiting budgets of €200,000 to €500,000 per department, even low-percentage savings are very valuable.
- Increased retention reduces the demand for new and replacement staff. This means that the recruiting costs will not just fall, but more and better training can be conducted with higher numbers of cases and better quality treatment. This supports the UKM and the department on the profit side and increases the appeal in the further training and additional qualification of specialist physicians.
- Through optimal staffing, not only will the treatment and training quality increase, but also the utilization of the most expensive rooms of the department—the operating rooms. Previous experience in operating room management at other hospitals shows considerably reduced set-up times before the first incision, improved time from skin incision to closure (ie, duration of operations), fewer complications, and higher satisfaction of medical personnel due to a better capacity to plan staffing.
- This improved staff planning should also lead to remuneration that is fair considering performance and qualification; although this is theoretically possible through tariffs, it is currently uncommon in practice. This means, for example, that in large proportions of on-call work, more than 49% of the time is worked, meaning that this should be paid at full rate and not at on-call rates. Better planning and clearer remuneration standards should increase the profitability and employer appeal at the same time.

Textbox 3. Expected organizational adaptations for improved employee retention.

- Structured training, even on-the-job, with appropriate, planned flexibility based on the specific staffing experiences of UKM and the value partners will be published in professional magazines.
- Questions regarding hospital financing including incentives for the hospital operators to provide resources for further training will be discussed with the associations and recommendations will be prepared in practice forums for hospital and special purpose associations.
- Specific measures will be recommended in the organizational guide for helping improve recruiting and retention in hospitals. Implementation experiences and successes will be published in specialist articles.
- Models of flexible and attractive training will be published in specialist articles and presented to an expert audience on professional conferences.
- Long-term change and adjustment requirements are being discussed with representatives from hospitals and professional associations in practice forums and recommendations are being derived. Implementation experiences will be published in specialist articles.
- To make allowances for the learning behavior of new generations, the use of new learning tools (eg, tablet PCs and mobile phones) and new training forms new forms of cooperative and media-supported learning will be developed.
- To achieve a structured and demand-oriented training, better personnel planning software, and electronic skills management systems are needed: in a standardized process, suitable software providers will be identified and with 1 of these software providers, a software solution will be implemented at UKM. IT solutions, once they have been developed, will be available to all hospitals.

Discussion

Project Status

Overall, utilization of the project results will lead to short-, middle-, and long-term effects. In the short-term, that is, during the project execution, an organizational guide with sample calculations for investment needs and cost reductions through flexible work and training offers is being developed, a series of events called "demography and competence management in hospitals" has been initiated together with the associations and interest groups represented in the project council [46] several articles have been published in practice-oriented journals [47] and volumes [48]. In addition, a personnel concept and an IT concept for a software program for flexible personnel planning in hospitals are under development. In the mid-term, within 2 to 3 years of project completion, we aim to develop recommendations for supporting flexible working and learning conditions in hospitals through associations based on project results documented in an organizational guide, to initiate a national platform for "demography and competence management in hospitals," based on the event series. Moreover, we prepare the publication and marketing of the new consulting portfolio for hospitals. In the long-term, we aim to develop recommendations for adjusting and opening tariff contracts and for financing flexible work and training offers in hospitals as part of the statutory payment system. Innovative software for personnel planning in hospitals will be implemented and tested as a new software package through software providers.

Outlook

In association with interest groups and medical associations FacharztPlus will support the structuring of further medical training through better controlling of training, and standardization of "learning analytics." The research project also promotes competence-based professional training instead of collecting "training credits" and helps to adjust education and further training of the medical profession to reflect current challenges in curative medical care (eg, increasing comorbidity). A special focus lies on the incorporation of gender-specific features into the job profile in order to be able to use more work hours from qualified and experienced female specialist physicians through the development of new gender- and generation-specific working time models. Finally, we want to motivate German health care policy to strive for tariff policy and regulatory framework conditions, which encourage flexible work and training as well as models of future financing of further specialist physician training and subsequent training for additional qualification of specialist physicians.

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Conflicts of Interest

None declared.

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Abbreviations

IT: information technology
HR: human resources
NGT: nominal group technique
UKM: University Hospital of Muenster

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Protocol

Taxonomy for the Rehabilitation of Knee Conditions (TRAK), a Digital Intervention to Support the Self-Care Components of Anterior Cruciate Ligament Rehabilitation: Protocol of a Feasibility Study

Emma Dunphy[1*], BSc (Hons), M Phil; Fiona L Hamilton[1*], MBBS, PhD; Kate Button[2], PhD

[1]EHealth Unit, Primary Care and Population Health, University College London, London, United Kingdom

[2]School of Healthcare Sciences, Cardiff University, Cardiff, United Kingdom

[*]these authors contributed equally

Corresponding Author:
Emma Dunphy, BSc (Hons), M Phil
EHealth Unit
Primary Care and Population Health
University College London
Upper Third Floor, University College London Medical School (Royal Free Campus)
Rowland Hill Street
London,
United Kingdom
Phone: 44 20 7794 0500 ext 38826
Fax: 44 20 7794 0500
Email: emma.dunphy@ucl.ac.uk

Abstract

Background: Rupture of the anterior cruciate ligament (ACL) is common, especially in the active population. In defining the problem of ACL rehabilitation, this study draws from the knowledge that improved self-care, strength, and fitness are associated with better outcomes. Traditional rehabilitation involves regular physiotherapy, but it is not clear what the optimal way for delivering rehabilitation is, and it varies widely across the world. Evidence for treatments are discussed in the literature, however standard length of rehabilitation and frequency of appointments are unknown. Additionally, current rehabilitation models in the National Health Service (NHS) struggle with catering to large volumes of patients and the lengthy time span over which rehabilitation is delivered. The use of eHealth (the Internet in health care) has been successful at delivering behavior change to a number of diverse patient groups. In physiotherapy, problems such as exercise compliance, exercise technique, and managing a broad program of rehabilitation and advice can be challenging. An eHealth intervention called Taxonomy for the Rehabilitation of Knee Conditions (TRAK) to support self-management and behavior change has been developed by patients and clinicians, and acceptability studies have yielded positive results. TRAK is not an exercise rehabilitation protocol; it is a tool to support ACL rehabilitation with personalized plans, prompts, and logs to help adherence and videos and instructions to improve quality and address queries. The patients have their own log-ins and can email their physiotherapist through the website. This novel platform is directly in line with current NHS England, National Institute for Health and Care Excellence, and NHS Improvement agendas that call for rehabilitation initiatives using both technology and supported self-management for patients. This study forms part of a research platform to identify a best practice model of ACL care from the literature and opinions of key stakeholders. Patients' exercise programs and duration of treatment are still based on individual needs, but use of the website may offer improved self-management and function and reduced health resource use.

Objective: This is a feasibility study to establish recruitment, retention, sample size estimates, and practicality of collecting outcome measures to inform a future trial comparing the TRAK intervention, which has been rigorously designed to address the challenges of ACL rehabilitation, to usual care.

Methods: This is a feasibility study comparing 2 groups: standard care and standard care plus eHealth. It will use convergent parallel mixed methods where both qualitative and quantitative data are sought for a more thorough understanding of the objectives. Primary outcomes relate to feasibility, including recruitment, retention, and usage. Secondary outcomes relate to health resource use and patient-rated outcome measures.

Results: This research expects to establish the feasibility of a full-scale randomized controlled trial to explore whether patients who use an eHealth intervention to support ACL rehabilitation have better outcomes plus improved self-efficacy and reduced health resource use than a usual care group.

Conclusions: The study will provide essential information to support the development and powering of a future clinical trial of eHealth and physiotherapy for patients with ACL reconstruction in the NHS.

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KEYWORDS

musculoskeletal; ACL; rehabilitation; eHealth; self management

Introduction

Background

Anterior cruciate ligament (ACL) rupture is a relatively common injury among those who are physically active [1-3]. Surgery is still the most common way to manage these patients and rehabilitation is essential [1-5] for "maximizing potential for patients to live a full and active life within their family, social networks, education/training and the workplace where appropriate" [5]. The optimal way for delivering rehabilitation is not clear, and current methods vary widely across the world [6-8]. Evidence for treatments is much discussed in the literature. This study addresses how current methods of service delivery in the National Health Service (NHS) struggle to cater to large volumes of patients and the lengthy time span over which rehabilitation is delivered [9-11]. Costing ACL rehabilitation in the NHS is not currently possible given that no standard guideline of care exists.

Some of the challenges of ACL rehabilitation include patient adherence, quality and type of exercises, motivation, and incomplete rehabilitation [3,4,6-8]. eHealth, defined as the use of the Internet in healthcare [12], could improve ACL rehabilitation when used as a tool to support behavior change and greater self-management [13,14]. To date, the use of eHealth has been successful at delivering behavior change to a number of diverse patient groups [12,15-17].

Taxonomy for the Rehabilitation of Knee Conditions (TRAK) is a website that targets behavior change to support self-management. It provides an individualized exercise program, progress log for key exercises, information section for each stage of rehabilitation, prompts, and videos and instructions to support the quality of rehabilitation [18] (see Multimedia Appendix 1). Patients log in to a personal account and have an embedded email link to the physiotherapist who oversees their program.

The TRAK intervention was developed at Cardiff University and has been the subject of a series of development studies to aid self-management in a cohort of patients with knee problems [10,19,20]. It is based on the TRAK ontology, which models standard care knee rehabilitation [20]. Further studies including an acceptability study of TRAK in an ACL population in the NHS are underway in a London hospital. TRAK is in line with current NHS England, National Institute for Health and Care Excellence (NICE), and NHS Improvement agendas and initiatives around rehabilitation using both increased technology and increased support for patients to self-manage [5,21,22].

Objectives

A feasibility study is needed to establish recruitment, retention, sample size estimates and the practicality of collecting outcome measures. It will illuminate the mechanisms that may affect a future clinical trial comparing the TRAK intervention, which has been rigorously designed to address the behavioral challenges of ACL rehabilitation, to usual care.

Methods

A Mixed Methods Randomized Feasibility Trial

This study will use convergent parallel mixed methods where an embedded qualitative study will help expose the mechanisms influencing feasibility data such as recruitment, retention, and usage [23,24]. An online randomization tool will be used to mitigate imbalance between the arms and to assess whether it is possible to recruit to both arms of the study: standard care and standard care plus TRAK. This study will provide essential information to support the development and powering of a future clinical trial of eHealth and physiotherapy for patients with ACL reconstruction in the NHS.

The study will aim to recruit participants from the ACL rehabilitation pathway at a North London NHS Hospital. It will explore patient acceptance of the randomization process and of the burden of participation in a study such as submitting to demography profiling and outcome collection, attending training sessions and interviews, and committing to use the intervention [25-27].

Collecting information for an economic evaluation as part of research is important for potentially informing policy [25]. The study will assess the feasibility of collecting EQ-5D-5L, a validated outcome measure for health status which can be used for health and economic appraisal. It is used to calculate quality-adjusted life-years (QALYs) in a full trial to appraise health resource use in both arms of the study [28]. Descriptive statistics and data completeness for patient-completed health care resource use questionnaires will be reported. Methods, ease, and data completeness of collecting number and duration of physiotherapy appointments will be a particular focus of the work. This work will be supervised by a clinical trials unit health economist who will inform the feasibility trial procedures, including how data is captured and reported and how to deal with uncertainty in the data.

A second part of the study will use semistructured interviews with patients and physiotherapists on their experiences of using TRAK. A schedule of questions will be used to provide an

in-depth understanding of the user perspective of the intervention and the participation burden of the study that may have implications for a future trial. Conversations will be taped, transcribed verbatim, and analyzed using a thematic analysis discussed below.

Selection Criteria

All adults immediately post ACL reconstruction who have been referred to the ACL rehabilitation program, are able to read and write English and give written informed consent, and have access to the Internet at home will be considered for this study. Individuals with complex comorbidities or surgeries such as multiligament reconstruction or fracture will be excluded from the study.

Potential Ethical Considerations

Ethical approval will be sought from the Health Research Authority. There is a risk that using TRAK will not address an individual patient's needs. The risk of this has been minimized by conducting a series of development research projects leading up to this study.

There is a risk that the participant's symptoms deteriorate but remote monitoring through email will not identify this quickly. Since face-to-face treatment still applies and the patient can be identified when attending the group, this risk will be minimized. Patients will also be encouraged to air concerns with their therapist via email through the website.

There is a burden of time placed on the patient whereby they have to learn to use the website and take the time to log in daily. However, participants will have access to many aspects of TRAK beyond completion of the study through remote log-in, and using TRAK for some individuals will mean that rehabilitation can fit in better around their lifestyle.

Consent

Treating clinicians will identify suitable participants when they attend the ACL group during their face-to-face consultation about their knee condition. If the individual is interested in finding out more about the study and gives verbal consent, the research team will be informed. All individuals will then speak to the lead applicant about the study and participation will be explained. The time of the lead applicant has been funded for this activity.

Sample Size

Eligible and consenting patients will be recruited from a North London physiotherapy department. Patient recruitment will begin following completion of preliminary work packages on July 1, 2018. There are on average 2 new patients per week in the ACL group based on local audit data, which equates to 60 patients over 30 weeks who may be eligible for recruitment. There is potential for 15 further patients to be recruited from the first phase of rehabilitation bringing the potential recruits to 75 patients [29,30]. As the inclusion criteria are broad, it is expected that most patients will be eligible, and early patient feedback indicates patients will be keen to partake. Recruitment stops after 30 weeks, which allows the last recruited patient 7 months to participate. This is enough time to deliver on the study objectives of measuring feasibility although not necessarily enough time for patients to complete the program [30].

A sample size of 35 in each arm is recommended in feasibility studies in order to provide sufficient data and precision of means and variances to inform a future randomized controlled trial (RCT) [30]. Once patients have given consent, baseline measures will be collected. Each participant will then be randomized to either treatment or standard care group. This will be done through an online randomizing service. All will be given standard induction and then a TRAK induction for the intervention arm.

Retention will be measured by follow-up outcomes at markers of 6 weeks, 3 months, 6 months, and end of care or the trial. Usage of the website to determine uptake will be measured by the frequency of log-ins, email contacts, and attendance at face-to-face sessions. This will inform the retention rate and the engagement of patients with the intervention.

To assess the acceptability of the website as a self-management support tool, the patients in the TRAK arm of the study will not be obliged to attend weekly face-to-face sessions (although a minimum attendance will be stipulated). Attendance becomes a key measure of self-efficacy, where less face time may indicate greater self-efficacy and therefore informs the possibility of reduced face time for eHealth users in a future RCT.

Patient and public involvement (PPI) feedback that informed this application has indicated it is acceptable to randomize to either arm of the study. However, retention and usage data will show this more accurately and have significant implications on understanding of demand, implementation, and practicality of researching this new intervention in further studies.

Arms of the Study

Treatment as Usual Group

ACL rehabilitation is an exercise group using evidence-based milestones to progress through a mix of strength and neuromuscular control exercises. Stages 1 and 2 are weekly, and stages 3 and 4 are every 2 weeks. Those who consent and are randomized to the usual care group will have a usual induction to the ACL rehab program, including

- Recommended amount of exercise
- Types of exercise (personalised, related to goals)
- Appropriate use of ice, crutches, or bracing as individually indicated
- Education on potential red flags, expected milestones, and challenges of each stage

Patients will progress through the 4 phases of rehabilitation according to their ability. At each face-to-face session they will be assessed by their physiotherapist for quality of movement, strength, and neuromuscular control toward goal achievement.

Intervention Group

If randomized to the intervention arm, patients will have initial education on the use of TRAK to support their rehabilitation. They will be offered follow-up teaching sessions if required. Patients will have access to the 5 dimensions of TRAK:

- Contact with the physiotherapist via email
- Expert knowledge base for each stage of the program detailing milestones, common problems, and a summary of the evidence base
- Individualized exercise program chosen by their physiotherapist, including videos and instructions of each session. There is a technique guide that advises the patient how to do the exercises correctly
- Exercise log to record exercise participation, progressions, and measures of leg strength and effort level
- Prompt system to remind patients to adhere

At each face-to-face session patients will be assessed by their physiotherapist for quality of movement, strength, and neuromuscular control and appropriate progressions toward goal achievement. Their exercises will be modified on their TRAK interface to reflect progress. Use of behavior change tools like logs, goal reviews, and use of prompts are recorded with usage data.

Outcome Measures

Patients will complete outcomes at 6 weeks, 3 months, 6 months, and final visit. This is in line with previous RCTs in the field [6,31-33].

Primary Outcomes

- Recruitment
- Retention
- Usage such as log-ins, number of pages visited, response to prompts, and log use will inform influence of behavior change tools
- Cost analysis
  - Face to face time with physiotherapists
  - Number of appointments
  - Consultant visits
  - General practitioner visits
  - Email contacts
  - Physiotherapist time outside of class

Secondary Outcomes

Patient-rated outcome measures (PROMs) are chosen as the most likely outcome measures for use in a full RCT, depending on feasibility results.

- Knee Injury and Osteoarthritis Outcome Score [34]
- Health Resource Use Questionnaire [35]
- Stanford Self-Efficacy Questionnaire [36]
- EQ-5D-5L [28]

Usage of TRAK Website

- Log-ins
- Pages visited
- Log input
- Strength progressions input
- Strength gains (Limb Symmetry Index and Return to Sport After Injury Scale)
- Email contacts to physiotherapists

Adverse Events

Adverse events such as infection, reinjury, or failure to progress are rare but will be monitored throughout at face-to-face sessions and via patient-clinician email. Patients will be alerted to these possibilities in their inductions, in the class, and on the TRAK website.

Methods for Protecting Against Bias

With the help of the clinical trial unit, an online randomizing process will be used for this trial to help control against bias. A physiotherapist who is blinded to treatment allocation will collect PROMs from patients. PROMs by their nature are bias-limiting because they are filled in by patients and not clinicians.

Data Analysis and Frequency of Analysis

Standard procedures of data collection will be adhered to and guided by practices of the clinical trials unit. The qualitative and quantitative data strands are to be collected and analyzed simultaneously and with equal priority [23].

Quantitative data will be analyzed as follows: binary and other categorical measures will be summarized using frequencies and percentages and continuous measures using means and standard deviations (or medians and interquartile ranges for very skewed distributions). All outcome measures will be summarized separately by study arm. Differences in outcomes between arms will be estimated using multilevel linear or logistic regression models with a random effect of person to account for the repeated measures on individuals over time. Potential therapist effects will be appropriately modelled. The precision of estimates will be assessed using 95% confidence intervals. Power analyses will be conducted to calculate the sample size necessary to detect an effect of the intervention in a future RCT.

The qualitative analysis will be done using a thematic analysis approach. This sees the data itself, rather than the theory, driving the process. The themes emerging from the interviews are grouped stringently so all the interview data relating to a particular theme are recorded. An explicit process of analysis will be outlined and reported, especially with regard to how data are weighted and reported secondary to frequency of occurrence or explanatory value [37]. The process will be largely inductive and will develop an epistemology of the ACL patient experience where preconceived ideas are suspended in favor of the unique perspectives of the participants. The patient's "perception, thought, memory, imagination, and emotional experience of an event" is liberated and fully informs our understanding [38]. Interview data will be analyzed by the chief investigator and cross-checked by another supervisor.

Expected outputs:

- Determining the feasibility of an RCT by gathering sufficient data to power a trial as outlined
- Determining the acceptability of TRAK as a tool of behavior change to physiotherapists and patients and illuminating the mechanisms that influence feasibility measures
- Determining the feasibility of gathering costing data to inform an economic analysis alongside a potential RCT

Patient and Public Involvement

Participant feedback will be sought from the patient steering group at quarterly meetings throughout the trial or by request. Patients were part of the design of TRAK, and they informed the content and filmed the exercise videos. They checked all lay project documents for the ethics process. A National Institute for Health Research PPI panel reviewed the study favorably, and changes were made based on feedback.

Results

Recruitment to this study will be pending successful funding of the study. Recruitment will aim to begin in July 2018 following completion of preliminary work packages. Ethical approval will be sought through the Health Research Authority in January 2017 pending successful funding of the study. The study will be overseen by a trial steering committee.

Discussion

Impact of the study will be the delivery of TRAK ready to test in an RCT at the end of the feasibility study. The feasibility of collecting data toward a phase 3 effectiveness and cost-effectiveness study and the future direction of eHealth interventions in the management of ACL patients in the NHS will be established.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Images from the Taxonomy for the Rehabilitation of Knee Conditions website.

[PDF File (Adobe PDF File), 141KB - resprot_v5i4e234_app1.pdf]

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Abbreviations

ACL: anterior cruciate ligament
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
PPI: patient and public involvement
PROM: patient-rated outcome measure
QALY: quality-adjusted life-year
RCT: randomized controlled trial
TRAK: Taxonomy for the Rehabilitation of Knee Conditions

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Protocol

Predictors of Vascular Cognitive Impairment Poststroke in a Middle Eastern (Bahrain) Cohort: A Proposed Case-Control Comparison

Claire Donnellan[1], BSc, RN, MA, DipStat, PhD; Mona Al Banna[2], BCh, BAO, MB, MSc; Noor Redha[2], MD; Adel Al Jishi[2], MD; Isa Al Sharoqi[2], MD; Safa Taha[3], PhD; Moiz Bakhiet[3], PhD, MD; Fatema Abdulla[2], MD; Patrick Walsh[4], PhD

[1]School of Nursing and Midwifery, Faculty of Health Sciences, University of Dublin, Trinity College, Dublin, Ireland

[2]Department of Clinical Neurosciences, Salmaniya Medical Complex, Salmaniya, Bahrain

[3]Department of Molecular Medicine, Princess Al Jawhara Center for Genetics and Inherited Diseases, Salmaniya, Bahrain

[4]School of Medicine, Royal College of Surgeons in Ireland–Bahrain, Busaiteen, Bahrain

Corresponding Author:
Claire Donnellan, BSc, RN, MA, DipStat, PhD
School of Nursing and Midwifery
Faculty of Health Sciences
University of Dublin, Trinity College
2 Clare Street
Dublin
Ireland
Phone: 353 1 8964109
Fax: 353 1 8963001
Email: cdonnel@tcd.ie

Abstract

Background: Poststroke dementia and cognitive impairment are associated with poor long-term outcomes after stroke. The contribution of genetic factors such as the presence of apolipoprotein (ApoE) 4 allele and its association with cognitive impairment poststroke remains inconclusive, particularly in Middle Eastern regions.

Objective: The aim of this study is to examine all correlates and potential predictors of cognitive impairment including self-awareness and regulation deficits in stroke patients and compare these functions with healthy older adults from a Middle Eastern population.

Methods: A prospective stroke sample of 200 patients (case group) and 100 healthy aging individuals (control group) will be recruited from the largest medical complex in Bahrain. A neuropsychological battery of cognitive assessments (global, executive, and metacognition) will be conducted on all participants. Participants will be categorized into 4 subgroups (nonvascular cognitive impairment, vascular cognitive impairment with no dementia, vascular dementia, and mixed dementia) using standardized cognitive assessment scores and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, dementia criteria. Biomarkers will include ApoE genotype, soluble form of receptor for advanced glycation end products, neprilysin, beta-secretase 1, biochemistry, and hematology measurements.

Results: The primary study outcome is to determine early risk factors for cognitive impairment after stroke in a Bahraini cohort. The study has received full ethical approval from the Bahrain Ministry of Health and from the affiliated university.

Conclusions: With increasing stroke incidence rates in the Middle East, this research study will provide useful biological and epidemiological data for future development and planning of health policies and guidelines for stroke care within the Gulf region.

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KEYWORDS

stroke; cognition; vascular dementia; assessment; biomarkers; protocol

Introduction

Stroke is becoming a major health problem in the Middle East as incidence rates are increasing comparably with western countries [1-3]. In tandem with this increasing number of new cases of stroke per annum are the growing demands and pressures impacting health systems in the region. Advances in stroke research internationally have aimed to improve patient care and quality of life while reducing the perceived burden and health care system demands. However, empirical evidence regarding the presentation of the most common consequences poststroke is currently not available in the Middle East.

Cognitive impairment is one of the most common sequelae following stroke with 40% to 75% of stroke survivors experiencing some sort of cognitive deficit [4,5]. For the majority of patients, some degree of cognitive impairment will be evident in the acute phase poststroke [6]. Predictors of cognitive impairment include type of stroke, recurrent episodes, the site and laterality of the lesion(s), volume of cerebral infarction, medial temporal lobe atrophy, and coexistent neurodegenerative pathology. Other biological factors known to exacerbate cognitive impairment further are aphasia, diabetes mellitus, atrial fibrillation, and depression [7]. Many of the cognitive problems resolve over time, but approximately 35% of individuals will be left with some residual cognitive impairment [8,9]. Poststroke dementia and cognitive impairment are associated with poor long-term outcomes, including survival and disability, up to 4 years after stroke [9,10]. There has been some investigation regarding the contribution of apolipoprotein (ApoE) 4 allele [11] and its association with cognitive impairment poststroke and overall disease outcome [12-17]. However, results remain inconclusive, and further research is required in order to determine and clarify the role of ApoE 4 allele in stroke incidence and outcome particularly in Middle Eastern regions.

Many studies have been performed concerning the effect of stroke on global and executive cognitive function [18-21]; however, fewer studies have been conducted on other higher-order cognitive functions such as metacognition [22,23]. The concept of metacognition consists of self-awareness, which includes knowledge about cognitive abilities and strategies, and self-regulation, which includes cognitive monitoring and cognitive control [24]. Therefore, metacognition involves conscious knowledge of cognitive processes as well as the ability to consciously monitor and regulate one's ongoing activities while engaging in a task [25]. These higher-order cognitive functions are required in order for individuals to recognize or be aware of their deficits post–brain injury so that they are capable of selecting activities within their capability for safe and independent functioning [26]. Deficits in relation to these cognitive functions can present significant problems in terms of motivation and goal attainment as part of rehabilitative programs. Assessment and test procedures for self-regulatory functions and metacognitive processes remain limited and are currently being considered to be included as part of cognitive function tests in future protocols [27]. The aim of this study is to examine all correlates and potential predictors of cognitive impairment including self-awareness and regulation deficits in stroke patients and compare these functions with healthy older adults from a Middle Eastern population.

Methods

Study Design

This is a case-control study. A longitudinal quantitative approach will be conducted to examine the research objectives.

Participants: Inclusion and Exclusion Criteria

The study will involve recruiting 2 separate sample groups. The first group, known as the case group, will include recruiting individuals within 4 weeks poststroke (see Textbox 1). The second group, known as the control group, will include recruiting healthy older adults who will be age- and gender-matched with the individuals in the case group (see Textbox 2). The case group will be recruited from the largest urban teaching hospital in Bahrain and the control group from 2 large primary health care centers within close geographical proximity to the recruiting hospital.

All consecutive admissions with a confirmed diagnosis of stroke (defined as symptoms of rapid onset lasting more than 24 hours and of presumed vascular origin reflecting a focal disturbance of cerebral function, excluding isolated impairment of higher function) [28] and in accordance with International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, diagnostic criteria will be tracked for eligibility to participate in the study.

Procedure and Measures

All stroke participants will be recruited to the study within 1 to 4 weeks poststroke and will be followed up 12 months later. Initial information collected from participants will include date of birth, gender, number of years spent in formal education, marital status, and living arrangements. Information regarding the participant's medical history will be retrieved from the healthy participants directly through interview and for stroke participants via their medical charts. This information will include past medical history of any conditions, history of medications, date of stroke, stroke type, localization of stroke, side affected, and computer tomography (brain) and/or magnetic resonance imaging (brain) results. Case and control groups will be administered the same questionnaires with the exception of the FAST, the National Institutes of Health Stroke Scale (NIHSS), and the Checklist for Cognitive and Emotional Consequences Following Stroke (CLCE-24), which will be assessed in the stroke participants only (see Table 1).

Textbox 1. Selection criteria for case group.

Inclusion criteria:

- ≥18 years of age
- Written informed consent to participate
- First-ever or recurrent stroke within 1 month of assessment
- Ability to participate in interview assessment with sufficient language (aphasia will be assessed using the shortened version of the Frenchay Aphasia Screening Test [FAST] with a cut-off score of ≥14)

Exclusion criteria:

- Transient ischemic attacks (TIAs) and related syndromes
- Nonverbal communication as a result of aphasia or as determined by a score of ≤13/20 on the shortened version of the FAST score
- Too medically unstable to participate in the study
- Formal diagnosis of prestroke vascular dementia or prestroke cognitive impairment
- Traumatic brain injury or traumatic intracranial or subarachnoid hemorrhage
- Visual or hearing impairment that would hinder participation in assessments
- Neurodegenerative disease (eg, Parkinson disease) or previously documented diagnosis of dementia

Textbox 2. Selection criteria for control group.

Inclusion criteria:

- Healthy adults both male and female
- Age and gender matched with case group participants
- English or Arabic speaking

Exclusion criteria:

- Previous use of psychotropic medication
- Neurodegenerative disease (eg, Parkinson disease, dementia, or stroke)
- Previous stroke or transient ischemic attack (TIA)
- Meets cognitive impairment criteria

The expected time for each stroke participant interview, including all assessments, should take 45 to 60 minutes, and for each healthy participant, the interview should take 20 to 40 minutes. The control group will include healthy individuals with no history of psychological or mental illness (including ever having been prescribed psychotropic medication) or any neurodegenerative diseases. Therefore, this group will create a baseline to identify the normal level of cognitive function that is age- and gender-matched to the case group individuals. In order for measurement to be relevant to the Bahrain region population, questionnaires have been translated into Arabic and either the English or Arabic battery of tests will be used depending on the participant's native tongue. All assessment tools have been translated from English to Arabic in accordance with international translation guidelines [29,30], and reliability tests (internal consistency) will be reported on all translated versions.

Cognition Assessment

The case group will be categorized into 4 subgroups [27,31,32] based on the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Trail-Making Test (TMT) scores alongside Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (DSM-IV) dementia criteria (see Textbox 3).

Table 1. Schedule of assessments and measures for case and control groups.

Generic variable name	Instrument/measure name	Case group		Control group
		4 weeks PS[a]	12 months PS	
Participant demographics	Age, gender, nationality, marital status, living situation, education and occupation, hand preference	x		x
Clinical details	Past medical history	x		x
	Oxfordshire Community Stroke Project classification	x		
	TOAST[b] classification of stroke	x		
	Lesion location	x		
	Affected side	x		
	Length of hospital stay	x		
Stroke severity	National Institute of Health Stroke Severity Scale	x		
Aphasia screening	Frenchay Aphasia Screening Test	x		x
Global cognition	Mini-Mental State Examination	x	x	x
	Montreal Cognitive Assessment	x	x	x
Executive function	Trail-Making Test (A+B)	x	x	x
Metacognition	Metacognitive Questionnaire-30	x	x	x
	Checklist for Cognitive and Emotional Consequences Following Stroke to be completed by participant and by proxy	x	x	x
Premorbid cognitive functioning	Informant Questionnaire on Cognitive Decline in Elderly	x	x	x
Mood	Hospital Anxiety and Depression Scale	x	x	x
Activities of daily living	Barthel Index	x	x	x
Biomarkers	Lipid profile, HbA1c[c], homocysteine levels, coagulation profile	x	x	x
	ApoE[d]	x	x	x
	sRAGE[e], BACE1[f] and NEP[g]	x		x

[a]PS: poststroke.

[b]TOAST: Trial of Org 10172 in Acute Stroke Treatment.

[c]HbA1c: hemoglobin A1c.

[d]ApoE: apolipoprotein E.

[e]sRAGE: soluble form of receptor for advanced glycation end products.

[f]BACE1: beta-secretase 1.

[g]NEP: neprilysin.

Clinical Laboratory Analysis

Blood will be drawn within 1 week of admission for the case group and after interview assessment for the control group. Blood specimens for the measurement of ApoE genotypes will be collected in edetic acid tubes. DNA will be purified from white blood cells using the MagNA Pure Compact Nucleic Acid Isolation Kit and stored at –20°C. ApoE genotype analysis will be performed by polymerase chain reaction–restriction fragment length polymorphism according to the method of Zivelin et al [33]. For the serum biomarkers (sRAGE, BACE-1 and NEP), blood will be collected in serum separator tubes, and the serum will be separated and stored at –80°C. The serum biomarkers will be measured using commercially available double sandwich enzyme-linked immunosorbent assay (ELISA) kits in conjunction with an ELISA plate reader. ApoE and serum biomarker analysis will be conducted at Princess Al-Jawhara Center for Genetics and Inherited Diseases. Routine biochemical analysis, including lipid profile, complete blood count, electrolytes, serum proteins, creatinine, homocysteine, and coagulation profile will be conducted at Salmaniya Medical Complex.

Sample Size

The number of participants required to produce a statistically meaningful change in cognition between the stroke patients and healthy controls was calculated using the following formula by Bland [34] for the comparison of 2 independent samples. A sample of 75 or more in each group will detect a minimum effect size in cognition and biomarkers with a power of 0.8 at a significance level of .05. Therefore, the study will aim to recruit a minimum sample size of 100 for both the case and control groups. For conducting multiple regressions models, the study will adhere to the Green proposal where the minimum

sample size should be greater than 50+8k, where k is equal to the number of independent variables [35]. Nonparametric statistical analysis will be conducted for the cognitive impairment groups' comparisons as classified in Textbox 3.

Textbox 3. Classification of cognitive impairment.

- Stroke with no vascular cognitive impairment:
  - MMSE score≥24 (with no education add 2 points, >80 years of age add 1 point)
  - MoCA score≥26 (add 1 point if≤12 years education)
  - TMT score: Trail A<78 seconds, Trail B<273 seconds
- Vascular cognitive impairment with no dementia:
  - Mild:
    - MMSE score 21-24
    - MoCA score 18-25
    - TMT score: Trail A>78 seconds, Trail B>273 seconds
  - Moderate:
    - MMSE score 10-20
    - MoCA score 10-17
    - TMT score: Trail A>78 seconds, Trail B>273
- Vascular dementia: classified according to the DSM-IV dementia criteria
- Mixed dementia: classified according to the DSM-IV dementia criteria

Statistical Analysis

All independent and dependent study variables will be reported using descriptive statistics. Comparisons between variables for control and case groups will be determined using independent *t* tests, analysis of variance, and multivariate analysis of variance where multiple variables will be analyzed together. Other statistical tests will include correlational analysis including uni- and multivariate analysis using Pearson's correlation and multiple regression. All variables will be checked for normal distribution in order to justify use of parametric statistics. Psychometric analysis will be conducted on all measures including and specifically those that are translated from English to Arabic (Metacognitive Questionnaire-30 and Hospital Anxiety and Depression Score). Nonparametric tests will be conducted for subgroup analysis where group sizes may be small using Spearman's correlation and Wilcoxon tests.

Estimated Study Outcomes

The effects of stroke will be determined by assessing all cognitive functions. The relationship between stroke severity and metacognitive functioning will be determined as will the association between cognitive impairment in the acute phase poststroke and the presence of ApoE and other biomarkers in a Middle Eastern cohort. Arabic versions of cognitive assessment tools will be validated.

Study Organization and Funding

The study protocol has been approved by the Ministry of Health, Kingdom of Bahrain, and the Royal College of Surgeons in Ireland–Bahrain (RCSI-Bahrain) research ethics committees. Research funding was awarded for this study from the RCSI-Bahrain (grant number BR00021). Written informed consent will be obtained from all participants willing to take part; they will be informed of the right to withdraw from the study at any time.

Results

See Table 2 for the baseline characteristics of the case and control group samples to date.

Table 2. Baseline characteristics of the first 51 stroke patients and 49 controls.

Baseline characteristics	Stroke	Healthy controls
Age in years, mean (SD)	59.33 (13.93)	57.51 (8.14)
Gender, n (%)		
Male	40 (78)	26 (53)
Nationality, n (%)		
Bahraini	31 (61)	46 (94)
Non-Bahraini	20 (39)	3 (6)
Living arrangement, n (%)		
Living alone	11 (22)	0 (0)
Living with others—family/friends	32 (63)	46 (94)
Other	8 (15)	3 (6)
Education, n (%)		
Primary	12 (23)	6 (12)
Secondary	20 (39)	22 (45)
Third level	10 (19)	14 (29)
Illiterate	9 (19)	7 (14)
Occupation, n (%)		
Manual	16 (31)	5 (10)
Nonmanual/self-employed	16 (31)	10 (20)
Unemployed/retired	19 (38)	34 (69)
History, n (%)		
TIA[a]	6 (12)	0 (0)
Stroke	9 (17)	0 (0)
Cardiovascular disease	9 (17)	6 (12)
Atrial fibrillation	5 (10)	4 (8)
Hypertension	32 (63)	27 (55)
Diabetes	20 (39)	22 (45)
Hyperlipidemia	19 (38)	24 (49)
Psychiatric conditions	1 (2)	0 (0)
Lesion location, n (%)		
Right hemispheric	26 (51)	—
Left hemispheric	20 (39)	—
Brainstem	5 (10)	—
Unknown	0 (0)	—
Stroke subtype, n (%)		
Ischemic	43 (84)	—
Hemorrhagic, intracerebral	8 (16)	—
Hemorhhagic, subarachnoid	0 (0)	—
OCSP[b] classification, n (%)		
Total anterior circulation	4 (8)	—
Partial anterior circulation	18 (35)	—
Lacunar	21 (41)	—

Baseline characteristics	Stroke	Healthy controls
Posterior circulation	8 (16)	—
TOAST[c] classification, n (%)		
Large artery atherosclerosis	14 (28)	—
Cardioembolic	2 (4)	—
Small artery occlusion	24 (48)	—
Determined or undetermined etiology	11 (20)	—
NIHSS[d], mean (SD)	5.77 (5.01)	—
0-4, n (%)	20 (39)	—
5-15, n (%)	30 (59)	—
≥16, n (%)	1 (2)	—
Cognitive status at baseline		
MMSE[e], mean (SD)	24.09 (4.81)	27.86 (2.42)
MoCA[f], mean (SD)	19.78 (6.64)	25.49 (3.60)
MCQ-30[g], mean (SD)	62.42 (14.29)	63.2 (15.60)
Barthel Index, mean (SD)	69.00 (31.07)	99.49 (2.10)
Independent, n (%)	13 (25)	49 (100)
Dependent, n (%)	38 (75)	—

[a]TIA: transient ischemic attack.

[b]OCSP: Oxfordshire Community Stroke Project.

[c]TOAST: Trial of Org 10172 in Acute Stroke Treatment.

[d]NIHSS: National Institute of Health Stroke Severity Scale.

[e]MMSE: Mini-Mental State Examination.

[f]MoCA: Montreal Cognitive Assessment.

[g]MCQ-30: Metacognitive Questionnaire-30.

Discussion

Advances in stroke research internationally have aimed to improve patient care and quality of life and reduce perceived burden and demands on health care systems. In terms of advancing the research agenda for the management of stroke in the Middle East, some strategic approaches may be considered from previous research reviews and studies conducted. Previous research studies and reviews have highlighted core aspects relevant for stroke management in terms of the adaptation process [36,37], clinical assessment, and adherence to evidence-based practice [38,39]. Therefore, moving the stroke research agenda forward in a region such as Bahrain requires stroke studies based on potential frameworks [40,41] that can address stroke management in the context of specific regional preferences. The aim of this research study is to investigate a very current topic in the field of stroke research regarding identifying the main correlates and predictors, including biological markers, for detecting those patients most at risk for developing cognitive impairment poststroke. This research study, in addition to addressing a relatively novel research area such as metacognition, will also record the clinical and demographical profile of stroke patients. Identifying core risk factors [42] in Bahrain will provide useful epidemiological data for future development and planning of health policies and guidelines for the overall prevention [43-45], management, and delivery of stroke care. These outcomes will aid in developing stroke management and rehabilitation within a contextual framework by tailoring the population's health needs based on specific cultural variations. Findings from these type of cognition studies will also inform future developments required for cognitive training interventions [46] specific for stroke patients and other populations with cognitive deficits as a result of neurological pathologies living in Middle Eastern countries. Finally this study will aim to ascertain recruitment considerations [47] for both healthy older adults and stroke patients who are at risk of developing dementia in this particular region.

Conflicts of Interest

None declared.

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Abbreviations

ApoE: apolipiprotein
BACE-1: beta-secretase 1

CLCE-24: Checklist for Cognitive and Emotional Consequences Following Stroke
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ELISA: enzyme-linked immunosorbent assay
FAST: Frenchay Aphasia Screening Test
MCQ-30: Metacognitive Questionnaire-30
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
NEP: neprilysin
NIHSS: National Institutes of Health Stroke Scale
OCSP: Oxfordshire Community Stroke Project
RCSI-Bahrain: Royal College of Surgeons in Ireland–Bahrain
sRAGE: soluble form of receptor for advanced glycation end products
TIA: transient ischemic attack
TMT: Trail-Making Test
TOAST: Trial of Org 10172 in Acute Stroke Treatment

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Protocol

App Chronic Disease Checklist: Protocol to Evaluate Mobile Apps for Chronic Disease Self-Management

Kevin Anderson[1], BComm, GradDipEd; Oksana Burford[1], BPharm, PhD; Lynne Emmerton[1], BPharm, PhD

School of Pharmacy, Curtin University, Perth, Australia

Corresponding Author:
Lynne Emmerton, BPharm, PhD
School of Pharmacy
Curtin University
GPO Box U1987
Perth, 6845
Australia
Phone: 61 892667352
Fax: 61 892662769
Email: lynne.emmerton@curtin.edu.au

Abstract

Background: The availability of mobile health apps for self-care continues to increase. While little evidence of their clinical impact has been published, there is general agreement among health authorities and authors that consumers' use of health apps assist in self-management and potentially clinical decision making. A consumer's sustained engagement with a health app is dependent on the usability and functionality of the app. While numerous studies have attempted to evaluate health apps, there is a paucity of published methods that adequately recognize client experiences in the academic evaluation of apps for chronic conditions.

Objective: This paper reports (1) a protocol to shortlist health apps for academic evaluation, (2) synthesis of a checklist to screen health apps for quality and reliability, and (3) a proposed method to theoretically evaluate usability of health apps, with a view towards identifying one or more apps suitable for clinical assessment.

Methods: A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was developed to guide the selection of the apps to be assessed. The screening checklist was thematically synthesized with reference to recurring constructs in published checklists and related materials for the assessment of health apps. The checklist was evaluated by the authors for face and construct validity. The proposed method for evaluation of health apps required the design of procedures for raters of apps, dummy data entry to test the apps, and analysis of raters' scores.

Results: The PRISMA flow diagram comprises 5 steps: filtering of duplicate apps; eliminating non-English apps; removing apps requiring purchase, filtering apps not updated within the past year; and separation of apps into their core functionality. The screening checklist to evaluate the selected apps was named the App Chronic Disease Checklist, and comprises 4 sections with 6 questions in each section. The validity check verified classification of, and ambiguity in, wording of questions within constructs. The proposed method to evaluate shortlisted and downloaded apps comprises instructions to attempt set-up of a dummy user profile, and dummy data entry to represent in-range and out-of-range clinical measures simulating a range of user behaviors. A minimum score of 80% by consensus (using the Intraclass Correlation Coefficient) between raters is proposed to identify apps suitable for clinical trials.

Conclusions: The flow diagram allows researchers to shortlist health apps that are potentially suitable for formal evaluation. The evaluation checklist enables quantitative comparison of shortlisted apps based on constructs reported in the literature. The use of multiple raters, and comparison of their scores, is proposed to manage inherent subjectivity in assessing user experiences. Initial trial of the combined protocol is planned for apps pertaining to the self-monitoring of asthma; these results will be reported elsewhere.

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KEYWORDS

health; mobile applications; app; smartphones; self-management; protocol; usability checklist; self-care; chronic disease

Introduction

Management of chronic conditions has evolved from traditional paper-based monitoring and action plans [1] to the use of mobile messaging [2], and now smartphone and other mobile apps to record and manage clinical data [3-5]. One such application of this technology involved a self-care app for salt intake, which has a protocol published for its use [6]. Although such apps are widely supported by health authorities and authors to enhance consumers' engagement with self-management, more long-term randomized controlled trials (RCTs) are required to measure their clinical effectiveness and frequency of use [7,8]. Additionally, self-care guidelines should be updated to incorporate engagement with mobile apps during RCTs [9].

Selecting a health app to facilitate self-care of a chronic condition can be overwhelming due to the increasing number of apps for a wide range of health conditions. Engagement with a health app lacking essential operational features, storage and calculation of clinical measures, and unaligned to the consumers' requirements, can result in declined usage of the app, potentially compromising self-care regimens [10].

Furthermore, many health apps lack a theoretical foundation, as identified in a news post by an emergency room doctor and medical professor in North Carolina [11]. Some apps are structured with a clinical appearance and facilitate data entry by consumers, but are created for entertainment purposes, as acknowledged by another journalist based on the same doctor's findings [12]. Additionally, consumers' decisions to select apps presented in the Apple App Store and the Google Play Store are clouded by marketing jargon and lay-user reviews, with an absence of official and consistent quality markers [13].

The certification of health apps to improve safety and quality in health care is an ongoing issue [14]; theory-based quality ranking of apps has begun [15] but is in an early stage. Proposed interventions include active review of every health app by app stores and/or regulators such as the Food and Drugs Administration (FDA) in the United States or the Therapeutic Goods Administration (TGA) in Australia [14]. This method is expected to be relatively slow and costly. Complicating this problem, many health apps do not fall within the jurisdiction of the FDA [5], TGA, or their overseas counterparts, particularly if the apps are not classified as medical devices and have no peripheral device requiring regulatory assessment. Consequently, the need for further research into the clinical integrity of health apps is warranted.

A recently published initiative using a rating scale for health apps named the Mobile Application Rating Scale (MARS) [16] was produced in Australia, and designed to aid app selection by researchers. The MARS appears comprehensive when rating mental health and general health apps, but has not been specifically designed for chronic conditions. Additionally, the 23 sub-categories of the MARS were not all grounded in health consumer mobile app experiences; some usability studies informing the MARS included health website evaluation [17], nonhealth website quality measurement [18,19], user experiences with online goods [20], and nonhealth-specific evaluation frameworks [21]. One recent study questioned the MARS' validity, since it has not been widely adopted [22]. However, building or updating an app to rate against the MARS requires due process, and more findings are expected since an Australian state government healthy body endorsed the scale, attracting media attention [23].

A number of other studies regarding the usability of health apps have reported findings [24-26], a content analysis guide [27], a mobile website framework [28], and an app design and development guideline [9]. One app-usability study [28] built upon Nielsen's usability heuristics [29], but was not health-tailored. Table 1 outlines health app usability studies that have produced checklists or rating scales; these are critiqued later in this paper. Growth in the health app market, both in terms of availability and adoption, warrants greater distinction between apps. A need exists for a protocol to guide researchers in their identification of apps suitable for assessment, and for developers to test their product against competitors' apps. This paper reports (1) a protocol to identify relevant apps for academic evaluation, (2) synthesis of a checklist to screen apps for quality and reliability, and (3) a proposed method to theoretically evaluate the usability of health apps, with a view towards identifying one or more apps that are suitable for clinical assessment.

Table 1. Commonalities and differences between health app usability studies.

Authors	Year	Name of rating scale or checklist	Purpose	Consumer vs academic use	Number of dimensions	Number of raters
Stoyanov et al [16]	2015	Rating scale[a]: Mobile Application Rating Scale (MARS)	Quality assessment	Academic	5	2
Nielsen [29]	1994	Checklist[b]: Nielsen's Usability Heuristics	Rectify usability problems	Academic	10	3-5
Hundert et al [5]	2014	Checklist: 7 criteria	Headache diary app evaluation (scored against 7 criteria)	Both help to inform health care professionals and potential users on the best available e-diary apps for headaches	7	2
Belmon et al [30]	2015	Rating scale: for app features, not complete apps; Behavior Change Techniques (BCT)	Young adults' opinion on BCT in physical activity apps	Consumer rating	3	N/A (179 young Dutch adults)
Patel et al [15]	2015	Rating scale: MARS [16]; (1) Weight loss/smoking cessation criterion score, (2) cultural appropriateness criterion score, and (3) cultural appropriateness criteria	Quality ranking	Academic	3 with 22, 23, and 6 subcriteria, respectively	2
Yanez Gomez et al [31]	2014	Mobile-specific usability heuristic checklist	Heuristic evaluation	Academic	13	As per Nielsen [29]

[a]A rating scale's results align a numerical value to constructs such as *Ease of Use*.

[b]A checklist can be a series of requirements necessary to achieve compliance without numerical values.

Methods

Phase 1: Development of an App Selection Protocol

Selection of relevant apps (and elimination of irrelevant apps) requires sequential consideration of the publicized and evident features of apps. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was deemed suitable for representation of the shortlisting process. In the absence of guidance from published literature, critical decisions for the purposes of shortlisting health apps were based on:

Relevance: limiting searches to the respective country's app stores ensures relevance to the local setting. Duplicate apps require removal from the shortlist. Preliminary trial of the PRISMA flow diagram has identified some apps available on both iOS and Android operating systems with similar names, requiring further examination of app logos and *screen dumps* available from the respective app store. Cases in which both an Apple and Android version of an app are available result in the Apple version being recommended to be retained, since health apps with clinical management in Australia are launched on iOS first (Brophy S, personal communication, 1 January 2015).

Availability in English: this enables evaluation of the app in the local environment. Preliminary trial of the selection process has indicated that some apps displayed in a language other than English are also available in English once the app has been downloaded.

Provision of clinical management: preliminary trial of the flow diagram suggests health apps can be classified into 5 categories. *Clinical management apps* require the user to input clinical readings such as peak expiratory flow (for asthma monitoring) or blood pressure (for hypertension monitoring), and may integrate gamification for sustained usage of the app. *Informational apps* or *eBooks* are simply digitized books containing information about a condition, without facilitating data input. *First aid apps*, ambulance apps or individual doctors' apps were classed as extraneous to the use of the app for self-monitoring of a medical condition. *Exercise or yoga apps* involve holistic management of the medical condition through techniques such as controlled breathing techniques or yoga poses. *Novelty apps* or apps for entertainment purposes include prank apps and games using fictional characters with the target condition. Certain apps, identified through searches restricted to Australia, are only available via an international account, and have been categorized accordingly.

Availability at no cost to consumers: if the purpose of the shortlisting and evaluating apps is to identify an app(s) suitable for formal evaluation via clinical trial, or as part of the outcome

measures in a trial, ideally the app(s) should be available at no cost to consumers. This parameter assumes that the cost of an app is unrelated to quality of the app.

Currency: the date of the most recent update is a particularly important eligibility criterion, since it represents the frequency with which developers respond to consumer feedback.

Phase 2: Development of the Evaluation Checklist

The app evaluation checklist was synthesized using peer-reviewed checklists and studies on the usability of health apps [5,15,16,25,27,29-35], supplemented with a qualitative study exploring consumer experiences with health apps [10]. Critique and comparison of the extant checklists, and the proposed checklist, are presented in the *Results* section. Criteria-based quality assessment was applied by creating the checklist in a number of iterations, data reduction [36,37], and assessment of face and construct validity by the authors. Face validity involved reviewing syntax and structure of checklist questions to ensure that questions reflect the research objectives. Construct validity required testing the definition of themes; these discrepancies were verified using definitions provided by similar studies, and cross-referenced with theoretical models.

This checklist was also created with reference to the principles of heuristic evaluation [29,38], which encompasses the construction of small but broad *usability principles* to evaluate an app's usability [29]. Heuristic evaluation has been applied successfully in the development of a number of health apps, such as headache diaries [5] and healthy eating apps [39], to guide design features such as the maximum number of items to maintain comprehensiveness, specificity, and efficiency. Nielsen's Usability Heuristics [29] were the foundation of several mobile app usability studies [5,28,31], and were applied here. The checklist was designed to enable rating by assessors, as per another Australian health app study [16]. For efficiency and to avoid transcription errors, the checklist should be created with survey software such as Qualtrics, rather than in hard copy.

Heuristic evaluation involved the application of 10 principles to each app, as reported by the Oracle Corporation [38]:

1. Visibility of system feedback: can the system show the user what part of the system is being accessed? Does the *back* button inform the user where they are returning to?

2. Complexity of the application: is the information technology and health literacy displayed in the app applicable to the target audience?

3. Task navigation and user controls: is the shortest possible path taken for users to perform tasks?

4. Consistency and standards: are industry standards adhered to, so users are not confused about the meaning of certain standards (eg, metric units) or conventions?

5. Error prevention and correction: are users prevented from making errors, such as entering letters in a numbers field?

6. Recognition rather than memory overload: does the system help people remember, rather than presenting all information at once?

7. Efficient to use: is there a basic and advanced mode to cater to different users?

8. Simplicity and appeal: is the system and design easy to use/appealing?

9. Be tolerant and reduce cost of errors: do errors provide avenues for further support? Can users move on after an error?

10. Help support: are there helpful suggestions for users to follow when unsure how to proceed?

Phase 3: Development of the Method to Evaluate the Usability of Health Apps

In order to apply the evaluation checklist to selected apps, a number of procedures are required: (1) determination of the number of independent raters; (2) moderation of differences between raters; (3) instructions for set-up and simulated use of the app, such as identification of a realistic user profile for all raters to enter; (4) standardization of time for initial navigation of the app; and (5) particular tasks to attempt to represent a range of user behaviors, and test the limits of the app. A simple summative scoring system is suggested to identify those apps considered to have met the criteria for formal evaluation or inclusion in a clinical trial. The scores of multiple expert raters should be compared using the 2-way mixed Intraclass Correlation Coefficient (ICC), since the same raters rate shortlisted apps using the same checklist. Consideration of interrater reliability using the ICC with SPSS version 23 (IBM Corp., Armonk, NY; 2015) is used. Utilization of the ICC is recommended to capture the varying *magnitudes of disagreement* [5] present in subjective usability metrics, and to measure homogeneity amongst raters. Internal consistency should be assessed using Cronbach alpha to ensure questions used in each section of the questionnaire are measuring the same construct [5,40]. Instructions for management of these calculations are presented in the *Results* section.

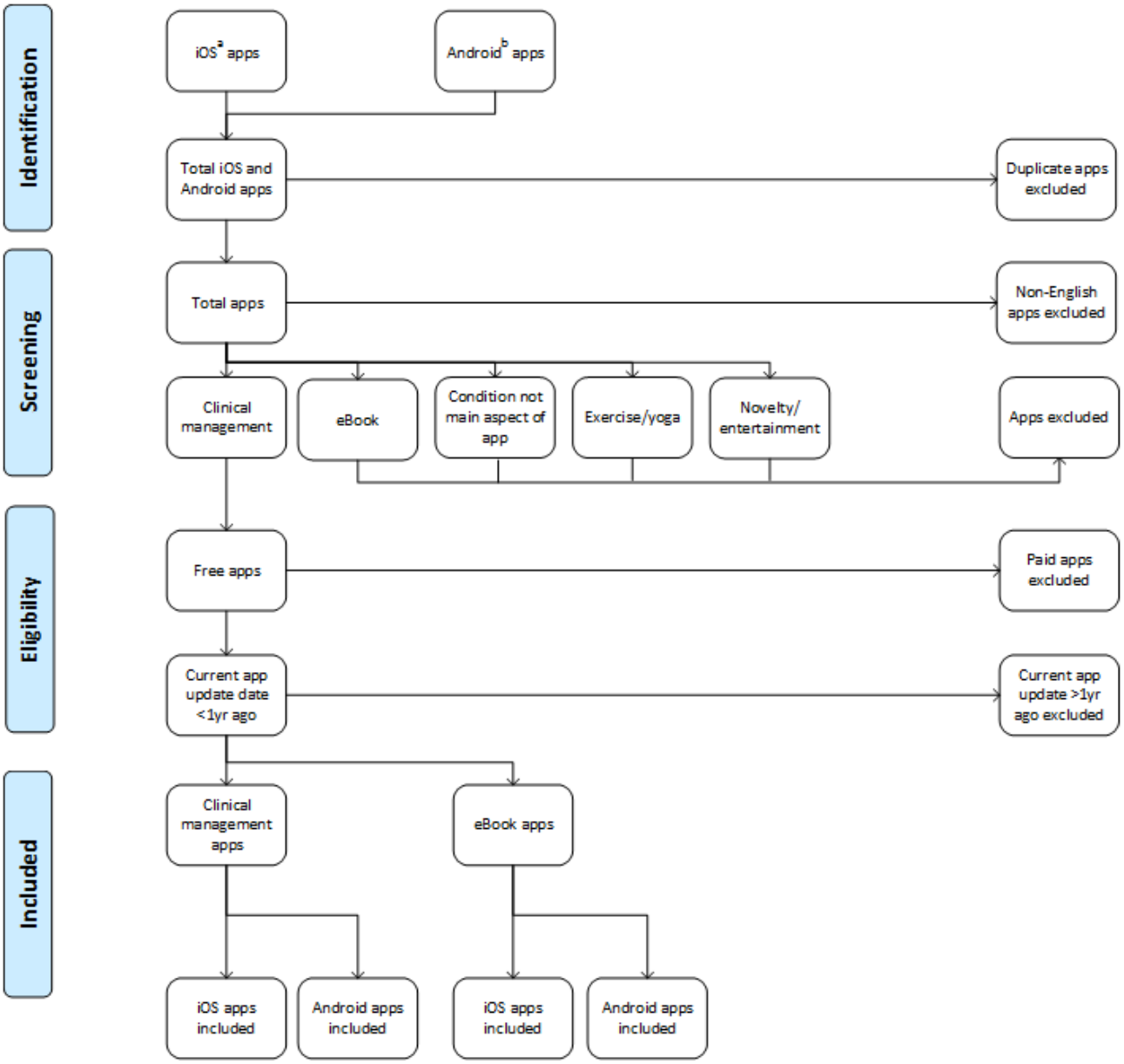
Results

Phase 1: Development of an App Selection Protocol

The process for filtering health apps available from the Australian Apple App Store and the Google Play Store to meet selection criteria is represented in Figure 1. In line with the 5 critical decisions described in the *Methods*, the flow diagram assesses relevance, English language, clinical management, free availability, and currency of the version.

This app-identification procedure uses the Australian Apple App Store and Google Play Store to locate apps specific to the target chronic condition. Subsequently, duplicate apps are removed, in addition to foreign language apps with no English language option. Apps not providing clinical management of the target condition are removed. Only free apps that have been updated less than 1 year ago are retained.

Figure 1. PRISMA flow diagram.[a]Via Australian iOS APP Store (iTunes),[b]Via play.google.com (Australian account).



Phase 2: Development of the Evaluation Checklist

In total, 6 peer-reviewed checklists focusing on usability of health apps were identified [5,15,16,29-31], as presented in Table 1. The MARS comprises 4 dimensions, totaling 19 items, with another subjective quality and app-specific category of 10 items [16]. Dimensions used in the 6 studies ranged from 3 to 13. Overall, there were consistent themes in the extant checklists, but subcomponents (ie, warnings about unhealthy values, user profile setup, and features available in offline mode) were lacking.

In addition to the studies described in Table 1, 1 app usability framework for health websites provided useful insight into theory underlying the Technology Acceptance Model (TAM) and user experience [28]. Another study [41] was not health related, but guided creation of the checklist, with reference to some common considerations regarding app usability, such as design and *help* features. Self-care guidelines when using an app were also instrumental in guiding the design of this protocol, although no rating scale or checklist were evident [9]. One content analysis guide for smoking apps [27] confirmed findings from the aforementioned studies including feedback, app content, user relevance, and user experience.

Other peer-reviewed studies have reported health app usability research without applying checklists, rating scales, guidelines, or frameworks. A New Zealand ranking system for weight loss and smoking cessation apps used 22 and 23 items respectively, considering social networking synchronization, daily activities (eg, record of food intake), personalized feedback and engagement, and using a Boolean operator to award points for scoring purposes [15]. The items listed in this New Zealand study were specific to the health condition, rather than considering other factors affecting app quality. Additionally, 2 studies presented methods to select the most popular apps to rate [15,27], rather than create a checklist or rating scale for comparative assessment of apps. Comparing and contrasting the aforementioned checklists confirmed the need for the design process to consider how consumers maintain self-care practices.

Table 2 lists the constructs, variables, and source(s) of each variable in the resultant checklist, named the App Chronic Disease Checklist (ACDC); the complete checklist is illustrated in Multimedia Appendix 1. In total, 4 constructs (*Engagement*, *Functionality*, *Ease of Use*, and *Information Management*), derived from thematic analyses of published checklists and qualitative research, are represented in the checklist. A qualitative study [10] informed the need to include *Ease of Use* as a construct (rather than *Aesthetics*, a theme from the MARS), and broaden the scope of the *Information Management* construct.

Table 2. Thematic synthesis of the ACDC checklist.

Construct	Variable	Source
Engagement	Gamification	[10,15,42]
	Customization	[10,16,33,43]
	Interactivity	[10,16]
	Positive Behavior Change	[10]
	Effectiveness	[16]
	Self-Awareness	[10,16,30]
Functionality	Health Warning	[10]
	Feedback	[10,16,27,29,31,34,39,44]
	Intuitive Design	[10,16,33,34]
	Connection to Services	[10,16,24]
	Performance Power	[10,16,29]
	Structural Navigation	[16,29,31]
Ease of Use	Usability	[10,16]
	Automation	[10,26]
	Medical and Technological Jargon	[10,39]
	User Profile Setup	[10]
	Offline Mode	[10]
	Reminders	[5]
Information Management	Statistics	[5,10]
	Privacy and Data Security	[10,43-46]
	Quality and Accuracy of Information	[10,29,34,39,46]
	Quantity of Information	[16,39]
	Visual Information	[10,16]
	Credibility	[16]

Face and construct validity were confirmed via discussion amongst the 3 authors. Construct validity guided the classification of, and ambiguity in, wording of questions within constructs, as guided by the TAM [47] and Health Information TAM [48]. The TAM confirmed alignment of questions relating to *Reminders* and *Automation* within the *Ease of Use* construct. This process was undertaken simultaneously with the consideration of usability heuristics. Lack of information in studies considering *Visual Appeal*, for example, was addressed by using Nielsen's Usability Heuristics [29] and integrated into the *Functionality: Feedback* and *Information Management: Visual Information* questions. Discussion amongst authors and consideration of extant checklists determined that a 3-point ordinal scale, appropriately worded for each question, would be used. Details of this scoring scale are described later in this paper.

Phase 3: Development of the Method to Evaluate the Usability of Health Apps

The evaluation should be completed as soon as possible after shortlisting of apps, to ensure version control and currency. In two studies, 2 raters were used to apply scores to apps [5,16], while 1 study used 5 raters to measure usability [9]. This approach was consistent with the recommendation by Nielsen [29] to use 3 to 5 experts. In line with these recommendations, and a number of other health app studies [5,16,41], this protocol suggests 3 expert raters with no experience or conflicts of interest with any of the apps.

All clinical management apps retained by the flow diagram should be rated without collusion between raters, and in their entirety, before proceeding to a subsequent app. Initially, a sample (approximately 10%) of these apps should be randomly identified using a randomization algorithm, and quarantined for

trial scoring by all raters, with results being moderated between the raters. Scores from this trial may be merged into the full scoring exercise if no significant changes have been made to the scoring protocol, as recommended by methodologists [40]. If a trialed app and a nontrialed app produce the 2 top scores, both scores should be moderated to identify the top-ranked app.

After proceeding with the assessment of the remaining shortlisted apps, raters' scores (saved in the online survey platform) will be imported to SPSS for calculation of usability scores and interrater and internal reliability. Each response on the 3-point ordinal scale will be assigned a value of 0 (where the feature is not evident or functional), 0.5 (where the feature is somewhat evident or functional), or 1 point (where the feature is clearly evident or functional), and summed to a total (out of 6) for each of the 4 constructs, as well as a total out of 24 for each app.

As established in the *Methods*, 2-way mixed ICC is recommended to measure interrater reliability [49]. The ICC should be calculated for the total score (out of 24) to compare the 3 raters, and the raters' totals for each construct: *Engagement*, *Functionality*, *Ease of Use*, and *Information Management*. Differences in scores should only warrant moderation if the ICC for each construct is nonsignificant ($P>.05$). Subjective questions, such as those within the *Ease of Use* construct, are expected to generate a lower ICC score in that construct, compared to more objective ratings of items relating to *Privacy* or *Ability to Export Data*.

One Cronbach alpha statistic should be calculated to measure correlation between the collective totals for each construct (out of 18 for each construct, if using 3 raters). Cronbach alpha should also be determined for the total score (out of 72) for the 3 raters collectively.

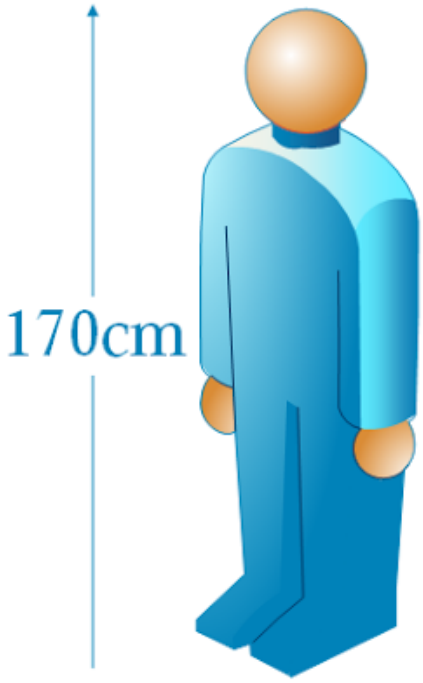
Before the apps are set up, instructions commence by entering all remaining shortlisted apps into a random list generator. The purpose of randomizing apps is to eliminate selection bias by balancing *unknown factors* [50]. Apple HealthKit apps actively monitor consumer readings, so raters should create unique logins that are clearly identified as being associated with trial of the app (eg, a consumer name such as *Test Dummy 1*); however, raters should provide authentic contact details for compulsory profile fields to facilitate receipt of outputs, if this is a function of the app. If raters encounter requests for additional data, the recommended approach is to refer to the Instructions for Raters (Multimedia Appendix 2).

Figure 2 illustrates the features of a dummy profile for entering clinical data into shortlisted apps to gauge the app's usability and functionality. The dummy profile comprises a range of realistic goals, and demographic and clinical data that reflect information that might be requested of new users. These data should be adjusted by the lead investigator to be realistic for the medical condition of interest (eg, obesity management).

As part of the dummy profile, raters should attempt to enter 1 week of realistic in-range clinical readings, taken with good compliance, with the recommended self-monitoring schedule for the relevant medical condition. This week should be followed by 1 week of readings representing poor control of the medical condition, with several days of poor compliance with self-monitoring. An example based on peak expiratory flow readings (for asthma monitoring) is provided in Figure 3, in which an adverse event such as a respiratory infection (in red) has affected a consumer's readings, and numerous readings are missing during this period of out-of-range data. Such variations in clinical data are important to gauge how the clinical management app responds to variable control of one's chronic condition and inconsistency in data entry. If raters encounter requests for additional data, the recommended approach is to discuss a course of action with other raters before proceeding.

Figure 2. Test dummy profile for clinical data entry.

Ms Test Dummy
01.01.1987 (F)



Profile
- Uncontrolled asthma since [appropriate age]
- Enters daily peak flow readings into app
- Understands a reading [above/below] 630 L/min requires adjustment of therapy
- Athletic
- Running three times per week
- Asthma since childhood
- Variable control over the years
- Hospitalized once after chest infection
- Compliance and adherence to medication generally good

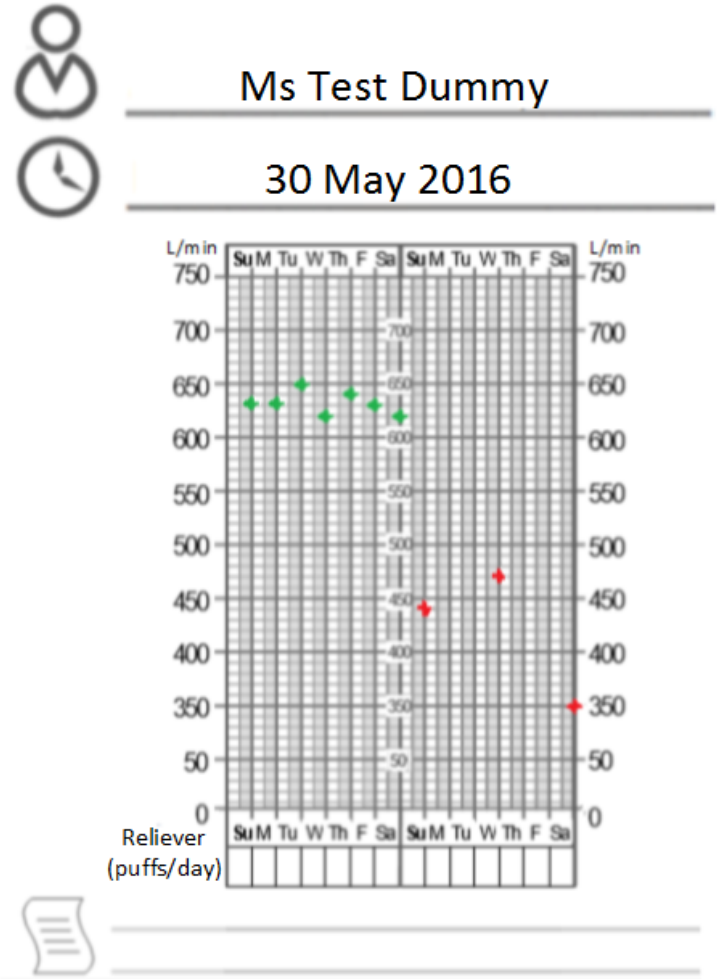
Triggers:
- Chest cold, pollen/fungal spores, sudden weather changes, cold/dry air, smoke, harsh chemicals, strong smells/sprays

Reliever:
- Ventolin (salbutamol)
  2 puffs as needed
  14.07.2014 – 14.07.2050

Preventer:
- Seretide (fluticasone 125mcg/salmeterol 25mcg)
  2 puffs/12 hours
  14.07.2010 – 14.07.2050

Assumptions:
- Acceptable reading technique
- Takes no other medication apart from [OTC tablets] when required
- To test reporting functions:
  GP: Dr Test Account [use 2nd rater's email]
  Next of Kin: Mummy Dummy [use 3rd rater's email]
- Postcode/ZIP: [20001]
- City: [Washington DC]
- Exacerbations during inconsistent self-management period: chest cough, wheezing, chest tightness

Figure 3. Peak flow values to input into shortlisted clinical management apps.



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Woolcock Institute of Medical Research, 2006
Reddel HK, Vincent SD, Civitico J. The need for standardisation of peak flow charts. Thorax 2005; 60: 146-7.

Discussion

Creating a health app selection protocol for developers and academics resulted in a guided and evidence-based procedure that aims to guide researchers to identify a health app with the highest level of usability and functionality characteristics. The identified app may then be the subject of a clinical trial as an independent intervention in health consumers' self-management of a chronic condition, or as an adjunct for other interventions. The need for evidence-based content when deciding which health app to use is also supported by a 2016 Australian review of mental health apps [51]. Consequently, consumers using top-ranking apps identified by this protocol are expected to demonstrate greater persistence with self-management of medical conditions. This theory, however, remains to be tested.

Dissemination of this protocol should also benefit app developers in their appreciation of usability heuristics and features of highly-functional, high-quality, and attractive apps. Future variations could include a developer-specific checklist, with design science and computer science-related constructs aiding the app design and development process.

The key contribution of this protocol to the body of research in this field lies in its comprehensiveness. This protocol incorporates a 3-stage method to shortlist apps, and then assesses the shortlisted apps using standardized instructions for a team of raters using an evidence-based checklist (the ACDC). The use of 3 expert raters is expected to be economical, without compromising robustness; trial of the protocol and determination of the interrater reliability statistics are required to confirm this theory.

While a previous study reported a brief flow diagram for the selection of an app [16], the inclusion of more selection criteria in the flow diagram enables more discriminatory filtering of available apps. The number of apps retained by this filtering process is expected to vary according to the chronic condition and number of marketed apps. Additional shortlisting criteria may be included if the final number retained apps remains unmanageable.

The ACDC draws most heavily on the MARS [16], with a number of differences informed from the review of other literature, and recognizes that findings from the MARS have not yet been published. First, *Ease of Use* has been identified

as a construct in the ACDC, rather than *Aesthetics* (in the MARS). This development was informed by qualitative research [10] that reported strong consumer sentiment in health app experiences. By including this consumer perspective, the ACDC recognizes the importance of a consumer's persistence with a health app for self-management of a chronic condition [10,52,53]. Second, the *Information Management* construct has been broadened in the ACDC to reflect data concerns in the information age, as informed by qualitative research [10]. Third, the ACDC was designed for use in apps for any chronic condition, not just mental health, which is the reported use for the MARS [16]. Fourth, a limitation of the MARS identified in the *Introduction* was the MARS's construction with reference to sources beyond health app usability studies. The ACDC was constructed via thematic synthesis from a body of literature specific to health app usability.

Apps are being launched with increasing frequency, and considering the ubiquitous nature of smartphones and electronic health strategies of hospitals and clinics, the use of health apps to facilitate self-care of chronic conditions will continue to expand. The authors acknowledge the release of Apple's ResearchKit [54] and the more individualized CareKit [55], which harbor the ability of researchers to embed surveys in Apple apps for data reporting. Android-based smartphones will soon have access to these open-source Apple apps (eg, Asthma Health [56]) that are available for American Apple account holders only. In the future, authors of clinical outcome questionnaires should enable researchers to integrate questions into platforms such as ResearchKit, for efficiency and convenience of data entry during clinical trials.

It is essential for developers and academics to employ a profile with dummy values to test the shortlisted apps, with the profile including compliant and noncompliant clinical readings, in addition to registering a real email account to which readings can be exported. One limitation of this approach is that a single dummy profile, even devised with in-range and out-of-range clinical data, is unlikely to test the full functionality of an app. However, a carefully constructed dummy profile and the use of 3 raters, each completing a 24-question assessment of the app, should enable thorough evaluation and ranking of the shortlisted apps.

This protocol offers a comprehensive procedure and straightforward checklist to guide selection of highly-functional and usable health apps for use in further research, or self-management by consumers. To date, the protocol has been partially tested; the first research study will apply this protocol to apps for asthma self-management.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

App Chronic Disease Checklist v1.0.

[PDF File (Adobe PDF File), 38KB - resprot_v5i4e204_app1.pdf]

Multimedia Appendix 2

Instructions for raters.

[PDF File (Adobe PDF File), 39KB - resprot_v5i4e204_app2.pdf]

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Abbreviations

ACDC: App Chronic Disease Checklist

BCT: Behavior Change Technique
FDA: Food and Drugs Administration
ICC: Intraclass Correlation Coefficient
MARS: Mobile Application Rating Scale
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial
TAM: Technology Acceptance Model
TGA: Therapeutic Goods Administration

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Protocol

Safety, Acceptability, and Use of a Smartphone App, BlueIce, for Young People Who Self-Harm: Protocol for an Open Phase I Trial

Paul Stallard[1*], PhD; Joanna Porter[2*], BSc (Hons); Rebecca Grist[1*], PhD

[1]Child and Adolescent Mental Health Group, Department for Health, University of Bath, Bath, United Kingdom

[2]Child and Family Mental Health, Temple House, Oxford Health National Health Service Foundation Trust, Keynsham, United Kingdom

[*]all authors contributed equally

Corresponding Author:
Paul Stallard, PhD
Child and Adolescent Mental Health Group
Department for Health
University of Bath
Wessex House
Claverton Down
Bath
United Kingdom
Phone: 44 1225 383282
Fax: 44 1225 383282
Email: p.stallard@bath.ac.uk

Abstract

Background: Up to 18% of adolescents will engage in an act of self-harm before young adulthood, with the majority of acts occurring in private. Mobile apps may offer a way of providing support for young people at times of distress to prevent self-harm.

Objective: This is a proof-of-concept study designed to explore the safety, acceptability, feasibility, and usability of a smartphone app, BlueIce, with young people who are self-harming.

Methods: In this phase I open trial we will evaluate BlueIce, a smartphone app developed and coproduced with young people with lived experience of self-harm. BlueIce includes a mood-monitoring diary, selection of mood-lifting techniques based on cognitive behavior therapy and dialectical behavior therapy, and direct access to emergency telephone numbers. We will recruit young people (n=50) attending specialist child and adolescent mental health services with a current or past history of self-harm to trial BlueIce as an adjunct to their usual care. Questionnaires and interviews will be completed at baseline, postfamiliarization (2 weeks), and at follow-up (12 weeks after baseline) to assess safety, app use, and acceptability. Interviews will be undertaken with clinicians to assess the feasibility of BlueIce within a clinical setting.

Results: Recruitment occurred between May and November 2016. The recruitment target was 50, and by the beginning of November 54 young people had been referred.

Conclusions: This study is the first to evaluate an app specifically developed with young people for young people (under the age of 18 years) who self-harm. It will determine whether BlueIce is acceptable, how often it is used, and whether it is safe and does not have any unintentional adverse effects. This information will determine whether a feasibility trial to test recruitment, randomization, retention, and appropriate outcome measures should be pursued.

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KEYWORDS

self-harm; smartphone app; BlueIce; adolescents; CBT; DBT

Introduction

Overview

Self-harm is defined as intentional self-poisoning or self-injury, irrespective of type of motive or the extent of suicidal intent [1]. Self-harm is a risk factor for suicide. Although suicide rates in those under the age of 18 years are comparatively low, approximately half of those who commit suicide have been found to have a previous history of self-harm [2]. However, the

majority of self-harm in adolescence is self-destructive and often occurs without suicidal intent (nonsuicidal self-injury).

While suicide rates in this age group are low, self-harm is unfortunately common with community studies from many countries consistently reporting a lifetime risk of 13% to 18% [3-7]. Of those who self-harm, half will report multiple self-harming events [6]. For example, in a UK community survey of young people aged 12 to 16 years from 8 schools, 15% reported acts of self-harm over the past 12 months with 55% reporting self-harm over 2 consecutive 6-month episodes [8].

In community surveys in developed countries, self-cutting is the most commonly reported method of self-harm whereas self-poisoning is more common in those who present at accident and emergency departments [5,6,9]. However, comparatively few episodes of self-harm result in hospital presentations with most being undertaken in private and remaining hidden [10].

Although suicide is comparatively uncommon in adolescents, it is the second or third leading cause of death within this age group [10]. Self-harm is associated with an increased risk of mortality and suicide. A 10-year follow-up study in the United Kingdom of young people who presented at hospital following an episode of self-harm found that of those who subsequently died, half had committed suicide [11].

In terms of risk factors, self-harm is associated with a range of sociodemographic and educational factors (eg, gender, lower socioeconomic status, sexual orientation), life events (eg, trauma, abuse, family breakdown), and psychological factors (eg, depression, drug and alcohol misuse, impulsivity) [10].

Interventions for Self-Harm

A UK review by the National Institute of Health and Care Excellence (NICE) recommends that all children under 16 years of age attending hospital following self-harm should be admitted to a pediatric ward and assessed by an experienced mental health practitioner [1]. In terms of interventions, NICE recommends a 3- to 12-session psychological intervention with the aim of reducing self-harm. NICE recommends that it is tailored to individual need and could include cognitive behavioral, psychodynamic, or problem-solving elements [1]. However, comparatively few trials of interventions for children and adolescents who self-harm have been reported. A recent UK Cochrane review concluded that “there is not much evidence on which to draw conclusions on the effects of interventions for self-harm in this population“ [12]. The review found little support for group-based therapy but suggested that therapeutic assessment, mentalization, and dialectical behavior and cognitive behavior therapy warrant further evaluation. Finally, it recommended that any new therapeutic interventions should be developed in collaboration with patients to ensure patients’ needs are met.

Telemedicine

Telemedicine is the use of information and communication technologies to increase access to care and improve health outcomes [13]. Adolescents are familiar with and frequent users of technology. A survey by the Office of Communications, the regulatory body supervising the communications industry in the United Kingdom, found that nearly all young people aged 12 to 15 years (98%) have Internet access [14]. Approximately 90% of 15-year-olds have a smartphone with ownership increasing with age. Smartphones therefore offer an accessible way of delivering and supporting mental health interventions for this age group.

One particular area that has seen a phenomenal expansion in recent years is the development of smartphone apps. Increasingly these have been developed to help with a range of mental health problems [15]. However their development has significantly outpaced research, and the evidence for their efficacy is largely unknown [15]. In terms of self-harm, no smartphone apps have been specifically developed for young people (under the age of 18) who self-harm.

BlueIce Development

The development of BlueIce has followed the Medical Research Council framework for the development and evaluation of complex interventions [16]. The original idea was discussed with a group of young people who had a lived experience of self-harm. The young people thought that a smartphone app could improve self-management and provide a helpful way to manage distress and prevent self-harm at times of crisis.

The content of the app was informed by theoretical approaches that appeared promising in treating self-harm—in particular, cognitive behavior therapy (CBT) and dialectical behavior therapy (DBT). The structured nature of these therapies facilitated the incorporation of core therapeutic techniques into a mobile app. BlueIce therefore includes ideas from CBT (behavioral activation, thought challenging, and mood lifting activities) and DBT (mindfulness and distress tolerance).

Further meetings with young people focused on app content, design, and presentation. A beta version of BlueIce was produced which was reviewed by the young people and a group of child mental health professionals. Further recommendations for content and design were suggested and these were incorporated into the second beta version. This was reviewed again with the young people who positively endorsed the app.

BlueIce was developed for Android operating systems and was coded natively. Although it does not connect or interact with existing health care systems, data stored on BlueIce can be reviewed with the young person’s mental health clinician during routine clinical appointments.

Aims of the Study

The aim of this study is to undertake a phase I trial to explore the safety, acceptability, feasibility, and usability of BlueIce with young people aged 12 to 18 years who are self-harming.

Methods

Study Design

This is a phase I open trial where eligible young people will be invited by their mental health clinician to use BlueIce. The study was funded by the Health Foundation (2143 Oxford Health National Health Service [NHS] Foundation Trust), and the

protocol was approved by the NHS South West—Exeter Research Ethics Committee (reference 16/SW/0018).

Setting and Participants

The study will be undertaken in specialist child and adolescent mental health services (CAMHS) provided by Oxford Health NHS Foundation Trust. The Trust serves a wide geographical area that includes Bath and North East Somerset, Buckinghamshire, Oxfordshire, Swindon, and Wiltshire.

Eligible participants will be aged 12 to 18 years with a history of repeated self-harm. Participants may be currently self-harming (within the past 4 weeks) or have a history of self-harm and feel that they will harm themselves again. BlueIce is designed to be used alongside specialist CAMHS so young people must be in receipt of an ongoing face-to-face intervention.

Young people will be excluded if they have active suicidal ideation and are seriously contemplating or planning a suicide attempt. Given that we do not know whether BlueIce will have any unintentional adverse consequences, it would not be safe to test it with a high-risk group who are actively suicidal. Second, young people will be excluded if they are diagnosed with psychosis or have a significant learning disability which might impede their ability to use the app. Third, we will exclude young people who have been subject to abuse within the last 6 months or are the subject of a safeguarding investigation. Finally, BlueIce is only available in English and we will therefore exclude those who are unable to understand English.

Recruitment and Consent

Project information will be provided to all clinical teams and staff across Oxford Health. This will be followed by meetings with clinical teams and interested clinical staff to demonstrate BlueIce. Clinicians will be provided with project information sheets which they will be asked to discuss with eligible young people whom they think will benefit from BlueIce. The clinician will pass details of interested young people to the research team. The researcher will contact the young person to discuss the project and obtain written consent. For those under the age of 16, parental consent will also be required.

Intervention

BlueIce is an Android smartphone app that has been coproduced with young people who have self-harmed. It contains a personalized toolbox of strategies that are available to the young person 24/7. It is designed to be used as an adjunct to therapy and includes a mood diary, a section of personalized mood-lifting techniques, and emergency contact numbers.

Mood Diary

Young people are able to monitor their mood each day. For each mood rating, they have the option of adding a note to record any particular reason why they might be feeling as they do. Their rating and notes are saved in a calendar which the young person and therapist can review to look for changes and patterns over time.

Mood Lifting

Young people who rate their mood as low will automatically be routed to the mood-lifting section of BlueIce. They can access this at any time directly from the main menu. This section contains a menu of mood-lifting activities personalized according to the interests of the young person. The activities are designed to counter the common reasons why young people self-harm (to punish themselves, emotional relief, feeling hopeless) and draws on common methods used in CBT and DBT. The mood-lifting section includes 8 activities:

- Photographs, inspirational quotes, and pictures that are associated with happy memories can be uploaded and saved. These can be reviewed when low to help young people remember the positive things in their life.
- A music player is included where young people can upload and store music they enjoy and which has a positive effect on how they feel. This playlist can be readily accessed as a way of improving their mood.
- Young people can create a personalized list of physical activities they enjoy like going for a run or riding a bike or playing with siblings for review when they are low.
- Young people can create a list of activities—like making a cake, watching an episode of a favorite TV series, reading a book, playing with a pet—that can be reviewed when they are feeling down.
- Audio-recorded instructions for a 10-minute mindfulness session, calming visualization, and a quick controlled breathing exercise (4-7-8 breathing) are included. These can be used to help young people manage any unpleasant emotions or distressing thoughts.
- Young people can record any troubling thoughts that are racing through their heads into the thought diary. These can be directly typed into BlueIce where they are saved and can be reviewed with the clinician at a later date. This allows identification of any particular themes that could be addressed during face to face work with their clinician.
- This section draws on ideas from DBT and helps young people tolerate their distress. This includes instructions for an ice dive, a sensory toolbox, and a pros and cons balance sheet for self-harming.
- The final section contains the phone numbers of 3 to 5 people whom the young people could contact if they were feeling low and in danger of self-harming. These would be people who make them feel happy and those they could talk with about how they are feeling. This section prompts the young person to reach out to others.

Emergency Contacts

The final section contains phone numbers young people can call which provide direct access to emergency support both nationally and locally.

Study Procedure

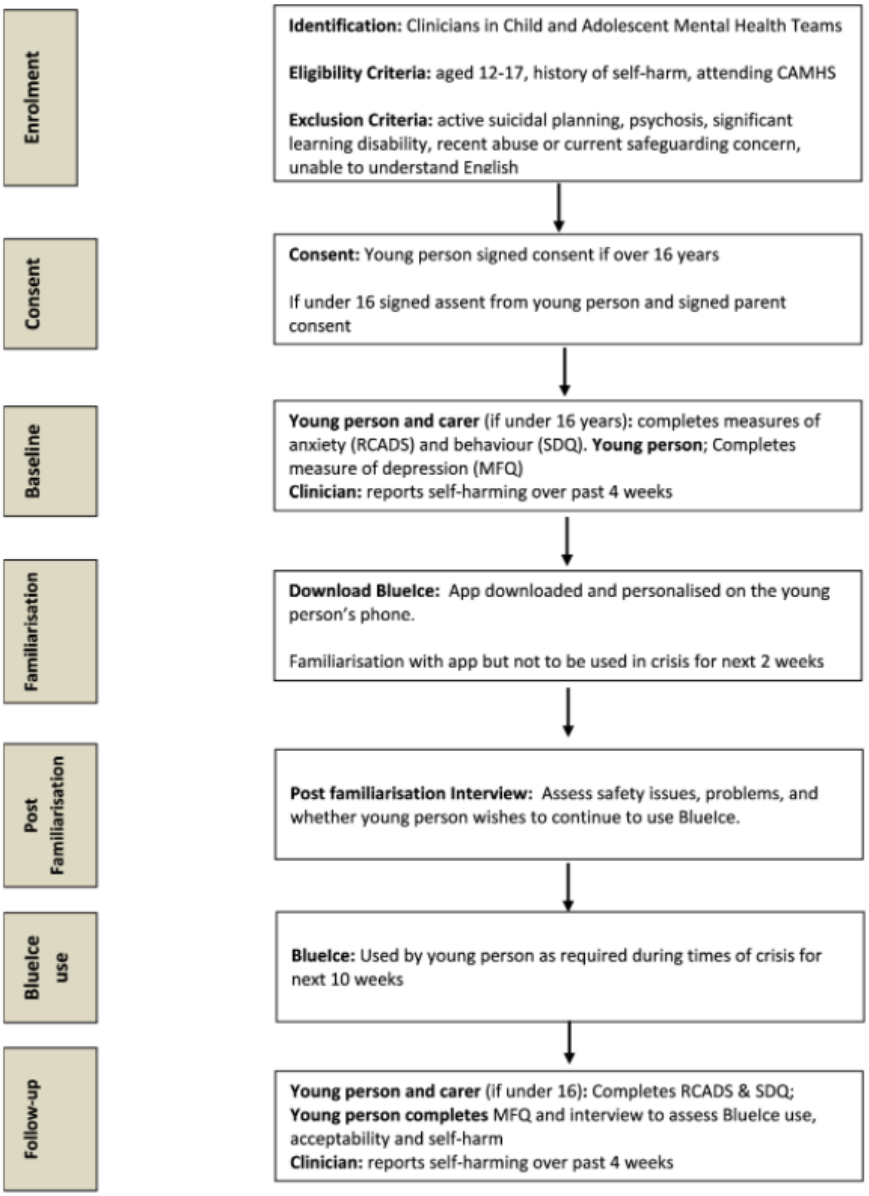
The study procedures are summarized in Figure 1. Clinicians will be invited to identify and discuss BlueIce with young people they were working with who meet inclusion criteria. If the young person is interested the clinician will contact the research team

and inform them whether the young person has self-harmed in the last 4 weeks.

The research team will arrange to meet with the young people and, if under the age of 16 years, their carers. The study will be discussed, informed consent obtained, and baseline assessments completed. BlueIce will then be downloaded on to the young person's phone and the sections in the mood lifter personalized.

In order to ensure safety, young people will be instructed to familiarize themselves with BlueIce but not to use it at times of crisis for the next 2 weeks. BlueIce will then be reviewed with the researcher after familiarization to discuss how they found the app and whether they encountered any problems. The young person will then choose to either continue using BlueIce for the next 10 weeks or to stop and have it removed from the phone. If they chose to use BlueIce, they can use it as often as they wish. Follow-up assessments will be completed with young people and the use and acceptability of BlueIce determined.

Figure 1. BlueIce study procedure. CAMHS: Child and Adolescent Mental Health Services; RCADS: Revised Child Anxiety Scales; SDQ: Strengths and Difficulties Questionnaire; MFQ: Mood and Feelings Questionnaire.



Outcome Measures

Mood

Young people and their carers (if under 16 years of age) will complete the Revised Child Anxiety Scales (RCADS) [17-19] and Strengths and Difficulties Questionnaire (SDQ) [20]. These provide an assessment of anxiety, depression, and behavioral problems. Young people will also complete the Mood and Feelings Questionnaire (MFQ) [21], a standardized measure to assess depression. All questionnaires will be completed at baseline and at follow-up after using BlueIce.

Safety

Semistructured interviews will be undertaken with young people postfamiliarization and at follow-up. These will focus on safety and in particular whether BlueIce worked as intended (ie, did not crash or freeze) and had no unintentional adverse effects. For example, constantly recording mood as low might increase thoughts of hopelessness and self-harm. Young people will also be asked to rate the extent to which BlueIce might make them self-harm and whether it might help.

Acceptability

Although BlueIce was developed with young people who had a lived experience of self-harm, we will assess whether the BlueIce layout and content are understandable and acceptable to those currently in crisis. This will be assessed during postfamiliarization and follow-up interviews and through ratings assessing ease of use, helpfulness, and whether to recommend BlueIce to a friend.

Usability

We will assess whether BlueIce can be easily downloaded and personalized on different Android phones. We will also check which parts of the app young people use and which they find most helpful.

Self-Harm

Information will be obtained from referring clinicians about whether the young person had been self-harming in the 4 weeks before using BlueIce and in the 4 weeks before the follow-up assessment. In addition, young people will be asked during the follow-up interview whether BlueIce had helped to prevent an episode of self-harm and if so, how many.

Feasibility

This will be assessed through the number of referrals per team and professional group and through interviews with referring clinicians. We will also undertake qualitative interviews with clinicians to determine usability, usefulness, and fit with clinical practice.

Sample Size

This is an initial feasibility study and as such no formal power calculation was undertaken. For this phase I safety trial we plan to recruit 50 young people, a sample that will be sufficient to reach saturation through analysis of data collected in semistructured interviews [22].

Statistical Analysis

We will describe the cohort in terms of age, gender, and previous self-harm and report recruitment, completion, and drop-out rates. Safety will be assessed by the percentage of participants who report problems, a worsening of mood, or an increase in self-harm. Mean and standard deviations of ratings (potential harm and help) will be reported.

Acceptability will be determined by satisfaction ratings and through analysis of semistructured interviews. Interviews will be audiorecorded and transcribed. They will then be analyzed using a predefined framework derived from the interview schedule and adapted and revised on the basis of participant responses [23]. The interviews will also assess usability and how often young people used the app and which features.

Feasibility will be assessed by examining referral flows by teams and professional groups. We will also interview referring clinicians to obtain their views about usability, usefulness, and fit with clinical practice.

Outcome data from standardized questionnaires and reported changes in self-harm will be treated as preliminary and will not be subject to extensive analysis. We will conduct an exploratory analysis using descriptive statistics, where appropriate, to report pre- and post-use changes.

Results

We have completed recruitment and are now undertaking post-use assessments.

Discussion

This study seeks to explore the safety, acceptability, feasibility, and use of a smartphone app for young people attending specialist CAMHS who are self-harming. Our study addresses an important problem and through the use of technology aims to empower young people to manage their unpleasant emotions and thoughts of self-harm at times of crisis. A particular strength of our intervention is the coproduction with young people who have a lived experience of self-harm. Young people have shaped the content, design, and appearance of BlueIce in order to ensure that it is acceptable and attractive to our intended users. A further strength of our design is the focus on evaluation and in determining safety. It is important that smartphone apps used as adjuncts to mental health interventions are subject to evaluation [24,25]. In particular, when dealing with sensitive issues such as self-harm, it is important to demonstrate that apps are safe and do not unintentionally cause any adverse events.

To our knowledge, this is the first smartphone app designed with and produced for young people under the age of 18 years who self-harm. Our study design does however have limitations—in particular our reliance on clinical staff to identify and recruit young people. Clinicians have been found to have negative views about eMental health as highlighted in studies looking at clinician attitudes to computerized interventions [26,27]. We are unsure about clinicians' views about smartphone apps as adjuncts to face-to-face care but are aware that uptake may be limited. We will attempt to minimize this risk through an active process of clinician engagement involving information-giving, demonstrations, and on-going email updates and informal meetings.

A second limitation is our reliance on retrospective self-report to assess the frequency of self-harm. Self-report may underestimate the number of events recalled, particularly for those young people who are engaging in regular and frequent harming. This limitation is acknowledged; although at this stage we are primarily focused on the app functionality and in assessing use, acceptability, and safety. Prospective reporting of self-harm (eg, through diaries) and objective measures of

self-harm (eg, accident and emergency attendances) will be considered in a subsequent phase II trial.

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Authors' Contributions

PS is the grant holder and principal investigator for the project. PS conceptualized the study design and drafted the manuscript. RG and JP are the researchers involved in the study. All authors read, contributed to, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CAMHS: Child and Adolescent Mental Health Services
CBT: cognitive behavior therapy
DBT: dialectical behavior therapy
MFQ: Mood and Feelings Questionnaire
NHS: National Health Service
NICE: National Institute of Health and Care Excellence
RCADS: Revised Child Anxiety and Depression Scale
SDQ: Strengths and Difficulties Questionnaire

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Protocol

Development and Feasibility Testing of PROMPT-Care, an eHealth System for Collection and Use of Patient-Reported Outcome Measures for Personalized Treatment and Care: A Study Protocol

Afaf Girgis[1,2], BSc (Hons), PhD; Geoff P Delaney[1,2,3], MBBS, PhD, MD; Anthony Arnold[1,4], BAppSc(MRS)RT; Alexis Andrew Miller[4,5], BSc, BMed, MInfCommTech (Res); Janelle V Levesque[1,2], BPsych (Hons), PhD; Nasreen Kaadan[1,3], BAppSc; Martin G Carolan[1,4,6], BSc (Hons), PhD; Nicole Cook[7], BPsych, MPsych (Clin), PGDip (Psych); Kenneth Masters[4], AdvDipBus; Thomas T Tran[1,3], BAppSc(MRS)RT; Tiffany Sandell[4], BSc, MPH, MSc (Health Management); Ivana Durcinoska[1], BBiotech, MIPH; Martha Gerges[1], BA (Psych); Sandra Avery[1,3], GradCert Business Technology; Weng Ng[1,3], BSc (Med), MBBS (Hons), PhD; Stephen Della-Fiorentina[8], MBBS; Haryana M Dhillon[9], BSc, PhD; Ashley Maher[10], BSc, MCS

[1]Centre for Oncology Education and Research Translation, Ingham Institute for Applied Medical Research, Liverpool, Australia
[2]Department of Medicine, South Western Sydney Clinical School, University of New South Wales, Sydney, Australia
[3]Liverpool Cancer Therapy Centre, Liverpool Hospital, Liverpool, Australia
[4]Illawarra Cancer Care Centre, Wollongong Hospital, Wollongong, Australia
[5]Centre for Oncology Informatics, University of Wollongong, Wollongong, Australia
[6]Illawarra Health and Medical Research Institute, University of Wollongong, Wollongong, Australia
[7]Cancer Institute New South Wales, Sydney, Australia
[8]Macarthur Cancer Therapy Centre, Campbelltown Hospital, Campbelltown, Australia
[9]Faculty of Science, Central Clinical School, The University of Sydney, Sydney, Australia
[10]Didymo Designs, Wollongong, Australia

Corresponding Author:
Afaf Girgis, BSc (Hons), PhD
Centre for Oncology Education and Research Translation
Ingham Institute for Applied Medical Research
Level 2, Ingham Institute Building
1 Campbell Street
Liverpool
Australia
Phone: 61 4 1214 2841
Fax: 61 2 9602 3221
Email: afaf.girgis@unsw.edu.au

Abstract

Background: Patient-reported outcome (PRO) measures have been used widely to screen for depression, anxiety, and symptoms in cancer patients. Computer-based applications that collect patients' responses and transfer them to the treating health professional in real time have the potential to improve patient well-being and cancer outcomes.

Objective: This study will test the feasibility and acceptability of a newly developed eHealth system which facilitates PRO data capture from cancer patients, data linkage and retrieval to support clinical decisions and patient self-management, and data retrieval to support ongoing evaluation and innovative research.

Methods: The eHealth system is being developed in consultation with 3 overarching content-specific expert advisory groups convened for this project: the clinical advisory group, technical advisory group, and evaluation advisory group. The following work has already been completed during this phase of the study: the Patient-Reported Outcome Measures for Personalized Treatment and Care (PROMPT-Care) eHealth system was developed, patient-reported outcomes were selected (distress, symptoms, unmet needs), algorithms to inform intervention thresholds for clinical and self-management were determined, clinician PRO feedback summary and longitudinal reports were designed, and patient self-management resources were collated. PROsaiq, a

custom information technology system, will transfer PRO data in real time into the hospital-based oncology information system to support clinical decision making. The PROMPT-Care system feasibility and acceptability will be assessed through patients completing PROMPT-Care assessments, participating in face-to-face cognitive interviews, and completing evaluation surveys and telephone interviews and oncology staff participating in telephone interviews.

Results: Over the course of 3 months, the system will be pilot-tested with up to 50 patients receiving treatment or follow-up care and 6 oncology staff at 2 hospitals in New South Wales, Australia. Data will be collected to determine the accuracy and completeness of data transfer procedures, extent of missing data from participants' assessments, acceptability of the eHealth system and usefulness of the self-management resources (via patient evaluation surveys and interviews), and acceptability and perceived usefulness of real-time PRO reporting (via oncology staff interviews) at the completion of the pilot phase.

Conclusions: This research investigates implementation of evidence into real world clinical practice through development of an efficient and user-friendly eHealth system. This study of feasibility and acceptability of the newly developed eHealth system will inform the next stage of larger scale testing and future implementation of the system as part of routine care.

ClinicalTrial: Australian New Zealand Clinical Trials Registry ACTRN1261500135294; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=369299&isReview=true (Archived by WebCite at http://www.webcitation.org/6lzylG5A0)

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KEYWORDS

patient-reported outcomes; eHealth, self-management; real-time report; oncology; patient-centered care; PROMPT-Care; electronic medical records; oncology information systems

Introduction

Patient reported outcome (PRO) measures have been widely used in a variety of settings including screening for depression, anxiety, and symptoms in cancer patients [1,2] and in the primary care [3] and rural settings [4]. There are many examples of computer-based applications that collect patients' responses and translate them in real time into a useable format for the treating health professional [1,2,5-8]. A systematic review undertaken by Chen et al [5] concluded that routinely collecting PRO measures enables better patient-centered care in cancer settings when a patient management plan is integrated with routine collection of PROs. This review identified strong evidence that well-implemented electronic PRO (ePRO) systems with timely feedback improved patient–health care provider communication and patient satisfaction and may also improve the monitoring of treatment response and detection of unrecognized problems [5]. The impact of ePROs on clinical and health service outcomes has also now been demonstrated with a large randomized controlled trial with cancer patients reporting significant outcomes including reduced emergency room visits, longer tolerability of chemotherapy, and improved survival [9].

We have previously published a discussion paper citing a lack of ePRO systems being implemented as part of routine oncology care in Australia and detailing our intention to develop an eHealth system, Patient-Reported Outcome Measures for Personalized Treatment and Care (PROMPT-Care), which has the potential to lead to improvements in patients' quality of life and health outcomes while reducing variations in cancer outcomes [10]. This PROMPT-Care system is based on a prototype system, PROsaiq, which was previously developed to import PRO surveys into a hospital's Oncology Information System (OIS) [11]. This protocol paper reports on the steps involved in developing this clinical system and the proposed testing of its acceptability and feasibility in 2 oncology care centers. At the time of publication, some of the work described was completed and some was pending.

The purpose of the PROMPT-Care eHealth system is to support the routine collection and analysis of PROs from cancer patients over time, from the time of being registered as a cancer patient, and make this information available to the patient and the health professionals involved in the delivery of their cancer care. The eHealth system will also deliver evidence-based self-management information to address patient-reported problems and empower patients to take a more active role in decision making and managing their ongoing care and recovery. Importantly, one of the key features distinguishing PROMPT-Care from previous eHealth systems used in the oncology setting is its integration into the hospital's point-of-care OIS.

The term "patient" used throughout this document encompasses all people diagnosed with cancer during and after their acute treatment phase including into longer term survivorship.

Methods

Study Design and Objectives

This is a feasibility study with the overall aim of developing and testing an integrated eHealth system to support and enable cancer patients to achieve and maintain improved health and well-being and better cancer outcomes.

The specific objectives are as follows:

1. Develop an eHealth system that is integrated into the hospital's OIS (MOSAIQ, Elekta Medical Systems, Sunnyvale, CA) to support assessment of cancer patients' PROs through the use of electronically administered standardized assessment tools, provision of real-time feedback of the results to the treating clinicians, and generation of links to self-management resources for patients that are tailored to their PROs. This

includes developing a production version of the PROsaiq prototype system [11].

2. Implement a pilot version of PROMPT-Care at 2 hospitals and test the feasibility and functionality of the system.

3. Test the acceptability of the pilot version of PROMPT-Care in a sample of cancer patients and clinicians at the 2 participating hospitals.

Setting

The feasibility study will be undertaken in the cancer centers of 2 public hospitals in New South Wales (NSW), Australia. Liverpool Hospital is the largest of the 6 hospitals in South Western Sydney Local Health District, a district with a population of over 820,000 people, comprising 12% of NSW residents. The communities in this district are socially, economically, culturally, and linguistically diverse, and the area contributes 10% of the total new cases of cancer load in NSW. Liverpool Hospital treats more than 81,000 patients annually. Wollongong Hospital is the largest of the Illawarra Shoalhaven Local Health District's 9 hospitals. This district has a population of more than 390,000 residents. and Wollongong Hospital, the region's tertiary referral hospital, treats more than 47,000 patients annually.

Ethics Approval and Consent to Participate

Ethics approval was obtained from the Human Research Ethics Committee of South Western Sydney Local Health District with site-specific ethics approvals obtained for Liverpool Hospital and Wollongong Hospital.

Development of the PROMPT-Care eHealth System

The PROMPT-Care system includes key features relating to system design, data collection, assessment reporting, and workflow integration that were identified from a review of 33 ePRO systems as being important to supporting a successful ePRO system [1]. We have previously summarized these recommended features [10].

Establishing Clinical, Technical and Evaluation Advisory Groups

A total of 3 expert groups were convened to inform the development and evaluation of the PROMPT-Care system: a clinical advisory group (CAG) and a technical advisory group will guide the content, development, and functionality of the system including transformation of PROsaiq from prototype to production, and an evaluation advisory group will guide the feasibility and acceptability testing of the developed system. Additionally, special working groups were convened, as required, to advise on specific aspects of the eHealth system development and content. The membership and roles and responsibilities of these groups are presented in Table 1.

Table 1. Patient-Reported Outcome Measures for Personalized Treatment and Care (PROMPT-Care) project advisory group membership, roles, and responsibilities.

Membership and expertise	Roles and responsibilities	Special working groups
Clinical advisory group		
Core members (n=38) with a range of expertise: radiation and medical oncology, nursing, allied health, psycho-oncology, hospital management, cancer systems innovation management, OIS[a] and electronic records management, and research.	Responsible for the overall content and implementation of PROMPT-Care[b] as part of routine care, including the clinician feedback system and the patient self-management system. The CAG[c] is responsible for decisions about: -The outcomes of cancer patients to be collected over time -The PRO[d] measures to collect the agreed patient outcomes -The frequency of measurement of the PROs -The modes of delivery of the PRO information to health professionals involved in the delivery of patient care in both summary and longitudinal format -The PRO score thresholds which will trigger recommended actions by the clinical team -The content of the evidence-based recommendations to be generated in response to each PRO that is above the predetermined threshold -The suite of evidence-based self-management information that will address patient-reported problems and enable patients to take an active role in decision making and managing their ongoing care and recovery	A clinical algorithms working group will be specifically focused on development of algorithms and evidence-based recommendations for clinicians, which are required for programming the clinician feedback reports. A self-management working group will identify suitable self-management resources for patients using the PROMPT-Care system.
Technical advisory group		
Core members (n=23) with expertise in cancer systems innovation, OIS and electronic records management, hospital information management and technical design, oncology informatics, and medical and radiation oncology.	Responsible for overseeing the development and implementation of the production information technology system (PROsaiq) and infrastructure to support PRO data capture and management including: -Integration of the pilot PROMPT-Care system with the existing hospital information technology systems and OIS to support real-time data access to all members of the care team, including network configuration, with special consideration of hospital security firewalls -Delivery of a patient assessment interface suitable for use on both desktop and mobile technology (eg, tablets) to support PRO data capture either within the clinic or from home at predefined periods	A MOSAIQ reporting working group will be specifically focused on display of the PRO data in MOSAIQ.
Evaluation advisory group		
Core members (n=10), with wide-ranging research and statistical expertise, particularly in psycho-oncology and clinical research.	Responsible for developing an evaluation plan to document the feasibility and acceptability of the PROMPT-Care system.	

[a]OIS: oncology information system.

[b]PROMPT-Care: Patient-Reported Outcome Measures for Personalized Treatment and Care.

[c]CAG: clincial advisory group.

[d]PRO: patient-reported outcome.

Selection of Patient-Reported Outcome Measures and Assessment Frequency

The CAG was consulted about which PRO domains were most important for informing patient care and amenable to evidence-based intervention. The CAG was presented with the following domains to consider: symptoms, distress, anxiety, depression, quality of life, and unmet needs. Following the selection of the domains to be assessed, a comprehensive review of specific measures was undertaken to select the final core set

of PRO measures. PRO measures that met the following recommended properties were favored for inclusion in the PROMPT-Care survey: simple, brief, informed by patients, reliable, valid and responsive to change, easily scored and interpreted, and free to use as well as those which predicate clinical action [12]. In an effort to minimize patient burden, an item map was developed during this phase to identify any significant duplication of items across the short-listed measures, and any redundant measures were excluded from the core PRO assessment. The final measures selected were: the Distress Thermometer (DT) [13] with the problem checklist [14], the Edmonton Symptom Assessment Scale (ESAS) [15] and the Supportive Care Needs Survey–Screening Tool 9 (SCNS-ST9) [16]. However, it is noteworthy that once the system has been set up and tested, changes in the PRO measures can be made in the future (ie, the initial decisions regarding PROs are not locked in long-term).

The CAG was also consulted about the frequency of patients completing the PRO assessments, with consideration given to (1) the timeframe for the response options for each of the selected PRO measures (eg, within the past week), (2) allowing sufficient time between 2 assessments for clinical recommendations to have been actioned, (3) minimizing patient burden and therefore improving compliance, and (4) whether the assessment frequency should differ for patients on-treatment versus those in follow-up. The CAG advised on the frequency of assessments for this phase of the PROMPT-Care program while acknowledging that the feasibility and acceptability testing would inform future assessment frequency.

Development of Algorithms to Guide Response to Patient-Reported Outcomes

For each of the selected PRO measures, item and scale cut-off scores differentiating between normal (below threshold) and clinical (above threshold) responses were determined from published sources [14,16,17]. These threshold scores informed the development of clinical and self-management recommendations. A multidisciplinary clinical algorithms working group was convened (medical and radiation oncologists, social worker, clinical psychologist, care coordinators) to develop actionable recommendations for each item that breaches the clinical threshold. A total of 15 actionable recommendations were developed after consultation with published guidelines [14,18]. These recommendations were tailored to the specific issue of concern (eg, symptom vs information need), and they ranged from "No action required" to "Clinically address as appropriate OR refer to [*types of specialties indicated here, depending on issue*] for further assessment and care."

Development of Patient-Reported Outcome Feedback Reports

The PROMPT-Care system is designed to allow any oncology staff member from the participating cancer centers to access their patients' PRO assessment reports. A total of 2 report formats were developed in consultation with the CAG members: (1) a summary report of the patient's most recent PROMPT-Care survey, which included recommendations for the care team to address the patient-reported concerns and (2) a longitudinal report summarizing the PROs over time to allow the clinical team to identify trends and determine whether previously implemented interventions have addressed patients' issues of concern. Consideration was given to the content and presentation of the feedback reports with a focus on minimizing any need for interpretation of scores and highlighting issues of concern (scores above predetermined thresholds) in red to readily draw attention to them. Refer to Multimedia Appendices 1 and 2 for examples of the clinician summary and longitudinal feedback reports.

Collation and Review of Patient Self-Management Resources

The PROMPT-Care assessment measures items in the domains of physical well-being (eg, fatigue, pain, mouth sores), emotional well-being (eg, anxiety, depression, loss of interest in activities), social and family well-being (eg, support from family and friends, problems with partner), and practical support (eg, transport, housing, being informed about test results). A self-management working group was established as a subgroup of the CAG to identify suitable, readily available self-management resources in each of these domains as well as in the "maintaining health and well-being" domain for general health issues. Identified resources were systematically reviewed on the basis of their quality (language used, links active and relevant, peer-reviewed resource, HonCode certification [19], currency, applicability and objectivity). Each resource was reviewed by a member of the working group, and the results were collated on an evaluation form that outlined whether or not the resource was to be included in the pilot project. Resources were sought from local NSW cancer websites and organizations in the first instance followed by reputable Australian sources and finally from international cancer organizations. These self-management resources will be accessible to participating patients via 5 domain-specific pages hosted on the Cancer Institute NSW (CINSW) eviQ website [20], with patients' responses to the PROMPT-Care assessment determining which pages they were able to access.

Participants

As this is a feasibility study, staff will be selected on the basis of their willingness to comprehensively test the PROMPT-Care system and provide feedback to inform any modifications required for the next phase of research. Clinicians will be asked to identify eligible patients for the pilot study who they perceive would also be willing to provide comprehensive feedback on the pilot PROMPT-Care system. Hence, the participant selection was purposive rather than representative.

Eligible patients are people who are either currently receiving cancer care (including follow-up care) or have recently been diagnosed with cancer and are scheduled to commence cancer treatment at one of the participating sites. Eligibility criteria include a confirmed diagnosis of cancer, age 18 years or over, cognitively able to provide informed consent and understand the surveys, and sufficient skills to complete the survey in English. Exclusion criteria are having a diagnosis of a blood cancer and not having access to the Internet outside of the clinic.

All staff who provide care in the oncology departments at the participating hospitals are eligible to participate. However, as

this is a small feasibility study, 3 clinicians from each hospital (6 in total) who were not directly involved in the development of any aspects of the PROMPT-Care system will be invited to participate. In this phase of research, only 3 staff were ineligible to participate due to their direct, rather than advisory, role in building the technical or clinical components of the PROMPT-Care system.

Measures

The system's functionality will be assessed over a 3-month period with some patients expected to complete only 1 PROMPT-Care assessment during this period (if recruited later in the study) and some completing up to 3 assessments (if recruited at the start of the study).

- The accuracy and completeness of data transfer procedures (from the point of the patient completing an assessment to a report appearing via MOSAIQ) will be assessed by comparison of data received by MOSAIQ to data presented in the clinical feedback reports.
- The extent of missing data from participants' assessments will be assessed through examination of the PROMPT-Care reports to determine whether there is any systematically missing data.

In this study, the main purpose of assessing acceptability is to identify any modifications necessary for improving patient and provider uptake of the system in the next phase of research. Hence, acceptability of the system to patients and staff will be assessed as follows:

- Patients will complete an evaluation survey and interview at the end of the pilot phase to determine their perceptions of acceptability of the eHealth system and usefulness of the self-management resources.
- Cancer center staff directly involved in the pilot phase will participate in an evaluation interview at pilot study completion. The interview will focus on their perceptions of the acceptability and perceived usefulness of the real-time PRO reporting.

Procedure

Oncology Team Training

During the set-up phase, oncologists and other staff (including nurse care coordinators and allied health staff) from the 2 participating cancer centers will be introduced to the PROMPT-Care program through presentations made by the chief investigator and directors of cancer services at both sites. They will receive training resources which include background information about the purpose of PROMPT-Care, the battery of PROs and interpretation of their outcomes, information on how to access the summary and longitudinal reports via their OIS, and strategies for discussing the PROMPT-Care outcomes with the patient. One-on-one and group meetings will be held with all clinicians involved in this feasibility phase to facilitate familiarity with and high utility of the PROMPT-Care system.

Patient Recruitment

Given the small number of patients required for the feasibility study, participating clinicians will review their patient lists for the upcoming 4 to 6 weeks to identify patients who meet the eligibility criteria. Research staff will then mail an information and consent pack to eligible patients and will telephone patients 2 weeks after mail-out to confirm receipt of study materials, answer any questions about participation, and initially obtain verbal consent. Patients who require a replacement invitation pack will be sent another one immediately. Patients who return a signed consent form or who provide verbal consent when phoned by research staff will be asked to attend a PROMPT-Care appointment 20 minutes prior to their upcoming scheduled appointment at the cancer center in order to complete study paperwork (including written consent if not already received) and their first PROMPT-Care assessment. Patients who are unable to be reached before their next scheduled clinic appointment or who require more time to consider their participation will have the opportunity to consent at a later time and complete a PROMPT-Care assessment prior to another upcoming clinic appointment. Research staff will be available to assist patients who need help completing the surveys.

PROMPT-Care Assessments

An assessment schedule will be established when the participant enters the study that indicates the frequency and pattern of assessments that the participant will receive. Patients who are on-treatment will complete the PROMPT-Care survey every 2 to 4 weeks, depending on the schedule of their review appointments. Patients on follow-up will complete assessment approximately monthly. It was agreed that patients completing the PROMPT-Care survey every 2 to 3 weeks would complete only the DT/Checklist and ESAS on every occasion with the SCNS-ST9 added to the battery for every second assessment, as that measure has been validated using a 4-week time frame. Participants completing the PROMPT-Care survey on a monthly basis would always complete the full assessment (ie, DT/Checklist, ESAS, and the SCNS-ST9).

Patients who are attending the clinic will complete the PROMPT-Care survey in the waiting area using an electronic tablet device provided by the research team. Follow-up patients will typically complete their PROMPT-Care survey from home via a link sent by email. However, if follow-up patients are attending the clinic for a review appointment, they will complete their monthly survey while in the waiting area. As this is a pilot project to determine the feasibility and acceptability of the PROMPT-Care system, patients who are due to complete their PROMPT-Care surveys from home will be sent a reminder email if they have not completed it within the requested timeframe (48 hours).

Access and Review of Reports

To facilitate rapid access and review of the patients' PRO reports, all patients participating in this PROMPT-Care feasibility study will be flagged as "PROMPT-Care Trial" participants on the OIS used by the participating sites. Clinicians are instructed to access the report during the consultation, review any issues flagged as problematic by the patient (ie, scores above threshold), discuss these with the patient, and take any appropriate actions to address the issues.

Patient Self-Management

Upon completion of the PROMPT-Care assessment, patients will receive an email with links to the website page(s) for each domain in which they breached threshold scores on any of the items in that domain. For example, if any of the physical domain items were breached, the link to that page would be included in the patient's email; if not, that link would be excluded. Patients who scored below threshold on all items would only receive the link to a "maintaining health and well-being" page.

Evaluation of Acceptability of PROMPT-Care

The purpose of the acceptability assessment is to identify any modifications required to the PROMPT-Care system in preparation for phase 2 of our research. Patients and oncology staff will participate in the assessment of system acceptability.

Cognitive interviews are a technique that will be used to assess patient understanding of the survey questions and response options. This technique requires participants to verbalize their thoughts as they process and answer questions in an attempt to identify issues pertaining to comprehension, inability to retrieve relevant data to accurately answer questions, errors in wording, and whether there is a discrepancy between the lived experience and response options in the survey [21]. The PROMPT-Care study will use a combined think-aloud and verbal probing technique [22] with standardized verbal prompts at various parts of the survey while also allowing spontaneous probes based on participant observations (eg, I noticed you started several thoughts when considering that answer. Can you tell me a bit more about them?) and conditional probes (eg, I noticed you paused for a long time before you answered. Could you tell me why?). A subset of participants will volunteer to take part in the cognitive interviews, which will be conducted during the first time patients complete the PROMPT-Care measures. The cognitive interviews will be recorded using Camtasia (TechSmith Corp) software and are expected to take approximately 45 minutes.

Participating patients will be asked to complete an evaluation survey and invited to participate in a brief telephone interview to determine their views on the eHealth system and the usefulness of the self-management resources at study completion.

Oncology hospital staff who have had direct contact with PROMPT-Care feasibility study patients will be invited to participate in a brief semistructured telephone interview to assess their views on the eHealth system at study completion. The interview will focus on determining staff's perceptions of technical issues relating to ease and timeliness of accessing the PROMPT-Care reports, usefulness of the reports' content and format, perceived impact (positive or negative) on workload, and perceived need for training to support wider scale implementation of the PROMPT-Care system.

Results

Descriptive data will be collected to inform accuracy and completeness of data transfer from the PROMPT-Care surveys to the OIS. All interviews with patients and oncology staff will be audiorecorded and transcribed verbatim with quotes extracted indicating patient and staff reflections on their engagement with the PROMPT-Care system and identification of access barriers or problems. Cognitive interviews will be reviewed and patient cognitive errors identified to highlight potentially problematic elements of the survey.

Discussion

This research investigates implementation of evidence into real world clinical practice through development of an efficient and user-friendly eHealth system to facilitate (1) PRO data capture, (2) data linkage and retrieval to support clinical decisions and patient self-management, and (3) data retrieval to support ongoing evaluation and innovative research. The system includes PROs which have been identified by a clinical advisory group as being appropriate and relevant for the clinical setting, overcoming documented barriers of acceptability and relevance [5]. Integration of the PRO measures into the existing hospitals' OISs enhances their relevance and usefulness in informing routine cancer care.

The data collected will inform the feasibility and acceptability of this system-level strategy and identify barriers which should be addressed to facilitate wider implementation of this system in clinical practice. Once fully established, the accumulated data from the PROMPT-Care system will inform population-level needs of cancer survivors to identify potential gaps in care. The systematic approach to data collection over time will also allow the assessment of the impact of changes in service delivery over time. In the future, the system can be adapted to collect PROs from the non-English–speaking cancer community, thereby extending our understanding of the needs of this vulnerable and underresearched group.

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prior to publication. The funding bodies were not involved in the overall design of the feasibility study; the collection, analysis, and interpretation of data; or the writing of this manuscript.

Authors' Contributions

All authors contributed to aspects of the development and content of the PROMPT-Care system and its implementation in participating centers, and all reviewed this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Clinician summary feedback report.

[PDF File (Adobe PDF File), 114KB - resprot_v5i4e227_app1.pdf]

Multimedia Appendix 2

Clinician longitudinal feedback report.

[PDF File (Adobe PDF File), 111KB - resprot_v5i4e227_app2.pdf]

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Abbreviations

CAG: clinical advisory group
CINSW: Cancer Institute New South Wales
DT: Distress Thermometer
ePRO: electronic patient-reported outcome
ESAS: Edmonton Symptom Assessment Scale
NSW: New South Wales
OIS: Oncology Information System
PRO: patient-reported outcome
PROMPT-Care: Patient-Reported Outcome Measures for Personalized Treatment and Care
SCNS-ST9: Supportive Care Needs Survey–Screening Tool 9 items

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Protocol

Quality of Mobile Phone and Tablet Mobile Apps for Speech Sound Disorders: Protocol for an Evidence-Based Appraisal

Lisa M Furlong[1], BSLT (Hons); Meg E Morris[2,3], PhD; Shane Erickson[1], PhD; Tanya A Serry[1], PhD

[1]School of Allied Health, Discipline of Speech Pathology, La Trobe University, Bundoora, Australia

[2]Healthscope Northpark Private Hospital & La Trobe University, Bundoora, Australia

[3]Centre for Sport & Exercise Medicine Research, Bundoora, Australia

Corresponding Author:
Lisa M Furlong, BSLT (Hons)
School of Allied Health
Discipline of Speech Pathology
La Trobe University
Kingsbury Drive
Bundoora, 3086
Australia
Phone: 61 457645539
Fax: 61 394791874
Email: l.furlong@latrobe.edu.au

Abstract

Background: Although mobile apps are readily available for speech sound disorders (SSD), their validity has not been systematically evaluated. This evidence-based appraisal will critically review and synthesize current evidence on available therapy apps for use by children with SSD.

Objective: The main aims are to (1) identify the types of apps currently available for Android and iOS mobile phones and tablets, and (2) to critique their design features and content using a structured quality appraisal tool.

Methods: This protocol paper presents and justifies the methods used for a systematic review of mobile apps that provide intervention for use by children with SSD. The primary outcomes of interest are (1) engagement, (2) functionality, (3) aesthetics, (4) information quality, (5) subjective quality, and (6) perceived impact. Quality will be assessed by 2 certified practicing speech-language pathologists using a structured quality appraisal tool. Two app stores will be searched from the 2 largest operating platforms, Android and iOS. Systematic methods of knowledge synthesis shall include searching the app stores using a defined procedure, data extraction, and quality analysis.

Results: This search strategy shall enable us to determine how many SSD apps are available for Android and for iOS compatible mobile phones and tablets. It shall also identify the regions of the world responsible for the apps' development, the content and the quality of offerings. Recommendations will be made for speech-language pathologists seeking to use mobile apps in their clinical practice.

Conclusions: This protocol provides a structured process for locating apps and appraising the quality, as the basis for evaluating their use in speech pathology for children in English-speaking nations.

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KEYWORDS

speech therapy; medical informatics; rehabilitation; mHealth, speech sound disorders

Introduction

mHealth

At the beginning of 2016, there were an estimated 7.4 billion mobile subscriptions worldwide, of which 3.4. billion were mobile phone subscriptions [1]. With the exponential increase in the use of mobile devices globally, there is increased interest from speech-language pathologists (SLPs), clients, and their families regarding how mobile apps can be used to enhance the management of childhood speech sound disorders (SSD).

The Global Observatory for eHealth of the World Health Organization defines mHealth as "medical and public health

practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants and other wireless devices" [2]. mHealth apps are software programs developed for handheld devices used to provide advice around prevention of disease and healthy living, to screen and support self-management of chronic diseases (eg, asthma, diabetes, cardiovascular disease), to support adherence to treatment regimes, promote behavior change, educate patients, and to offer providers and consumers access to health care–related information and services [3-7].

Mobile Apps for Speech Sound Disorders

For SLPs, mobile apps for SSD are becoming prevalent in clinical practice [8]. There is an opportunity for mobile apps to assist in the clinical management of SSD, for example, by supplementing speech therapy, increasing practice time, offering biofeedback or information relating to the accuracy of the user's attempt, enhancing families' engagement with speech therapy, and by strengthening SLPs' ties with clients by offering them extended treatment throughout the day [8]. Mobile apps are arguably cost effective, accessible, and convenient [7]. For SLPs, apps allow access to otherwise expensive equipment like decibel readers and voice recorders, at an affordable price. Apps are easy to store and transport, and are durable, unlike traditional paper-based resources and games, which are subject to wear and tear. Apps also save time, offering SLPs the convenience of automatic record keeping and monitoring of progress (eg, tallies/scoring) as well as by reducing SLPs' preparation time. Many apps also have the option to customize or personalize particular features (eg, by adding personal photos and pictures).

However, the magnitude and rapid explosion of available apps poses a challenge for how SLPs and clients can find them and determine which ones to use. Due to the constraints of clinical practice, SLPs do not always have the time to find suitable apps or to critically appraise their quality. The resources available to SLPs and other consumers (eg, parents, caregivers, teachers) to choose or recommend particular apps can be scant. Instead, SLPs and other consumers may have to rely on subjective 'star rating systems' or user reviews, which may not accurately reflect the efficiency, effectiveness, or quality of the app. They are unlikely to be able to ascertain the extent to which the app was developed in reference to principles of evidence-based practice [7].

Children with SSD have "any combination of difficulties with perception of speech sounds, articulation/motor production, and/or phonological representation of speech segments (consonants and vowels), phonotactics (syllable and word shapes), and prosody (lexical and grammatical tones, rhythm, stress and intonation)" [9]. To promote gains in speech production accuracy and reduce the risk of later social, academic, or emotional difficulties [10,11], these children benefit from frequent, effective, and intensive therapy [12]. The efficiency and effectiveness of therapy is dependent on a range of factors relating to service delivery (eg, therapy setting, therapy schedule, family support and involvement), client factors (eg, age, motivation, attention, self-awareness), and the treating SLP (eg, experience, expertise) [13].

The use of mobile apps as a technology-based intervention has the potential to influence some of these factors. They have the potential to influence or enhance the efficiency and effectiveness of traditional therapy. In other domains of speech pathology, the use of technology-based interventions has been shown to increase intervention intensity [14,15], which may allow clients to reach expected outcomes earlier but without the need for simultaneous increased direct contact time with a SLP. Technology-based interventions allow for practice between therapy sessions in a variety of settings [16,17], which may be particularly beneficial in generalizing communication skills. Using technology has also been shown to increase enjoyment, motivation, and compliance for therapy both within [18,19] and outside of the clinic [20].

Such benefits have been demonstrated in recent studies, which have specifically evaluated health-related mobile apps, for example, for the self-management of chronic conditions (eg, diabetes, asthma, depression) [21], for treatment adherence in patients with bipolar disorder [22], and for the provision of lifestyle interventions for weight-loss in cancer survivors [23].

An initial step in understanding how mobile apps can be used in to enhance the management of SSD is to identify mobile apps that are currently available for this client population. The evidence base for use of mobile apps in the management of childhood SSD is sparse. Despite there being a number of Web-based app catalogues, reviews, blogs, and recommendations for the use of mobile apps in speech pathology (typically authored by SLPs); to the authors' knowledge, there are no published reviews on this topic. While the use of mHealth holds promise for this client population, the feasibility of implementing mHealth depends on the quality of available apps.

Aim

We provide the protocol for a systematic review of currently available mobile apps for children with SSD. A systematic process of selection and evaluation of apps from the app stores of the 2 largest operating platforms will take place. Two certified practicing SLPs will evaluate the included apps using a structured quality appraisal tool. This shall enable a quality assessment of available apps across the indicators of engagement, functionality, aesthetics, information quality, subjective quality, and perceived impact [24]. This content will be summarized and presented in a way that aids decision making for both SLPs and consumers when selecting an app for this client population.

Methods

Design

The systematic review will be conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). PRISMA is an evidence-based minimum set of items designed to help authors improve the reporting of systematic reviews and meta-analyses. Since its inception, it has been applied to other types of research (eg, evaluations of interventions) and has recently been applied in a review of health-related mobile apps [25].

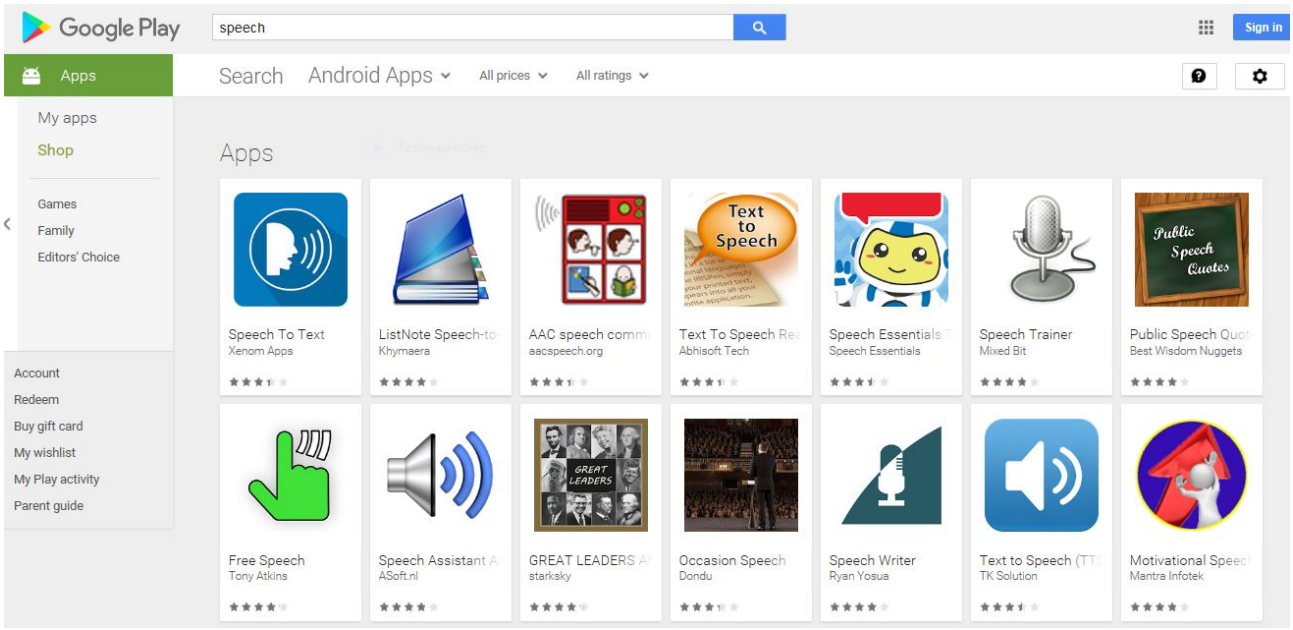
Sources, Search Terms, and Search Strategy

The Google Play store and Apple iTunes Store will be searched. These 2 stores have been selected because they are linked to the 2 most widely used operating platforms, Android and iOS. The selection of these operating platforms is based on their substantial share in the mobile app market. According to the International Data Corporation shipment figures, the most popular operating platforms by market share in the second quarter of 2015 were Android (82.8%) and iOS (13.9%) [26]. While this information is specific to the worldwide mobile phone market, these data support our rationale to use these 2 operating platforms in our review of mobile apps for both mobile phones and tablets. Previous reviews evaluating health-related mobile apps have also sourced apps solely from these 2 operating platforms [7,27,28].

Using the Web interface of the Google Play and Apple iTunes stores, a list of defined terms will be entered into the search fields. This method was chosen following phone consultations with specialists at Apple Support and Google Play. This search method has also been used in other studies evaluating mobile apps in the areas of asthma [27], bipolar disorder [1,7], and health care–associated infection prevention [28]. The search terms were defined in consultation with experts in the field of childhood SSD and app specialists from Apple Support and Google Play. In the Apple iTunes Store, the search terms will be entered within 2 separate categories: apps for iPhone and apps for iPad. In the Google Play store, search terms will be entered only once as there is no capacity to search by device. Rather, apps will be later categorized according to device compatibility.

Search terms include relevant synonyms and layperson terms to account for the wide variety of consumers accessing the app stores. The search terms are: “speech, phonology, phonological, articulation/artic, talk, pronunciation, speak, say, chat, speech therapy, speech pathology.” Figure 1 shows an example search of the Google Play store.

Figure 1. Example search of Google Play store. Google and the Google logo are registered trademarks of Google Inc., used with permission.



Eligibility Criteria and App Selection

The aim of the selection process is to find mobile apps that can be used in the management of childhood SSD. This process will be performed using the following eligibility criteria: provision of activities or tasks requiring production of speech by the user (ie, not just listening or auditory discrimination tasks), developed for speakers of English, free or paid, running on Android or iOS, and available on mobile phone or tablet. Exclusion criteria are: apps that provide speech production training for second language learners (ie, accent modification), apps that teach foreign languages, speech to text/text to speech apps, alternative and augmentative communication apps, apps designed for clients with voice disorders, apps designed to develop receptive or expressive language skills (eg, following directions, semantics, syntax), and apps providing assessment only. To screen apps for inclusion in the review, a 3-step process will be used: (1) collation, (2) broad screening, and (3) focused screening.

Collation of Titles Generated by the Search

A research assistant will enter the defined search terms into the search field of the Web interface for both the Google Play and Apple iTunes stores. The titles and icons of all resulting apps of all resulting apps will be entered into a spreadsheet, organized according to the app store in which they were located. Duplicate applications using different search terms from the same app store will be removed. For apps that are compatible with both tablets and mobile phones, both will be included to investigate the differences that may exist between the 2 versions.

Broad Screening

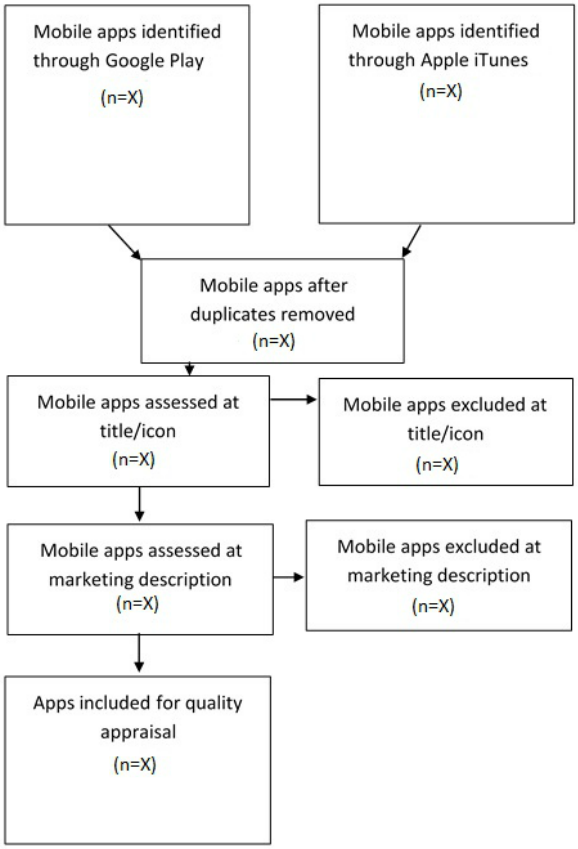
First, manual inspection of titles within the spreadsheet will be screened independently for inclusion criteria by 2 independent reviewers; both certified practicing SLPs. Following this, reviewers will meet and each present a list of apps for inclusion and subsequent screening. Discrepancies between the lists will be identified and discussed until consensus can be reached. If

consensus cannot be reached, consultation with a third reviewer will occur. Majority rule will be used to determine inclusion.

Focused Screening

The research assistant involved in step 1 of the screening process will return to the Google Play and Apple iTunes stores to extract the marketing description of all apps included at broad screening so that further screening can take place. Marketing descriptions will be entered into the same spreadsheet used in step 2, alongside the app title, icon, and source (app store). The same 2 reviewers involved in step 2 (broad screening) will independently review the full marketing description of the included apps within the spreadsheet. Apps will be selected based on the eligibility criteria described above. A list of apps for qualitative assessment will be compiled independently by each reviewer. Reviewers will meet to discuss apps for final inclusion. Consensus will be reached through discussion. If consensus cannot be reached, a third reviewer will be consulted. Majority rule will be used to determine inclusion. Apps meeting inclusion criteria at this final screening stage will be downloaded for further evaluation. Figure 2 displays the search and selection strategy

Figure 2. Search and selection process.



Data Extraction

Apps meeting inclusion criteria will be downloaded onto 4 devices: a Samsung Galaxy Tab A 8.0 WiFi 16GB (Android Version 5.0 [Lollipop]), an iPad 3 (iOS Version 9.3.4), an Android phone (to be specified), and iPhone 5S (iOS Version 9.3.4) for complete assessment. App classification data will be extracted from the marketing description in the app stores by the first author (involved in the screening process) and entered into a spreadsheet: app name and version, time of latest update, app update frequency (average), number of updates, rating current version/all versions, developer, number of ratings for current versions/all versions, cost (basic version/upgrade version), platform, marketing description [24], and device compatibility. A second reviewer will independently extract the same data for 10% of the included apps. Interrater reliability for data extraction will be determined by comparing the 15 data points.

Data Analysis

The quality of the apps will be evaluated by the 2 reviewers involved in the screening process, using the Mobile Application Rating Scale (MARS) [24]. Both reviewers are certified practicing SLPs with clinical experience in the management of childhood SSD. The MARS is a tool for assessing the quality of mHealth apps. It was developed by an expert multidisciplinary team from the Institute of Health and Biomedical Innovation and Queensland University of Technology, as part of an Australian Government Initiative [24]. The MARS evaluates app quality using a 5-point scale (1-inadequate, 2-poor, 3-acceptable, 4-good, 5-excellent) across the indicators of: engagement, functionality, aesthetics, information quality, subjective quality, and perceived impact [24]. The MARS provides a total mean score for the overall quality of an app. The highest potential mean score is 145 (29 questions across 6 indicators). Mean scores can also be calculated for each indicator to clearly identify the strengths and weaknesses of the app.

In its 2014 pilot study, the MARS total score assigned to the 50 apps included in the pilot, achieved high levels of interrater reliability (two-way mixed intraclass correlation coefficient [ICC]=.79; 95%CI 0.75-0.83) [24]. Concurrent validity was determined by comparison of the MARS total score with the Apple iTunes App Store star rating for 15 of 50 apps involved in the pilot. A moderate correlation between the MARS total score and the Apple iTunes star rating (r_{15}=.55, P<.05) [24] was reported.

In accordance with the recommendations provided by the MARS developers, the 2 raters involved in the quality assessment of the included mobile apps will complete the Web-based MARS training module prior to the quality assessment taking place. Completion of this training module will ensure that the raters understand the purpose of the MARS and how to use it. Completion of this training module should also improve interrater reliability. In keeping with the guidelines provided by the MARS developers, assignment of app quality ratings will initially be piloted with 5 apps not included in the review to establish interrater reliability [24]. A two-way mixed ICC will be used to determine how consistent the 2 raters are, relative to each other. An ICC above 0.75 is indicative of "good reliability" [29] and this will need to be achieved before the apps included in the review are appraised. If this level of reliability is not achieved following piloting of the MARS with these 5 apps, further training around the use of the MARS will take place. This may involve a repeat viewing of the Web-based training module, discussion around the MARS indicators, consultation with the MARS developers, and/or further piloting of the MARS with additional apps. Following appraisal of the included apps, the two-way mixed ICC will again be calculated for the MARS total score and each MARS subscale.

The Pearson product-moment coefficient of correlation will be calculated to determine whether a correlation exists between the MARS score assigned by the certified practicing SLPs to each app and the star ratings assigned by users of each app in the Apple iTunes and Google Play stores.

Data Synthesis

The results will relate to the data extracted and quality assessment performed on the included apps. Descriptive and technical information relating to the included apps will be presented in a table and summarized narratively within the text. Graphs and tables will enable comparison of the quality of included apps across the MARS indicators of engagement, functionality, aesthetics, information quality, subjective quality and perceived impact. The 10 mobile apps achieving the highest total mean score for quality will be described in detail to provide consumers with a list of the Top 10 Mobile Apps for Children with SSD.

Results

Searching of the 2 app stores is currently underway. Broad and focused screening will commence toward the end of 2016. Data extraction and quality appraisal of the selected apps will commence in 2017.

Discussion

Implications

This protocol paper presents and justifies the methods for a systematic review of mobile apps for children with SSD. The aim of the systematic review is to identify the types of apps currently available for Android and iOS mobile phones and tablets and to critique their design features and content using a structured quality appraisal tool.

Conclusions

Amid a plethora of mobile apps for children with SSD, it is becoming increasingly difficult for SLPs to identify high quality apps for clinical use. This protocol describes a systematic search, selection, and appraisal process of mobile apps for children with SSD. This review will provide descriptive and technical information in addition to a quality assessment for the included apps. These results will assist SLPs in making an informed choice when selecting and recommending apps for the clinical management of this client population.

Authors' Contributions

The first author wrote the protocol with contributions and feedback from all coauthors. All authors read and approved the final protocol.

Conflicts of Interest

None declared.

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Abbreviations

ICC: intraclass correlation coefficient
PRISMA: preferred reporting items for systematic reviews and meta-analyses
MARS: mobile application rating scale
SLP: speech-language pathologist
SSD: speech sound disorders

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Protocol

Data Analysis Protocol for the Development and Evaluation of Population Pharmacokinetic Models for Incorporation Into the Web-Accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo)

Alanna McEneny-King[1], MSc; Gary Foster[2,3], PhD; Alfonso Iorio[4,5], MD, PhD; Andrea N Edginton[1], PhD

[1]School of Pharmacy, University of Waterloo, Waterloo, ON, Canada

[2]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada

[3]Biostatistics Unit, The Research Institute, St Joseph's Healthcare, Hamilton, ON, Canada

[4]Health Information Research Unit, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada

[5]Hamilton Niagara Hemophilia Program, Department of Medicine, McMaster University, Hamilton, ON, Canada

Corresponding Author:
Alfonso Iorio, MD, PhD
Health Information Research Unit
Department of Clinical Epidemiology and Biostatistics
McMaster University
CRL 140
1280 Main Street West
Hamilton, ON, L8S 4K1
Canada
Phone: 1 90552529140 ext 20152
Fax: 1 905 526 8447
Email: iorioa@mcmaster.ca

Abstract

Background: Hemophilia is an inherited bleeding disorder caused by a deficiency in a specific clotting factor. This results in spontaneous bleeding episodes and eventual arthropathy. The mainstay of hemophilia treatment is prophylactic replacement of the missing factor, but an optimal regimen remains to be determined. Rather, individualized prophylaxis has been suggested to improve both patient safety and resource utilization. However, uptake of this approach has been hampered by the demanding sampling schedules and complex calculations required to obtain individual estimates of pharmacokinetic (PK) parameters. The use of population pharmacokinetics (PopPK) can alleviate this burden by reducing the number of plasma samples required for accurate estimation, but few tools incorporating this approach are readily available to clinicians.

Objective: The Web-accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo) project aims to bridge this gap by providing a Web-accessible service for the reliable estimation of individual PK parameters from only a few patient samples. This service is predicated on the development of validated brand-specific PopPK models.

Methods: We describe the data analysis plan for the development and evaluation of each PopPK model to be incorporated into the WAPPS-Hemo platform. The data sources and structure of the dataset are discussed first, followed by the procedures for handling both data below limit of quantification (BLQ) and absence of such BLQ data. Next, we outline the strategies for building the appropriate structural and covariate models, including the possible need for a process algorithm when PK behavior varies between subjects or significant covariates are not provided. Prior to use in a prospective manner, the models will undergo extensive evaluation using a variety of techniques such as diagnostic plots, bootstrap analysis and cross-validation. Finally, we describe the incorporation of a validated PopPK model into the Bayesian post hoc model to produce individualized estimates of PK parameters.

Results: Dense PK data has been collected for more than 20 brands of factor concentrate from both industry-sponsored and investigator-driven studies. The model development process is underway for the majority of molecules, with refinement and validation to be completed in 2017. Further, the WAPPS-Hemo co-investigator network has contributed more than 300 PK assessments for use in model development and evaluation. This constitutes the largest repository of this type of PK data globally.

Conclusions: The WAPPS-Hemo service aims to eliminate barriers to the uptake of individualized PK-tailored hemophilia treatment. By incorporating this tool into routine practice, clinicians can implement a personalized dosing strategy without performing rigorous sampling or complex calculations. This service is centred on validated models developed according to the robust approach to PopPK modeling described herein.

ClinicalTrial: ClinicalTrials.gov NCT02061072; https://clinicaltrials.gov/ct2/show/NCT02061072 (Archived by WebCite at http://www.webcitation.org/6mRIXJh55)

(JMIR Res Protoc 2016;5(4):e232) doi:10.2196/resprot.6559

KEYWORDS

hemophilia; population pharmacokinetics; factor VIII; factor IX; tailored prophylaxis

Introduction

Background

Hemophilia is an inherited bleeding disorder caused by a deficiency in clotting factor VIII (FVIII, hemophilia A) or factor IX (FIX, hemophilia B). FVIII and FIX are key constituents in the coagulation cascade, which produces fibrin clots in response to blood vessel injury [1]. Consequently, hemophiliacs suffer from spontaneous, often recurring, joint bleeds, eventually leading to arthropathy. Hemophilia A is the more common form of the disease, affecting approximately 1 in 5000 males, while hemophilia B is considerably more rare (approximately 1 in 20,000) [2].

Modern hemophilia treatment consists of replacement of the deficient factor [3]. Replacement therapy began with the introduction of plasma-derived clotting factor concentrates in the 1960s, and advances in DNA technologies in the 1990s propelled the development of recombinant coagulation factors and the more recent design of longer-lasting recombinant products [4,5]. Clotting factor replacement therapy may be administered according to two main treatment strategies: episodic and prophylactic. The concept of prophylaxis, initiated by Nilsson and colleagues in the 1970s [6,7], is derived from the clinical observation that patients with moderate hemophilia (ie, those with clotting factor activity greater than 1% of normal) are less prone to the spontaneous bleeds and consequent arthropathy seen in those with severe hemophilia [8]. Today, there is global unanimity that prophylaxis should be initiated in young children before joint disease is apparent [9-11], as episodic treatment has been shown to be ineffective for the prevention of arthropathy [10]. However, implementation of the prophylactic approach varies considerably between countries [12]. The cost and availability of factor concentrates are major barriers to its widespread adoption, as is the challenge of patient compliance [13].

Despite its proven clinical benefit, an optimal dosing strategy for prophylaxis has yet to be determined. Evidence suggests that treatment should be individualized for best results, both from a therapeutic and economic perspective [14]. Typically, the pharmacokinetic (PK) properties of factor concentrates are assessed with classical PK studies, which are carried out in a small homogeneous group of participants, usually young and healthy. Subsequently, patients are empirically dosed by weight based on average PK estimates without taking into account individual variation in PK parameters beyond what can be predicted by age and weight [15]. Indeed, participants who appear similar may exhibit different PK behavior due to unpredictable variability. For example, Collins et al examined the variability in time to reach a critical factor level and found significant variation not only between children and adults, but within each group as well [16]. Unfortunately, performing an individual PK study with a classical approach requires 11 samples – 4 in the distribution phase (0 to 1 h) and 7 in the elimination phase (up to 48 h for FVIII, 72 h for FIX) – as outlined in recommendations from the International Society on Thrombosis and Haemostasis [17], making individualized PK-tailored dosing a difficult approach to apply in a clinical setting, especially when it involves pediatric patients.

One opportunity to overcome some of the limitations and barriers discussed above is offered by population pharmacokinetic (PopPK) modeling. Indeed, PopPK studies can make use of both rich and sparse sampling, which allows for a larger and more heterogeneous group of participants (eg, pediatric, elderly, and critical care patients) to be included due to less demanding sampling schedules [18]. Moreover, the PopPK approach allows for the partitioning of the total variability in PK response in a population into predictable and unpredictable variability. Predictable variability can be attributed to covariates that influence PK, such as body weight, age, and disease phenotype, and the identification of meaningful covariates can help to recognize at-risk subpopulations [19]. Unpredictable variability may occur both between subjects (BSV) and within a single subject (WSV), and a main goal of PopPK is to estimate the magnitude of these unexplained sources of variability so that a suitable dosing strategy may be determined [20,21]. In the case of hemophilia, WSV is small relative to BSV [15], so an individualized dosing regimen is appropriate. This approach is used in the therapeutic monitoring of several other conditions [22-24], and a 2010 study by Björkman et al indicated that a PopPK model combined with a limited sampling strategy could be as useful for the prediction of individual FVIII PK as a classical study [25]. However, adoption of this method has been hampered due to the complexity of the models needed to describe clotting factor PK and a relative shortage of PK data due to the rarity of the disease.

In response, the Web-Accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo, NCT02061072) project was launched in April 2013 at McMaster University, Hamilton, Ontario, Canada. A detailed description of the project methodology, objectives and progress is published separately [26]. In brief, WAPPS-Hemo aims at supporting clinicians in

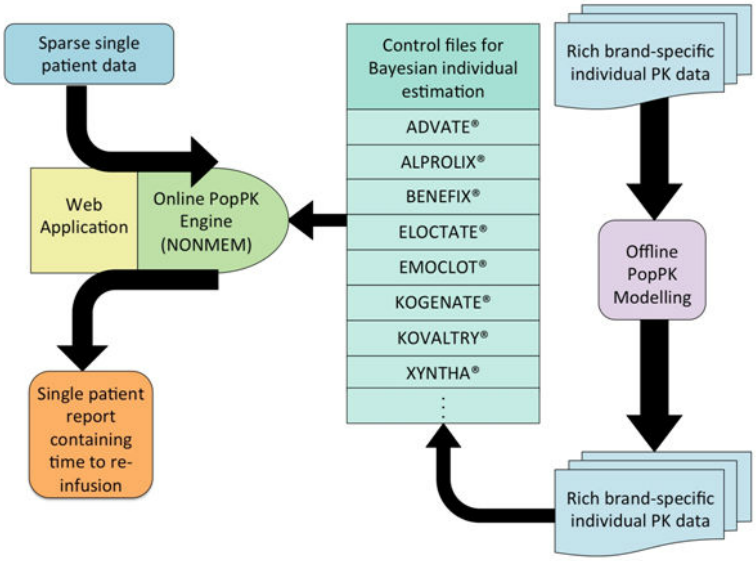
assessing individual PK for more informed dosing decisions (Textbox 1). The goal of the WAPPS-Hemo project is to set up a centralized, dedicated, Web-accessible, actively moderated service, allowing for (1) the input of anonymized and certified patient data by clinicians; (2) automatic estimation of patient-specific PK parameters; (3) expert validation of the estimation process; and (4) reporting of estimates to clinicians (Figure 1). WAPPS-Hemo represents the first non-industry sponsored, Web-based PopPK Bayesian calculator providing individualized PK estimates.

This report outlines the methods used for the development of brand-specific PopPK models, which form the knowledge base of the WAPPS-Hemo Bayesian individual forecast platform.

Textbox 1. The Web-Accessible Population Pharmacokinetic Service - Hemophilia project summary.

In the framework of the population pharmacokinetic (PopPK) approach, estimating reliable outcomes by the Web-Accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo) service requires that underlying PopPK models are well developed using a sufficiently large population of individuals. The WAPPS-Hemo project has assembled a vast database of clotting factors VIII and IX pharmacokinetic (PK) data across numerous brands and this represents the largest repository of this type of data globally. The repository includes PK data from industry sponsors and independent investigators; furthermore, clinical sites contributing data to the WAPPS-Hemo repository for individual estimation agreed upon subsequent use of those data for modeling. Indeed, onboarding of clinical sites requires that each participating site enters the network by signing a data transfer agreement where the site commits to data provision and takes responsibility for clinical use of the results. The principal investigator of WAPPS-Hemo, Dr Alfonso Iorio, agrees to share ownership of the database and authorship on any publication stemming from the project. Clinicians contribute to the repository by submitting to the website as few as 3 to 4 factor levels per patient along with demographic information. The appropriate PopPK control file is selected for the brand of factor concentrate identified in the patient data file. The online PopPK engine automatically estimates the relevant individual PK parameters. Following expert validation, a patient report is generated and sent to the clinician that includes the time when the factor level reaches a specified value, for example 0.05, 0.02 or 0.01 international units (IU) per mL, along with credibility intervals.

Figure 1. The Web-Accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo) platform uses brand-specific population pharmacokinetic models and submitted patient data to generate reports of individual pharmacokinetic profiles and estimates.



Objectives

The primary objective of this report is to outline the methods for developing PopPK models on dense FVIII and FIX data obtained from the Data Sources to better understand the relationship between blood plasma concentration and time for each molecule investigated. PopPK model estimates will be entered as priors in subsequent Bayesian post hoc analyses to predict the most reliable function between blood plasma concentration and time for patients with sparse data. This function will be used to inform clinicians when the next dose of a particular FVIII or FIX molecule should be administered.

Methods

Data Sources

Dense individual PK data on 878 participants using 21 different molecules from 17 different sources have been collected as part of industry-sponsored or investigator-driven studies. Most of the data in the derivation cohort are provided as both clotting and chromogenic assay results, but we plan to model exclusively with data from clotting assays, as the data received from participating clinical sites is almost uniquely of this type. Characteristics of some of the dense data that has been obtained for the WAPPS-Hemo project are summarized in Table 1. All datasets reported the age and weight of the participants; certain studies also reported additional covariates such as hematocrit, von Willebrand factor levels, and blood type, which can be tested during covariate analysis. In addition, individual patient data is being collected continuously through the WAPPS-Hemo

co-investigator network that currently has 47 active hemophilia treatment centers registered. To date, close to 300 profiles have been submitted.

Table 1. Summary of some dense data used for initial population modeling.

Brand	Type	N[a]	Age, years	Weight, kg	Hematocrit included	vWF[b] level included	Blood type included
Advate	FVIII[c] recombinant	25	15-62	53.8-127.4	No	Yes	No
Alprolix	FIX[d] recombinant	129	12.1-71.5	45.0-186.7	Yes	No	No
Benefix	FIX recombinant	80	4.3-58.5	17.9-186.7	Yes	No	No
Eloctate	FVIII recombinant	167	12-65	42.0-129.2	No	Yes	Yes
Kogenate	FVIII recombinant	40	13.0-56.1	47.4-124.2	No	No	No
Kovaltry	FVIII recombinant	23	12-51	46.3-124.2	No	No	No
Xyntha	FVIII recombinant	30	14-57	50.7-117.2	No	No	No

[a]N: number of participants.

[b]vWF: von Willebrand factor.

[c]FVIII: clotting factor FVIII.

[d]FIX: clotting factor FIX.

Dataset Assembly

Rich Dataset

Rich data used for PopPK modeling are provided by the data sources. These data will be received in various software packages and in a variety of formats, so they will be re-formatted into a standard comma-separated values (CSV) file for input into the PopPK modeling software, NONMEM (v 7.3.0; ICON Development Systems, Ellicott City, MD, US). Where possible, the dataset will consist of the variables shown in Table 2. AMT, DV, TIMEH, AGE, and BW are required to be provided by the data source. The optional covariates (HT, VWF, RACE, BTYPE, and HCT) are collected if possible.

Structure of the NONMEM Dataset

The record for each patient is organized as follows. The first record is used to read in the pre-dose amount, which accounts for the patient's endogenous factor level and any residual factor from a previous dose, if measured. The TIMEH entry for the first record is set to zero, and this is the reference point for the time for all subsequent records in the dataset. The first record also contains the BASELINE value, which corresponds to the patient's endogenous factor level. If a baseline level of the factor was measured, the measured value is entered; if not, a baseline value of 0.005 IU/mL (0.5% of normal factor activity) is assumed.

The second record is used to read in the dose administered (AMT). For this entry, the TIMEH column contains the time (in hours) that was required to administer the dose (eg, 0.1666 for a 10-minute administration). The amount and time are used to calculate the rate (RATE=AMT/TIMEH). For all subsequent records, AMT and RATE are set equal to zero.

The third record contains the first valid observation of the plasma concentration and subsequent records contain subsequent valid observations of the plasma concentration. The one exception to this is records following a valid observation that refer to samples that are below the limit of quantification (BLQ). Because the information from these different events (eg, PREDOSE, BASELINE, concentration observations, and BLQ events) needs to be handled in different ways, indicator variables MDV3 and MDV5 are included to designate how each entry should be used.

Table 2. Typical variables in NONMEM datasets.

Variable	Description	Units
Required variables		
CID	Patient identification number	Positive integer
OCC	Dose occasion	Positive integer
TIMEH	Time for each concentration measurement from start of bolus	Hours or fraction of hours (minimum of 4 decimal places)
AMT	Total dose	IU[a]
RATE	Rate of entry of drug: AMT/TIMEH	IU/h
DV	Plasma concentration of valid observation or BLQ[b]	IU/L
AGE	Age	Positive integer, years
BW	Weight	Positive integer, kilograms
EVID	Event identification variable	Positive integer (0=valid observation, 1= dose, 3=BLQ observation)
DOSE	AMT/BW	Positive number, IU/kg
PREDOSE	Plasma concentration at time of start of bolus	Zero or positive integer if measured, –1 if not measured (IU/L)
MDV5	Missing dependent variable	0=valid observation; 1=dose or BLQ observation; MDV5=MDV when no BLQ
BASELINE	Endogenous plasma concentration	Positive integer if known, –1 if not known, IU/L
BLQ	Below limit of quantification	≤ 0=non BLQ measurement, positive integer=BLQ value, IU/L
MDV3	Missing dependent variable	0=valid observation or BLQ; 1=dose; MDV3=MDV when BLQ is present
Optional covariates		
HT	Height	Positive integer, centimeter
VWF	von Willebrand factor	Percentage
RACE	Race	Positive integer (1=White, 2=Black, 3=…)
BTYPE	Blood type	Positive integer (1=A, 2=B, 3=AB, 4=O)
HCT	Hematocrit	Percentage

[a]IU: international unit.

[b]BLQ: below the limit of quantification.

Data Checking

Errors and Missing Data

Prior to analyzing the data, the integrity of the data will be scrutinized to identify potential data errors. Errors can exist for a number of reasons. For example, following a dose, plasma concentrations typically decline with time so if a plasma concentration for a record is higher than the plasma concentration for a previous record, that record will be flagged to be checked. If any data are missing they will be flagged to be checked. Similarly, outlying covariate values for continuous variables (eg, AGE, BW, or HT) will be flagged to be checked. Any categorical variable that has a value that is not expected will be flagged to be checked. Duplicate records within a patient's data will also be flagged.

Procedures for Handling Data Errors

All potentially erroneous data will be reported and discussed. If a resolution to the error is forthcoming, it will be documented and the appropriate changes will be made to the dataset. If no resolution is found, the error will be documented and the data will be excluded from subsequent analyses.

Data Modeling Methods

Software, Subroutines, and the Handling of Data Below the Limit of Quantification

Nonlinear mixed effects modeling and Bayesian post hoc estimations will be completed in NONMEM and PDx-Pop (v 5.10; ICON Development Systems, Ellicott City, MD, US). PopPK modeling will be performed using the first order conditional estimation with interaction (FOCEI) method. The ADVAN and TRANS subroutines for each model, which specify the model structure and parameterization, respectively, are shown in Table 3.

Table 3. NONMEM subroutines used to implement kinetic equations for linear models following intravenous administration.

Model	ADVAN subroutine	TRANS subroutine
1-compartment	ADVAN1	TRANS2: CL, V
2-compartment	ADVAN3	TRANS4: CL, V1, Q, V2
3-compartment	ADVAN11	TRANS4: CL, V1, Q2, V2, Q3, V3

Severe hemophilia patients have, by definition, an endogenous coagulation factor level below 0.01 IU/mL, which is also often cited as the limit of quantification (LOQ) for coagulation activity assays [27-29]. As a result, trough concentrations are often BLQ and several methods exist for the handling of samples that are BLQ. Simpler methods exclude BLQ data or replace these points with LOQ/2; this protocol makes use of the M3 method described by Beal in 2001 [30].

Structural Model Building

The first step in model development will be a naïve pooled analysis, which allows for preliminary exploration of model structure and mean estimates of PK parameters. Further definition of the model structure (ie, number of compartments) will be determined using a combination of graphical techniques and numerical goodness-of-fit measures. Models will be evaluated using an objective function value based on a summation of the residual error. One model is considered to be superior to a similar hierarchically well-formulated model with one more degrees of freedom if the objective function decreases by 3.84 units or more, based on the assumption of a chi squared (χ^2) distribution. Models will also be evaluated using diagnostic plots (Textbox 2).

Textbox 2. Diagnostic plots used to evaluate the models.

- Observed values vs individual/population predicted values
- Conditional weight residuals (CWRES) vs predicted values
- CWRES vs time
- Observed and predicted values vs time
- Normal QQ-plots
- CWRES histogram
- Eta histograms
- Population covariate plots

In the event that it is difficult to determine which structure best characterizes the data, it may be helpful to fit each subject individually to explore the reasons for unexplained variability. For example, some factor concentrates may exhibit different structures between patients, which may in turn require estimates to be derived from both models followed by a comparison of the effects on population estimates and individual dosing decisions; as a rule of thumb, we will always take the most conservative approach.

The goal of PopPK is to describe the concentration-time profile for each subject using a series of mathematical equations in a hierarchical manner (Figure 2). Observed concentrations are expressed as a function of an individual's PK parameters (θ) and time (t), with a residual error term (ε) to account for unexplained variability within the individual (Figure 3, Equation 1).

The appropriate structure for the residual unexplained variability (RUV, ε) will be determined using graphical goodness-of-fit plots (including histograms of the residuals, normal QQ plots, and plots of the residuals vs predicted values) and numerical measures (such as objective function value and shrinkage). Possible models for the RUV are shown in Figure 3 (Equations 1-4) where ε's are independent and normally distributed, with a mean of zero and variance of σ^2. The combined additive-proportional error model (Figure 3, Equation 4) is most commonly used in PK modeling.

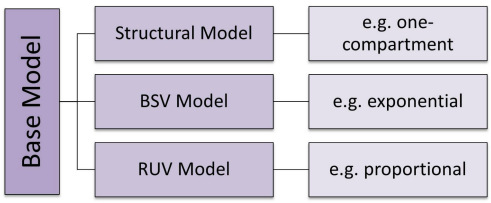
From a population of participants, an estimate of the typical value of the relevant PK parameters can be obtained. A new parameter, η, can then be used to describe how an individual's parameter deviates from the typical value (ie, the BSV, Figure 3, Equation 5).

The BSV (η) of PK parameters will be estimated using the relationship shown in Equation 8 (Figure 3) where θ_{ij} is PK parameter i for the j^{th}individual, $TV(\theta_i)$ is the population mean value of the parameter, η_{ij} is the subject-specific deviation from the population mean of PK parameter i for individual j. The η 's are normally distributed, with a mean of zero and a variance-covariance matrix, ω^2. The functional form chosen for the BSV is based on the assumption that PK parameters are log-normally distributed. In the event that this model does not provide a good fit, other functional forms may be explored.

Initially, BSV will be included on all PK parameters, and the necessity of all these terms will be investigated both graphically and using formal hypothesis tests. Once the significant random effects have been identified, the structure of the variance-covariance matrix (ω^2) can be explored. All prior model development assumes a diagonal variance-covariance

matrix (ie, no correlation between random effects). Comparing models with diagonal and unstructured variance-covariance matrices will test for the correlation between random effects.

Figure 2. Illustration of the various components of the base model for a one-compartment model with exponential between subject variability and proportional residual unexplained variability.



$$Y_{ij} = \frac{Dose}{V_i} e^{-\frac{CL_i}{V_i} t_{ij}} (1 + \varepsilon_{ij})$$

$$\varepsilon_{ij} \sim N(0, \sigma^2)$$

$$CL_i = TV(CL) e^{\eta_{CL_i}}$$

$$V_i = TV(V) e^{\eta_{V_i}}$$

$$\eta_i = \begin{pmatrix} \eta_{CL_i} \\ \eta_{V_i} \end{pmatrix} \sim BVN(0, \omega^2)$$

Figure 3. Equations for defining different aspects of the population pharmacokinetic models including residual unexplained error (1-4), between subject variability (5-6), and covariates (7-10).

$$Y = f(\theta, t) + \varepsilon \quad (1)$$

$$Y = f(\theta, t) \cdot (1 + \varepsilon) \quad (2)$$

$$Y = f(\theta, t) \cdot e^{\varepsilon} \quad (3)$$

$$Y = f(\theta, t) \cdot (1 + \varepsilon_1) + \varepsilon_2 \quad (4)$$

$$Y = f(\theta, t, \eta) + \varepsilon \quad (5)$$

$$\theta_{ij} = TV(\theta_i) \cdot e^{\eta_{ij}} \quad (6)$$

$$\theta_{ij} = TV(\theta_i) + \theta_{Var} \cdot Var_j \quad (7)$$

$$\theta_{ij} = TV(\theta_i) \cdot e^{\theta_{Var} \cdot Var_j} \quad (8)$$

$$\theta_{ij} = TV(\theta_i) \cdot Var_j^{\theta_{Var}} \quad (9)$$

$$\theta_{ij} = TV(\theta_i) \cdot \left(1 + \theta_{Var} \cdot Var_j\right) \quad (10)$$

Covariate Model Building

In order to minimize the unexplained portion of the BSV, covariates will be added to the model. Potential covariate relationships will first be explored by examining plots of the included η ’s against each covariate. From these plots, the covariates that are most likely to be significant can be identified, and then tested formally in the model. Various functional forms describing the relationship between the covariates and the PK parameters are possible. Examples of commonly used functional forms are shown in equations 7-10 of Figure 3 where Var_j is the covariate value for individual j and θ_{Var} describes the magnitude and direction of the correlation between the covariate and parameter. Often, covariates such as weight and age will be centered or scaled by the mean or median; this assists in the interpretation of the estimates and helps to stabilize the estimation procedure. Covariates will be added to the model in a stepwise manner by considering formal hypothesis test results, precision of the parameter estimates and graphical techniques.

All model-building datasets include age and weight as parameters, but data for certain brands of factor concentrate could also include height, hematocrit, von Willebrand factor level and blood group as possible covariates. Where available, these covariates can be tested in model development and, if fitting the above criteria for retention, be included in the final model. However, the choice of model would need to take into account the fact that clinicians using WAPPS-Hemo for individual PK estimations are required to include age and weight when requesting PK estimates from the WAPPS-Hemo platform, whereas inclusion of other covariates listed above is optional. Therefore, it is possible that a covariate may significantly influence the PK of a molecule, but may not be recorded at the clinical site. In order to reconcile significant covariates and available information, multiple models may be produced for a single molecule and a process algorithm for determining which model to use in a given situation will be incorporated into the WAPPS-Hemo platform. The decision tree may also incorporate different structural models for molecules that behave differently between subjects, and the model that provides the most precise estimates will be selected. In all cases, the clinician will receive a single report corresponding to whichever model was chosen for the data provided.

Population PK Model Evaluation

The first step in model evaluation includes the use of the diagnostic plots outlined above to ensure that all model assumptions are being met (eg, independent and normally distributed residual error, normally distributed random effects). Also, metrics such as the condition number and the variance inflation factor may be used to assess collinearity. A bootstrap analysis will also be performed to ensure that the model is stable and provides precise estimates for all parameters.

Next, the models will be evaluated using cross-validation techniques with the rich data. Either the holdout method or a *k*-fold cross-validation technique will be employed, depending on the size of the dataset in question. The bias and accuracy of the models will be assessed using the metrics of mean error and mean squared error.

Following evaluation with rich data, the models will be validated using sparsely sampled data to ensure that they perform adequately with the type of data that will be provided by clinicians using the WAPPS-Hemo platform. Validation with sparse data presents some challenges, since the typical methods discussed above cannot be employed. However, a number of strategies for evaluating models using sparse data have been reported. These include using a subset of a complete sampling scheme to compare performance [31,32], performing Monte Carlo simulations [32], and examining predictive distributions of the observed concentrations [33]. Our preferred method is the use of a subset of a complete set of samples.

Bayesian Post Hoc Model

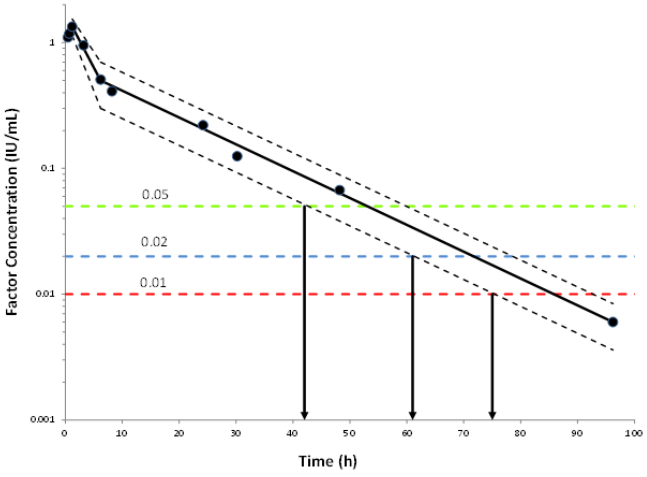
Bayesian estimations will also be performed in NONMEM, using the parameter estimates from the PopPK models as informative priors for the relevant PK parameters (eg, volume of distribution, clearance). This step will use the same model structures and estimation methods as previously described, and will handle the presence or absence of PREDOSE, BASELINE, and BLQ values in the same manner as outlined above. From the output files, the time from dose initiation to various concentrations (eg, 0.05, 0.02 or 0.01 IU/mL) or the concentration at different times (eg, 24, 48, and 72 h) can be reported with the accompanying 95% credibility intervals. The times reported to the clinician will be the times at which the lower boundary of the 95% credibility interval for concentration first reaches each of these three concentration thresholds (Figure 4). For concentrations at specified times, the credibility interval would report the lower and higher concentration value estimated at that given time.

We have opted to use the credibility interval as the most efficient and understandable way to report the amount of "shrinkage" of the patient data to the population model. The interval will be larger or smaller depending upon the amount of information that is used either from the population (ie, larger band where most values within the population are possible for the patient) or the individual (ie, smaller band where more rich patient data reduces variability). The Bayesian approach used allows this variability to vary across different segments of the curve, being large where no or little information is provided and small where informative points are provided.

Reporting

A comprehensive PopPK report will be assembled for each brand-specific model that is developed, according to the Food and Drug Administration (FDA) guidance on PopPK reporting [34]. The recommended sections included are shown in Textbox 3. These guidelines apply to reports submitted to the FDA, which are not directly available to the public; however, a close approximation of the reports we will be generating for each model for peer-review publication is provided by Rajagopalan and Gastonguay [35].

Figure 4. Factor concentration as a function of time (symbols: patient data, black line: predicted individual pharmacokinetic profile) where time to the lower 95% credibility interval bound for each of the 0.05 (green line), 0.02 (blue line) or 0.01 (red line) IU/mL thresholds is reported to the clinician. Time 0 represents time of dose initiation.



Textbox 3. Recommended sections included in the comprehensive population pharmacokinetics report.

- Summary
- Introduction
- Objectives, Hypotheses and Assumptions
- Materials and Methods
  - Assay
  - Data
  - Data Analysis Methods
- Results
- Discussion
- Application of Results
- Appendix

Results

Dense PK data has been collected for more than 20 brands of factor concentrate. Models have been developed for all but three molecules, and we expect to receive data for one additional molecule in early 2017. All models will undergo further refinement and validation, and be submitted for publication in 2017. From the WAPPS-Hemo co-investigator network, we have collected 300 PK assessments to date and expect to reach the 500-assessment mark by early 2017.

Discussion

Risks and Barriers

The main risk associated with the use of the WAPPS-Hemo service is the possibility that the specific patient is outside of the covariate space used to build the models. In such cases, the individual estimated PK parameters may be imprecise or essentially “wrong” and could result in suboptimal treatment decisions. In light of this, we plan to implement risk minimization procedures. First, we provide both average estimates as well as their associated credibility intervals. In cases where the patient is outside of the model development space, we expect the intervals to be large such that clinical usage of the predictions is discouraged. Second, each forecasted PK is reviewed individually by an expert and appropriate warnings will be added as needed. Third, as a general policy for WAPPS-Hemo users, we recommend that the PK prediction is used as a tool to speed up treatment optimization. To this end, we recommend prospective testing with sampling around specific times that would be valuable in decreasing uncertainty.

One of the main goals of the WAPPS-Hemo program is to eliminate barriers to the uptake of an individualized PopPK-driven approach to hemophilia treatment. By adopting this tool, clinicians require fewer blood samples and circumvent the complex calculations usually needed to implement a tailored dosing strategy. However, the current output report may be a potential hindrance. Although the report contains times to critical factor levels as well as concentrations at convenient time points, these results only pertain to the dose that was administered. A proposed clinical module will allow clinicians to input two parameters among dose, frequency, and desired factor level to calculate the third. This additional functionality will allow those that treat hemophilia to evaluate the theoretical effect of changing dose and frequency on future plasma levels in real time without having to submit multiple profiles through the WAPPS-Hemo platform.

Conclusions

In summary, the WAPPS-Hemo service is predicated on valid PopPK models. This report focuses on describing the process for model development and evaluation, which all brand-specific models will undergo. Rich data has been, and continues to be, the main source of data for model development. However, as clinical sites contribute sparse data to the repository, a greater breadth of PK data and covariates will allow for continuous quality improvements in the models.

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Conflicts of Interest

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Abbreviations

BLQ: below the limit of quantification
BSV: between subject variability
CWRES: conditional weight residuals
FIX: clotting factor IX
FVIII: clotting factor FVIII
LOQ: limit of quantification
PK: pharmacokinetic
PopPK: population pharmacokinetics
WAPPS-Hemo: Web-Accessible Population Pharmacokinetic Service - Hemophilia
WSV: within subject variability

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Protocol

Using Patient Flow Information to Determine Risk of Hospital Presentation: Protocol for a Proof-of-Concept Study

Christopher M Pearce[1], MBBS, MFM, PhD; Adam McLeod[1], BNursing, MHInf; Jon Patrick[2], PhD; Douglas Boyle[3], PhD; Marianne Shearer[1,4], MBL, GradCertCommLaw, GradDipMgt, GradDipComputing; Paula Eustace[1,5], PhD; Mary Catherine Pearce[1], BSc (Biomed), PhD

[1]Melbourne East General Practice Network, Burwood East, Australia

[2]Health Language Analytics, Eveleigh, Australia

[3]Research Information Technology Unit, Health and Biomedical Informatics Centre, The University of Melbourne, Parkville, Australia

[4]Gippsland Primary Health Network, Moe, Australia

[5]Eastern Melbourne Primary Health Network, Box Hill, Australia

Corresponding Author:
Christopher M Pearce, MBBS, MFM, PhD
Melbourne East General Practice Network
6 Lakeside Drive
Burwood East,
Australia
Phone: 61 3 8822 8444
Fax: 61 3 8822 8550
Email: cpearce@megpn.com.au

Abstract

Background: Every day, patients are admitted to the hospital with conditions that could have been effectively managed in the primary care sector. These admissions are expensive and in many cases are possible to avoid if early intervention occurs. General practitioners are in the best position to identify those at risk of imminent hospital presentation and admission; however, it is not always possible for all the factors to be considered. A lack of shared information contributes significantly to the challenge of understanding a patient's full medical history. Some health care systems around the world use algorithms to analyze patient data in order to predict events such as emergency presentation; however, those responsible for the design and use of such systems readily admit that the algorithms can only be used to assess the populations used to design the algorithm in the first place. The United Kingdom health care system has contributed data toward algorithm development, which is possible through the unified health care system in place there. The lack of unified patient records in Australia has made building an algorithm for local use a significant challenge.

Objective: Our objective is to use linked patient records to track patient flow through primary and secondary health care in order to develop a tool that can be applied in real time at the general practice level. This algorithm will allow the generation of reports for general practitioners that indicate the relative risk of patients presenting to an emergency department.

Methods: A previously designed tool was used to deidentify the general practice and hospital records of approximately 100,000 patients. Records were pooled for patients who had attended emergency departments within the Eastern Health Network of hospitals and general practices within the Eastern Health Network catchment. The next phase will involve development of a model using a predictive analytic machine learning algorithm. The model will be developed iteratively, testing the combination of variables that will provide the best predictive model.

Results: Records of approximately 97,000 patients who have attended both a general practice and an emergency department have been identified within the database. These records are currently being used to develop the predictive model.

Conclusions: Records from general practice and emergency department visits have been identified and pooled for development of the algorithm. The next phase in the project will see validation and live testing of the algorithm in a practice setting. The algorithm will underpin a clinical decision support tool for general practitioners which will be tested for face validity in this initial study into its efficacy.

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KEYWORDS

electronic health record; data linkage; primary care; machine learning; avoidable presentation

Introduction

Overview

Primary care management of patients makes good economic sense. When compared to the high-cost, high-intensity activities of secondary or tertiary care systems [1,2], primary care provides a low-cost, low-intensity approach to health care that is ideally suited to addressing both illness management and prevention [2,3].

Many people have multiple risk factors for more than one health problem, and it is well recognized that the risk effect is magnified when risk factors are combined. Reducing and minimizing risks through attention to preventative measures, timely intervention, and optimal use of support strategies and services can minimize the risk of harm and encourage better use of hospital resources. Missing preventative opportunities, on the other hand, can result in a higher dependency on limited and expensive hospital resources.

Although many conditions cannot be prevented and will at some point require management in a hospital, a great number will be well managed at home, in general practice, or by community-based services. These ambulatory care–sensitive conditions (ACSCs) are conditions for which management is influenced by primary care access, care funding, and the patient's socioeconomic status, as well as the medical condition itself [4]. More vulnerable groups within the community, such as elderly patients [5], Aboriginal and Torres Strait Islanders [6], and patients of low health literacy [7], are considered more likely to present for emergency care. Both incentivizing care in order to lower direct primary care costs to patients and improving the management of such conditions in primary care may affect hospital admissions for those conditions [8].

In Australia, programs such as the Hospital Admission Risk Program (HARP) model in Victoria have specifically targeted patients at high risk of emergency department presentation [9]. Selection for these programs has been based on the number of admissions or presentations or the chronic disease—predominantly chronic obstructive pulmonary disease, congestive heart failure, and diabetes. There is, however, an inherent difficulty in obtaining all the relevant information when considering access to such programs because the large number of variables is beyond what can be documented and widely understood in the set of admission criteria. For example, in any clinical interaction, the recorded data is only a subset of the actual data. By using a computerized clinical decision support system (CCDSS) to assess all available historical data rather than simply the most recently collected data, we hope to improve the decision-making process. There is evidence to suggest such systems can improve chronic disease management and in some cases patient outcomes as well; however, further work is required to fully understand the limitations of the CCDSSs that are currently available and in use. The key to developing a good system will certainly lie with developing a good predictive algorithm or model [10].

Several admission prediction models have been implemented in the United Kingdom, where a unified health system allows for unified patient flows [11]. One of the most widely reported models was the Patients at Risk of Rehospitalization (PARR++) Combined Predictive Model [12]. This model, like many other models of this kind, primarily used hospital data for predicting risk of emergency department (ED) readmission and proved relatively ineffective in changing clinical outcomes. A more complex model, involving over 30 variables, is based on general practice data alone [13]. Other approaches have taken a disease-specific view rather than a whole of population view [14]. In Australia and other countries with nonunified health care systems, isolated datasets have been used to build similar models. One such model, the Patient Admission Prediction Tool, has been implemented in Queensland, Australia, in order to improve bed management in hospitals where demand is ever increasing [15,16]. This model used hospital admission data to forecast future ED presentation; however there was no link to diagnosis. While the tool was deemed successful at forecasting attendance, very little impact was made on the key markers of hospital overcrowding, a failing that highlights the importance of preventing the hospital attendance in the first place.

A possible solution to identifying the potential ED presentation in general practice involves using prehospital presentation markers from general practice attendances. In order to reduce the number of preventable ED presentations, data linkage models generated [17] across health care settings are needed. The problem is that delivering data in a real-time mode to the point-of-care in order to most effectively influence care remains a significant challenge.

The Population Level Analysis and Reporting (POLAR) diversion project will set up the facility to test the hypothesis that risk reduction for multiple patient demographics and conditions can be achieved in the Australian context through strategic syntheses and intersects of extracted clinical data. This will build on ontological work conducted in the Australian context to more reliably flag conditions associated with increased hospital admission, such as diabetes, from routine data [18].

In doing so it attempts to address a significant gap in suitable strategies currently available, which are aimed at identifying avoidable ED presentations. The process aims to add a further depth and breadth to the clinical decision aids available at point-of-care. It particularly aims to facilitate the preventative orientations called for by best practice approaches [4,17], focusing the attention of busy general practitioners on risk reduction over crisis management.

This proof-of-concept study develops and tests the risk prediction process. Development of this risk prediction tool will use data housed in a warehouse that feeds the POLAR tool, a resource for health professionals used to analyze and interpret health records. The ultimate outcome of this study will be to implement a predictive model in general practices aimed at reducing avoidable presentations to hospital EDs.

Study Aims

Primary Aims

- Develop a predictive risk identification tool, which may be a risk tree or risk score
- Determine the validity of the data extraction/risk algorithm integration process by testing with a select number of practices
- Implement in the general practice environment to test the validity of the risk report
- Demonstrate the feasibility of a broader program roll-out and assess the general practitioner–defined interventions initiated in response to the risk reports

Secondary Aims

- Identify and construct ontologies that identify people with conditions, multimorbidity, and other risk factors (eg, economic disadvantage) associated with hospital admission
- Highlight gaps in data quality that might restrict the use of the predictive tool
- Identify decision-support strategies for use by general practices in maintaining and improving vigilance of patients with specified morbidities and comorbidities
- Improve timeliness of interventions in actual and potential complications
- Improve patient care at home and in the community
- Provide informed estimation of generated cost savings by costing analyses of resources used (at the general practice level) versus resources saved (at the hospital level)
- Support clinical governance in general practice

Methods

Setting

The Melbourne East General Practice Network (MEGPN) is a not-for-profit organization offering primary care services and supporting general practices in the area. It holds and manages the data warehouse that is integrated with the POLAR tool. Regular downloads are added from contributing general practices in the catchment, thus continually expanding the data pool. In a previous incarnation, MEGPN was funded by government to support general practices in the eastern suburbs of Melbourne, Australia's second largest city [19]. For over 10 years, MEGPN has been offering practices quality improvement activities using the Plan/Do/Study/Act method. Central to the entire program has been MEGPN's active encouragement through its practice feedback reporting of consistent data governance [20] and its independent data quality activities aimed at improving the data analysis used in the feedback visions [21].

Ontologies for High Risk Conditions

We will develop clinical surrogates (eg, use medication data) and other markers that flag from routine data the risk of admission. This study will specifically examine general practice patients from the MEGPN region. There are currently 1.3 million deidentified records in the MEGPN general practitioner dataset, which includes many patients from outside the catchment. In Australia, patients are not bound to a specific practice or general practitioner and can visit any number of practices in a given time frame. Initial data on emergency presentations will be obtained from Eastern Health, the main provider of secondary care services to the region.

Population

No distinction will be made with regard to any aspect of a patient's medical history or demographics; any patient who meets the criteria in the algorithm will be highlighted to the general practice. The implementation phase evaluating the reporting process will use data from 6 to 10 practices from the pool that contributed to the research dataset.

Ethics

As this is a multifaceted project, there are several aspects to the ethics applications involving various partner institutions and elements of the project. MEGPN has ethics approvals for the use of deidentified data in its database for the purposes of research and for reporting such data to general practice as well as additional approval for linking MEGPN data with deidentified hospital data. Separate ethics approval has been granted for a focus group interview informing selection of key algorithm components.

Governance

The project has an advisory group consisting of general practitioners and hospital representatives and representatives from state and federal governments and the Australian Institute of Health and Welfare. The group provides an important validation mechanism and project advice around practitioner needs and clinical assumptions. The advisory group also assists in developing the specific alert criteria of the risk identification algorithm through a range of best practice clinical guidelines.

Model Development

The first phase of the study involves understanding the general practice journeys of patients who attend the ED. To do this, data have been extracted from general practices in the area and linked with hospital emergency admission data. The hospital data has been collected from the Victorian Emergency Minimum Dataset (VEMD) where hospitals contribute all records for emergency admissions and includes demographic data, referral/arrival information, triage category, diagnosis and procedures, and discharge information.

In order to obtain the necessary granular general practice data, the project is implementing a data extraction tool. The Generic Health Network Information Technology for the Enterprise (GRHANITE) tool [22] extracts patient-centered data from the practices. The collected data include diagnoses (active and inactive), serial visit information, reason for encounter, procedures, referrals, pathology and diagnostic results, and comprehensive prescription information, as well as demographic data. Within GRHANITE is the ability to generate a unique encrypted hashtag linkage key to allow linking of individual patient data across sites. Both sets of data are therefore stripped of any identifying information but can be linked by the hashtag linkage key applied by the GRHANITE tool. The hospital data, which is episode-based, is then linked with the patient-centered data from general practice. We will therefore be able to detect those patients who have attended the local ED and any general

practice in the area. The POLAR data warehouse holds ED data from over a 5-year period, and we will build a database of general practitioner attendances across all practices for the 6 months prior and 3 months after each admission.

A model will be developed using a predictive analytic machine learning algorithm. The modeling process will require us to build attribute sets around 14 groups of variables. Models will be built by omitting each attribute set to determine their effects on the models. They will then be evaluated by 10-fold cross validation on a support vector machine, identifying the precision and recall for each class. In an effort to create more refinement in the model, domains will be compacted where possible, most often to 3 values: below normal, above normal, and normal. This is a method for densifying the statistical sample and hopefully reinforcing weak effects. Some analysis will be performed using information gain to understand the level of contribution of each attribute set to the predictive model. Other exploration will be made with the number of classes that produced the most effective classification because classes for 60-day, 90-day, 180-day, and 365-day periods proved particularly difficult to model reliably.

Based on the model, an at-risk report will be created with these flags for the general practitioner: (1) patients deemed to be at heightened risk of increasing morbidity related to specific, targeted health states and (2) the parameters and thresholds exceeded that place them at current risk of presentation to the hospital. In order to continuously improve the quality of the report, we will request additional information from the general practitioner be provided that could enhance the accuracy of the predictive algorithm.

Upon completion of model development, consent will be obtained for validation by practices from their representatives, and individual general practitioners will be contracted for their evaluations in return for small incentive payments designed to cover their expenses in using the tool and providing feedback. Patients will be alerted that the practice is involved in the study, as per the responsible Human Research Ethics Committee requirements.

Risk Score Implementation

Implementation of the risk report will be initiated in multiple practices that are already providing data to POLAR. Essentially, practices will have a regular data extraction that will be then run through the algorithm; the results will be uploaded to the practice in deidentified form for reidentification on a patient-by-patient basis by the practice software. The report is issued by internal identifier that can be cross-matched by practice staff to identify patient details within the practice. Thus patients can be identified only at the point-of-care. No identifying information will be kept centrally. General practitioners will be recruited to participate in focus groups and interviews on the impact on their personal practice of the algorithm-informed risk reporting process.

The risk report will serve as a clinical decision aid to be used with normative clinical discretion. It is not intended as either a clinical directive or a prescription for management. Rather, it flags for the general practitioner patients who meet at-risk criteria and reports on the parameters exceeded and parameter/morbidity combinations that trigger the alert. Data quality issues will also be raised with general practitioners, with the research team outlining missing information in the record (that if complete might mean better risk stratification).

During the study, practices will receive a series of reports showing estimated risk of ED presentation across the time periods 1 month, 3 months, and 12 months. General practitioners will be asked their thoughts on the clinical accuracy of the prediction against their clinical knowledge. This will be followed with a brief questionnaire asking details about changes to patient management (if any). These might include changes to medications, mobilization of extra services, or regular monitoring.

After 3 months of regular reporting, general practitioners will be interviewed about their experiences, and the pooled data will be used in a final report.

Results

At the time of writing we are running the data linkage process over 700,000 hospital presentations from a 10-year time frame and anticipate 100,000 unique patient records. We will then begin the process of stratifying the identified admissions into unavoidable, ambulatory sensitive, and other and perform the analysis. Following the analysis, we expect to provide a weighting to the various factors that will indicate risk of hospital admission and potentially a time frame. The combination will inform the general practitioners of the relative probability of hospital admission attributed to at-risk patients, thus allowing them to recommend appropriate interventions.

Discussion

Potential Implications

In the Australian context, this project is significant in two ways. In the first instance, the distributed nature of Australian general practice, with no formal registration to practices and split funding streams (general practice is federally funded and hospitals state funded), mitigates against quality data collection across the data silos. For that reason, the linking of data in these settings (a first for Australia) allows for investigations not previously possible. The second is the potential of delivering an almost real-time report to general practitioners to enable them to mobilize available resources to patients at the time. These resources may be from within the practice or from programs run by community or hospital services.

Limitations

Data quality will always be a limitation in the data linkage process. The tool generation process is reliant on data quality from both the ED and the general practices. The ED dataset is derived from a set used to create the VEMD that is used for state-wide analysis and planning. It is collected by hospitals from their existing systems as a by-product of clinical and administrative processes. Similarly, the general practice data, while a more complete set, is also derived from data used for patient care. MEGPN has been involving practices in data

quality and clinical governance reviews for 10 years; for certain fields the data are reliable and valid (prescribing, diagnoses) while for others (smoking status) the data are less reliable. This is one of the reasons data feedback loops are built into the program.

Conclusions

With the agenda of keeping people out of hospital, the POLAR diversion project targets risk-of-presentation identification at general practice level. It aims to contribute meaningfully to the systematic, multifaceted approach to quality improvement that is inherent in good clinical governance and essential to best managing patients with complex problems.

By creating linkage between general practitioner and hospital records, we have been able to generate unique patient flow information. This will allow algorithms to be designed that will identify patients at risk of taking the less desirable care pathway via the local hospital ED, where resources are thinly spread. Design of a user-friendly report that can provide real-time data to primary care services will help direct patients to intervention services (eg, HARP, additional health care services), thus reducing the burden on the hospital system. By reducing ED traffic, patient outcomes are expected to improve via tailored care in a less acute environment.

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Conflicts of Interest

None declared.

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Abbreviations

ACSC: ambulatory care–sensitive conditions
CCDSS: computerized clinical decision support system
ED: emergency department
GRHANITE: Generic Health Network Information Technology for the Enterprise
HARP: Hospital Admission Risk Program
MEGPN: Melbourne Eastern General Practice Network
PARR++: Patients at Risk of Rehospitalization
POLAR: Population Level Analysis and Reporting
VEMD: Victorian Emergency Minimum Dataset

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Protocol

ENHANCE—(Electronic Hydroxyurea Adherence): A Protocol to Increase Hydroxyurea Adherence in Patients with Sickle Cell Disease

Susan Creary[1], MSc, MD; Deena J Chisolm[2], PhD; Sarah H O'Brien[1], MSc, MD

[1]Nationwide Children's Hospital, The Ohio State University School of Medicine, Columbus, OH, United States

[2]Nationwide Children's Hospital, The Ohio State University, Columbus, OH, United States

Corresponding Author:
Susan Creary, MSc, MD
Nationwide Children's Hospital
The Ohio State University School of Medicine
700 Children's Drive
Columbus, OH, 43205
United States
Phone: 1 614 722 3569
Fax: 1 614 722 3559
Email: susan.creary@nationwidechildrens.org

Abstract

Background: Hydroxyurea (HU) is the only disease-modifying medication for patients with sickle cell disease (SCD). HU can reduce SCD-related complications but only 35% to 50% of pediatric patients adhere to HU at the rates achieved in clinical trials and this limits its clinical effectiveness. Mobile Directly Observed Therapy (Mobile DOT) is a pilot-tested, electronic, multidimensional, HU adherence intervention that targets many components of the Health Behavior Model.

Objective: The aim of this study is to evaluate the impact of Mobile DOT on HU adherence in children with SCD. The objective of our study is to inform the development of future adherence interventions and pediatric SCD protocols.

Methods: This is a single-arm crossover study of pediatric patients with SCD. Participants self-record videos of their daily HU administrations and receive text message alerts to take HU, feedback on their HU adherence, and incentives when they achieve adherence goals during the 6-month Mobile DOT phase. Participants' HU adherence during the Mobile DOT phase is compared with their baseline HU adherence (6 months prior to study entry) and to their HU adherence 6 months after completing the Mobile DOT phase. The primary outcome of this study is HU adherence measured by medication possession ratio.

Results: The trial is ongoing. Preliminary review of participant satisfaction results suggest that most participants can complete Mobile DOT in less than 5 minutes per day and are satisfied with the intervention.

Conclusions: If effective, the Mobile DOT strategy will increase HU adherence and this could improve patients' clinical outcomes and reduce costs of care.

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KEYWORDS

hydroxyurea; children; sickle cell disease; adherence intervention

Introduction

Sickle cell disease (SCD) is a chronic, inherited, red blood cell disorder that affects approximately 28,000 children in the United States and leads to substantial morbidity, premature mortality, and annual health care costs of approximately $335 million [1-4]. Vaso-occlusive pain and acute chest syndrome episodes are the 2 most common SCD-related complications [2]. Hydroxyurea (HU) is the only disease-modifying medication for patients with SCD. HU is a once-daily medication taken by mouth that comes in a capsule or liquid formulation and clinical trials indicate that HU reduces the frequency of vaso-occlusive pain and acute chest syndrome episodes, mortality, and health care costs for pediatric patients [5-8]. In a randomized, controlled study of HU for pediatric patients with SCD, 90% of patients achieved ≥80% HU adherence [9]; however, studies that measure HU adherence in clinical practice suggest that only

35% to 50% of pediatric patients achieve this high adherence rate [10,11]. Children who have poor HU adherence also have worse health outcomes and increased health care costs compared with those who have high adherence [11], but targeted adherence interventions to increase HU adherence remain untested.

HU adherence in pediatric patients with SCD is challenging for multiple reasons. First, children with SCD in the United States are primarily African American. African American children are more likely to live in poverty than non-Hispanic White [12], and impoverished patients are more likely to face systematic medication adherence barriers, such as poor access to pharmacies and higher medication copays than those of higher economic status [13]. Second, HU is a chronic medication, not curative, and the clinical benefits may take months to manifest [14]. Third, children and adolescents with SCD are also a diverse patient population with age-specific adherence barriers. Young children rely on caregivers to administer their medications and may be uncooperative with their medication administration. Adolescents have developmental and psychosocial factors, such as failing to accept that they have a chronic disease that can reduce their adherence [15]. Parents of children with SCD report that dealing with competing responsibilities are a barrier to HU adherence and that receiving support and the positive impact of HU on their children's health facilitate adherence [10]. Finally, it is difficult to determine which patients have poor HU adherence or if interventions are successful at increasing adherence because validated HU adherence measures (eg, self-reported adherence, biomarkers, and refill rates) do not exist for this population of patients or for this medication.

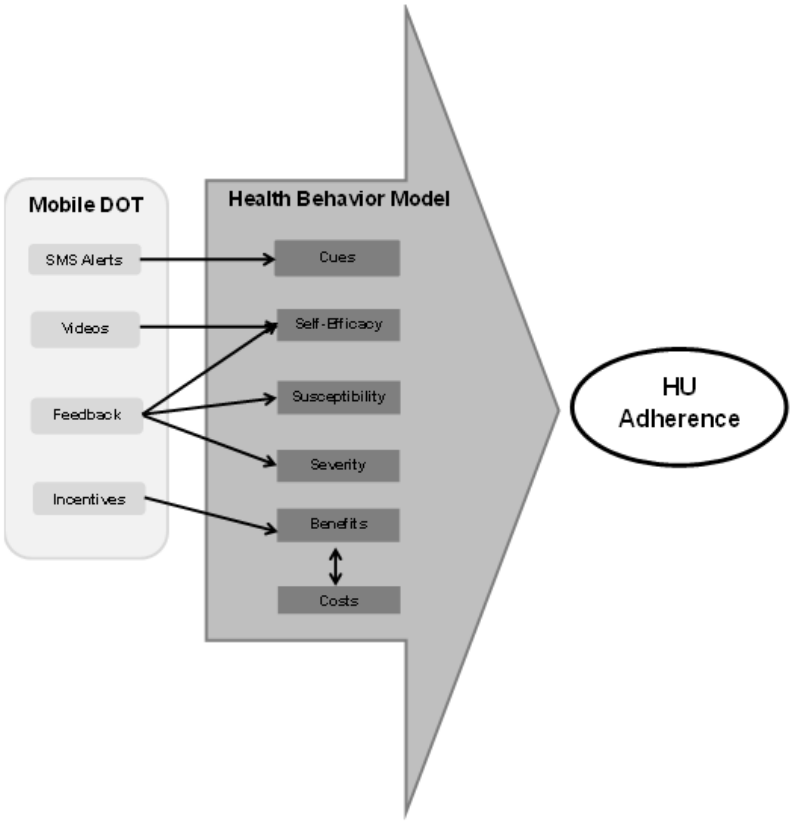
The Health Behavior Model is a theoretical model commonly used to explain patients' medication adherence behavior. The Health Behavior Model suggests that the variables that predict medication adherence behavior are patients' perceived susceptibility, perceived disease severity, perceived benefits, perceived costs, cues to action, and self-efficacy (Figure 1) [16]. Perceived susceptibility is the level to which patients accept that they have a disease, and perceived disease severity is their valuation of whether that disease should receive treatment. Patients balance their perceived benefits of medication (eg, feeling better) with their perceived costs of a medication (eg, side effects). Cues remind patients to take medications and can be internal, such as experiencing a symptom that reminds them to take medication to alleviate that symptom, or external, such as receiving a prompt from another person to take medication. Finally, self-efficacy is patients' confidence in their ability to adhere to a medication [17] and it can be influenced by patients' prior experiences, their observations of others, and by the external input or support that they receive from others.

Many adherence interventions that target individual Health Behavior Model variables exist, but each has its limitations for use in children with SCD. For example, electronic alerts can provide cues to patients to prevent forgetting, but these devices can be expensive and they do not have the ability to remind, monitor, and encourage patients in a single application [18]. Electronic monitoring and providing feedback to patients is a feasible intervention that has been used in high risk, minority children with asthma, and can be an effective strategy because it serves to promote self-efficacy and also educate patients and parents about their disease severity and susceptibility [19-20], but it can be time consuming. Contingency management, or providing monetary incentives to patients for completing a healthy behavior [21-23], increases the benefit of being adherent to patients but can also be expensive and may not sustain adherence long-term [19]. Finally, directly observed therapy (DOT) involves health care workers traveling to observe patients ingest medications. It supports and encourages patients to administer their medications and it is the most successful medication adherence intervention for communicable diseases, including tuberculosis and human immunodeficiency virus [24,25]. However, it is unclear if DOT is effective for a noncommunicable disease or for chronic medications or if it would be cost-effective for these conditions or treatments long-term.

To overcome the multiple adherence barriers that exist for HU and children and adolescents with SCD, we created Mobile Directly Observed Therapy (Mobile DOT), an innovative, multidimensional adherence strategy. We pilot-tested Mobile DOT and found that a small population of children and adolescents with SCD could achieve ≥90% HU adherence using this strategy [26]. Adherence experts suggest that smartphone technology has the potential to improve medication adherence in children with chronic diseases because it takes advantage of a medium that youths already frequently use [27,28]. We designed Mobile DOT to target multiple Health Behavior Model variables using this widely available technology to deliver this multifaceted adherence approach without requiring additional software. Mobile DOT sends text message reminder alerts to cue patients to take HU. Patients record videos of their daily HU administrations to promote self-efficacy through experiential learning. Patients receive feedback from the research staff to increase self-efficacy and impact their perceived susceptibility to SCD-related complications and their perceived SCD severity. Finally, patients receive monetary incentives when they achieve adherence goals to increase the perceived benefits of taking HU (Figure 1).

The current study aims to determine if Mobile DOT increases HU adherence in children with SCD. This paper describes the study protocol in detail, the different components of the Mobile DOT intervention, and the measures that will be obtained. In addition, we will also determine if other measures (biomarkers, self-reported adherence, and refill adherence) are valid HU adherence measures. Finally, since adolescents with SCD are at particularly high risk of complications and death due to poor self-management skills at the time of transition to adult care [4,29], we will explore the impact of Mobile DOT on adolescents' self-management skills. If effective, Mobile DOT has the potential to improve these patients' health outcomes and significantly reduce their costs of care.

Figure 1. Mobile Directly Observed Therapy (Mobile DOT) and the health behavior model. HU: hydroxyurea; SMS: short message service.



Methods

Study Design, Study Visits, and Data Collection

This is an 18-month, single-arm, crossover study that includes both young children and adolescents with SCD (Table 1). Participants' receive 6 months of the Mobile DOT intervention. Their HU adherence during their Mobile DOT phase is compared with their HU adherence during the 6 months prior to enrollment (baseline), and their HU adherence during the 6 months after they receive Mobile DOT (observation). Study visits occur during standard of care monitoring visits and the visit windows are wide to increase this study's feasibility and appeal and to prevent influencing patients' adherence behavior with more frequent visits. Participants receive a US $25 gift card after they complete each study visit for the time they spent completing study surveys.

Setting

Nationwide Children's Hospital (NCH) is a comprehensive, pediatric, tertiary care center. NCH provides care for approximately 380 patients, ages 0-21, with SCD. The principal investigator is a hematologist who provides clinical care for patients with SCD at NCH.

Participants

All participants must provide informed consent to participate. Participants who are <18 years at enrollment are required to have their consenting caregiver provide consent, and participants 9-17 at study entry are required to provide assent. Eligibility criteria include the following: (1) age ≤19 years, (2) diagnosis of SCD (any genotype), (3) prescribed HU for at least the previous 6 months to allow time for patients to have achieved a stable HU dose, (4) planning to receive SCD-related care at NCH for the study duration, (5) participants ≥18 years must have personal daily access to a smartphone capable of recording and submitting videos to Mobile DOT, (6) consenting caregivers of participants <18 years must have daily access to a smartphone capable of recording and submitting videos to Mobile DOT and agree to participate in the participant's HU administration routine, and (7) participants and/or the consenting caregivers must speak English. Patients who receive concurrent, chronic, red cell transfusion therapy (simple or exchange transfusion) are excluded because red cell transfusions affect HU biomarkers. Participants 16- to 19-years old at enrollment are considered adolescents. Participants are recruited using recruitment letters and approached when they present for care. If a prospective participant does not enroll on the study, the reason for why he or she did not enroll is recorded. The enrollment and withdrawal data are reviewed at least monthly during the study to ensure that recruitment and attrition goals are achieved and modification to these procedures are not required to achieve the aims of the study.

Mobile DOT

Mobile DOT includes four aspects: reminder text message alerts, participant videos, feedback on adherence, and monetary incentives. Participants receive a Mobile DOT tutorial after enrollment to confirm that they receive the text message alerts, are able to send acceptable and viewable videos as an email attachment, and understand what is required to receive adherence incentives. Participants also receive a study sheet with information on what to do if they temporarily lose their smartphone and how to contact the research team if they have

technical problems. Participants' telephone numbers are confirmed at each study visit, and participants are responsible for notifying the research team if they change their telephone number or lose or break their smartphone. During the first 2 weeks of the study, the research team follows closely with participants (up to daily) by telephone, text message, or email, if necessary, to resolve any technical issues. The research staff also communicates with participants throughout the study to resolve technical issues by telephone, text message, email, or during appointments at NCH if participants notify the research team that they are having issues.

Secure Mobile DOT Website

A secure Mobile DOT website was built by the research technology team at NCH to send the text message alerts and to receive, store, and view participant videos. The Web application runs under an Apache Web server (version 2.2.15; Apache Software Foundation), was written in the Perl and Javascript languages, and runs on a 64-bit CentOS 6.5 Linux operating system. A secure Microsoft Exchange mail server sends the automated text message alerts to the participants and the background scripts retrieve the emails with the video attachments. All participant videos are stored locally on the operating system in a directory with restricted access. All information about the participants, the emails, and videos received from the participants are stored in a local SQLite (SQLite Consortium) database.

Text Message Reminder Alerts

Participants select their preferred HU medication administration time and create their own personalized text message reminder alerts at enrollment. For example, 2 participants selected, "It's Go Time!" and "Reminder! It's Meds Time" to be sent to remind them to take HU. Up to 4 of these alerts and one confirmation message (if a video is received) are sent to participants and/or the consenting caregivers each day. The alerts are discontinued for that day, once a video is received.

Videos

Participants record their daily HU administration with their smartphone and deliver these videos to the secure website by attaching the video to an email, which they send to the secure server. Participants are informed during the consent process that there is a risk that these videos could potentially be intercepted during the delivery process but that they are secure once they are received by the website. This information is also included specifically in their informed consent document. Participants are instructed to take the HU dose prescribed by their provider, have their labeled HU medication bottle and dose ready when they begin recording their video, and that each video be brief, unique, and continuously recorded in high enough definition to allow for easy recognition of the participant and HU in its capsule or liquid formulation. They are trained so that the videos include the participant ingesting HU and the participant opening their mouth after they ingest HU. Participants are told to submit each video on the day that it was recorded, but videos that are received after that date are still considered valid if they are received within 7 days or if technical issue occurred.

Consenting caregivers are responsible for informing other supervising adults how to submit the videos if they are not available. In the unusual event that participants are instructed to temporarily discontinue HU by their SCD providers, participants are instructed to continue to submit daily videos stating this. Participants are not required to submit videos if they are seen in the emergency department. If they are hospitalized, their electronic medical administration records are used to confirm HU adherence. Temporary lapses (up to 5 days) in smartphone access are allowed, but participants must email, text message, or leave a voicemail for the research team each of these days to confirm that HU was taken.

Adherence Feedback

The research staff observes all submitted videos within 72 hours of receipt and provides feedback to study participants to encourage HU adherence. This communication occurs after each missed video and after adherence goals are achieved (≥90% HU video adherence for 30 days). The research staff determines whether this feedback should occur via text message, email, or telephone call, so that it does not become intrusive and the type of communication that is used is documented.

Incentives

Participants receive a US $30 gift card within 2 weeks if they achieve ≥90% video HU adherence for each 30-day period during the Mobile DOT phase of the study. Partial compensation is not provided. The 30-day study periods during the Mobile DOT phase are sequential, but participants who miss more than 3 videos early in a period can begin the next 30-day period early, if they submit at least 5 consecutive videos.

Measures

Medication Possession Ratio

Participants sign a pharmacy release form at enrollment and the list of pharmacies that they use is reviewed with the research staff at each study visit. Participants' HU refill records and hospitalization medication administration records are used to calculate their medication possession ratio (MPR) for each study phase using the following formula: MPR is the total number of days the participant had access to HU during the study phase divided by the total number of days that the participant was prescribed HU during the study phase.

Laboratory Data

Participants' laboratory studies are obtained per NCH standard of care for patients prescribed HU. This monitoring includes measuring mean corpuscular volume (MCV) and fetal hemoglobin (HbF) at each monitoring visit. Prior studies show that HU induces HbF production and increases MCV [30,31], but it is unknown if these routinely obtained biomarkers are valid HU adherence measures. HbF at NCH is measured using Sebia Zone Electrophoresis and MCV is measured using a standard coulter counter.

Urine Assay

In addition to standard laboratory tests, participants provide urine samples at their study visits (Table 1). These urine samples are analyzed using gas chromatography mass spectrometry to

detect if HU is present. This method will be used to detect recent HU exposure and can detect HU in concentrations >1 µg/mL in the urine [32]. We will use this data to classify patients as adherent if they have levels >1 µg/mL and nonadherent if they have undetectable levels. Because HU adherence over multiple months is required to achieve a clinical benefit and this method can only determine if recent HU exposure has occurred, we will determine if intermittently detecting HU in the urine at study visits is correlated with video observed adherence.

Morisky Medication Adherence Scale, 4-Item

Participants complete the Morisky Medication Adherence Scale, 4-item (MMAS-4) at multiple time-points during the study (Table 1). The MMAS-4 is a validated, self-report adherence survey for adults that includes 4 yes/no questions [33-35], but it is unknown if this survey is valid in children with SCD.

Transition Readiness Assessment Questionnaire

Adolescents' (16-19 years) self-management skills before and after receiving Mobile DOT are measured using the Transition Readiness Assessment Questionnaire (TRAQ) 5.0 (Table 1). The TRAQ 5.0 is a 20-item validated, patient-centered instrument that has 2 domains, self-management and self-advocacy [36].

Newest Vital Sign

Because health literacy has the potential to influence self-management [34], adolescent participants complete the newest vital sign (NVS) before and after receiving Mobile DOT (Table 1). The NVS is a validated survey that identifies patients at risk for low health literacy [37,38].

Satisfaction Survey

Participants complete the 5-point Likert scale Mobile DOT satisfaction survey that was created and modified during the pilot study to determine if participants found Mobile DOT intrusive, usable, and sustainable (Table 1). Participants are also asked to estimate the amount of time it takes to record the daily videos and to rate the importance of the incentives on their adherence behaviors.

Survey Completion

Participants complete all the surveys independently if they are ≥14-years old. Consenting caregivers of participants complete the surveys if the participant is <14. Surveys are completed electronically on an iPad and data is stored in a secure REDCap (REDCap Consortium) database.

Clinical Outcomes

Participants' electronic medical records are used to track the frequency of SCD-specific clinical outcomes (eg, vaso-occlusive pain episodes, acute chest syndrome episodes, or need for acute red cell transfusion) that were reduced with HU in the prior pediatric clinical trials [5-8].

Study Withdrawal

Participants who do not send videos or respond to communications for more than 30 days during the Mobile DOT phase are withdrawn from the study because we are unable to confirm that they still have smartphone access and are receiving all of the Mobile DOT components. Participants are also able to voluntarily withdraw from the study at any time. Withdrawn participants complete a final study visit and we record the reason for withdraw (Table 1).

Statistical Analysis

To determine if Mobile DOT improves HU adherence, we will compare the proportion of participants who achieve ≥80% HU adherence by MPR during the Mobile DOT phase with the proportion that achieved this level of adherence at baseline. This adherence level was chosen because improved clinical outcomes were seen when 90% of patients achieved this level of adherence during a large pediatric HU clinical trial [5,9]. We assume that we will have a 20% attrition rate and plan to enroll 72 participants to have 60 evaluable participants. This sample size will have 80% power, with an odds ratio of 6.869, using a one-sided McNemar test, and a significance level of .05.

We will use Spearman correlation coefficient to determine the correlation between video observed HU adherence and the other collected HU adherence measures (MMAS-4, MPR, MCV, HbF, and urine HU assay). Our sample size will have 80% power, at an alpha=.05, to detect a correlation coefficient ≥.35 between video adherence and the other adherence measures. To explore the impact of Mobile DOT on adolescents' self-management skills, we will use McNemar test, and we will have 80% power to detect an effect size of 0.54, with a mean difference of 1 and standard deviation equal to 1.85, using a two-sided paired *t* test, with alpha=.05.

Table 1. Study design, visits, and data collection.

	Study phase						
	Baseline	Mobile DOT[a]			Observation		Off study
Study visit	No visit	1	2	3	4	5	Withdraw
Study day	−180 to 1	0	30-136	165-211	240- 316	345- 391	Anytime
Data collection							
Demographic data		x					
Hydroxyurea dose (mg/kg/d)	x	x	x	x	x	x	x
Pharmacy list		x	x	x	x	x	x
Medication possession ratio[b]	x			x		x	x
Phone numbers		x	x	x	x	x	x
Morisky Medication Adherence Scale, 4-item		x	x	x	x	x	x
Satisfaction survey			x	x			x
Newest vital sign[c]		x		x		x	x
Transition Readiness Assessment Questionnaire 5.0[c]		x		x		x	x
Laboratory data		x	x	x	x	x	x
Urine assay		x	x	x	x	x	x
Indication for withdraw							x

[a]Mobile DOT: Mobile Directly Observed Therapy.

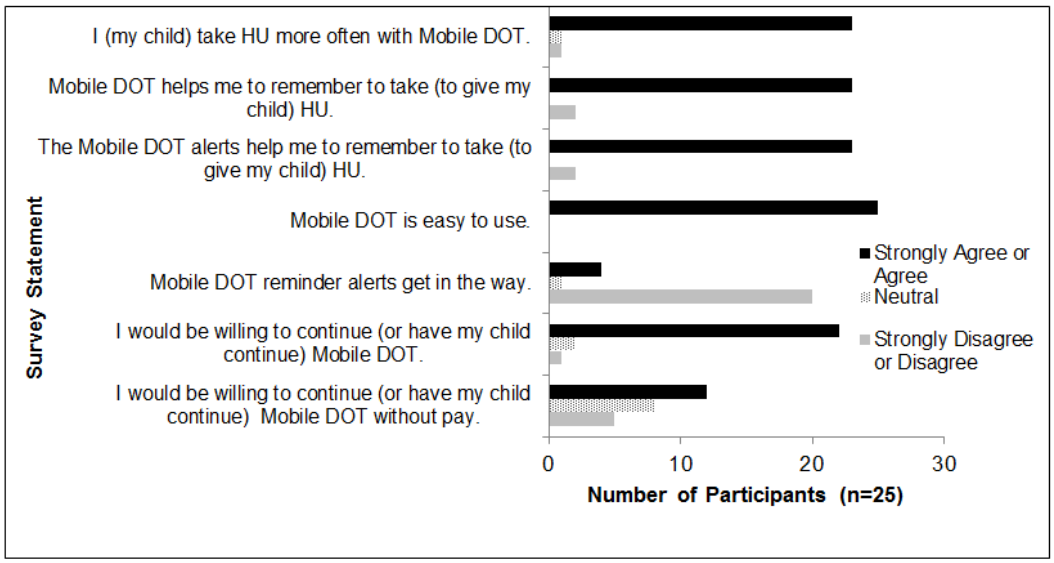
[b]Medication possession ratio is calculated for each study phase and calculated after participants complete the study.

[c]Only for adolescent participants (those who are 16- to 19-years old) at enrollment.

Results

This project was funded by the National Heart, Lung, and Blood Institute in September 2015. Participant enrollment is ongoing and we anticipate that all participants will have completed the study by early 2018. To date, we have approached 65 patients, enrolled 45, and 39 have either withdrawn (n=14) or completed their Visit 3 (n=25). Preliminary review of the satisfaction survey results show that most participants (n=38) complete Mobile DOT in less than 5 minutes each day. Most of the participants who completed the Mobile DOT phase of the study (n=25) also reported that they were satisfied with the intervention (Figure 2). Patients have withdrawn from the study because they either stopped HU or moved out of the country (n=2), stopped sending videos and responding to communications (n=6), had smartphone technical issues (n=1), lived in multiple homes that did not all have reliable smartphone access (n=3), or did not like receiving the text message alerts and did not have reliable smartphone access (n=2).

Figure 2. Preliminary satisfaction survey responses for participants that have completed the intervention phase. Mobile DOT: Mobile Directly Observed Therapy; HU: hydroxyurea.



Discussion

Recruitment and Study Progress

We are successfully recruiting a large number of eligible patients. Similar to other feasibility studies of electronic interventions studies in minority populations [20], our preliminary satisfaction survey results suggest that participants who complete the intervention report that it improves their HU adherence. Our study attrition rate (31%) has been higher than anticipated. Because inconsistent access to a smartphone was a common reason for attrition in early participants, we have modified our eligibility criteria, which previously stated that participants had to "have access to a smartphone" to be more specific and specifically state that participants "have daily access to a smartphone" to limit future attrition.

Future Implications

Despite demonstrated efficacy of HU, poor adherence is common among pediatric patients, and results in worse health outcomes [9-11]. Mobile DOT has the potential to fill an important gap in treating children with SCD by targeting specific adherence barriers for this patient population and multiple Health Behavior Model constructs. It leverages widely available smartphone technology to deliver a multifaceted adherence approach to a diverse patient population. If successful, it will increase HU adherence, which has the potential to improve patients' clinical outcomes and reduce health care costs.

In addition, this study has the potential to inform other aspects of SCD-related patient care and the medication adherence field. First, determining the validity of other potential HU adherence measures will allow SCD providers and investigators to determine if routinely obtained (HbF and MCV), or easily obtained measures (MMAS-4 or a urine assay) can be used to identify patients with poor HU adherence and measure the effect of HU adherence interventions. Second, if Mobile DOT is successful in this complex patient population, this strategy could be tested in other patient populations where medication nonadherence is common and challenging. Lastly, exploring the effect that Mobile DOT has on adolescents' self-management skills may inform future interventions to improve adolescent transition and result in improved health outcomes in these high-risk patients.

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Conflicts of Interest

None declared.

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Abbreviations

HbF: fetal hemoglobin
HU: hydroxyurea
MCV: mean corpuscular volume
MPR: medication possession ratio
Mobile DOT: Mobile Directly Observed Therapy
MMAS-4: Morisky Medication Adherence Scale
NCH: Nationwide Children's Hospital
NVS: newest vital sign
SCD: sickle cell disease
TRAQ: Transition Readiness Assessment Questionnaire

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Protocol

A Checklist for the Conduct, Reporting, and Appraisal of Microcosting Studies in Health Care: Protocol Development

Jennifer Prah Ruger[1,2], MA, MSL, MSc, PhD; Marian Reiff[3], MSc, PhD

[1]School of Social Policy & Practice, University of Pennsylvania, Philadelphia, PA, United States

[2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

[3]Department of Medical Ethics & Health Policy, University of Pennsylvania, Philadelphia, PA, United States

Corresponding Author:
Jennifer Prah Ruger, MA, MSL, MSc, PhD
School of Social Policy & Practice
University of Pennsylvania
3701 Locust Walk
Philadelphia, PA, 19104
United States
Phone: 1 215 746 1330
Fax: 1 215 573 2099
Email: jenpr@upenn.edu

Abstract

Background: Microcosting is a cost estimation method that requires the collection of detailed data on resources utilized, and the unit costs of those resources in order to identify actual resource use and economic costs. Microcosting findings reflect the true costs to health care systems and to society, and are able to provide transparent and consistent estimates. Many economic evaluations in health and medicine use charges, prices, or payments as a proxy for cost. However, using charges, prices, or payments rather than the true costs of resources can result in inaccurate estimates. There is currently no existing checklist or guideline for the conduct, reporting, or appraisal of microcosting studies in health care interventions.

Objective: The aim of this study is to create a checklist and guideline for the conduct, reporting, and appraisal of microcosting studies in health care interventions.

Methods: Appropriate potential domains and items will be identified through (1) a systematic review of all published microcosting studies of health and medical interventions, strategies, and programs; (2) review of published checklists and guidelines for economic evaluations of health interventions, and selection of items relevant for microcosting studies; and (3) theoretical analysis of economic concepts relevant for microcosting. Item selection, formulation, and reduction will be conducted by the research team in order to develop an initial pool of items for evaluation by an expert panel comprising individuals with expertise in microcosting and economic evaluation of health interventions. A modified Delphi process will be conducted to achieve consensus on the checklist. A pilot test will be conducted on a selection of the articles selected for the previous systematic review of published microcosting studies.

Results: The project is currently in progress.

Conclusions: Standardization of the methods used to conduct, report or appraise microcosting studies will enhance the consistency, transparency, and comparability of future microcosting studies. This will be the first checklist for microcosting studies to accomplish these goals and will be a timely and important contribution to the health economic and health policy literature. In addition to its usefulness to health economists and researchers, it will also benefit journal editors and decision-makers who require accurate cost estimates to deliver health care.

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KEYWORDS

microcosting; economic evaluation; cost analysis; checklist; guidelines

Introduction

As health care costs increase worldwide, there is growing pressure to more efficiently use our limited health care resources. Economic evaluations are used to identify, measure, and compare the costs of health interventions and programs in order to help make decisions about resource allocation and program implementation [1]. A first step for controlling costs is the accurate measurement of the true costs of health interventions and programs. Many economic evaluations in health and medicine use charges, prices or payments as a proxy for cost. However, using charges, prices or payments rather than the true costs of resources can result in inaccurate estimates [2,3]. Microcosting is a cost estimation method that provides detailed and accurate cost data by direct enumeration and costing of all the resources used in the provision of an intervention [4,5]. In contrast to gross-costing studies, which use reimbursement amounts or charges or aggregate cost estimates, microcosting requires the collection of detailed data on resources utilized and the unit costs of those resources in order to identify actual resource use and economic costs. Microcosting findings more accurately reflect the true costs of an intervention to health care systems and to society, and are able to provide transparent and consistent estimates. Microcosting has been shown to improve the validity and reliability of total cost estimates for hospital services and for diagnostic or treatment interventions where costs are not available or evolving [6-9]. Microcosting involves the direct measurement of cost by observation and survey and is especially useful for identifying the actual costs of new health interventions or programs, when existing administrative data are not sufficiently sensitive or when there are no established estimates for their aggregate costs [10-12]. There is an increasing need for microcosting in decision making in health policy, and it is important that studies are conducted according to consistent principles and that they are reported in a way that allows for transparency and comparability across studies.

The importance of rigor and transparency in reporting of health economic evaluations has been addressed by systematic reviews of economic evaluation studies and the development of standards and guidelines for the conduct and reporting of economic evaluations of health interventions [11,13-16]. However, the existing guidelines and checklists do not provide sufficient detail for the methods and techniques involved in microcosting studies [6,10,11,13,17-19]. These instruments do not provide a methodological framework and analytic components specific to the inclusion of items to evaluate microcosting studies. The value of checklists for improving the quality of studies and reports in health care has been demonstrated [20,21]. However, there is currently no existing checklist or guideline for the conduct, reporting or appraisal of microcosting studies in health care interventions. We propose to develop a formal checklist, informed by a theoretically- and empirically-based framework, for the conduct, reporting, and appraisal of microcosting studies in health care. The checklist will (1) provide a framework and guidance for the conduct of microcosting studies; (2) assist in the development of manuscripts reporting microcosting studies and reviewing the manuscripts for publication; and (3) lead to more consistency and transparency in conducting and reporting of microcosting studies, allowing for comparison of the studies' findings. Ultimately, this protocol will lead to the development of a checklist for the conduct, reporting, and appraisal of microcosting studies in health care, improving the quality of these studies.

Methods

The design of this protocol for the development of a microcosting checklist utilizes recommendations in the Guidance for Developers of Health Research Reporting Guidelines [20,22], and draws on approaches described in published reports of checklist development for reporting and appraisal of economic evaluations of health interventions [13-16,23-29].

The checklist will be developed in the following four stages: (1) identification of appropriate potential domains and items, (2) tem selection, formulation, and reduction, (3) external review (further item reduction and revision), and (4) testing and assessment.

Identification of Potential Checklist Items

To identify the important domains and items to be considered for inclusion in a standardized conducting and reporting guideline for microcosting studies in health care, the following three methods will be used: (1) systematic review of microcosting studies (Method 1), (2) review of checklists and guidelines for economic evaluations of health interventions, and selection of items relevant for microcosting studies (Method 2), and (3) theoretical analysis of economic concepts relevant for microcosting (Method 3). Triangulation of the three methods will produce a preliminary list of items that will be more comprehensive and inclusive than items identified from any one method alone.

Method 1

A systematic review is being conducted of all published microcosting studies of health and medical interventions, strategies, and programs [19]. A comprehensive database has been created, consisting of all microcosting studies published in English. A research objective is to evaluate the quality of published microcosting studies in health care. Details of the search criteria and methodology for data extraction are published elsewhere [19].

The research team will critically assess the quality of each microcosting study included in the systematic review using checklists recommended by the Campbell and Cochrane Economic Methods Group [30] for appraising reporting and methodological quality of economic evaluations. Specifically, the Drummond checklist [31] and the Evers checklist [26] will be used to evaluate the quality and risk of bias of single effectiveness studies; the Philips checklist [32] will be used to evaluate the quality and risk of bias of studies that use decision analytic modeling. The Fukuda and Immanaka criteria [16] will be used to assess the transparency of cost estimates. The Consolidated Health Economic Evaluating Reporting Standards (CHEERS) checklist will be used to assess reporting quality [14]. These criteria categorize studies into levels of transparency based on whether the study clarifies the cost components included, reports the quantity and unit price of resources

separately, and reports an estimate of each component. These checklists were employed because they provided the most relevant criteria for assessing economic evaluations including costing, even though they were not developed specifically to assess microcosting studies.

The checklist items will be filled out independently by the two reviewers conducting the systematic review. Disagreements will be discussed and resolved by the two reviewers, and a third researcher will be consulted if needed. The strengths, inadequacies, and redundancies of the existing checklists used to assess quality and bias of the microcosting studies in the systematic review will be documented. Experience with using the existing checklists (ie, Drummond, Evers, Philips, Fukuda, and CHEERS) for study quality and risk of bias in economic evaluations in the systematic review will demonstrate which items are relevant to assessing the quality and reporting of microcosting studies and which are not. Items are scored as "yes", "no", "not clear" or "not applicable". Those that are scored as "not applicable" by all three reviewers for all studies will be excluded. We will document which items in the existing checklists successfully identified relevant criteria for microcosting. Only the relevant items will be selected for consideration for a preliminary list of items to be included in the checklist. Some items may be modified to fit the needs of a microcosting evaluation. We will also note whether the checklists lacked items to assess specific criteria that are relevant, and should be included, for microcosting studies. Criteria that are inadequately covered will be identified and new items will be formulated for these criteria in the new checklist.

The research team conducting the systematic review will extract data from the microcosting studies using a standardized data collection form based on the CHEERS guidelines [14,15], guidance from the Campbell and Cochrane Economics Methods Group [30], and the research team's previous experience with systematic reviews of health economic studies and microcosting studies [33-38]. Data will be extracted from microcosting studies in a number of areas including (1) cost components included (eg, personnel costs, consumables/materials/supplies cost, medication costs, facility costs, transportation costs, productivity loss); (2) whether the study reports input utilization quantity and unit cost data separately; (3) method of quantity data collection used (eg, time-motion study, patient self-report, cost-accounting database, provider/staff interview); and (4) method of unit cost data collection (eg, invoice amount, hospital/clinic/provider price catalogue, standard fee schedule) [19]. New items will be formulated by the research team conducting the systematic review based on the data extracted from and critical review of the published microcosting studies.

Method 2

A comprehensive search for published checklists and guidelines used to evaluate the quality, conduct, and reporting of costing in economic analyses of health interventions and programs will be performed. References to published articles describing reporting guidelines or checklists to evaluate the quality of economic evaluations of health interventions will be identified. The references in the selected articles will also be manually reviewed in an iterative process to identify all relevant checklists and guidelines. We will also manually review the references from systematic reviews conducted to evaluate the conduct and reporting of economic evaluations of health interventions including the CHEERS statement [14,15], and the "Best practices for conducting economic evaluations in health care: a systematic review of quality assessment tools" AHRQ report [13].

The search will include the articles in the systematic review (Method 1). In addition, the terms used to index the relevant articles will be identified and used to perform a broad electronic literature search to identify additional checklists and guidelines. Searches based on terms identified to date include (1) ("microcost" OR "microcost") AND ("questionnaire" OR "checklist" OR "guideline"); and (2) ("cost" OR "cost analysis") AND ("questionnaire" OR "checklist" OR "guideline") AND "health care quality, access and evaluation"). We will search PubMed, EconLit, BIOSIS Previews, Embase, Scopus and the National Health Service Economic Evaluation database (NHS EED) to identify relevant English language articles.

From the checklists and guidelines identified in the selected publications, the items relevant for assessing or reporting costing of health interventions or programs will be extracted. These items will be compiled into a comprehensive list and categorized into domains. Within each domain, we will review and narrow down selection of items and will remove any duplicates. Only items considered relevant to microcosting will be retained based on consensus of the research team. We will provide the rationale for inclusion or exclusion of each item and domain.

Method 3

A theoretical analysis of economic concepts relevant for microcosting will be conducted. A search has been done for literature in welfare economics and microeconomics and for literature in costing that defines microcosting and differentiates microcosting from gross costing and other costing methods. The latter search included articles in the systematic review, references from these articles, and references from checklists for economic evaluations. The difference between the use of charges, prices, or payments to assess costs and estimates of the real costs of resources will be examined. An analytical framework for conducting microcosting studies will be developed and conceptual domains relevant for microcosting will be discussed. Any domains that are missing or not adequately represented in any current economic evaluation checklist will be identified. Newly formulated checklist items (not included in existing checklists) will be developed for each conceptual domain for inclusion in the new checklist.

Creation of an Initial Item Pool

Items derived using each method (ie, the systematic review, checklist review, and theoretical analysis) will be compiled into a comprehensive list. The overlap and variation in domains and items will be documented and any duplicate or redundant items will be removed. The pool of remaining items will be discussed and evaluated by research team members.

New items may be formulated based on the findings of criteria deemed relevant and necessary for microcosting studies but inadequately covered by existing checklists or guidelines. The

addition of new items will also be guided by the analysis of the systematic review and by the theoretical analysis. Through deliberation and discussion, items will be refined and a consensus will be reached in the selection of items to be included in a preliminary list.

External Review by Expert Panel

The checklist will be developed using a modified Delphi method, designed for reaching consensus among an expert panel. Delphi is a "method for structuring a group communication process" [39]. It consists of an iterative multistage process with the goal of consensus among a group of experts [40,41]. In conventional Delphi exercises a list of issues to be considered is usually developed by open-ended questions in the first round, and the participants usually remain anonymous. The following two major modifications that have been reported in the literature will be employed: (1) the use of a literature review to determine in advance the list of issues to be considered and ranked by the panel [40-42], and (2) the possible addition of an online/electronic panel discussion or workshop following the survey rounds to resolve any lack of consensus [40,43,44]. Usually not all panel participants are able to attend the online/electronic panel or workshop, and the discussion will breach the anonymity of participants who attend. If a panel or workshop is held, permission will be obtained from participants to use their names in any acknowledgements in subsequent publications. These modifications to the traditional Delphi process can save time and financial resources, and are appropriate for our topic, which is limited in scope and requires a narrow range of expertise for which there are only a limited number of qualified panel members [40,43]. Our Delphi process will be similar to that described by Husereau et al in the development of the CHEERS report [15].

An international expert panel will be recruited and a modified Delphi exercise will be conducted to rank the items in the preliminary list. Panel participants will be selected based on their expertise in the conduct and reporting of economic evaluations, and specific expertise in microcosting studies and methodology. Potential panel participants will include (1) content specialists who have conducted and published full microcosting studies and who are identified in the course of the systematic literature review; (2) international researchers who have expertise in economic evaluations for health interventions with specific interest in costing studies; (3) journal editors interested in publishing microcosting studies; and (4) methodologists with expertise in checklist development. Invitation emails will be sent to potential members of the expert panel, including a description of the project and the expected timeline. We will invite participants to complete an initial survey to rank the items and provide comments, and if possible, to complete a follow-up survey and discussion and/or workshop electronically, with results reported according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [45].

The preliminary list of items will be sent to panel participants in the form of a survey. The procedures used in the development of the CHEERS checklist will be followed to obtain feedback from the panel participants [15]. Each panel participant will be asked to rate the importance of each item by using a 10-point Likert scale from 1 ("not at all important") to 10 ("extremely important"). In addition, they will rate their confidence in judging the importance of each item on the basis of their current knowledge from 1 ("not confident") to 3 ("very confident"). The participants will also be asked to comment on the wording and options for scoring, and recommend deletion or addition of items. The survey will be accessible either online or in print depending on the preference of the respondent.

Survey responses from round 1 will be recorded in an electronic spreadsheet. The items will be ranked by importance scores weighted by confidence ratings. Categories of importance will be created based on previous published reports [15,22]. Items will be labeled according to their weighted average score. There are various approaches to items rank ordering. We will pilot test the method where items with a weighted average score of more than 8 will be labeled as "very important/included", 7-8 as "high importance/likely included", 5-6 as "moderate importance/possibly included", and 0-4 as "low importance/not included". Comments for each item will be collated and summarized. The research team will review and revise the item list through discussion based on survey responses.

A revised list of items will be compiled including the information about item ranks and averages, and sent to members of the expert panel who agreed to participate in a second round of review. Respondents will be informed that items with a score of 6 or less (labeled "possibly included") will be included in the final checklist only if they receive a higher score. Item-specific comments from round 1 will be included below each ranked item. After round 2, items with a score of 6 or less will be labeled "rejected" and not considered for the final checklist [15]. Responses will be categorized as for round 1, and comments will be collated and reviewed by the research team. An online meeting may be convened for expert panel participants to discuss the remaining items. The research team will revise the checklist based on the comments and discussion in the meeting.

Pilot Test

A selection of the full and predominant microcosting articles from the systematic review data will be used to pilot test the new checklist. The articles will be rated by two independent reviewers. Reliability estimates will be calculated and discrepancies will be discussed with the research team. Items may be modified or further explained in order to improve clarity and comprehension. The checklist scores will also be compared with scores for the coded checklists used in the systematic review (eg, the Drummond, Evers, Philips, Fukuda, and CHEERS checklists) in order to assess external validity.

Results

The project is currently in progress.

Discussion

Principal Findings

Currently, health systems in the United States and internationally are faced with increasing costs and limited resources. Accurate

cost assessments are essential in order to plan programs and enact health care policies in a cost-efficient manner. Microcosting involves the direct measurement of cost by observation and survey and is used to find the actual cost of new health interventions and programs, or when existing administrative data are not sufficiently sensitive [10,12]. The concepts and methodologies for microcosting studies have been evolving over the past three decades [2,6,10,11,17-19,34-36,46-57], and an increasing number of studies have utilized microcosting techniques in recent years. However, existing instruments and guidelines for economic evaluations lack the framework and specific components required to guide the conduct and reporting of microcosting studies. The aim of this project is to develop a checklist, based on theoretical and empirical research and expert review, to assist with the conduct and reporting of microcosting studies. Standardization of the methods will enhance the consistency, transparency, and comparability of future microcosting studies.

Our review of guidelines and checklists included those that were intended for the conduct, reporting, and appraisal of economic evaluations for health interventions. In some cases, the specific purpose was stated, for example the stated purpose of the CHEERS guidelines is for reporting (and not for conduct) of studies. Several checklists have been designed specifically for quality assessment (eg, Drummond, Evers, Philips). These checklists consist of items that may be relevant for a combination of conduct, reporting, and appraisal without indicating a specific intention. In some cases, the content of the item may be similar, but the wording may indicate the relevance for conduct or reporting (eg, “resource use included” vs “resource use stated”). Checklists may not separate the quality of reporting from the validity of the design and conduct of a study, and elements of checklists intended for evaluating the quality of reporting may therefore be used as guidance in designing studies [13]. Our checklist is intended to provide a framework to consider when conducting, reporting, and/or appraising a microcosting study. In designing our checklist, we will be attentive to the purpose of each domain and each item, and will indicate the relevance for conduct, reporting and appraisal.

This protocol draws on recommendations for developing reporting guidelines [20,21], and on methodologies for developing published checklists for economic evaluations of health interventions [13-16]. Initial steps will include identifying a need for new guidance through a systematic literature review of microcosting studies, and a literature search to identify items used for costing in checklists for health economic evaluations and theoretical analyses. These three activities will be used to generate a preliminary list of items to include when conducting and reporting microcosting studies. The preliminary list will be disseminated to members of an expert panel, identified by the research team as having particular expertise in microcosting analysis and economic evaluation. Panel members will be asked to rate the importance of each item on a Likert scale and the average scores, weighted by confidence level, will be used to rank items. Items will then be categorized and ranked by the research team, based on scores and comments of panel members. Panel members will participate in a second round of review and possibly an online meeting to discuss items to be included in the final checklist. The checklist will be evaluated through a pilot test conducted by the research team in order to assess reliability and validity. The pilot test will also identify any issues that require clarification and determine how useable the checklist is in the real world [20].

Conclusion

This will be the first checklist for the conduct and reporting of microcosting studies, and will be a timely and important contribution to the health economic and health policy literature. In addition to its usefulness to health economists and researchers, it will also benefit journal editors and decision-makers who require accurate cost estimates in order to meet the goals of the health system to efficiently deliver health care, including electronic health (eHealth) interventions [58]. This framework will help to standardize the methods of microcosting, thereby allowing for greater transparency and comparability of costs among different health care interventions and programs.

Conflicts of Interest

None declared.

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Abbreviations

CHEERS: Consolidated Health Economic Evaluating Reporting Standards
CHERRIES: Checklist for Reporting Results of Internet E-Surveys

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Protocol

Stigma and Its Impact on Glucose Control Among Youth With Diabetes: Protocol for a Canada-Wide Study

Anne-Sophie Brazeau[1], PhD, RD; Meranda Nakhla[1], MD, MSc, FRCPC; Michael Wright[2], DEC; Constadina Panagiotopoulos[3], MD, FRCPC; Daniele Pacaud[4], MD, FRCPC; Mélanie Henderson[5], MD, PhD, FRCPC; Elham Rahme[1], PhD; Deborah Da Costa[1], PhD; Kaberi Dasgupta[1], MD, MSc, FRCPC

[1]Department of Medicine, McGill University, Montreal, QC, Canada

[2]Concordia University, Montreal, QC, Canada

[3]BC Children's Hospital, University of British Columbia, Vancouver, BC, Canada

[4]Alberta Children's Hospital, University of Calgary, Calgary, AB, Canada

[5]Centre Hospitalier Universitaire Sainte-Justine, Université de Montréal, Montreal, QC, Canada

Corresponding Author:
Kaberi Dasgupta, MD, MSc, FRCPC
Department of Medicine
McGill University
687 Pine Avenue West, V-Building (V1.08)
Montreal, QC, H3A 1A1
Canada
Phone: 1 514 934 1934 ext 44715
Fax: 1 514 934 8293
Email: kaberi.dasgupta@mcgill.ca

Abstract

Background: Stigma in chronic disease involves unwarranted rejection, judgement, or exclusion by others based on the chronic disease itself.

Objective: We aim to determine the prevalence of stigma among youth and young adults with type 1 diabetes in Canada, to assess associations between stigma and glycemic control, and to explore ways to address stigma related to type 1 diabetes.

Methods: The study includes 3 distinct phases: (1) refinement of survey questions, (2) assessment of test-retest reliability, and (3) a data collection and analysis phase (online survey and mailed-in capillary blood sample to assess hemoglobin A1c). A total of 380 youth and young adults (14 to 24 years old) with type 1 diabetes are being recruited through social media and clinic posters.

Results: Phases 1 and 2 are complete, and phase 3 is in progress. Thirty participants completed phase 2. The survey includes the Barriers to Diabetes Adherence in adolescent scale (intraclass correlation [ICC]=0.967, 95% CI 0.931-0.984), the Self-Efficacy for Diabetes Self-Management measure (ICC=0.952, 95% CI 0.899-0.977), the World Health Organization-5 Well-Being Index (ICC=0.860, 95% CI 0.705-0.933), 12 closed-ended questions, and an additional 5 open-ended questions to explore challenges and solutions developed by the team of experts, including a patient representative.

Conclusions: This will be the first large-scale survey to estimate the prevalence of stigma in young people with type 1 diabetes. The results of this study will allow for an appreciation of the magnitude of the problem and the need for developing and implementing solutions. This work is intended to provide an initial understanding of youth perspectives on the challenges of living with type 1 diabetes and will serve as a foundation for future research and action to help youth improve their experience of living with diabetes.

Trial Registration: ClinicalTrials.gov NCT02796248, https://clinicaltrials.gov/ct2/show/NCT02796248 (Archived at http://www.webcitation.org/6mhenww3o).

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KEYWORDS

type 1 diabetes; youth; stigma; perception; well-being

Introduction

Many youth with diabetes struggle with self-esteem, body image, social role definition, and peer-related issues [1]. During adolescence, peer relationships and acceptance by friends are essential [2]. In an effort to avoid being perceived as different by their peers, adolescents may engage in passive coping strategies such as withdrawal, avoidance of activities, and nonadherence to treatment regimens [3-5]. These behaviors may continue into early adulthood, now termed emerging adulthood. This period between the ages of 18 and 30 years is characterized by the challenges of establishing autonomy, personal identity, and making vocational and educational choices [6]. Emerging adults with diabetes must contend with complex developmental tasks while also dealing with their condition and its treatment [7].

Stigma related to chronic disease may be defined as, "negative social judgement based on a feature of a condition or its management that leads to perceived or experienced exclusion, rejection, blame, stereotyping and/or status loss" [8]. Adolescence and young adulthood are life stages that may be particularly vulnerable to stigma and its adverse impacts.

Canadian Chronic Disease Surveillance System data (2008/09) indicate that 20,492 children and adolescents (aged 10-19 years old) and 15,861 young adults (aged 20-24 years old) have diabetes [9]. Type 1 diabetes accounts for approximately 95% of diabetes in childhood and adolescence, and a large proportion of diabetes in emerging adults [10]. The universal and persistent need for insulin therapy in type 1 diabetes may compound the likelihood of stigma. Another reported cause of stigma is the loss of control resulting from hypoglycemia [11]. There is a paucity of evidence-based strategies to help people live with type 1 diabetes. Living with diabetes implies not only achieving control of blood glucose levels, but also feeling empowered, healthy, and happy. These factors have positive effects on quality of life [12]. Stigma may adversely impact diabetes management, mood, and a sense of well-being; longitudinal studies indicate that even mild emotional distress, a potential consequence of stigma, predicts *worse-than-expected* clinical and psychological outcomes [13]. Conversely, addressing stigma has the potential to enhance emotional states and health behaviors.

Stigma in diabetes has been understudied. Some recent investigations have examined stigma in adults with type 1 diabetes through in-depth interviews [8,14]. Such qualitative evaluations provide important insights into the causes and experiences of stigma, but cannot capture the prevalence of the problem. This issue is a key component that will be addressed in this study using a large, nation-wide sample.

The primary objective of this study is to determine the prevalence of stigma among youth and young adults with type 1 diabetes in Canada, through a nation-wide online survey. The survey includes a key subset of stigma-related questions used in a previous study [15]. In addition, in partnership with patient representatives and health care providers we selected, refined, and developed a set of both closed-ended and open-ended questions to more broadly capture the construct of stigma (sources, experiences, and consequences of stigma) and the challenges of living with type 1 diabetes. An innovative aspect of our study is that we are asking participants to mail in a capillary blood sample for assessment of glycemic control (hemoglobin A1c, a measure that captures overall glucose control over the prior 2-to-3 months [16]). Using these samples, in addition to the survey questions, we will assess the associations between stigma and hemoglobin A1c levels, hypoglycemia frequency, psychological well-being, and health behaviors (ie, potential consequences of stigma). Finally, by analyzing free text responses to open-ended questions, we will identify potential strategies to address stigma.

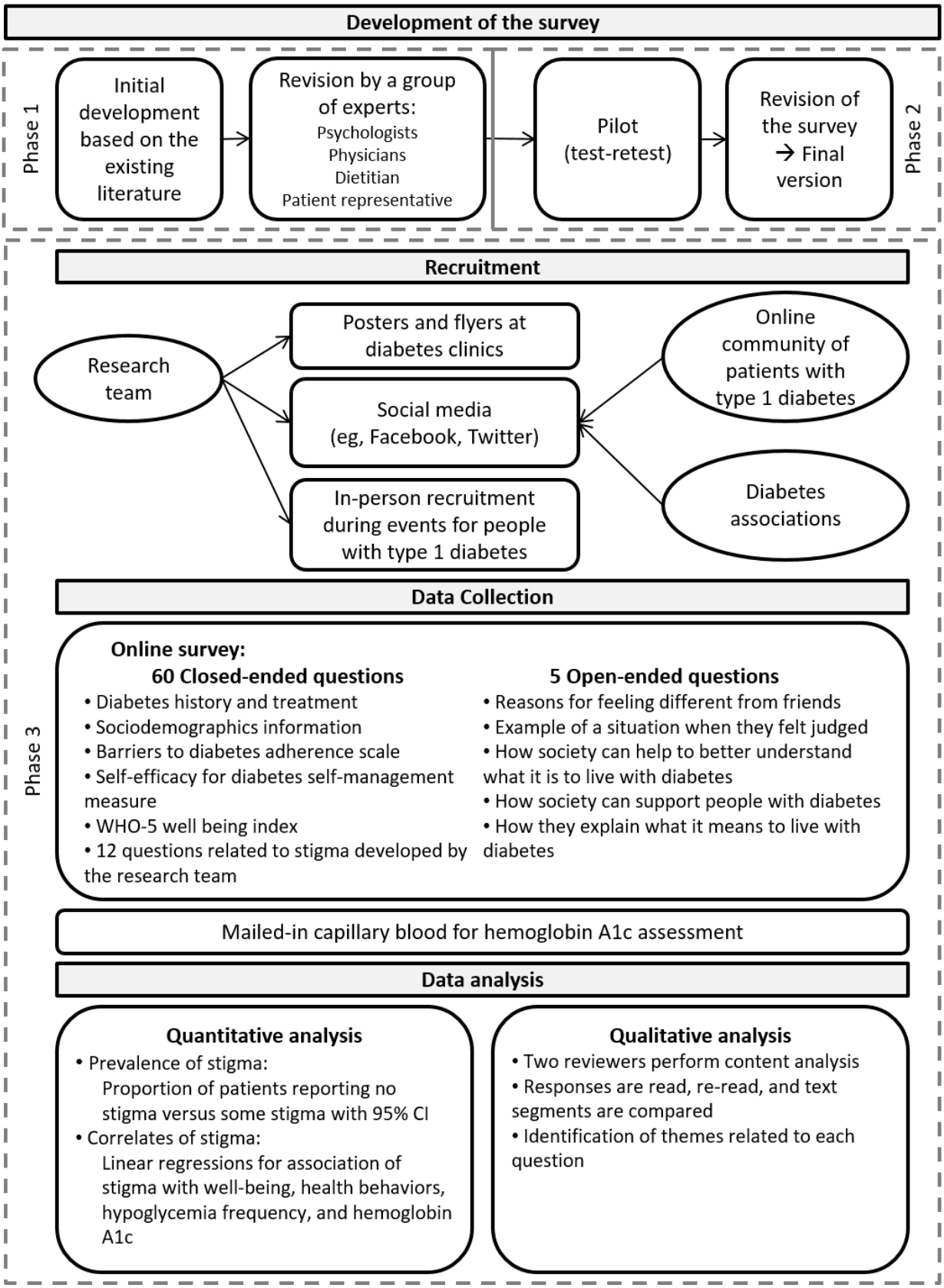
Methods

All study procedures were reviewed and approved by the Institutional Review Board of the McGill University Health Centre. Electronic consent was obtained prior to completion of the survey.

Study Design

This 1-year project is a cross-sectional online survey combined with mailed-in capillary blood samples for hemoglobin A1c assessment (Figure 1). The study includes 3 distinct phases: (1) survey question refinement and creation of an online questionnaire, (2) a pilot testing phase consisting of 30 participants completing the questionnaire on two separate occasions, and (3) a data collection phase (survey and hemoglobin A1c testing and analysis). Phases 1 and 2 have been completed.

Figure 1. Study design.



Phase 1: Selection of Questions to Capture Stigma and Development of the Survey

A key set of questions included in our survey are derived from the Barriers to Diabetes Adherence (BDA) questionnaire developed by Mulvaney et al [15]. This 21-item tool includes 6 questions specifically addressing stigma, as well as 4 other aspects related to living with diabetes (stress and burnout, time pressure and planning, social support, and parental autonomy

support). The BDA is reported to have good overall internal consistency (Cronbach alpha=.88) [15].

To gain a broader understanding of stigma in our specific population of interest, we included additional questions, guided by the revised framework for understanding diabetes-related stigma developed by Browne et al [8]. These investigators have highlighted the importance of addressing the causes, experiences, and consequences of stigma. *Causes* refer to the sources of stigma and features of the condition (ie, type 1 diabetes) and its management, *experiences* include judgment by others and stigmatizing practices, and *consequences* refer to the psychological, behavioral, and medical impact of diabetes-related stigma.

The questionnaire was developed by our research team, comprised of pediatric endocrinologists, clinician scientists, psychologists, a dietitian, and a patient representative. We conducted a survey of the literature and existing instruments, and developed our own questions.

The online questionnaire (French and English versions) was programmed into FluidSurveys [17], which is a low-cost online survey design tool used by researchers and government organizations. Data generated through FluidSurveys are stored in Canada. Participants can complete the survey directly online, or offline on tablets, laptops, or cell phones. The survey platform also allows participants to upload documents (eg, pictures, videos, or text). Participants can interrupt survey completion as needed, and continue at a more convenient time.

Phase 2: Pilot Testing

Thirty youth and young adults with type 1 diabetes were asked to complete the survey twice, spaced by one week, to assess test-retest reliability (see *Data Analyses*). Participants for the pilot phase were recruited through social networks (see *Recruitment*).

Phase 3: Data Collection

Following some adjustments to the survey tool based on the pilot phase, the final survey was programmed into FluidSurveys.

Recruitment

Adolescents and emerging adults with type 1 diabetes aged 14-25 years are eligible for this study. Specifically, the study is publicized through posters at diabetes clinics, on Facebook pages, via Twitter messages, and on websites of diabetes organizations (eg, Canadian Diabetes Association, Diabète Québec). We also ask the organizations to email their members directly to inform them about the study, with a link embedded in the email message. We are also willing to be present at chapter meetings to provide information about the study. Flyers promoting the study are also posted at hospital centers in which study investigators are based. To further publicize the study, our patient representative (MW) communicates with potential participants through social networks for youth with type 1 diabetes.

Once participants have been directed to our website, they register to receive an emailed personal link to the survey. Upon completion of the survey, an Amazon.ca gift card is sent to them (Can $10). Participants are also asked if they are willing to mail in a capillary blood sample, as described below. When we receive the mailed-in sample, the participants are provided with a second gift card (Can $10).

Glucose Control

Survey participants willing to mail in a capillary blood sample receive a kit for hemoglobin A1c testing (DTIL Laboratories, Inc., Thomasville, GA, USA) with a prepaid envelope for mailing the sample back to Montreal (QC, Canada). The kit includes a sample vial that contains a preservative (ethylenediaminetetraacetic acid), a vial holder, a single use lancet, a capillary tube device to draw up a small amount of blood after lancing, and a Ziploc bag. We batch ship the samples to a laboratory in the United States. The AccuBase A1c Test Kit is a nonfasting, finger stick, whole blood mail-in test requiring a very small blood volume (0.001 milliliters). Upon collection, samples are stable for 45 days without refrigeration. Samples are analyzed using a two-step process: the screening step detects hemoglobin variants and/or disturbed erythrocyte kinetics by ion-exchange high performance liquid chromatography; the second step includes the use of an interference-free procedure (high performance liquid chromatography-boronate affinity) that provides a hemoglobin A1c value free of possible interferences, including chemically modified derivatives [18].

Sample Size

To date, no data exists regarding the prevalence of stigma in adolescents and emerging adults with type 1 diabetes. We estimate a 50% prevalence for sample size calculations, as this is the proportion that mandates the largest sample size. Given that approximately 34,535 adolescents and emerging adults in Canada have type 1 diabetes (95% of 36,353 diabetic individuals [9]), to detect a 50% proportion with stigma to an accuracy of 5% would require 380 survey completers (two-sided 95% CI for a single proportion with normal approximation, using nQuery Advisor 7.0). Based on our previous experience [19], we estimate that 52% of the respondents will complete the mailed-in hemoglobin A1c test. Thus, a subsample of 200 participants will provide objective data on hemoglobin A1c levels.

Data Analyses

Development and Pretesting

The test-retest reproducibility of the scales was determined by comparing results on the two separate occasions that the questionnaire was completed (30 participants). Test-retest reliability was examined using single-measure intraclass correlation coefficients (ICC) and 95% CIs, with ICC <0.40 indicating poor agreement, 0.40-0.74 indicating fair to good agreement, and >0.75 indicating excellent agreement [20].

Participant Characteristics

Means and standard deviations (SDs), medians and interquartile ranges, or proportions are being used (as appropriate) to report participant characteristics.

Prevalence of Stigma

For the primary analysis, we will evaluate the responses to the 6 questions addressing stigma in the BDA questionnaire [15]. Each of the items involves a 1-to-5 Likert scale. For our purposes, *no stigma* will be a score of 6 out of a potential 30. We will determine the proportion of individuals with a score >6 and the corresponding 95% CI. We will then examine individual questions addressing stigma through our questionnaire, selecting a cutoff score tailored to each question. Our data will give us the ability to estimate an overall prevalence of diabetes-related stigma among youth and young adults with type 1 diabetes. We will then estimate the prevalence of stigma in subgroups (ie, boys, girls, ethnocultural groups, teens, and young adults)

Correlates of Stigma

Linear regression will be used to evaluate associations of stigma with psychological well-being, health behaviors, hypoglycemia frequency, and hemoglobin A1c, with additional potential predictors included in the models (eg, age, sex, sexual orientation/gender identification, ethnocultural background).

Analyses of Responses to Open-Ended Questions

Two reviewers will perform qualitative content analysis of responses to open-ended questions (one of whom is a patient representative). The responses will be read twice, and text segments will be compared, seeking similar or repeated ideas. The final step will involve labeling identified themes for each question. We have employed a similar analytical strategy for qualitative studies in diabetes [21,22].

Results

Phase 1

In addition to the BDA, we considered 2 additional questions developed by Folias et al to capture stigma (as reported in an American Diabetes Association abstract [23]), as well as other questions related to lived experiences with type 1 diabetes and managing young people with type 1 diabetes (eg, stigma within social media networks) [24].

In addition to stigma, we query peer support, quality of life and well-being, diabetes history and current treatment, and socio-demographic information. We considered several existing tools and instruments, such as the Hypoglycemia Patient Questionnaire [25], the Self-Efficacy for Diabetes Self-Management measure (SEDM; 10 items, test-retest ICC=0.89, Cronbach alpha=.90 [26]), the Problem Areas in Diabetes Scale (a 20-item measure assessing feelings related to living with diabetes and its treatment, including guilt, anger, frustration, depressed mood, worry, and fear; Cronbach alpha=.92 [27]), the Pediatric Quality of Life Inventory Generic Core Scales and Diabetes Module (a 28-item questionnaire, age-specific for 13-18 year-olds; Cronbach alpha=.88 [28]) and the World Health Organization (WHO)-5 Well-Being Index, (a validated 5-item questionnaire assessing subjective psychological well-being [29]).

Demographic factors including age, sex, sexual orientation/gender identification, and ethnocultural background are queried to ascertain the prevalence of diabetes-related stigma in different demographic subgroups. Owing to their potentially sensitive nature, however, the questions regarding sexual orientation/gender orientation are explicitly optional [30]. Following completion of closed-ended questions, participants respond to open-ended questions that seek to capture experiences and perceptions of stigma, as well as ideas about how stigma may be effectively addressed. Participants are permitted to upload explanatory materials (eg, videos, testimonials, pictures, drawings).

The survey that underwent pilot testing included 7 socio-demographic questions, 5 questions regarding diabetes history and treatment, the BDA scale, the SEDM scale, and the WHO-5 Well Being Index, as well as 12 questions related to stigma developed by the team (eg, *reasons for feeling judged*, *by whom they feel being judged the most*) and an additional 4 open-ended questions (eg, *describe a situation in which you felt judged*, *how can society can better understand what it is like to live with type 1 diabetes?*).

Phase 2

The mean age of the 30 participants in the pilot phase was 20 years, and type 1 diabetes duration averaged approximately 9 years (Table 1). A large majority of participants were female, and half used multiple daily injections of insulin, while half were on insulin pump therapy (Table 1). The mean hemoglobin A1c value was slightly above target (ie, 7.0% [16]) at 7.6%, and the average number of hypoglycemic episodes in the prior week was approximately 3 (Table 1).

Table 1. Participants' characteristics.

Characteristics	Mean (SD) or frequency (%)
Age, years	20.5 (2.8)
Age at diagnosis, years	11.3 (5.5)
Diabetes duration, years	9.2 (5.1)
Sex	
Female	24 (80%)
Male	6 (20%)
Language	
English	19 (63%)
French	11 (37%)
Last hemoglobin A1c, %	7.6 (1.4)
Insulin treatment	
Multiple daily injections	15 (50%)
Continuous subcutaneous insulin injection (insulin pump)	15 (50%)
Number of hypoglycemic events in the previous week	3.1 (2.6)

In the pilot phase, the average time between the two completions of the survey was 9.8 days (SD 4.5). A mean of 20:19 minutes (SD 8:52) were required to complete the survey. ICCs were high for the three scales included in the pilot version of the survey (BDA ICC=0.967, 95% CI 0.931-0.984; SEDM ICC=0.952, 95% CI 0.899-0.977; and WHO-5 Well Being Index ICC=0.860, 95% CI 0.705-0.933). Following the analyses of the pilot phase, minor modifications were made to the survey. The final version includes 60 closed-ended questions and five open-ended questions. Data collection is in progress.

Discussion

Our study will be the first nation-wide evaluation of stigma in youth and young adults with type 1 diabetes. Previous studies have largely been qualitative; our investigation will include qualitative components but will also permit an estimate of prevalence. This strategy will allow for an appreciation of the magnitude and scope of the problem, and the development of strategies to help patients live better lives. Novel aspects of our methodology include (1) the use of an online survey, permitting evaluation across a large geographic area and inclusion of many individuals; (2) incorporation of a mailed-in capillary blood sample, allowing for objective assessments of glycemic control; (3) use of social media to enhance recruitment; and (4) inclusion of a patient representative on the research team, which provides an expert on the experience of living with type 1 diabetes. The questionnaire has been developed and pilot tested, and demonstrates good test-retest reproducibility. Our work is intended to provide an initial understanding of youths' perspectives on difficulties and potential solutions for a normal life, and to serve as foundation for future research that helps people with type 1 diabetes achieve a good quality of life.

Online surveys are useful tools for achieving wide geographic coverage (which are particularly useful in large countries like Canada) and a large sample size, at relatively low cost. A survey-based approach in a private location may be preferable to interviews and/or witnessed survey completion when dealing with sensitive topics [31]. We have used online surveys as part of a prospective study examining depressive symptoms in 622 men (mean age 34.3 years, SD 5.0) during the first postnatal year with a newborn [32]. Participants completed standardized online self-report questionnaires measuring depressed mood, physical activity, sleep quality, social support, marital adjustment, life events, financial stress, and demographic factors during their partners' third trimester of pregnancy. We determined that >10% of men experience depressed mood in the first year after their child's birth [32]. We have adopted a similar method in the current study to capture the concept of stigma. Stigmatizing practice can come from family members, friends, health care providers, classmates, teachers, colleagues, and employers, among others. A self-report method, rather than interviews, was considered an ideal method to question this young population due to the high level of privacy that this approach affords.

We hypothesize that prevalence of stigma will be high in this age group, and may negatively impact diabetes management, as reflected through hemoglobin A1c (ie, high values reflect high blood glucose) and frequency of hypoglycemia episodes. To measure hemoglobin A1c, we are using mailed-in capillary blood samples. In a previous study, we used mailed-in capillary blood samples to measure glucose levels, in an effort to determine the prevalence of diagnosed and undiagnosed diabetes in the province of Quebec [19]. In that study, 52.2% (954/1829) of survey respondents provided mailed-in blood samples, of which approximately 90% were analyzable [19]. To our knowledge, no previous study has specifically examined the relationship between stigma and diabetes control in type 1 diabetes, although positive associations between emotional distress and prolonged suboptimal glycemic control have been reported [33]. This study will allow us to determine whether important medical consequences are associated with stigma (ie,

an association between stigma and high hemoglobin A1c levels and/or hypoglycemia frequency).

Our previous studies have largely relied on in-person recruitment, even when the survey instruments are online (eg, introductions by clinic staff, clinic posters). However, the present study has largely relied on online and social media-based recruitment strategies. We have contacted many small diabetes organizations that focus on youth and young adults with type 1 diabetes. Many of these organizations are local initiatives that have generously tweeted about our study or posted it on their Facebook pages. This recruitment strategy appears to be particularly effective in this young, social media-savvy patient population.

Our team includes a patient representative, which is critical to the relevance of this study. There is an increasing recognition of the importance of patient representatives in health care research, due to their insights into defining research questions, adapting tools, interpreting results, and participating in knowledge translation efforts [34]. Patients are recognized as experts in their experience of disease. Our team includes such a representative, who has participated in all aspects of this study to date, and is remunerated for his work. This representative was instrumental in the selection of questions that were included in the survey, and assisted with participant recruitment via social media. This team member is also participating in the identification of themes by reviewing the responses to our open-ended questions.

Limitations of our study include potential selection bias; those who opt to participate may experience more (or less) stigma than others with type 1 diabetes, and may therefore be more likely to complete the survey. Recruitment in general is challenging, as even online surveys may be perceived as burdensome. Additionally, some participants may be reluctant to mail in capillary blood samples, even though this patient population is accustomed to capillary blood sampling for self-monitoring purposes. Our study will not capture the directly-reported perspectives of family members or friends, although we may address these factors in a future study.

Regarding future research directions, we are exploring the possibility of developing a more comprehensive stigma scale for this population. We plan to use the information from the present study to design a follow-up survey, similar to the scale developed for type 2 diabetes [35]. Such a tool could permit evaluation of trends and changes over time, with potential for incorporation into national surveys such as the biennial Canadian Community Health Survey [36].

Our study will highlight the importance of stigma in the day-to-day lives of young people with type 1 diabetes, as well as its association with diabetes control and adherence to treatment in a Canadian population. Stigma is a social construct, and therefore differs widely across societies [37]. It is important to gather information reflective of various populations. Patient-derived potential solutions will be formulated to reduce stigma in this clinical population.

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Authors' Contributions

ASB and KD designed the study, wrote the protocol, and drafted the manuscript, with valuable input from MN, CP, DP, MH, DDC, and MW.

Conflicts of Interest

None declared.

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Abbreviations

BDA: Barriers to Diabetes Adherence
CI: confidence interval
FRQS: Fonds de recherche du Québec-Santé
ICC: intraclass correlation
SD: standard deviation
SEDM: Self-Efficacy for Diabetes Self-Management
WHO: World Health Organization

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Original Paper

A Web-Based Psychosocial Intervention for Family Caregivers of Older People: Results from a Mixed-Methods Study in Three European Countries

Francesco Barbabella[1,2], PhD; Arianna Poli[1,3], MPsych; Frida Andréasson[2,4], MA Sociology; Benjamin Salzmann[1,5], MSW; Roberta Papa[1], BSc; Elizabeth Hanson[2,4,6], PhD; Areti Efthymiou[6,7], MPsych; Hanneli Döhner[5,6], PhD; Cristina Lancioni[1], MSc (Tech); Patrizia Civerchia[8], MPsych; Giovanni Lamura[1], PhD

[1]Centre for Socio-Economic Research on Ageing, National Institute of Health and Science on Ageing (INRCA), Ancona, Italy

[2]Department of Health and Caring Sciences, Linnaeus University, Kalmar, Sweden

[3]National Institute for the Study of Ageing and Later Life, Linköping University, Norrköping, Sweden

[4]Swedish Family Care Competence Centre (NKA), Kalmar, Sweden

[5]wir pflegen e.V., Berlin, Germany

[6]Eurocarers, Brussels, Belgium

[7]Cyprus University of Technology, Limassol, Cyprus

[8]Neurology Unit, National Institute of Health and Science on Ageing (INRCA), Ancona, Italy

Corresponding Author:
Francesco Barbabella, PhD
Centre for Socio-Economic Research on Ageing
National Institute of Health and Science on Ageing (INRCA)
Via S. Margherita 5
Ancona, 60126
Italy
Phone: 39 0718004799
Fax: 39 07135941
Email: f.barbabella@inrca.it

Abstract

Background: Informal caregiving is the main source of care for older people in Europe. An enormous amount of responsibility and care activity is on the shoulders of family caregivers, who might experience problems in their psychological well-being and in reconciling caregiving and their personal sphere. In order to alleviate such burden, there is increasing interest and growing research in Europe on Web-based support addressing family caregivers and their needs. However, the level of development and penetration of innovative Web-based services for caregivers is still quite low and the access to traditional face-to-face services can be problematic for logistic, availability, and quality reasons.

Objective: As part of the European project INNOVAGE, a pilot study was conducted for developing and testing a Web-based psychosocial intervention aimed at empowering family caregivers of older people in Italy, Sweden, and Germany. The program offered information resources and interactive services to enable both professional and peer support.

Methods: A mixed-methods, sequential explanatory design was adopted. Caregivers' psychological well-being, perceived negative and positive aspects of caregiving, and social support received were assessed before and after the 3-month intervention. Poststudy, a subsample of users participated in focus groups to assist in the interpretation of the quantitative results.

Results: A total of 94 out of 118 family caregivers (79.7%) from the three countries used the Web platform at least once. The information resources were used to different extents in each country, with Italian users having the lowest median number of visits (5, interquartile range [IQR] 2-8), whereas German users had the highest number (17, IQR 7-66) (P<.001). The interactive services most frequently accessed (more than 12 times) in all countries were the social network (29/73, 40%) and private messages (27/73, 37%). The pretest-posttest analysis revealed some changes, particularly the slight worsening of perceived positive values of caregiving (Carers of Older People in Europe [COPE] positive value subscale: P=.02) and social support received (COPE quality-of-support subscale: P=.02; Multidimensional Scale of Perceived Social Support subscale: P=.04), in all cases with small effect size (r range -.15 to -.18). Focus groups were conducted with 20 family caregivers and the content analysis of discussions

identified five main themes: online social support, role awareness, caregiving activities, psychological well-being, and technical concerns. The analysis suggested the intervention was useful and appropriate, also stimulating a better self-efficacy and reappraisal of the caregivers' role.

Conclusions: The intervention seemed to contribute to the improvement of family caregivers' awareness, efficacy, and empowerment, which in turn may lead to a better self-recognition of their own needs and improved efforts for developing and accessing coping resources. A major implication of the study was the finalization and implementation of the InformCare Web platform in 27 European countries, now publicly accessible (www.eurocarers.org/informcare).

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KEYWORDS

caregivers; frail elderly; Internet; social support; social networking; health education

Introduction

A significant portion of adult individuals worldwide are experiencing increasing responsibilities of, and effects from being involved in, informal care for relatives with long-term care needs. For instance, it is estimated that the number of family caregivers over 18 years of age who care for older people and disabled adults are around 58 million in the European Union (EU) (15% of the adult population) [1] and 34 million (14% of the adult population) in the United States [2]. In the European context, the number of family caregivers is twice the entire health care workforce, with the economic value of informal care covering between 50% and 90% of overall costs for long-term care in EU member states [3]. The impact of caregiving on individuals' lives is often remarkable and associated with different health and social issues. The prevalence of mental health problems among caregivers seems to be 20% higher than among noncaregivers [4], especially in terms of anxiety, depression, and distress attributed to their caring situation. Other risks for caregivers concern the possibility of encountering financial problems and difficulties in reconciling care with family activities and social life [4-6].

Recently, research in the European Union has increasingly concentrated on the development and testing of innovative solutions for providing support services to family caregivers of older people, especially in terms of Web-based programs with psychoeducational and psychotherapeutic purposes [7,8], or with multicomponent approaches including both professional and peer online support [9-11]. Although reviews in this field recommend more in-depth research for clarifying the effectiveness of Web-based interventions, preliminary evidence at the international level suggests that these should be multicomponent and tailored to caregivers' actual needs and preferences, in order to impact effectively on caregivers' psychological well-being, self-efficacy, and social inclusion [12-17]. This can be achieved by integrating the availability of information and educational modules with both professional and peer support, for instance, via interactive tools like discussion forums, chat rooms, and group videoconferencing [10,11,18-20].

So far, however, the level of development and coverage of Web-based programs for family caregivers has been rather low and fragmented in the European Union, with a number of small initiatives having limited scope and being sustained by poor funds and resources [21,22]. This fits into the broader picture of a general lack of formal support services dedicated to family caregivers [5,6]. This is further exacerbated in some EU countries—especially in Southern and Eastern Europe—by low policy, social, and cultural recognition of family caregivers' roles, including a lack of legal rights, benefits, and support actions from public institutions and society [3].

As part of the wider INNOVAGE project, cofunded by the European Union, we addressed this systematic lack of online supports for caregivers by promoting a new social innovation at the European level (ie, an innovative solution to meet health and social needs of caregivers, to sustain their empowerment, and to improve their well-being) [23]. This social innovation was constituted by the new InformCare Web platform, which was intended to act as a first point of access to a variety of information, education, and social support opportunities at the country level for family caregivers, as well as an opportunity for formal services and nonprofit organizations in the field. Our research had the ultimate goal to implement the InformCare Web platform in 27 European countries in their official languages in order to allow caregivers from any involved nation to benefit from a set of minimum information and support. Research, development, and implementation activities were coordinated by the Italian National Institute of Health and Science on Ageing (INRCA) and the European nonprofit organization Eurocarers, with the support of the Swedish Family Care Competence Centre (NKA) and a wide network of national nonprofit organizations in the European Union.

Thus, this article reports the results from the pilot-testing in three European countries of a multicomponent, Web-based intervention delivered through the InformCare Web platform. The work is based on the assumption that caregiving activities can lead the caregiver to experience both negative feelings, such as subjective burden, stress, and depression [24,25], and positive ones, for instance, gain, reward, and satisfaction [26,27]. The goal of this pilot study was to verify the impact of the Web-based psychosocial intervention on caregivers, primarily in terms of benefits for psychological well-being, self-efficacy, and self-perception of both negative and positive aspects of caregiving, and secondarily as a potential driver of personal development and access to coping resources.

Methods

Design

The multicenter pilot study was conducted in Italy, Sweden, and Germany, and employed a mixed-methods, sequential explanatory design. Structured questionnaires with quantitative measures of the main outcomes were administered to enrolled family caregivers both at baseline and at 3-months postintervention; the study took place from April to July 2014. Postintervention, results from the structured questionnaires were used to organize a focus group in each country, at which a subgroup of users participated. The aim was to gain a more in-depth understanding of caregivers' experiences, support the final analysis, and better interpret the results. The design and methods of the study were evaluated by competent local ethics committees in each country.

Development of the Web Platform

The design and development of the Web platform was based on a review of the main needs and preferences expressed by family caregivers [5,28], as well as the areas of online health information and support [15,29-31]. A consultation process was also carried out via online surveys administered to 58 family caregivers, external experts, and stakeholders from different European countries, reached by means of national and international networks of partner organizations, in order to identify Web tools to include for addressing caregivers' needs.

Individual user tests with 10 family caregivers were conducted on a first prototype of the Web platform in order to gain preliminary insights on its usability. Based on the feedback received, the platform was further refined for the pilot intervention.

Intervention Conditions

In all three countries, the Web platform included both information resources and interactive services areas, developed in their national official languages. Access was restricted by means of an individual username and password given to each caregiver at the beginning of the study. An overview of the main characteristics of the information and services and a screenshot of the home page are provided in Table 1 and Figure 1, respectively.

Within the information resources area, four main sections were developed in order to improve knowledge and self-awareness, mainly concerning the caregiver's role, coping strategies, and support available. Contents regarding the national range of services, benefits, and contacts available were appositely written by project staff and double-checked by external experts. Contents concerning general information on diseases, coping, and reconciliation strategies were provided by selected reliable websites in English managed by nonprofit organizations with a long-standing expertise in this field. Translation into national languages was carried out by national project staff and double-checked by senior project staff.

The interactive services area enabled communication among caregivers, as well as between caregivers and professional staff. The area included a set of Web tools: a dedicated social network, a forum, a private message feature, a chat feature, and a videochat feature. Interactive services were aimed specifically at improving caregivers' psychological well-being, self-efficacy, and self-perception of caregiving situation. These services were delivered by means of individual and group online support provided in terms of information, advice, counseling, and emotional and social support. In each country, an interactive services area was managed by a professional moderator—a psychologist in Italy, and social workers in Sweden and Germany—who acted as an online counselor.

Some additional structured services and tasks were also proposed in order to better customize service provision to the sociocultural peculiarities and digital skills of national samples (see Table 1). The choice of services and tasks took into account that the main profiles of caregivers recruited in the three countries differed in terms of age and relationship with the older person, as well as of education and employment status, confirming what was highlighted by a previous European study [5,32].

Guidelines for moderators, who were trained prior to the intervention, were developed based on the main recommendations available in the field [33-35]. This aimed to clarify how support and interactions with users should be performed by moderators, and to set limits and standards of such support.

Sample

The recruitment process adopted a convenience sample approach. Brochures and promotional materials were distributed in order to reach caregivers through available institutional and informal channels. In Italy, all participants were recruited through the Alzheimer Evaluation Unit at INRCA in Ancona, thus including family caregivers of people with Alzheimer's disease or other dementias. In Sweden, caregivers were enrolled by exploiting existing networks of the NKA, the Swedish Dementia Association, Carers Sweden, and Linnaeus University in Kalmar and Växjö. In Germany, the nonprofit caregiver organization wir pflegen e.V. and local social care services contributed to recruitment by approaching family caregivers through their networks and websites.

Selection criteria for including family caregivers in the study were the following: (1) providing informal caregiving in activities of daily living (ADLs) and/or instrumental activities of daily living (IADLs) for an older person aged 60 years or more; (2) having basic digital skills, allowing the use of an Internet browser on a computer and/or mobile device; (3) having ordinary access to a computer and/or mobile device with Internet connection.

Figure 1. Screenshot of the home page of the InformCare Web platform for family caregivers of older people (example of Italian version).

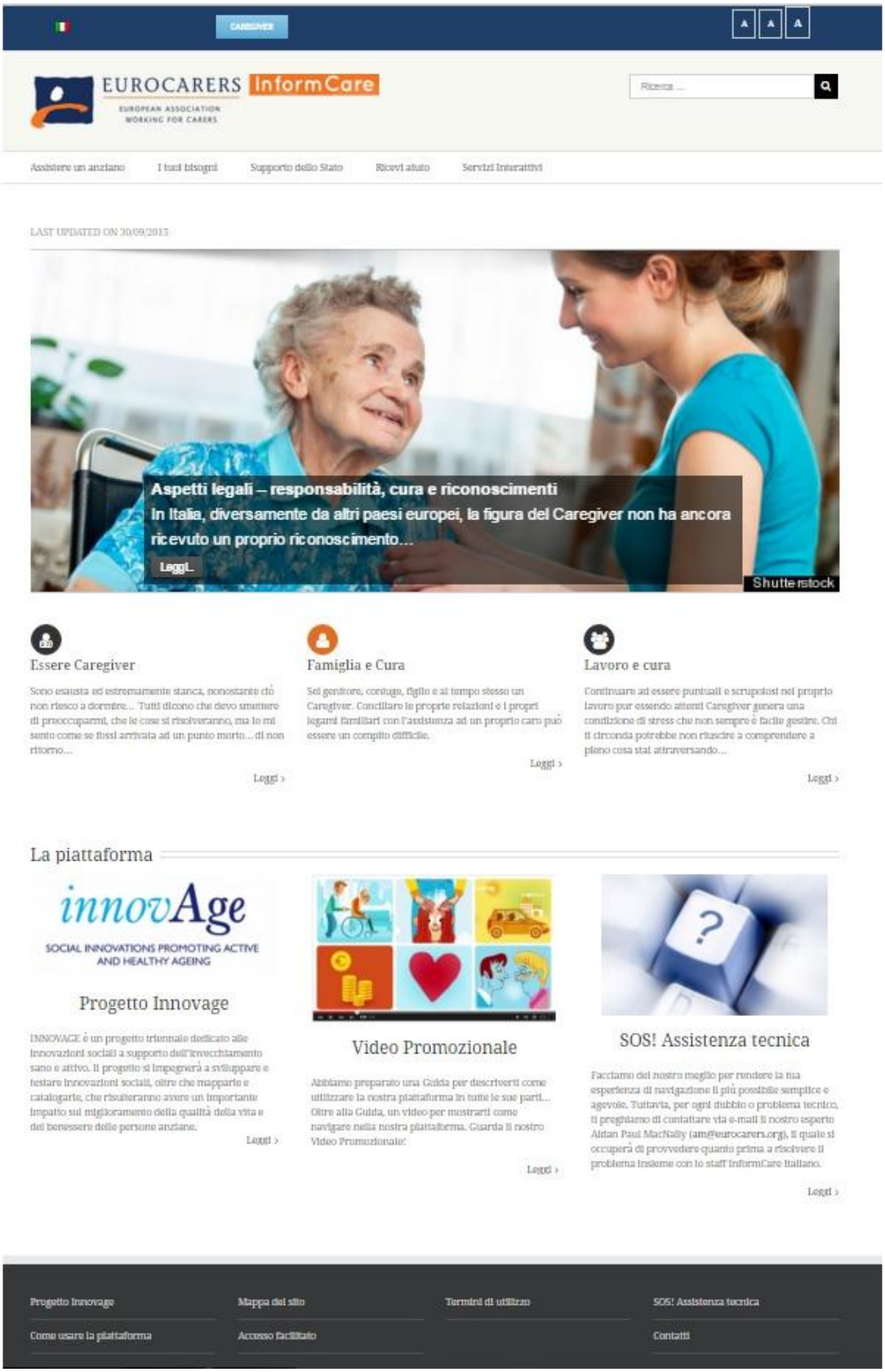

Table 1. Characteristics of information resources and interactive services.

Resources and services	Characteristics
Information resources	
Caring for the older person	Symptoms, diagnosis, and treatments of the 10 most common chronic conditions
	Long-term care services at country level
	Environmental security
Your own needs	Coping strategies
	Reconciliation with family and work
	Physical exercise
Support by the state	Legal issues (eg, responsibility, rights, and competency)
	Economic and social insurance benefits
Get help	Contacts for crisis or emergency
	List of relevant nonprofit associations
	List of other Web-based support programs
Interactive services	
Social network	Channel: asynchronous group communication
	Possible user's tasks: to see and read other caregivers' profiles and posts; to post, comment, and share information and multimedia on personal and others' walls
	Moderator's role: to post regularly, both useful information (from the Web and the information resources area) and emotional statements; to interact with users by commenting on their posts and periodically leaving messages on their walls
Forum	Channel: asynchronous group communication
	Possible user's tasks: to open discussion threads on personal doubts and requests; to comment on others' open threads
	Moderator's role: to stimulate interactions by opening new discussion threads and/or commenting appropriately on users' threads and comments
Private messages/emails	Channel: asynchronous interpersonal or group communication
	Possible user's tasks: to ask for direct support from the moderator; to contact other users
	Moderator's role: to monitor and support users by sending periodical or ad hoc messages
Chat and videochat/	Channel: synchronous interpersonal or group communication
videocommunication tools	Possible user's tasks: to ask for direct support from the moderator; to contact other users
	Moderator's role: to support users by participating in individual or group discussions
Additional structured services (country specific)	
E-learning course and virtual desk (Italy)	E-learning: multimedia training units with a focus on caregiving activities and long-term care services
	Virtual desk: weekly availability of moderator and other psychologists via chat, videochat, and forum for providing individual support
Writing tasks in forum (Sweden)	Biweekly writing exercises alternating time management and emotional writing, managed by the moderator
Videoconferencing groups (Germany)	Two weekly videoconferencing groups with three family caregivers each, managed by the moderator

Procedure

At the outset, each participant caregiver signed an informed consent form and received a guide for accessing and using the platform in both paper and electronic versions. Preliminary face-to-face or videoconferencing meetings were organized on an individual or group basis for presenting and showing the platform.

Participants were invited to use the Web platform whenever they needed to find information, ask advice, or get support. Stimulation strategies were planned according to social and cultural preferences (eg, short message service [SMS] text messages and emails).

Technical support was guaranteed by both the moderator—for immediate help and clarification—and the Web developer—for fixing technical problems. A set of earphones was given to each caregiver allowing for the use of videochat and videocommunication tools.

Quantitative Measures and Statistical Analysis

The primary outcome measures were represented by the caregivers' psychological well-being and self-perception of both negative and positive aspects of caregiving. A secondary outcome was the social support the caregiver perceived from significant others and from services. Variables were measured with a structured questionnaire administered to all participants,

both prior to and after the 3-month intervention, through an online system or, if requested, by post or email.

Sociodemographic characteristics and health problems of family caregivers and of their cared-for older persons—with the caregiver answering as a proxy—were asked through ad hoc categorical or binary questions. Other details were also asked about the care setting and access to public services (eg, home care and care allowances) and private services (eg, privately employed care assistant). As for the older person, ADLs and IADLs were measured, respectively, by means of the Barthel Index [36] (range 0-20, where 20 refers to a person who is independent in all activities) and the Duke Older Americans' Resources and Services (OARS) scale [37] (range 0-6, where 6 is the highest number of activities for which the person needs help). Health status of the caregiver was assessed through a single item—health status 1 variable (HS1): self-perceived general health—retrieved from the Minimum European Health Module [38], whose results were recoded in three categories: good, fair, and bad.

Among the outcome measures, the 5-item World Health Organization Well-being Index (WHO-5) [39] was used to assess the level of psychological well-being perceived by the caregiver. It uses a 6-point Likert scale (ranging from *at no time* to *all of the time*) to rate statements such as "I have felt cheerful and in good spirits" and "I have felt calm and relaxed," referring to the last 2-week period. Its percentage score was calculated by multiplying the raw score by 4 (ranging from 0 to 25).

The Carers of Older People in Europe (COPE) Index (15 items) [40,41] was included to ask about the perceived impact of the caregiving situation. The COPE Index uses a 4-point Likert scale (ranging from *never* to *always*) and includes three subscales concerning the following: negative impact, with seven items such as "Do you find caregiving too demanding?" (score range 7-28); positive value, with four items such as "Do you find caregiving worthwhile?" (score range 4-16); and quality of support, with four items such as "Do you feel well supported by friends or neighbors?" (score range 4-16). Negatively worded items of the negative impact subscale were reverse coded. A high score in a subscale indicated the following: low level of subjective burden (negative impact subscale); high level of positive feelings (positive value); and high level of support received by community, including family, friends, and formal services (quality of support).

Furthermore, the Multidimensional Scale of Perceived Social Support (MSPSS) (12 items) [42] measured the level of perceived social support received by the family caregiver. The MSPSS uses a 7-point Likert scale (ranging from *very strongly disagree* to *very strongly agree*) and includes three subscales asking to rate family (four items; eg, "My family really tries to help me"), friends (four items; eg, "I have friends with whom I can share my joys and sorrows"), and social support (four items; eg, "I have a special person who is a real source of comfort to me"). Each subscale ranges from 4 to 48 points, where 48 is the best support received, and a total score was calculated by summing the scores from all subscales.

Data about access to the information resources area of the platform were tracked through Google Analytics software. The number of times participants used single features of each interactive service were self-reported, then summed and categorized for each service as follows: never (no use), low use (6-12 times), and medium-high use (more than 12 times).

The Kolmogorov-Smirnov test was used to check for normal distribution of quantitative data. Data were expressed as frequencies for categorical variables, and as median (interquartile range [IQR]) and mean (SD) for continuous ones. Bivariate analysis was performed between the country variable and both sociodemographic characteristics and usage of the platform using the chi-square or Kruskal-Wallis tests for categorical or continuous variables, respectively. Comparison of paired data—medians before and after the intervention—on the primary outcome variables was carried out by the nonparametric Wilcoxon signed-rank test for dependent samples; effect size (r) was calculated as the Z value divided by the square root of the number of observations. A value of $P<.05$ was accepted as statistically significant. SPSS for Windows, version 16.0 (SPSS Inc) was used for the creation of the database, data cleaning, and data analysis.

Focus Groups and Qualitative Data Analysis

A focus group was organized in each country after the intervention for further evaluation, especially with regard to the aspects of self-efficacy and support received online. Standard operative guidelines and a common set of topics to be covered were adopted for all focus groups, including the following: (1) appropriateness and usefulness of the intervention to meet own needs, (2) personal evaluation of using online services, and (3) perceived changes and improvements connected to the use of the services. Moderators of focus groups were senior project staff, whereas other trained researchers participated as observers and note takers.

Participants constituted a subgroup of the overall sample of family caregivers who used the platform. All focus groups took approximately 90-120 minutes; discussions were audiotaped and transcribed, with the support of field notes. Transcriptions and field notes were used for a conventional content analysis [43], based on a constant comparative approach [44], which aimed at exploring similarities and differences across the three country samples. By making systematic comparisons across units of data—participants' comments and answers, and observations—researchers subsequently identified themes of discussion and selected relevant quotes from the focus groups [44,45]. Credibility of qualitative research was assured mainly by the following: prolonged engagement (eg, project staff's long-standing experience of research and practice on Web-based support for caregivers); persistent observation (eg, direct knowledge gained by moderators and researchers on Web platform usage by caregivers, including types and frequency of peer and professional interactions); and peer debriefing, including the continuous involvement of an external advisory board (15 international experts) and the validation of final study results in an expert evaluation meeting (6 international experts) [46].

The analysis of qualitative data integrated quantitative results in an explanatory sequential process [47].

Results

Descriptive Statistics

Overall, 123 family caregivers were initially recruited to the study—59 in Italy, 44 in Sweden, and 20 in Germany—completing both the informed consent form and baseline questionnaire. A total of 5 participants dropped out during the intervention—1 in Italy, 3 in Sweden, and 1 in Germany—due to the death of the older person, changed life circumstances, or lack of time. At the end of the intervention, 94 out of 118 caregivers (79.7%) had accessed the Web platform at least once—42 in Italy, 36 in Sweden, and 16 in Germany.

Table 2 describes the sociodemographic characteristics of both the participating caregivers and the older persons they cared for. The median age of the older persons in the total sample was 80 years (IQR 74-85), the group consisted of mostly women in both Italy and Germany (79% and 69%, respectively), and they had different levels of ADL and IADL dependency.

Family caregivers who used the Web platform at least once were mostly women (64/94, 68%) with a median age of 58 years (IQR 51-69). In Italy, participants were mostly children and children-in-law of the older person, with low confidence with the Internet and high participation rates in the labor market, providing medium-low intensity of informal care. German caregivers were mostly unemployed children or children-in-law with a medium-high education, whereas the Swedish subsample included mostly retired spouses with high education.

Usage

Table 3 shows how access to the two areas of the Web platform varied across countries. In general, the majority of caregivers in all countries accessed the platform two or more times—74% in Italy, 83% in Sweden, and 94% in Germany.

Concerning the information resources area, German and Swedish users made more visits than Italian ones in absolute terms ($P<.001$). The median number of visits ranged between 5 (IQR 2-8) in Italy and 17 (IQR 7-66) in Germany, with relevant differences in the number of pages visited ($P=.001$) and overall time spent ($P=.002$). In terms of interactive services, social network and private messages were used by the majority of participants. In particular, Swedish caregivers tended to use the forum more often (58% overall), followed by the chat feature (62%), and the videochat feature or other videocommunication tools (31%). German users displayed similar behaviors, whereas Italian caregivers hardly used the videochat feature (only 3% accessed it) and reported lower levels of access to both the forum and the chat feature (20% and 26%, respectively).

Table 2. Characteristics of older persons, family caregivers, and care settings by country.

Participant and setting characteristics	Italy (n=42)	Sweden (n=36)	Germany (n=16)	Total (n=94)	P[a] value
Older person					
Gender (woman), n (%)	33 (79)	13 (36)	11 (69)	57 (61)	<.001
Age (years), median (IQR[b])	82 (76-87)	76 (72-82)	82 (69-87)	80 (74-85)	.03
ADL[c] index, median (IQR)	15 (11-18)	11 (4-17)	5 (1-8)	13 (5-18)	<.001
IADL[d] index, median (IQR)	4 (2-6)	4 (2-6)	6 (4-6)	4 (2-6)	.05
Family caregiver					
Gender (woman), n (%)	28 (67)	26 (72)	10 (63)	64 (68)	.73
Age (years), median (IQR)	53 (47-58)	68 (57-73)	56 (53-67)	58 (51-69)	<.001
Relationship to the older person, n (%)					<.001
Spouse/partner	1 (2)	27 (75)	3 (19)	31 (34)	
Child/child-in-law	31 (74)	7 (19)	10 (63)	48 (51)	
Other	10 (24)	2 (6)	3 (19)	15 (16)	
Children (yes), n (%)	31 (74)	30 (83)	9 (56)	70 (75)	.20
Grandchildren (yes), n (%)	10 (24)	22 (61)	2 (13)	34 (36)	<.001
Health status, n (%)					.11
Bad	1 (2)	4 (11)	2 (13)	7 (7)	
Fair	13 (31)	17 (47)	8 (50)	38 (40)	
Good	28 (67)	15 (42)	6 (38)	49 (52)	
Education, n (%)					<.001
Low	9 (21)	3 (8)	2 (13)	14 (15)	
Medium	25 (60)	7 (19)	5 (31)	37 (39)	
High	8 (19)	26 (72)	9 (56)	43 (46)	
Employment (yes), n (%)	25 (60)	15 (42)	4 (25)	44 (47)	.04
Living status (with respect to cared-for person), n (%)					.002
Same household	9 (21)	24 (67)	8 (50)	41 (44)	
Within walking distance	13 (31)	4 (11)	5 (31)	22 (23)	
Beyond walking distance	20 (48)	8 (22)	3 (19)	31 (33)	
Confidence with Internet, n (%)				<.001	
None/low	10 (24)	1 (3)	1 (6)	12 (13)	
Medium	24 (57)	8 (22)	8 (50)	40 (43)	
High	8 (19)	27 (75)	7 (44)	42 (45)	
Care setting					
Informal care provided per week (hours), median (IQR)	12 (6-24)	32 (6-70)	30 (9-144)	15 (6-40)	.02
Duration of caregiving period (years), median (IQR)	3 (2-4)	3 (2-7)	7 (2-9)	4 (2-5)	.09
Home care (yes), n (%)	2 (5)	14 (39)	6 (38)	22 (23)	<.001
Cash allowances received by older people and/or family caregivers (yes), n (%)	22 (52)	4 (11)	12 (75)	38 (40)	<.001
Privately employed care assistant (yes), n (%)	18 (43)	11 (31)	7 (44)	36 (38)	.38

[a]Results of chi-square or Kruskal-Wallis tests for categorical and continuous variables, respectively. Sum of percentages may not be 100% because of rounding.

[b]IQR: interquartile range.

[c]ADL: activities of daily living.

[d]IADL: instrumental activities of daily living.

Table 3. Usage of the online information resources and interactive services by country.

Usage of resources and services	Italy (n=42)	Sweden (n=36)	Germany (n=16)	Total (N=94)	*P*[a] value
Information resources area, median (IQR[b])					
Number of visits	5 (2-8)	13 (3-41)	17 (7-66)	7 (2-20)	<.001
Number of pages visited	123 (75-186)	267 (66-790)	423 (121-926)	157 (67-362)	.001
Time spent (minutes)	102 (53-163)	177 (65-755)	432 (113-689)	139 (57-405)	.002
Pages per visit	25 (18-40)	20 (13-34)	21 (11-25)	22 (14-35)	.07
Time per visit (minutes)	24 (16-30)	19 (10-27)	19 (10-25)	21 (14-29)	.048
Interactive services area (Italy n=35; Sweden n=26; Germany n=12; total n=73), n (%)					
Social network					.001
Never	20 (57)	2 (8)	4 (33)	26 (35)	
Low use	8 (23)	8 (31)	2 (17)	18 (25)	
Medium-high use	7 (20)	16 (61)	6 (50)	29 (40)	
Private messages					.007
Never	16 (46)	4 (15)	6 (50)	26 (36)	
Low use	12 (34)	8 (31)	0 (0)	20 (27)	
Medium-high use	7 (20)	14 (54)	6 (50)	27 (37)	
Forum					.006
Never	28 (80)	11 (42)	5 (42)	44 (60)	
Low use	6 (17)	7 (27)	5 (42)	18 (25)	
Medium-high use	1 (3)	8 (31)	2 (16)	11 (15)	
Chat					.02
Never	26 (74)	10 (38)	7 (58)	43 (59)	
Low use	8 (23)	8 (31)	3 (25)	19 (26)	
Medium-high use	1 (3)	8 (31)	2 (17)	11 (15)	
Videochat/ videocommunication tools					<.001
Never	34 (97)	18 (69)	5 (42)	57 (78)	
Low use	1 (3)	4 (15)	2 (16)	7 (10)	
Medium-high use	0 (0)	4 (15)	5 (42)	9 (12)	
Specific country services or tasks, n (%)					
E-learning course (Italy) (yes)		25 (60)	N/A[c]	N/A	N/A
Writing task in forum (Sweden) (yes)		N/A	8 (22)	N/A	N/A
Videoconferencing sessions (Germany) (yes)		N/A	N/A	6 (38)	N/A

[a]Results of chi-square or Kruskal-Wallis tests for categorical and continuous variables, respectively. Sum of percentages may not be to 100% because of rounding.

[b]IQR: interquartile range.

[c]N/A: not applicable.

Table 4. Impact of the Web-based intervention on users.

Outcomes	Baseline measurement (T0)		Postintervention measurement (T1)		P^b value	Effect size, r^c
	Mean (SD)	Median (IQR[a])	Mean (SD)	Median (IQR)		
WHO-5[d]	44.5 (24.2)	40 (24-60)	43.4 (23.0)	40 (24-60)	.41	-.06
COPE[e] Index						
Negative impact	20.9 (4.1)	21 (19-24)	20.4 (4.2)	21 (18-23)	.22	-.09
Positive value	12.6 (2.2)	13 (11-14)	12.1 (2.1)	12 (11-14)	.02	-.18
Quality of support	10.4 (2.8)	10 (8-12)	9.8 (2.7)	9 (8-12)	.02	-.18
MSPSS[f]						
Family	21.0 (5.8)	22 (17-26)	20.1 (5.9)	20 (16-25)	.04	-.15
Friends	17.8 (6.1)	18 (13-23)	17.5 (6.1)	18 (13-22)	.71	-.03
Social support	21.9 (5.8)	23 (18-27)	21.1 (5.5)	21 (17-26)	.04	-.16
Total score	60.7 (14.2)	63 (50-73)	58.7 (14.2)	60 (47-69)	.11	-.12

[a]IQR: interquartile range.

[b]Wilcoxon signed-rank test for dependent samples, calculated between median values before and after the intervention.

[c]Effect size, *r*, is calculated as the Z value divided by the square root of the number of observations.

[d]WHO-5: 5-item World Health Organization Well-being Index.

[e]COPE: Carers of Older People in Europe.

[f]MSPSS: Multidimensional Scale of Perceived Social Support.

Outcomes

Primary and secondary outcomes were assessed before (T0) and after (T1) the 3-month Web-based intervention (see Table 4). At baseline, the median scores of negative impact and positive value COPE subscales were relatively high (13 out of 16 points, negative impact; 21 out of 28 points, positive value), indicating quite low levels of subjective burden and a high positive experience of caregiving. The level of perceived social support was moderate, as suggested by midrange values in the COPE quality-of-support subscale and MSPSS, whereas the level of psychological well-being was quite low (median 40 out of 100 in the WHO-5 Index).

Concerning the pretest-posttest scores, the analysis showed that participants changed their perception toward different aspects. There was a statistically significant decrease of values concerning the positive value of caregiving (-1; P=.02) and the quality of support received by significant others (-1; P=.02) (COPE Index subscales), as well as by family (-2; P=.04) and social support in general (-2; P=.04) (MSPSS subscales). A small effect size [48] was found for all significant variables (ranging from -.15 to -.18). The scores concerning the other scales related to the negative impact of caregiving, support by friends, and psychological well-being showed no changes in values.

Content Analysis of Focus Groups

A total number of 20 caregivers attended the focus groups: 7 in Italy, 7 in Germany, and 6 in Sweden. All participants in the three countries generally had a positive and satisfying experience with the platform, although there were slight differences in the emphasis of certain aspects. Data analysis identified five main themes: online social support, role awareness, caregiving activities, psychological well-being, and technical concerns. Theme analysis and relevant quotes are provided below (users' names are fictional).

1. Online Social Support

A consensus across the three focus groups was reported about the positive effects on social inclusion and support derived from using the interactive services. The platform was perceived as a safe virtual environment, which addressed caregivers' needs to communicate with others and share personal experiences, more than any other available, mainstream, open-access social network (ie, Facebook). The possibility to interact in a protected environment with other people experiencing similar issues—although users did not know each other at first—led to increased mutual learning and understanding, as well as the recognition of not being alone in this condition. Both group and individual support provided by professional counselors was considered optimal and brought clear benefits. In particular, Swedish caregivers openly described that social recognition and confirmation by peers was useful for raising their own self-esteem, mastery over life, and sense of competence.

> *On other platforms, when I write something about my situation I have to explain. On this platform I don't need to explain why I feel like I do, the other caregivers understand and know we have difficult times now and then.* [Nils, Swedish adult son]

> *Even just knowing that these kinds of support services exist and trustworthy people are working behind them, it is really important and helpful for family caregivers.* [Patrizia, Italian adult daughter]

2. Role Awareness

Caregivers expressed that they felt a change in their understanding of their caregiving situation, claiming especially of having been stimulated to reflect about and understand more their own condition and needs. In Italy and Germany, participants agreed that reading and sharing caregivers' experiences was emotionally difficult, but helpful in order to understand and better appraise their roles. Furthermore, many caregivers expressed that they had a better understanding about the future development of the older person's condition, and what they could expect to face in the months or years to come. In Sweden, older female spouses emphasized the valorization of their role as a direct effect of online interactions, one of them even reporting that she could now see her activity more as a proper "job" and better accept this role.

> *You got the impression that you are understood, able to talk openly and got to reflect on your own situation. This motivates you to take on new steps to improve your personal situation.* [Stefanie, German adult daughter]

> *I have felt that my experiences are worth something, that I am not only an old lady in her 70s who should just sit and be quiet.* [Lisa, Swedish older female spouse]

3. Caregiving Activities

Most caregivers in Italy and Germany underlined that information available on the platform, as well as tips and advice from other users, were useful to improve caregiving activities and better approach the cared-for person. Talking retrospectively, many users said their lives could have changed if they had had access to the platform earlier, because it could have helped them to recognize certain symptoms and help provide the older person with more adequate care.

> *My caregiving situation has improved by the tips I got from the other caregivers.* [Phillip, German older male spouse]

> *If this Web platform existed when our mum looked upset without any clear reasons, we would have realized more easily what she needed and would have avoided her having to suffer so much.* [Roberta, Italian adult daughter]

4. Psychological Well-being

In terms of subjective well-being, some users in Sweden (both children and spouses) said they felt less burdened after the intervention, especially because they could better accept both positive and negative feelings arising from the caregiving situation. The possibility to express and share them with others, without being judged but rather receiving social recognition and confirmation of their own efforts by peers, helped them to cope with the situation and to reduce their perceived stress.

> *I feel happier and calmer when I can share the positive and negative things that happen in my situation as a caregiver. I don't know if I would have coped with the situation [without the platform] actually.* [Nils, Swedish adult son]

> *I feel less stressed and that can be a result of other people's posts that I allow myself to have negative feelings and thoughts.* [Anna, Swedish older female spouse]

5. Technical Concerns

Despite the majority of participants who judged the usability of the platform as sufficient or good, some of them did mention technical or usability issues as a reason for not having used some of the available interactive services more. In particular, Swedish users reported problems with using the mobile version and specific features of some services (eg, uploading pictures on the social network, and using the chat and videochat features), whereas in Italy some caregivers found it difficult to find and reach some internal pages or services. In Sweden, an alternative videocommunication system was used with the moderator in order to overcome technical issues arising with the videochat feature. Support guaranteed by the moderator was in any case highly appreciated by all users across the three countries.

Discussion

Results from our pilot study showed a statistically significant change of the perception by caregivers of some aspects related to the caregiving context. At the end of the intervention, caregivers reported slightly lower levels of positive feelings and social support received, whereas subjective burden and psychological well-being did not change. On the other hand, qualitative findings from the focus groups pointed out the usefulness and appropriateness of support received by caregivers from information and communication with moderators and peers. The major benefit for users seemed to be their empowerment, by means of increased self-efficacy, role awareness, and social recognition.

An interpretation of these ambivalent results can be that the intervention actually stimulated a new appraisal of the caregiving situation, including coping resources and social support available in the community, with caregivers recognizing ultimately a lack of adequate (external and/or professional) support from family, significant others, and formal services. The online information and support received via the platform could have produced a reappraisal of their own situation, thus allowing participants to identify more clearly and/or for the first time multiple issues of caregiving previously unrecognized, and to understand hidden needs for support.

Our results seem to be in line with previous international research in this field. Studies delivering multicomponent programs comparable to our intervention, that included unstructured support by professionals and peers, did not show significant changes in psychological well-being and burden [49], especially over a short time frame [9,11]. Overall, only some structured psychoeducational and psychotherapeutic programs were found to have an impact on caregiver burden and psychological well-being outcomes [7,18,19,50-52], whereas other studies highlighted mainly mixed or inconclusive results [8,53-56].

Furthermore, there is a lack of empirical literature regarding the effect of Web-based programs on perceived positive aspects of caregiving [13], which limits the possibility of comparisons with our partly unexpected findings. However, another short-term study found that some caregivers receiving the Web-based program had higher levels of stress at the end of the intervention than at baseline [8], a result that has been similarly explained as the possible consequence of caregivers' enhanced awareness of their challenging caring situation. However, the worsening of positive feelings toward caregiving was narrow (median decreased from 13 to 12 in the 4-16 subscale range) and did not imply serious consequences for caregivers, also given the high level of initial scores and the qualitative findings collected in this respect.

Available literature also suggests that guidance from a professional counselor or coach is an effective way to address specific needs of caregivers [13,57]. As well, peer support in online communities can lead to increased confidence and self-efficacy [13-16,30], sense of belonging, and social inclusion [11,20,31]. Qualitative findings from our pilot study seemed to confirm these positive effects in the three countries, with major benefits for addressing social isolation for Swedish older spouses, also in line with available research [58].

Despite the lack of evidence in terms of burden and psychological well-being, the piloted intervention seemed able to provide useful and adequate online support services for family caregivers of older people, even in a short-term time frame, which might lead to increased efforts to alleviate stress by accessing coping resources and social support in the community [20,24,59]. In this respect, however, the challenge of tailoring the Web platform and tools to users' digital skills and preferences represents a crucial issue to be considered for guaranteeing their usability and friendliness. This is especially true for caregivers with little experience of using Web services [10,15], as shown by the problems experienced by the Italian subsample, mainly due to low digital skills.

This study has some limitations to be taken into account and results cannot be generalized without caution. First, the study was conceived as a pilot test of a new Web-based program, able to carry out only a short-term and limited assessment of the intervention. Second, although the adopted mixed-methods approach gave the opportunity to integrate quantitative and qualitative results, associations between variables and causal relations could only be inferred. Third, despite the fact that the study was designed to include the main variables of interest, due to project constraints we could not include a control arm and cannot therefore exclude the influence of external variables on the outcomes. Fourth, only a subgroup of caregivers could be enrolled in the focus groups; indeed, we cannot fully exclude the influence of a selection bias in the qualitative findings. In general, the recruitment process was based on a convenience sample approach and bias in the profiles of the recruited caregivers was possible. Difficulties in approaching family caregivers [5], especially in testing Web-based services [7,8], are well-known in the literature, and they might have led to a slight imbalance of country subsamples concerning numbers and characteristics of caregivers involved.

Despite these limitations, it should be underlined that only a few studies have been able to involve similar or higher numbers of family caregivers in Web-based intervention research [7,9,19,50], and almost none have had a multi-country perspective [9]. Furthermore, the refinement and implementation of the InformCare Web platform at the European level within the INNOVAGE project was a direct consequence of this study. Based on results and indications from the pilot intervention, the project team managed an adjustment of information resources and a revision of guidelines for implementing and moderating interactive services, an effort conducted together with a network of appointed stakeholders—nonprofit organizations and experts—in the EU countries. This constitutes a remarkable, concrete added value of this research, since the platform has been accessible since mid-2015 in 27 EU countries via the Eurocarers website [60]. It includes 32 national versions, with some countries having more than one official language, and more than 2500 Web pages in the information resources area, which are publicly available and tailored to country characteristics. According to the availability and resources of national nonprofit organizations appointed in each country, a selection of interactive services may have been activated for national caregivers as well. Therefore, this study represents a unique example of translational research, which aims to contribute to the overcoming of social and cultural barriers for family caregivers that still exist in many countries by exploiting the potential of Web-based support. Future work might be based on this pilot experience and the implementation of the InformCare Web platform for conducting more in-depth and robust studies, especially on how to provide effective and tailored support for family caregivers, as well as for enabling cross-country, comparability research with a common set of intervention tools and guidelines.

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Conflicts of Interest

None declared.

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Abbreviations

ADL: activities of daily living
COPE: Carers of Older People in Europe
EU: European Union
FP7: Seventh Framework Programme
HS1: health status 1 variable
IADL: instrumental activities of daily living
INRCA: Italian National Institute of Health and Science on Ageing
IQR: interquartile range
MSPSS: Multidimensional Scale of Perceived Social Support
N/A: not applicable
NISAL: National Institute for the Study of Ageing and Later Life
NKA: Swedish Family Care Competence Centre
OARS: Older Americans' Resources and Services

SMS: short message service
T0: baseline measurement point
T1: postintervention measurement point
WHO-5: 5-item World Health Organization Well-being Index

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Original Paper

Teaching Intuitive Eating and Acceptance and Commitment Therapy Skills Via a Web-Based Intervention: A Pilot Single-Arm Intervention Study

Sara Boucher[1,2], PhD; Olivia Edwards[1], MDiet; Andrew Gray[2], BCom (Hons); Shyamala Nada-Raja[2], PhD; Jason Lillis[3], PhD; Tracy L Tylka[4], PhD; Caroline C Horwath[1], PhD

[1]Department of Human Nutrition, University of Otago, Dunedin, New Zealand

[2]Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand

[3]Department of Psychiatry and Human Behavior, Brown University Medical School, Providence, RI, United States

[4]Department of Psychology, The Ohio State University, Columbus, OH, United States

Corresponding Author:
Caroline C Horwath, PhD
Department of Human Nutrition
University of Otago
PO Box 56
Dunedin,
New Zealand
Phone: 64 3479 7946
Fax: 64 3479 7958
Email: caroline.horwath@otago.ac.nz

Abstract

Background: Middle-aged women are at risk of weight gain and associated comorbidities. Deliberate restriction of food intake (dieting) produces short-term weight loss but is largely unsuccessful for long-term weight management. Two promising approaches for the prevention of weight gain are intuitive eating (ie, eating in accordance with hunger and satiety signals) and the development of greater psychological flexibility (ie, the aim of acceptance and commitment therapy [ACT]).

Objectives: This pilot study investigated the usage, acceptability, and feasibility of "Mind, Body, Food," a Web-based weight gain prevention intervention prototype that teaches intuitive eating and psychological flexibility skills.

Methods: Participants were 40 overweight women (mean age 44.8 [standard deviation, SD, 3.06] years, mean body mass index [BMI] 32.9 [SD 6.01] kg/m^2, mean Intuitive Eating Scale [IES-1] total score 53.4 [SD 7.46], classified as below average) who were recruited from the general population in Dunedin, New Zealand. Module completion and study site metrics were assessed using Google Analytics. Use of an online self-monitoring tool was determined by entries saved to a secure online database. Intervention acceptability was assessed postintervention. BMI, intuitive eating, binge eating, psychological flexibility, and general mental and physical health were assessed pre- and postintervention and 3-months postintervention.

Results: Of the 40 women enrolled in the study, 12 (30%) completed all 12 modules (median 7.5 [interquartile range, IQR, 2-12] modules) and 4 (10%) used the self-monitoring tool for all 14 weeks of the intervention period (median 3 [IQR 1-9] weeks). Among 26 women who completed postintervention assessments, most women rated "Mind, Body, Food" as useful (20/26, 77%), easy to use (17/25, 68%) and liked the intervention (22/25, 88%). From pre- to postintervention, there were statistically significant within-group increases in intuitive eating (IES-2 total score $P<.001$; all IES-2 subscale scores: $P \leq .01$), psychological flexibility ($P=.01$), and general mental health ($P<.001$) as well as significant decreases in binge eating ($P=.01$). At the 3-month follow-up, IES-2 improvements were maintained, and there were further improvements in binge eating ($P<.001$) and general mental health ($P=.03$), and a marginal yet nonsignificant tendency for further improvement in psychological flexibility ($P=.06$). There were no significant within-group changes in BMI from pre- to postintervention and postintervention to 3-month follow-up ($P=.46$ and $P=.93$, respectively).

Conclusions: The "Mind, Body, Food" prototype Web-based intervention is appealing to middle-aged women and may be a useful tool to help women learn intuitive eating and ACT skills, reduce binge eating, and maintain weight over 3 months. Further

work to improve the user experience and engagement is required before testing the online intervention in a randomized controlled trial.

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KEYWORDS

Web-based intervention; overweight; obesity; prevention; middle-aged women; BMI; intuitive eating; acceptance and commitment therapy

Introduction

Despite the high prevalence of reported attempts at weight control, obesity rates worldwide continue to increase [1-3]. Since obesity is associated with many adverse health consequences [4], and weight loss interventions have shown modest long-term success [5-7], there is an increasing focus on the prevention of weight gain [8,9]. Among middle-aged women (40-50 years), weight gains of 0.5 to 0.7 kg per year have been observed [10-12], and there is evidence that the greatest risk for weight gain is among women who are already overweight or obese [10]. Around menopause, weight gain is associated with increases in cardiovascular risk factors such as blood pressure, total cholesterol, low-density lipoprotein cholesterol, triglycerides, and fasting insulin [12]. For these reasons, effective weight gain prevention has been identified as an important goal for premenopausal women [12], because even among middle-aged women who report following healthy weight control behaviors (eg, decreased food quantity, exercise, reducing fat intake), weight gain is observed [1].

Intuitive eating is a nondieting, adaptive approach to eating behavior characterized by eating for physical rather than emotional reasons, relying on internal hunger and satiety cues, unconditional permission to eat when hungry and what food is desired, and choosing nutritious foods to help one's body function well [13-15]. Although intuitive eating shares similarities with mindful eating, there are differences. Mindful eating involves paying attention, without judgment, to the eating experience and to hunger/satiety cues and eating attentively without distraction [16]. However, intuitive eating also takes nutrition into consideration when choosing foods to enhance/support body function and involves giving oneself unconditional permission to eat not only when hungry but those foods one truly feels like eating [13-15]. Cross-sectional research has shown intuitive eating to be positively related to body appreciation, self-esteem, and satisfaction with life and inversely related to eating disorder symptomatology, poor interoceptive awareness, body surveillance, body shame, body mass index (BMI), and internalization of media appearance ideals [14]. Intuitive eating was inversely associated with BMI in a nationwide sample of middle-aged women [17] and intuitive eating interventions have lowered cholesterol levels, blood pressure, disordered eating, body dissatisfaction, and depression and improved diet quality, physical activity, stress management, and self-esteem [18,19]. Compared to diet group participants, participants who practice intuitive eating have been shown to maintain improvements in metabolic function (eg, blood pressure, blood lipids) even in the absence of weight loss, whereas little improvement was sustained in diet group participants [19]. A recent review of 20 studies evaluating intuitive eating interventions [18] reported reductions in weight in 6 studies, weight maintenance in 8 studies, and mixed results in 2 studies.

Long-term weight management is enhanced by effective emotion regulation skills [20,21]. A growing body of evidence supports the effectiveness of acceptance and commitment therapy (ACT) in the management of obesity [22-27]. ACT-based interventions focus on improving psychological flexibility, which is the ability to remain mindfully aware and accepting of one's experience in the present moment (eg, thoughts, feelings, bodily sensations) while also clarifying one's values and choosing to engage in behavior that is consistent with those values [28]. ACT-based skills do not teach control or avoidance of eating triggers but rather develop skills that create a different relationship with these triggers: allowing individuals to be present without acting on the triggers (ie, acceptance). Acceptance-based interventions (ie, teaching skills such as values clarity and behavioral commitment, awareness of decision-making processes, and distress tolerance) have been shown to increase psychological flexibility and improve weight control, particularly for those who tend to eat in response to emotional and environmental triggers [29]. In randomized controlled trials (RCTs) among adults attempting weight loss, brief (ie, 6-8 hours) ACT-based interventions have been reported to be more effective for weight loss compared to no-treatment [25,27]. Tapper's [27] findings suggest that the effect of the intervention on BMI was largely brought about by reductions in binge eating, while Lillis [25] reported that weight-specific acceptance and psychological flexibility significantly mediated BMI outcomes. Recently, Sairanen et al [30] reported that among overweight adults, the ability to recognize and accept aversive internal experiences (without reacting to them) was positively associated with eating for physical rather than emotional reasons.

Intuitive eating and ACT appear to be particularly well suited for integration, and to our knowledge, this is the first study to test them when used together. Both approaches focus on fostering a mindful, accepting, and open stance to one's experiences. Intuitive eating teaches individuals to be more mindfully aware of and follow the body's hunger and satiety cues, while ACT teaches individuals how to cope more effectively with negative and unwanted cognitive and emotional cues through awareness and acceptance. ACT skills may complement intuitive eating by helping to decouple eating behavior from emotional cues and external triggers, allowing for hunger and satiety cues to play a stronger role in regulating eating behavior.

Web-based interventions have the ability to have a major public health impact. They can present complex health information in

simple formats (eg, video, graphic, audio) [31], overcome time and travel barriers of face-to-face interventions [32], reach a large audience [33], reduce stigma related to being overweight or obese [34], and facilitate weight management [35]. ACT interventions have been adapted for Web-based delivery and have been shown to be effective in teaching ACT-based skills to manage conditions such as tinnitus [36], chronic pain [37], work-related stress [38], and multiple behavioral health risks [39]; however, there are no published studies testing Web-based ACT for eating behavior interventions. Although a small number of studies have investigated Web-based healthy eating interventions based on nondiet and size acceptance approaches among young adults [40,41], no published study to date has, to our knowledge, designed and evaluated an online intuitive eating intervention. Integrating ACT and intuitive eating is a novel approach to changing eating behavior that when delivered online would provide an accessible weight management intervention grounded in evidence-based theory.

We developed an online intuitive eating intervention called "Mind, Body, Food," based on the intuitive eating principles set forth by Tribole and Resch [15] and incorporating ACT-based skills. The aim of "Mind, Body, Food" was to teach middle-aged women intuitive eating skills facilitated via acquiring ACT-based skills. It was theorized that increased psychological flexibility resulting from the acquired ACT-based skills will further enable women to eat more intuitively by helping them to handle feelings, thoughts, urges, or cravings that can trigger eating when not physically hungry. The aim of this pilot study was to design an evidence-based prototype online intuitive eating intervention and investigate its acceptability, feasibility, and usage among middle-aged women.

Methods

Research Design and Setting

For this prospective single-arm pilot intervention study, participants were recruited from the community in Dunedin, New Zealand, and assessed preintervention, postintervention, and at 3-month follow-up. They accessed the intuitive eating intervention directly via the Internet. The University of Otago Human Ethics Committee granted ethical approval (reference code: H13/057). The Ngāi Tahu Research Consultation Committee approved the research methods as being consistent with the needs of the Ngāi Tahu iwi (South Island Māori, the indigenous population of New Zealand).

Participants and Recruitment

Women aged 40 to 50 years (inclusive) were eligible to participate in the study if they were able to communicate in English, able to engage in gentle physical activity (ie, walk at a leisurely pace for 10 minutes or more), premenopausal (ie, having a menstrual period in the preceding three months or currently being on any form of hormonal contraceptives that stopped menstruation [42]), and regularly accessed the Internet and email at least three days per week. To target women with the greatest potential to benefit from training in intuitive eating, we further restricted inclusion to women with below average Intuitive Eating Scale scores (IES) [13] (summed total IES score less than 65, based on nationwide survey data for overweight NZ women [17]) and with a BMI of at least 26.5 kg/m^2 (calculated using measured height and weight). Women were excluded if they were pregnant or lactating, taking hormone replacement therapy, or a current smoker or if they had a history of hysterectomy, oophorectomy, diabetes, cancer, cardiovascular disease, or eating disorder. Additionally, women were excluded if they currently were taking a medication that may affect their appetite or were enrolled in any weight loss program.

To recruit women from a diverse range of socioeconomic and ethnic backgrounds, recruitment materials were circulated through local health promotion and social service networks, low socioeconomic neighborhoods, and organizations servicing Pacific and Māori populations. Recruitment materials were framed in the context of encouraging women interested in learning intuitive eating skills for long-term weight management. The study was also promoted in a local newspaper article.

Sample Size

We aimed for a sample size of 40 participants at the 3-month follow-up visit in order to investigate acceptability and usability as well as providing sufficiently precise estimates of outcome measure variability, correlations between repeated measures, and retention rates. The sample size was not determined according to statistical principles but was the number judged to be suitable for achieving the study objectives. The recruitment target was set at 58 women to account for an estimated 30% attrition rate, based on previous research [43].

"Mind, Body, Food" Intervention

The 12-module self-guided "Mind, Body, Food" intervention was developed through an iterative process involving extensive input from end-users. The content was guided by evidence-based research in the field [25,27] and the researchers' own experience teaching intuitive eating (CCH, SB, TLT) and ACT skills (CCH, JL) face-to-face. A paper-based intervention prototype was pretested in focus groups and interviews with members of the target audience, followed by pretesting of a Microsoft PowerPoint-based prototype of the intervention. Following this, expert review of the intervention material, with a particular focus on intuitive eating (TT) and ACT (JL) content, was undertaken to ensure clarity and fidelity to the underpinning theoretical basis for the intervention. "Mind, Body, Food" content was then translated by a professional Web developer into a Web-based prototype (Figures 1 through 5), which was not compatible with mobile browsers. The Web-based prototype underwent usability and heuristic testing before the current study.

"Mind, Body, Food" consists of 12 modules, each covering skills related to intuitive eating and taking 15 to 20 minutes to complete. Table 1 presents "Mind, Body, Food" module titles and key skills and activities delivered. In each module, the key skills and their rationale were introduced in a 3- to 5-minute video featuring a discussion among three women (one dieter and two women who had learned intuitive eating). Each video commenced with discussion of a challenge related to eating (eg, recognizing physical hunger) before introducing the new skills and a discussion of the women's experience of practicing the skills. Each module followed with a guided audio activity and

typed activity. Guided experiential audio activities were used to deliver training in recognition of hunger and fullness signals and many of ACT's core skills (eg, awareness and acceptance of thoughts and feelings; "surfing" urges to eat when not physically hungry [ie, acceptance]; visualizing placing thoughts on leaves floating in a stream [ie, ACT's cognitive defusion skill]). Typed activities encouraged participants to reflect on how practicing the skills would make a difference to their life (ie, clarification of values). At the end of each module, users were encouraged to practice intuitive eating skills every day. Starting in Module 2, use of the Eating Awareness Tracker (EAT), a self-monitoring tool for recording nonjudgmental observations of eating-related experiences, was encouraged, and a library of additional resources was provided. The EAT enabled participants to monitor hunger, fullness, and mindfulness ratings during eating, each using 0 to 10 scales. Beginning in Module 1, the EAT was presented as an essential part of the intervention. Participants were encouraged to log into "Mind, Body, Food" to use the EAT as often as possible after meals or snacks and were provided an opportunity to practice using the EAT during Modules 2-11 by recording the most recent eating experience. At the end of each module, participants could choose to receive, via email or short message service (SMS), up to three daily prompts to use the EAT.

Figure 1. "Mind, Body, Food" log-in page.

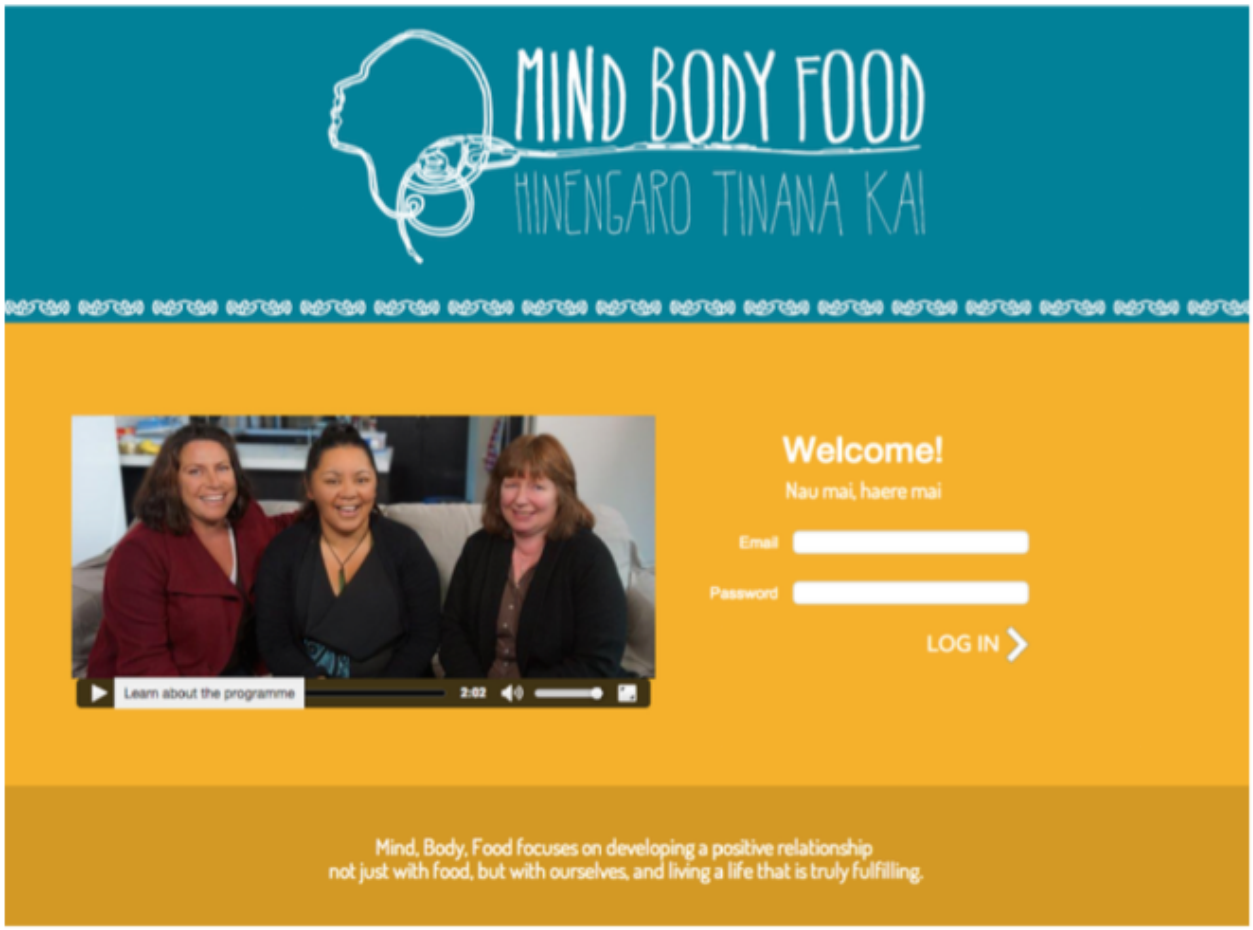


Table 1. "Mind, Body, Food" modules (including the te reo Māori titles) and key skills taught in each module.

Module	Title	Key skills	Activities
1	Ditch the Diets / Whakarerea te whakapuango	Giving self permission to eat wide range of foods. Guiding food choices based on what feels enjoyable and satisfying.	Practice before each snack/meal asking self, "It's okay to have this, but will I truly enjoy this and feel satisfied?" Typed and audio activities: reflection on past experience of dieting, or labeling foods "forbidden."
2	Tuning into Hunger / E rongo ana i te hikai	Recognizing what physical hunger feels like. Before eating, rating physical hunger on a scale 0 (absolutely empty) to 10 (sick from overeating). Initiating eating when hunger is rated 3 or 4.	Guided audio activity: scan of mouth, throat, and stomach to recognize physical signals of hunger. Typed activities: reflect on sensations of hunger (or lack of) before typical eating experiences, and reflect on how life would be different if body signals were listened to more often before eating.
3	Am I Full? Kua puta a pito?	Recognizing what fullness feels like and knowing when to take the last bite. While eating, rating fullness on a scale of 0 (absolutely empty) to 10 (sick from overeating). Finishing eating when fullness is rated 6 or 7.	Guided audio activity: awareness of stomach sensations to recognize physical signals of fullness. Typed activities: reflect on sensations of fullness after eating, and reflect on how life would be different if body signals were trusted to guide how much to eat.
4	One Bite at a Time / Kei ia ngau; ka ngau, a, ka ngau	Eating with nonjudgmental awareness (ie, mindfulness). Rating mindful eating on a scale from 0 (mindless eating) to 10 (mindful eating). Mindfully eating in 7 to 10 rating range.	Guided audio activity: practice mindfully eating a piece of dried fruit. Typed activity: reflect on usual level of mindfulness when eating and how the experience of eating would differ if more attention was paid to the food and how food affects the body.
5	Coping with Cravings / Whakataha atu te wararwara	Coping with urges to eat when not physically hungry (ie, acceptance).	Guided ACT audio activity: "urge surfing" to cope with a craving to eat when not physically hungry. Typed activities: reflect on common triggers to eat when not physically hungry and how life would be different if response to cravings was asking, "Am I physically hungry?" and "Is this food really what I feel like in this moment?"
6	Emotional Eating / Ka kai ki te whakarata i te mānuka	Identifying emotional triggers to eat (ie, acceptance). Coping with emotions without using food.	Guided ACT audio activity: practice making space for emotions (ie, not struggling to change them or get rid of them). Typed activities: reflect on common triggers to eat emotionally and how life would be different if allowing uncomfortable feelings to be present and not eating to change feelings. Ask, "Is emotional eating in line with what matters most in life?"
7	Every Body Deserves Respect / He mana tō ia tinana	Shifting focus from body appearance to appreciating body functions.	Guided audio activity: body scan with appreciation of body functions. Typed activities: describe self with nonjudgmental (ie, neutral or positive) words, and reflect on how life would be different if focus shifted from changing body's appearance to appreciating body's functions.
8	Dealing with Pressures to Diet / Whaihangatia ngā pēhanga o te whakapuako	Handling pressures to diet or engage in "fat talk."	Audio activity: review of diet cycle, encourage body appreciation and reflection on positive experiences with intuitive eating to reinforce motivation to eat intuitively. Typed activities: reflect on positive changes made since beginning "Mind, Body, Food," and identify responses to pressures to diet and "fat talk."
9	Taming the Inner Critic / Whakarata te kaiwhakatāwai o roto	Distancing self from negative thoughts (ie, cognitive defusion).	Guided ACT audio activity: visualize placing unhelpful thoughts on leaves in a stream. Typed activities: identify techniques to "unhook" from unhelpful thoughts, and reflect on how life would differ if not attached to unhelpful thoughts.
10	Get Active Your Way / Kei a koe te tikanga korikori	Engaging in enjoyable physical activities every day.	Guided audio activity: Walking mindfully (ie, tuning into bodily sensations and surroundings while walking). Typed activities: reflect on benefits of physical activity and how to include physical activity in daily routine.

Module	Title	Key skills	Activities
11	Fine Tuning Food Choices / Āta whiria te kai	Selecting healthier food options without feeling deprived.	Guided audio activity: mindful food shopping. Typed activity: identify enjoyable ways to eat more fruits and vegetables and choose lower fat foods without feeling deprived.
12	Staying on Track / Kia mau, kia ū	Staying motivated to maintain changes and recovering from "slips."	Guided audio and typed activities: reflect on positive changes made since starting "Mind, Body, Food," and identify barriers to eating intuitively and coping strategies.

Participants completed the 12 modules over a 14-week period and were reminded by email during the first 12 weeks when each new module became available. A new module became available only once the previous module was completed (as defined by clicking Done on the last page of the module). Participants could also receive a weekly notification via SMS that each new module was available. No recommendations were given regarding how frequently the intervention should be accessed. The "Mind, Body, Food" intervention was available until the final 3-month follow-up assessment, allowing participants to revisit and revise previous material.

Figure 2. Video activity.

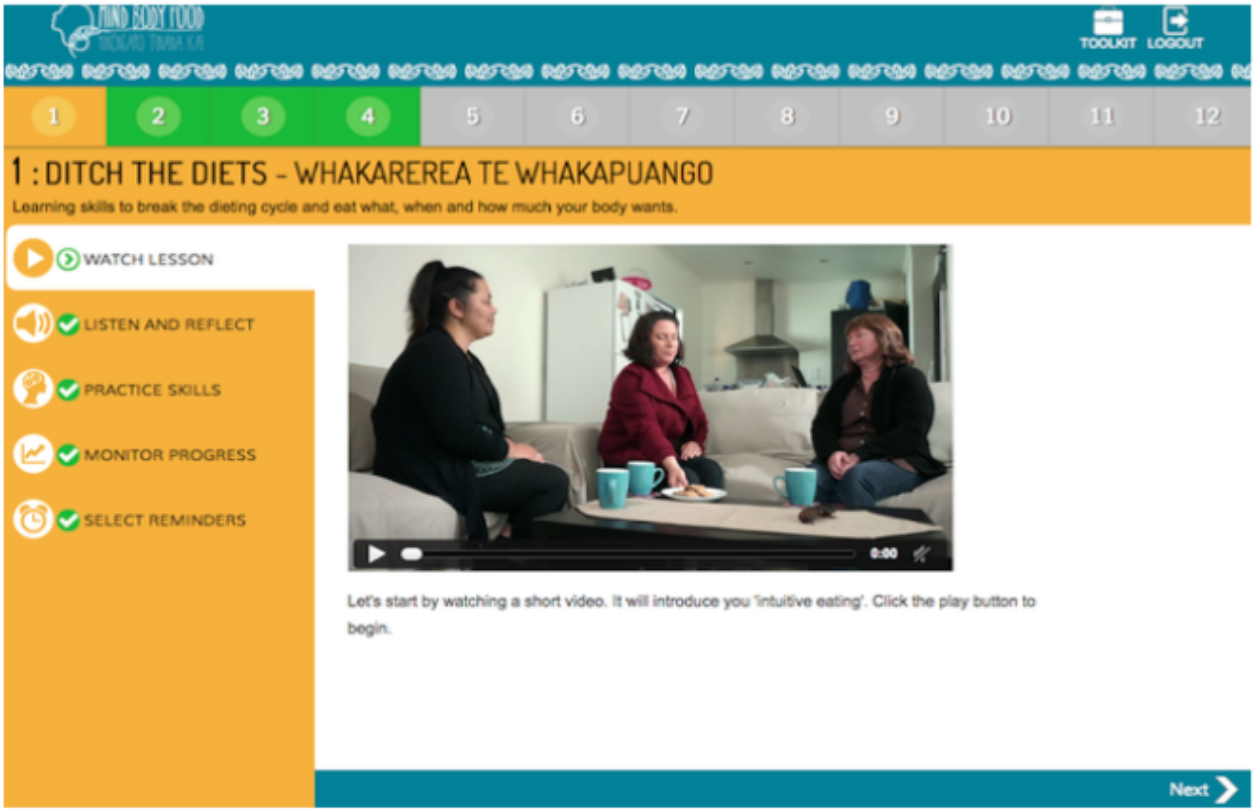


Figure 3. Audio activity.

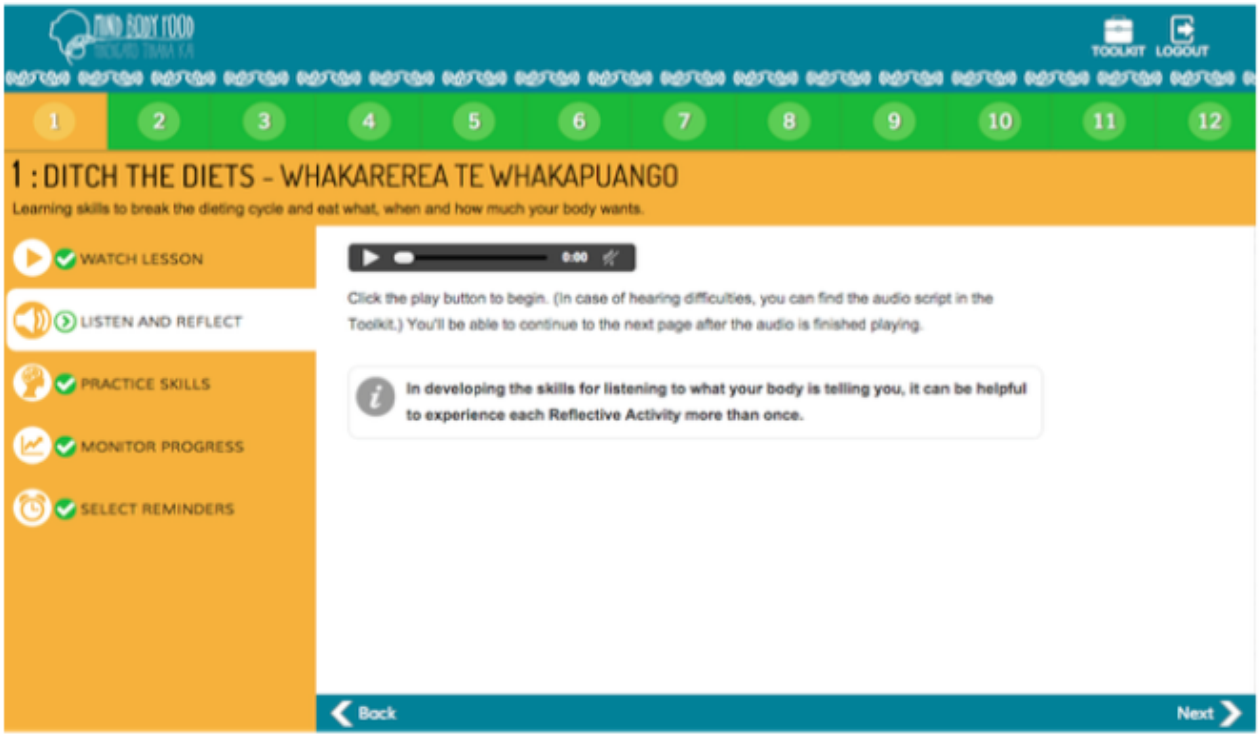


Figure 4. Typed activity.

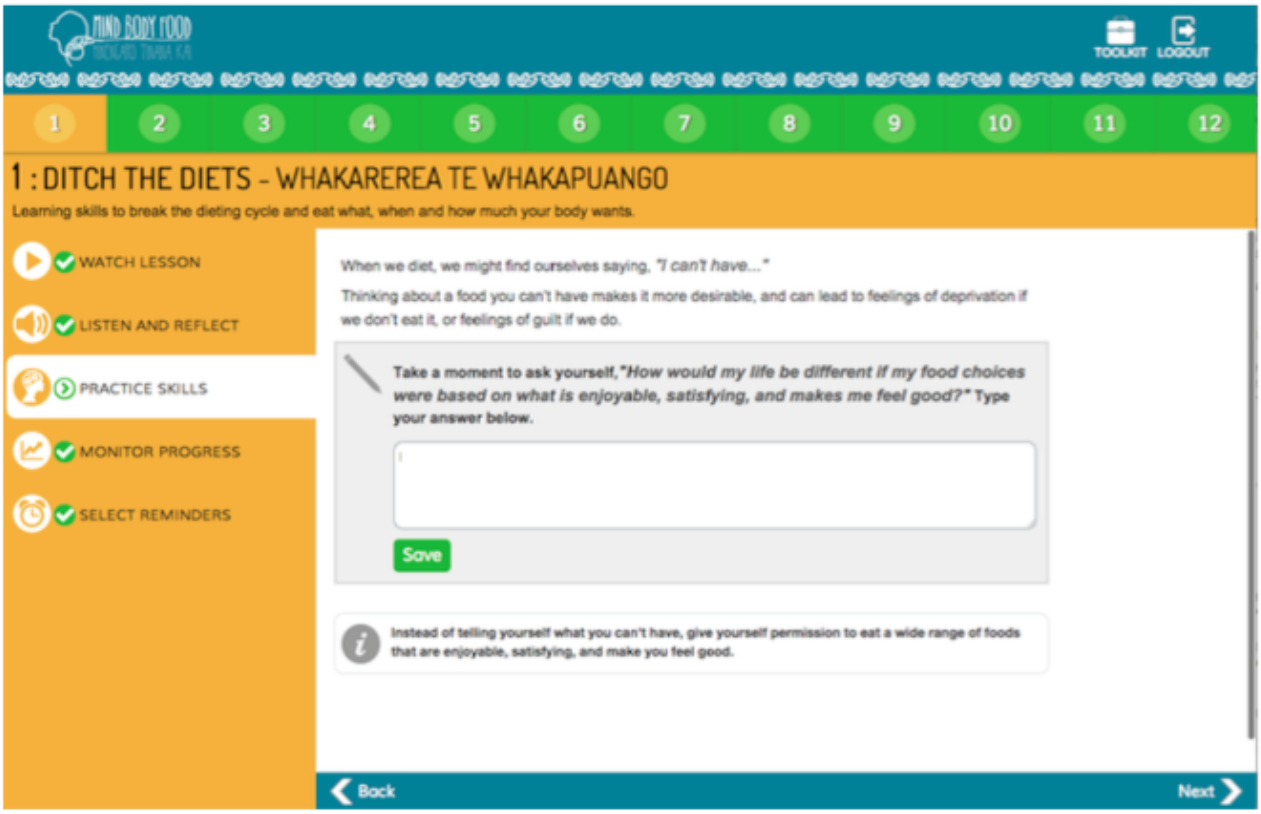
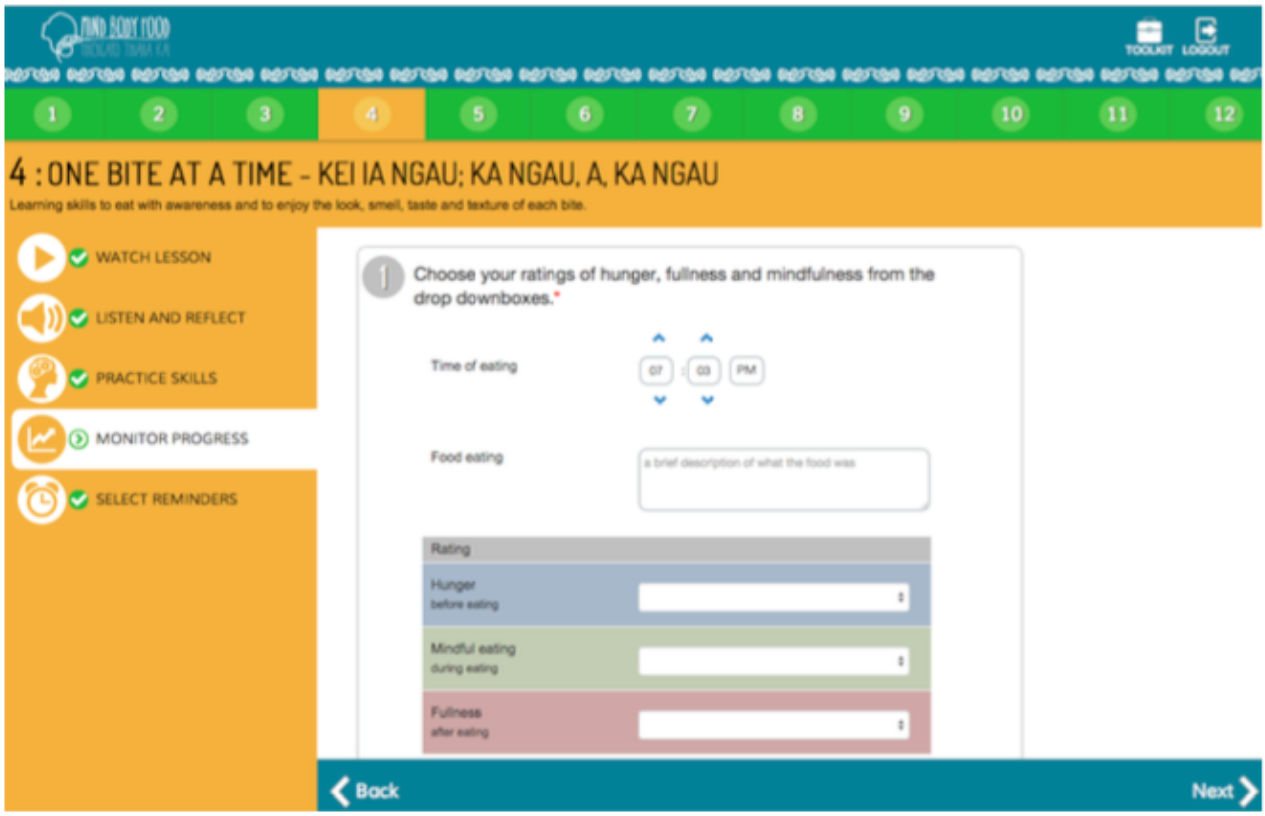


Figure 5. Eating Awareness Tracker (EAT) self-monitoring tool.



Procedures

During the initial contact, a preliminary check of eligibility criteria was conducted. Preliminary screening criteria included premenopausal status, 40 to 50 years of age, and BMI greater than 26.5 kg/m^2 based on self-reported height and weight. Women satisfying initial eligibility criteria were then emailed a Web-based screening questionnaire to evaluate exclusion criteria and Participant Information and Consent Form. Women who satisfied all inclusion and exclusion criteria were invited to participate in the study and were asked to complete the preintervention assessment by visiting the clinic located on campus. Women who did not meet eligibility criteria were offered a list of nondieting resources (eg, books, websites).

At the preintervention assessment, participants provided informed consent and upon enrollment in the study were assigned a username and passcode. At this time, they were given a brief tour of a module to familiarize them with the Web application. An intervention evaluation was completed online after the 12th module or during the postintervention clinic visit. At the final clinic visit, participants received a $20 grocery voucher as reimbursement for their costs in traveling to measurement sessions.

Measures

Usage

Google Analytics [44] was used to record usage data for measuring the mean number of modules completed and mean session duration (one session was defined as a group of interactions with “Mind, Body, Food” until a log-out action or a period of 30 minutes of inactivity). User identification tracking (using email addresses at log-in) was enabled in Google Analytics to show data from individual users. The total number of modules completed was determined by the exit page (the last page a user viewed before exiting “Mind, Body, Food”) for each participant over the course of the study to identify the highest module number viewed. EAT usage was determined by the mean number of weeks participants saved at least one EAT entry to a secure online database over the 14-week trial. To determine if illness or technical difficulties affected EAT usage, all participants were asked in the postintervention questionnaire to report if for more than five days over the past 14 weeks their appetite had been affected or if their access to “Mind, Body, Food” had been limited.

Acceptability

A 32-item Web-delivered postintervention evaluation was developed to assess the acceptability of “Mind, Body, Food.” Acceptability questions were informed by the technology acceptance model [45] and focused on perceived usefulness (ie, the extent that using “Mind, Body, Food” enhances one’s ability to learn intuitive eating skills), ease of use, and user satisfaction. Questions such as “Overall, to what extent was ‘Mind, Body, Food’ useful to you?” were answered using 5-point Likert-type items (1—not useful to 5—extremely useful).

Participant Pre-, Post-, and 3-Month Follow-Up Characteristics

Paper-based questionnaires were administered during the preintervention assessment (62 items) and during both postintervention and 3-month follow-up assessments (56 items). All questionnaires were checked for completeness during the

clinic visit, and participants were asked to answer any missed questions at that time.

The 23-item IES-2 [14] was used to measure women's tendency to eat intuitively. The subscales measure eating for physical rather than emotional reasons, unconditional permission to eat, reliance on hunger and satiety cues to guide eating, and body-food choice congruence (eg, choosing to eat foods that provide energy and stamina). Statements (eg, "I trust my body to tell me when to eat") were rated using subscales comprising 5-point Likert-type items (1—strongly disagree to 5—strongly agree). Providing evidence of its construct validity, the IES-2 total score and subscale scores have been positively related to body appreciation, self-esteem, and satisfaction with life and inversely related to eating disorder symptomology, poor interoceptive awareness, body surveillance, body shame, BMI, and internalization of media appearance ideals among women [14]. The IES-2 has also been found to yield internally consistent and stable scores with samples of women, providing evidence of reliability [14]. Preintervention, postintervention and 3-month follow-up IES-2 total score Cronbach alphas were .86, .90, and .91, respectively. Of the IES-2 subscales, all Cronbach alphas were .74 or higher (considered to be acceptable [46]) with three exceptions: preintervention Body-Food Choice Congruence subscale, postintervention and 3-month follow-up Unconditional Permission to Eat subscale Cronbach alphas were .61, .60, and .64, respectively.

Two questions were adapted from the Eating Disorder Examination-Screening Version (EDE-S) [47] to measure recent binge eating behavior. The first question asked, "Over the past 4 weeks (28 days), have there been any times when you have eaten what other people would regard as an unusually large amount of food?" to which participants were asked to respond Yes or No. Responses to this question were used to create a dichotomous variable (ie, binge eating vs no binge eating). The second question asked, "On how many days out of the last 28 have you had episodes like this when you may have also felt either unable to prevent them or unable to stop them once they had started?" Participants were asked to respond with the number of days. The EDE-S has high sensitivity (.90-.94) and specificity (.80-.96) in detecting eating disorders in community samples [47].

Height and weight were measured to calculate BMI for investigating preliminary effectiveness for weight gain prevention. A trained research assistant measured height to the nearest 0.1 centimeters using a stadiometer. Shoes were removed prior to the measurement. Weight was measured to the nearest 0.1 kilogram using a standard electronic scale while participants wore light clothing. Both height and weight were measured twice at each assessment and the mean values were used.

ACT-based processes (ie, psychological flexibility) were measured using the 7-item Acceptance and Action Questionnaire-II (AAQ-II) [48]. Items such as "My painful experiences and memories make it difficult for me to live a life that I would value" were answered using 7-point Likert-type items (1—never true to 7—always true). Higher scores reflected higher psychological *inflexibility*. The AAQ-II has good validity and reliability with various samples including college students and community-based adults [48]. Preintervention, postintervention, and 3-month follow-up AAQ-II scores had excellent Cronbach alphas (.91, .92, and .94, respectively).

Quality of life was measured by the Short Form 12-item Health Survey (SF-12v2) [49]. The SF-12v2 assesses eight domains of health, which are collapsed into two component summary measures of health: physical (incorporating Physical Functioning, Role-Physical, Bodily Pain, and General Health subscales) and mental (incorporating Vitality, Social Functioning, Role-Emotional, and Mental Health subscales) [50]. The component summaries have good reliability and validity among large community samples [51]. Preintervention, postintervention and 3-month follow-up SF-12v2 scores had acceptable Cronbach alphas (for physical summary measure: .79, .87, and .78, respectively; for mental summary measure: .84, .85, and .83, respectively).

Items assessing ethnicity, highest educational level, occupation status, and employment status were obtained from Statistics NZ's Census 2006 [52]. Ethnicity data were used to assign responders to one of five categories in the following order: Māori, Pacific Islander, Asian, Other and NZ European. Occupational status was used to assess socioeconomic status using the NZ Socioeconomic Index (NZSEI-06) [53]. Classification codes were retrieved from an online searchable database provided by Statistics New Zealand to identify the appropriate NZSEI-06 score [53]. When participants recorded a partner's occupation, the higher index score among the two was used to estimate household socioeconomic status. NZSEI-06 scores range from 10 to 90 with higher scores indicating higher socioeconomic status.

Statistical Analysis

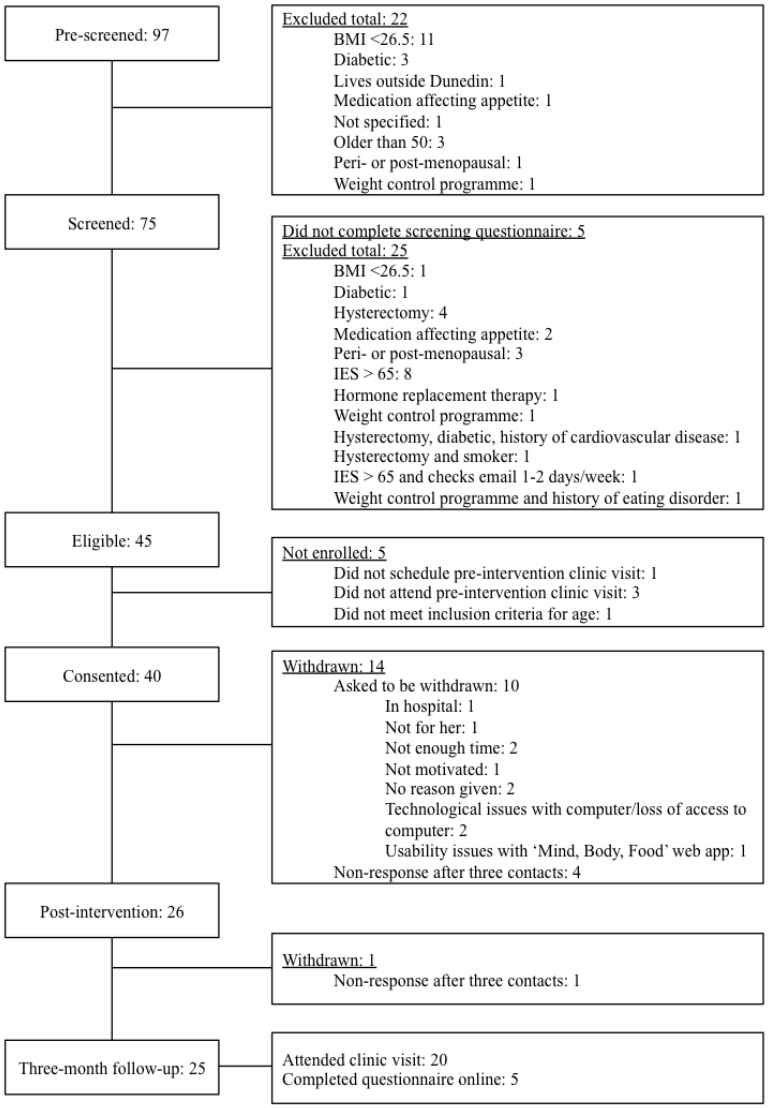
Mainly descriptive analyses were conducted due to the exploratory nature of the pilot study. Analyses were conducted using all available data. Means and standard deviations (SDs) for continuous variables and frequencies and percentages for categorical variables were calculated to describe the study sample. Analyses of differences between those completing and not completing the study and the within-group changes during the intervention were performed according to modified intention-to-treat principles, including all eligible women with available data but irrespective of their degree of participation with the intervention. Chi-squared tests and two sample *t* tests examined whether baseline characteristics predicted retention. Paired *t* and Wilcoxon matched-pairs signed-rank tests were performed to assess the overall significance of within-group changes over time among continuous variables, and McNemar tests were used in the same way for categorical variable comparisons. Spearman correlations were used to assess associations between changes from preintervention to postintervention in each of total IES-2 scores, the four IES subscale scores, BMI, and AAQ-II scores. Statistical analyses were performed using Stata 11.2 software (StataCorp LP) using 2-sided tests with the level of statistical significance set at $P<.05$.

Results

Recruitment and Retention

During recruitment, of the 97 women who expressed interest in the study, 75 women met preliminary screening criteria and subsequently were invited to complete the online eligibility assessment. Five women did not complete the online eligibility assessment, and only 45 women met the study inclusion criteria (see Figure 6 for reasons women were excluded). A total of 40 women were enrolled in the study from August to September 2014. The postintervention retention rate was 65% (26/40) and 63% (25/40) at the 3-month follow-up. Although the attrition rate was similar to that predicted (30%), the sample size at follow-up was lower than had been aimed for due to the number of women not meeting eligibility criteria. Figure 6 presents the flow of participants through the study.

Figure 6. "Mind, Body, Food" study participant flow diagram.



Baseline Characteristics

Table 2 presents the sample's demographic characteristics at baseline in comparison with corresponding NZ Census data. The sample was overrepresentative of NZ European women (30/37, 81.1% vs 69.8%) but similarly representative of Māori (4/37, 10.8% vs 11.7%) and Pacific (1/37, 2.7% vs 4.4%) women. University-educated women were overrepresented (21/37, 56.8% vs 17.7%). Women with NZSEI-06 (estimating socioeconomic status) scores in the lower two quartiles were underrepresented (10-33: 2/37, 5.4% vs 23.1%, 34-44: 3/37, 8.1% vs 29.4%). Half (18/36, 50.0%) of women reported dieting for 20 years or longer. There were no statistically significant differences in demographic characteristics or other measures such as intuitive eating, binge eating, general mental health, psychological inflexibility, and BMI between women who were retained and not retained at 3-month follow-up.

Table 2. Baseline characteristics of "Mind, Body, Food" participants (n=40).

Characteristic	All participants	National data
Age, years, mean	44.8	—
IES-1[a] summed total score [17], mean	53.4	69.4
Ethnicity [54], %[b]		
New Zealand European	81.1	69.8
Māori	10.8	11.7
Pacific	2.7	4.4
Other	5.4	4.6
Highest level of education attained [54], %[b]		
Secondary school or less	16.2	59.1
Technical/trade school or polytechnic	27.0	23.2
University	56.8	17.7
Employment [55], %[b]		
Employed	89.2	81.2-81.8
Employed full time	59.5	—
Employed part time	29.7	—
Homemaker	5.4	—
Other	5.4	—
Socioeconomic status (NZSEI-06)[c] [56], %[b]		
62-90 (higher socioeconomic status)	48.6	26.0
45-61	37.8	21.5
34-44	8.1	29.4
10-33 (lower socioeconomic status)	5.4	23.1
BMI[d] (kg/m^2) [57], mean	32.92	27.8
IES-2[e] total, mean	2.53	—
UPE[f], mean	3.06	—
EPR[g], mean	2.17	—
RHS[h], mean	2.33	—
B-FCC[i], mean	2.85	—
AAQ-II[j], mean	22.01	—
PCS[k], mean	50.01	—
MCS[l], mean	46.32	—
Binge eating, %[m]		
Yes	46.2	—
No	53.8	—
Dieting history, %[n]		
0-4 years	27.8	—
5-19 years	22.2	—
20+ years	50.0	—

[a]IES-1: Intuitive Eating Scale-1 (summed scores have potential range 21-105).

[b]Missing data, n=3.

[c]New Zealand Socioeconomic Index.

[d]BMI: body mass index.

[e]IES-2: Intuitive Eating Scale-2 (mean scores have potential range 1-5).

[f]UPE: Unconditional Permission to Eat subscale.

[g]EPR: Eating for Physical Rather than Emotional Reasons subscale.

[h]RHS: Reliance on Internal Hunger and Satiety cues.

[i]B-FCC: Body-Food Choice Congruence.

[j]AAQ-II: Acceptance and Action Questionnaire-II.

[k]PCS: Short Form 12-item (version 2) Health Survey Physical Component Summary.

[l]MCS: Short Form 12-item (version 2) Health Survey Mental Component Summary.

[m]Missing data, n=1.

[n]Missing data, n=4.

Usage During the 14-week Intervention

Google Analytics recorded "Mind, Body, Food" online traffic for 37 participants for 92 days at the end of the 14-week trial. A programming delay prevented monitoring from the start of the study, which explains missing usage data for three women. Of the 37 participants for whom usage data were available, 12 (32%) completed all 12 modules, 11 (30%) completed 7 to 11 modules, 12 (32%) completed 1 to 6 modules, and two women (5%) completed no modules. The median number of modules completed was 7.5 (interquartile range [IQR] 2-12) modules. The median number of sessions during the monitored period was 7 (a minimum of 1 session to a maximum of 66 sessions). The median session duration during the monitored period was 12 minutes, 54 seconds (a minimum of 3 minutes, 58 seconds, to a maximum of 100 minutes, 8 seconds). The median number of EAT entries over the 14-week intervention was 7 (a minimum of 1 entry to a maximum of 314 entries). The median number of weeks that participants recorded eating experiences in the EAT was 3 (IQR 1-9) weeks. Of the 40 participants enrolled in the study, 4 women (10%) used the EAT for at least 12 weeks of their intervention period, 7 (18%) used the EAT for 7 to 11 weeks, 20 (50%) used the EAT for 1 to 6 weeks, and 9 (23%) did not use the EAT during their intervention period.

Eleven women had limited access to "Mind, Body, Food" for more than 5 days, predominantly due to being away from home (n=8) or technical issues (n=3). Technical issues that prevented module completion included attempting to access "Mind, Body, Food" from an incompatible browser (n=3), using incorrect login details (n=1), and other issues not described (n=1). Seven women reported appetite being affected for more than 5 days (eg, due to illness) during the 14-week intervention.

Acceptability

A total of 26 women completed acceptability measures, and of these 12 had completed all modules, 10 completed 7 to 11 modules, and 4 completed 2 to 6 modules. Table 3 shows that participants' overall impression of "Mind, Body, Food" was positive. Most participants liked "Mind, Body, Food" and found the intervention useful (20/26, 77%), easy to use (17/25, 68%), easy to understand (23/25, 92%), and would recommend the program to others (21/25, 84%). Nearly half (12/25, 48%) of participants reported that "Mind, Body, Food" made it easy to learn intuitive eating skills.

Of all module components, the videos were more frequently rated as being quite or extremely useful by participants compared to the audio and typed activities (Table 3). Five out of 24 women (21%) women rated the EAT self-monitoring tool as quite or extremely useful, 3 out of 19 women (16%) found email reminders to use the EAT useful, and 4 out of 12 women (33%) found SMS reminders to use the EAT useful (not shown). In regards to reminders sent to begin the next module, 17 out of 26 women (68%) rated the email reminders as quite or extremely useful. Of the women (9/24, 38%) who chose to receive SMS reminders to begin the next module, 6 (67%) rated the reminders as useful (not shown).

Of the 20 women who currently owned a smartphone, 16 (80%) reported that if it were available a mobile version of "Mind, Body, Food" would be quite or extremely useful to them.

Table 3. User experiences of "Mind, Body, Food" (n=26).

Acceptability measures	n (%)	Median
Overall impression		
Overall, to what extent did you like "Mind, Body, Food?"		4
Disliked very much	0 (0)	
Disliked somewhat	0 (0)	
Neither liked nor disliked	3 (12)	
Liked somewhat	10 (40)	
Liked very much	12 (48)	
Missing	1	
Overall, to what extent was "Mind, Body, Food" useful to you?		4
Not useful	0 (0)	
A little useful	2 (8)	
Somewhat useful	4 (15)	
Quite useful	9 (35)	
Extremely useful	11 (42)	
Overall, to what extent did you find "Mind, Body, Food" easy to use?		4
Not at all easy	0 (0)	
Not very easy	3 (12)	
Somewhat easy	5 (20)	
Very easy	12 (48)	
Extremely easy	5 (20)	
Missing	1	
Overall, to what extent did you find "Mind, Body, Food" content easy to understand?		4
Not at all easy	0 (0)	
Not very easy	0 (0)	
Somewhat easy	2 (8)	
Very easy	15 (60)	
Extremely easy	8 (32)	
Missing	1	
Overall, to what extent did "Mind, Body, Food" make it easy for you to learn intuitive eating skills?		3
Not at all easy	0 (0)	
Not very easy	2 (8)	
Somewhat easy	11 (44)	
Very easy	9 (36)	
Extremely easy	3 (12)	
Missing	1	
Would you recommend "Mind, Body, Food" to others?		5
No, definitely wouldn't	0 (0)	
No, probably wouldn't	0 (0)	
Unsure	4 (16)	
Yes, probably would	8 (32)	
Yes, definitely would	13 (52)	
Missing	1	

Acceptability measures	n (%)	Median
Usefulness of program features		
How useful did you find the videos?		4
Not useful	0 (0)	
A little useful	4 (16)	
Somewhat useful	4 (16)	
Quite useful	7 (28)	
Extremely useful	10 (40)	
Missing	1	
How useful did you find the audio activities?		3
Not useful	4 (16)	
A little useful	5 (20)	
Somewhat useful	7 (28)	
Quite useful	7 (28)	
Extremely useful	2 (8)	
Missing	1	
How useful did you find the typed activities?		3
Not useful	4 (16)	
A little useful	3 (12)	
Somewhat useful	11 (44)	
Quite useful	4 (16)	
Extremely useful	3 (12)	
Missing	1	
How useful did you find the E.A.T.?		2
Not useful	5 (21)	
A little useful	9 (38)	
Somewhat useful	5 (21)	
Quite useful	3 (13)	
Extremely useful	2 (8)	
Missing	2	
How useful did you find the email reminders to begin the next module?		3
Not useful	2 (8)	
A little useful	1 (4)	
Somewhat useful	5 (20)	
Quite useful	9 (36)	
Extremely useful	8 (32)	
Missing	1	

Changes in Eating Behavior

The study was not designed to detect the effects of the intervention on the outcome measures (no control group was included), but within-group comparisons were performed as part of the feasibility component of the pilot study. From pre- to postintervention, there were statistically significant increases in IES-2 total scores and all four IES-2 subscale scores (Table 4). There was no evidence that these improvements diminished at the 3-month follow-up. Based on use of the dichotomous variable (ie, binge eating vs no binge eating), 7 out of 14 women who reported eating a significantly large amount of food (ie, binge eating) at the preintervention assessment reported no binge eating at the postintervention assessment. There were no women who transitioned from no binge eating at the preintervention assessment to binge eating at the

postintervention assessment or at the 3-month follow-up; 4 women who reported binge eating at postintervention no longer reported binge eating at the 3-month follow-up. McNemar's test revealed a significant decrease in the proportion of women binge eating from the pre- to postintervention visits (P=.01) and a significant decrease from postintervention to follow-up (P<.001). The median days women who were categorized as binge eaters reported binge eating at preintervention was 4.25 (IQR 2.5-10) days, at postintervention was 4 (IQR 2-8) days, and at the 3-month follow-up it was 2 (IQR 2-4) days. A Wilcoxon matched-pairs signed-rank test was used to examine changes in the reported number of days women were unable to prevent or stop episodes of eating an unusually large amount of food and revealed a significant decrease from pre- to postintervention (P=.03) and no evidence of a change from postintervention to follow-up (P=.57).

Psychological Inflexibility, Quality of Life, and BMI

Psychological inflexibility decreased significantly from pre- to postintervention (mean change −4.23 [SD 7.13], P=.006), and there was a tendency for a further decrease in psychological inflexibility from postintervention to 3-month-follow-up (mean change −2.60 [SD 6.58], P=.06) (Table 4). There were no significant changes in general physical health from pre- to postintervention (pre- to postintervention PCS scores: mean change 0.29 [SD 9.35], P=.88; postintervention to 3-month follow-up PCS scores: mean change 1.26 [SD 10.46], P=.55). However, general mental health improved significantly from pre- to postintervention with a further improvement postintervention to 3-month follow-up (mean change 5.07 [SD 6.31], P<.001; mean change 3.45 [SD 7.71], P=.03, respectively). There were no statistically significant changes in BMI from pre- to postintervention or postintervention to 3-month follow-up (mean change −0.13 [SD 0.88], P=.46 and mean change −0.01 [SD 0.57], P=.93, respectively).

Associations Between Changes in Intuitive Eating With BMI and Psychological Inflexibility

Spearman correlations showed a statistically significant inverse relationship between pre- to postintervention change in total intuitive eating scores and pre- to postintervention change in BMI (r_s=−.43, P=.03). Thus, greater decreases in BMI were associated with greater increases in intuitive eating. However, when relationships with individual subscales were examined, a significant association was found for only one subscale: greater decreases in BMI were associated with greater increases in eating for physical rather than emotional reasons (r_s=−.56, P=.003). There was also a statistically significant inverse relationship between change in psychological inflexibility scores and change in intuitive eating scores (r_s=−.52, P=.006); that is, greater improvements in psychological flexibility were associated with greater increases in total intuitive eating scores. Furthermore, larger improvements in psychological flexibility were associated with greater increases in two subscale scores: eating for physical rather than emotional reasons (r_s=−.41, P=.04) and reliance on hunger and satiety cues (r_s=−.62, P<.001). A greater reduction in psychological inflexibility scores was also associated with a greater decrease in BMI (r=.41, P=.04).

Table 4. Changes from pre- (n=26) to postintervention (n=26) and from postintervention to 3-month follow-up (n=25).

Characteristic	Mean (SD)	Change (SD)[a]	95% CI	*P* value[b]
IES-2[c] total				
Preintervention	2.54 (0.58)	—	—	—
Postintervention	3.45 (.55)	0.94 (0.67)	0.67, 1.21	<.001
3-month follow-up	3.53 (.61)	0.08 (0.55)	−0.15, 0.31	.47
UPE[d]				
Preintervention	3.07 (0.73)	—	—	—
Postintervention	3.56 (.54)	0.52 (0.87)	0.17, 0.87	.01
3-month follow-up	3.47 (.58)	−0.09 (0.64)	−0.36, 0.17	.76
EPR[e]				
Preintervention	2.19 (0.96)	—	—	—
Postintervention	3.21 (.89)	1.08 (0.96)	0.69, 1.46	<.001
3-month follow-up	3.49 (.88)	0.28 (0.89)	−0.09, 0.65	.13
RHS[f]				
Preintervention	2.33 (0.77)	—	—	—
Postintervention	3.58 (.76)	1.28 (0.98)	0.89, 1.68	<.001
3-month follow-up	3.55 (.81)	−0.03 (0.68)	−0.31, 0.25	.81
B-FCC[g]				
Preintervention	2.87 (0.61)	—	—	—
Postintervention	3.59 (.81)	0.74 (0.61)	0.50, 1.00	<.001
3-month follow-up	3.72 (.72)	0.13 (0.87)	−0.23, 0.49	.45
BMI[h] (kg/m^2)				
Preintervention	32.93 (4.85)	—	—	—
Postintervention	32.81 (5.31)	−0.13 (0.88)	−0.48, 0.23	.46
3-month follow-up[i]	32.80 (5.29)	−0.01 (0.57)	−0.28, 0.26	.93
AAQ-II[j]				
Preintervention	22.46 (8.67)	—	—	—
Postintervention	18.23 (8.14)	−4.23 (7.13)	−7.11, -1.35	.006
3-month follow-up	16.08 (7.73)	−2.60 (6.58)	−5.32, 0.16	.06
SF-12v2 PCS[k]				
Preintervention	50.46 (7.83)	—	—	—
Postintervention	50.87 (11.02)	0.29 (9.35)	−3.49, 4.06	.88
3-month follow-up	52.13 (6.78)	1.26 (10.46)	−3.06, 5.58	.55
SF-12v2 MCS[l]				
Preintervention	45.63 (6.31)	—	—	—
Postintervention	50.24 (7.41)	5.07 (6.31)	2.52, 7.61	<.001
3-month follow-up	53.70 (4.99)	3.45 (7.71)	0.27, 6.63	.03

[a]Changes from pre- to postintervention and postintervention to 3-month follow-up.

[b]Paired *t* tests were used to compare IES-2 scores, BMI, AAQ-II scores, and SF-12v2 scores.

[c]IES-2: Intuitive Eating Scale-2.

[d]UPE: Unconditional Permission to Eat subscale.

[e]EPR: Eating for Physical Rather than Emotional Reasons subscale.

[f]RHS: Reliance on Internal Hunger and Satiety cues.

[g]B-FCC: Body-Food Choice Congruence.

[h]BMI: body mass index.

[i]BMI change from postintervention to 3-month follow-up (n=20).

[j]AAQ-II: Acceptance and Action Questionnaire-II.

[k]PCS: Short Form 12-item (version 2) Health Survey Physical Component Summary.

[l]MCS: Short Form 12-item (version 2) Health Survey Mental Component Summary.

Discussion

Principal Findings

This pilot study is the first evaluation of an online intuitive eating intervention and demonstrated that middle-aged overweight women perceived the intervention to be an acceptable and useful way to learn intuitive eating skills. Among those women who completed all assessments, both psychological flexibility and all aspects of intuitive eating improved at the end of the intervention and were sustained at the 3-month follow-up. Binge eating and general mental health improved from preintervention to postintervention and there were further improvements in these outcomes at the 3-month follow-up. Results are consistent with the hypothesis that improvements in psychological flexibility may be linked with eating more intuitively.

To our knowledge, only one other published intuitive eating intervention (a face-to-face intervention) [58] has shown improvements in all aspects of intuitive eating (ie, unconditional permission to eat when hungry and what food is desired, eating for physical reasons, trusting bodily cues to determine when and how much to eat), as has been demonstrated in this pilot study. An innovative feature and major strength of the present study is the integration of intuitive eating with ACT skills. Many ACT skills are designed to build awareness and acceptance of internal experiences, which may in turn foster the ability to tune into and trust the body's hunger and satiety cues and not react to emotions and cravings by eating. ACT's focus on values-guided behavior may strengthen women's commitment to eating intuitively by helping them to clarify the value of shifting to eating behavior that is enjoyable, sustainable, empowering, and health-focused rather than weight-focused. The ACT elements of the intervention may have also improved nonjudgment towards thoughts about food or feelings about one's body and reduced reactivity towards experiences (ie, responding to internal and external experiences in deliberate and meaningful ways). Furthermore, the significant increase in psychological flexibility suggests the ACT strategies were active in the intervention. This study demonstrates support for and justifies further exploration of our innovative approach of integrating intuitive eating with ACT.

The significant reduction in binge eating behavior in this study is consistent with previous intuitive eating interventions [19] and ACT-based interventions [25,27]. Those who learn intuitive eating appear to be able to reduce the loss of control that often follows self-imposed restriction [18], and this ability may be enhanced by improved coping with emotional distress through development of ACT skills.

Improvements in women's general mental health may be explained by the ACT-based skills taught in "Mind, Body, Food;" however, intuitive eating interventions which do not specifically incorporate ACT skills have also been reported to improve psychological well-being [18]. Enhanced awareness and being less judgmental may have benefited women in areas of life beyond their eating experiences, allowing them to respond to situations in more personally meaningful ways. Physical activity was not addressed until the tenth module, which was viewed by a minority of participants, and this may contribute to the absence of changes in general physical health.

It is encouraging that numerous improvements occurred in spite of only 30% of the sample completing all 12 modules. Low completion rates are typical of Web-based interventions [43,59,60]. A systematic review of trials of Web-based health promotion interventions reported that on average 50% (minimum 1%; maximum 93%) of study participants completed all intervention modules (with interventions typically 10 modules long and meant to be used once a week) [60]. However, in this review, 76% of the interventions included interaction of the participant with a counselor, a factor which predicted significantly better adherence [60] but was lacking in our "Mind, Body, Food" intervention. A recent Web-based weight gain prevention intervention more similar to ours has reported the percentage of women completing all modules to be lower than in our study [61]. Low completion rates in such interventions, including our own, may reflect waning interest, perceiving the early modules of the intervention as sufficiently useful for learning new skills and thereby feeling it unnecessary to complete the rest, or a lack of social support [62]. Further investigation could assist in determining how many and which combination of modules are associated with optimal improvement in intuitive eating prior to a future RCT. Another contributor to noncompletion may be the desire for weight loss rather than a shift in focus towards long-term healthier lifestyle behaviors [62], particularly among women starting at a higher BMI [63] or among those with high body dissatisfaction.

Low use of the EAT and the importance of self-monitoring to successful behavior change [64-66] suggest that simplification and improvement of the self-monitoring tool is needed. In response to feedback from target users during intervention development, women had to choose to receive reminders to use the EAT rather than receiving automatic reminders, and this may also have contributed to low usage. However, the reported improvements in intuitive eating and binge eating may suggest that for some women, a self-monitoring tool may not have been essential for learning intuitive eating.

Strengths and Limitations

The study strengths include an intervention that integrates two empirically tested approaches to eating behavior change (intuitive eating and ACT), use of an intervention design that was informed by input from end-users and underwent rigorous pretesting with women in the target audience prior to the pilot study; objective measures of BMI and intervention usage; validated measures of intuitive eating, binge eating, psychological flexibility, and quality of life; and a 3-month follow-up. The most significant limitations of the study were the lack of a comparison group, small sample size, analyses conducted on the subset of participants who were exposed to the intervention and had not dropped out for any reason, and delayed monitoring via Google Analytics; however, the pilot study was undertaken to inform improvements to the intervention prior to proceeding to an RCT incorporating a control group. The pilot study shared the high attrition common to many Web-based interventions and results were based on a small group completing the study. The high rate of attrition observed during the study (35% were lost by postintervention and 37% by 3-month follow-up) and the expectation that missing data from health-focused studies involving overweight participants will generally be informative means that we cannot be certain that those dropping out did not experience negative outcomes that could attenuate or even negate the positive findings reported here. Prior to a future randomized trial, further research is needed to determine ways to increase engagement and improve program completion. This may be achieved by making the tool smartphone compatible since accessing the program on the go is likely to be helpful to women in applying the skills in real-world settings. A reduction in the number of modules may also be useful. The sample was overrepresentative of highly educated women, which has been noted in several studies of Web-based weight management interventions [67-69], and results may not generalize to less educated women. The positive self-reported outcomes may reflect regression to the mean, repeated administration of the questionnaires, or social desirability bias.

Conclusion

To our knowledge, “Mind, Body, Food” is the first intervention to combine teaching intuitive eating skills and ACT-based strategies for behavior change. It is also the first Web-based intuitive eating intervention. The “Mind, Body, Food” intervention was generally acceptable to the target audience, and the pilot study showed improvements in intuitive eating, binge eating behavior, psychological flexibility and general mental health, in addition to weight maintenance. Given the 3-month follow-up period and lack of a control group, it is important that an improved version of the intervention is evaluated in an RCT to investigate its longer-term effectiveness. The RCT will also examine the hypothesized mechanism that greater psychological flexibility leads to more intuitive eating, which leads to prevention of weight gain.

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Conflicts of Interest

None declared.

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Abbreviations

AAQ-II: Acceptance and Action Questionnaire
ACT: acceptance and commitment therapy
B-FCC: body-food choice congruence
BMI: body mass index
EAT: Eating Awareness Tracker
EDE-S: Eating Disorder Examination-Screening Version
EPR: eating for physical rather than emotional reasons
IES: Intuitive Eating Scale
IES-2: Intuitive Eating Scale-2
IQR: interquartile range
MCS: Mental Component Summary

NZSEI-06: New Zealand Socioeconomic Index
PCS: Physical Component Summary
RCT: randomized controlled trial
RHS: reliance on internal hunger and satiety cues
SD: standard deviation
SES: socioeconomic status
SF-12v2: Short Form 12-item (version 2) Health Survey
SMS: short message service
UPE: unconditional permission to eat

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Original Paper

Developing a Web-Based Weight Management Program for Childhood Cancer Survivors: Rationale and Methods

Fang Fang Zhang[1], PhD, MD; Susan Meagher[2], PhD; Michael Scheurer[3], PhD; Sara Folta[4], PhD; Emily Finnan[4], MS, RD; Kerry Criss[4], MS; Christina Economos[4], PhD; ZoAnn Dreyer[3], MD; Michael Kelly[2], MD

[1]Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA, United States

[2]Tufts Medical Center, Boston, MA, United States

[3]Baylor College of Medicine, Houston, TX, United States

[4]Tufts University, Boston, MA, United States

Corresponding Author:
Fang Fang Zhang, PhD, MD
Friedman School of Nutrition Science and Policy
Tufts University
150 Harrison Ave, Jaharis 235
Boston, MA
United States
Phone: 1 617 636 3704
Fax: 1 617 636 3727
Email: fang_fang.zhang@tufts.edu

Abstract

Background: Due to advances in the field of oncology, survival rates for children with cancer have improved significantly. However, these childhood cancer survivors are at a higher risk for obesity and cardiovascular diseases and for developing these conditions at an earlier age.

Objective: In this paper, we describe the rationale, conceptual framework, development process, novel components, and delivery plan of a behavioral intervention program for preventing unhealthy weight gain in survivors of childhood acute lymphoblastic leukemia (ALL).

Methods: A Web-based program, the Healthy Eating and Active Living (HEAL) program, was designed by a multidisciplinary team of researchers who first identified behaviors that are appropriate targets for weight management in childhood ALL survivors and subsequently developed the intervention components, following core behavioral change strategies grounded in social cognitive and self-determination theories.

Results: The Web-based HEAL curriculum has 12 weekly self-guided sessions to increase parents' awareness of the potential impact of cancer treatment on weight and lifestyle habits and the importance of weight management in survivors' long-term health. It empowers parents with knowledge and skills on parenting, nutrition, and physical activity to help them facilitate healthy eating and active living soon after the child completes intensive cancer treatment. Based on social cognitive theory, the program is designed to increase behavioral skills (goal-setting, self-monitoring, and problem-solving) and self-efficacy and to provide positive reinforcement to sustain behavioral change.

Conclusions: Lifestyle interventions are a priority for preventing the early onset of obesity and cardiovascular risk factors in childhood cancer survivors. Intervention programs need to meet survivors' targeted behavioral needs, address specific barriers, and capture a sensitive window for behavioral change. In addition, they should be convenient, cost-effective and scalable. Future studies are needed to evaluate the feasibility of introducing weight management early in cancer care and the efficacy of early weight management on survivors' health outcomes.

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KEYWORDS

weight management; childhood cancer survivors; obesity; Web-based; development; nutrition; physical activity

Introduction

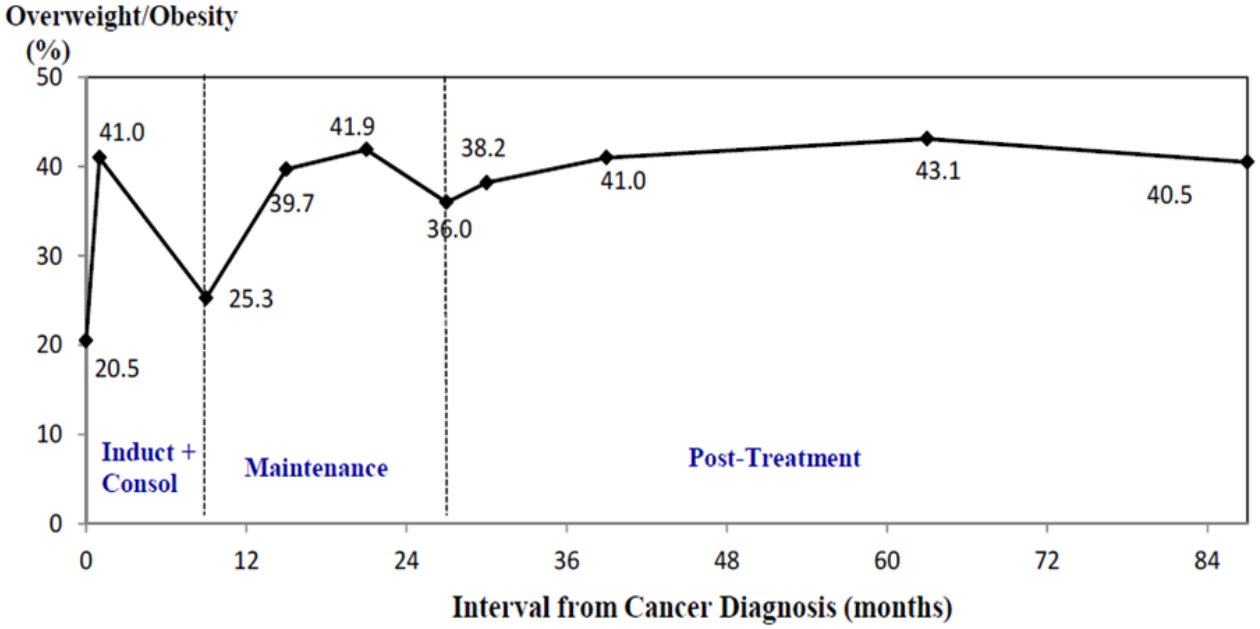
Dramatic improvements in the diagnosis and treatment of cancer in childhood have led to a rapidly growing cohort of survivors, now estimated to exceed 450,000 in the United States [1]. However, this success is associated with the recognition that childhood cancer survivors have significantly elevated risks of premature mortality and serious morbidity [2,3]. Recent studies have shown that childhood cancer survivors not only have significantly higher body mass index (BMI) than their peers [2] but also experience unhealthy weight gain early in treatment, and increases in weight are sustained throughout treatment and beyond [3-5]. Obesity is an established risk factor for cardiovascular diseases (CVD). Childhood cancer survivors are 7 times more likely to die of cardiac causes than the general population [6,7]. They also develop dyslipidemia, hypertension, and insulin resistance or diabetes at a much younger age [8]. Lifestyle interventions are clearly a priority for preventing the early onset of obesity and associated cardiometabolic conditions in this population.

Few interventions are designed to promote lifestyle modifications in childhood cancer survivors to reduce obesity and CVD risk [9]. To our knowledge, none have focused on initiating interventions soon after the survivors complete intensive cancer treatment to prevent the early onset of obesity and CVD morbidities. Strong evidence supports that unhealthy weight gain and development of CVD risk factors occur early in treatment and persist beyond treatment completion. For example, in a retrospective cohort of 83 patients of childhood acute lymphoblastic leukemia (ALL) at Tufts Medical Center, we found the percentage of children who were overweight or obese increased from 20% at diagnosis to approximately 36% at the end of intensive cancer treatment (ie, induction and consolidation phases of the treatment, which last between 7 and 9 months for most of the treatment protocols) (see Figure 1). After patients started maintenance chemotherapy (ie, maintenance phase of the treatment, which lasts approximately 18-24 months), the percentage of being overweight or obese increased to 40% at 6 months into maintenance and persisted beyond treatment completion [5]. The early onset of obesity is similarly observed in other studies [3,4] and in a meta-analysis from 21 studies that assessed longitudinal trend of weight patterns in pediatric ALL survivors [10].

Although cancer treatment can directly impact weight patterns, children also develop adaptive behaviors such as poor eating habits and physical inactivity during treatment. We conducted preliminary studies that identified intake patterns and levels of total energy expenditure in young survivors of pediatric ALL and lymphoma [11,12]. These intake and activity patterns were originally thought to be adaptive responses to cancer treatment but tend to last beyond treatment completion and are particularly difficult to reverse in long-term survivors. For example, prior studies have provided consistent evidence that childhood cancer survivors are less active than their peers [13,14]. Our study in survivors of childhood ALL and lymphoma found that the mean level of total energy expenditure (2073 kcal/day) was nearly 500 kcals lower than the estimated energy requirement, supporting the need of increasing physical activity to fill this gap [11]. Such a large gap is unlikely to be reversed by exercise alone. Our prior study [12] and those of others [15-17] have also shown that childhood cancer survivors have poor adherence to existing dietary guidelines. Their intake patterns are particularly low in fiber and whole grains and high in sodium and empty calories (calories from solid fats and added sugars), all of which are established risk factors for obesity and CVD-related morbidities. Further, family environment plays an important role in shaping children's dietary and activity behaviors [18-23], and parenting style and practices can be particularly important for children diagnosed with cancer at a young age [24] (eg, the peak age of ALL diagnosis in children is 2-5 years old [25]). As reported in qualitative research, parents practice permissive parenting related to unhealthy eating and sedentary behavior while the child is going through cancer treatment, which they find difficult to reverse following treatment completion [26]. Survivors' poor intake patterns and sedentary behaviors, which are closely related to parenting style and practices in young survivors, are established risk factors for obesity and cardiometabolic conditions.

Based on these findings, we developed a Web-based weight management program, the Healthy Eating and Active Living (HEAL) program, tailored for families with patients and survivors of childhood ALL, the most common cancer in children. Here we describe the conceptual framework, development process, novel components, and delivery plan of the HEAL program.

Figure 1. Change in prevalence of overweight and obesity during and after treatment in childhood acute lymphoblastic leukemia survivors (reproduced with permission from Pediatric Blood & Cancer [7]).

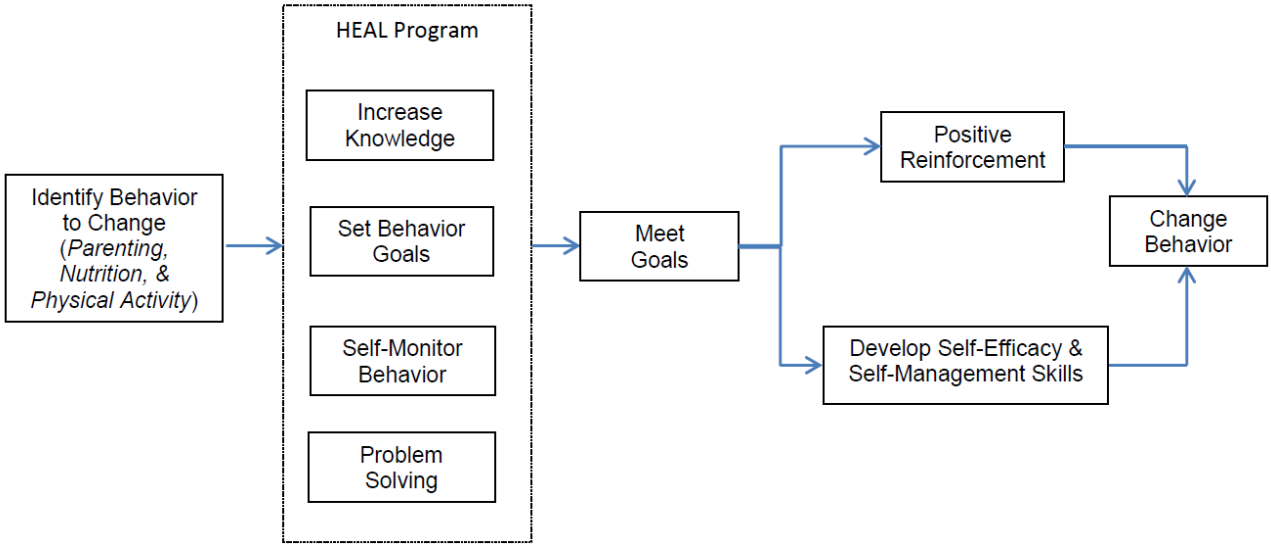


Methods

Overview

A multidisciplinary team of researchers (nutritional epidemiologist, pediatric oncologist, nutrition scientist, pediatric dietitian, behavioral scientist, and clinical psychologist) met weekly and identified behaviors that are appropriate targets for weight management in childhood cancer survivors and formulated the intervention components. Guided by strong evidence in childhood cancer survivors and informed by obesity prevention programs in the general pediatric population, we identified parenting, nutrition, and physical activity as 3 behaviors to change for the development of the HEAL program. Following the identification of behaviors to change, we used a basic framework of core behavioral change strategies as a foundation to formulate program goals and components. These core behavioral change strategies are grounded in theoretical models (eg, social cognitive and self-determination theories) [27,28], including increasing knowledge, developing behavioral skills (goal-setting, self-monitoring, and problem-solving), increasing self-efficacy, and providing positive reinforcement (Figure 2) [26].

Figure 2. Conceptual framework of the Healthy Eating and Active Living program for childhood cancer survivors.



Increasing Knowledge

Parental perception of their child's weight status is a key factor in determining parents' readiness for weight management for their child [29]. The curriculum therefore starts with increasing knowledge on the patterns of weight gain and the importance of healthy lifestyles in long-term health of childhood ALL survivors, as well as information on how cancer diagnosis and treatment may impact survivors' weight, eating habits, and

physical activity. Following this introduction, the curriculum focuses on 3 areas:

- The parenting focus is to improve parenting practices that facilitate healthy eating and active living in the family. The HEAL program engages parents as the agent of change, because the program targets on young children with ALL who largely fall into the age range of 4 to 10 years old when they start maintenance therapy or within 2 years of treatment completion. It emphasizes parents' roles in transitioning the family toward healthy eating and active living through modifying the family environment. It also addresses common barriers that parents face in implementing change at the family level.
- The nutrition focus is to enhance diet quality by (1) limiting consumption of sugar-sweetened beverages (SSBs) and foods high in empty calories; (2) limiting consumption of processed foods and snacks high in sodium; and (3) increasing consumption of vegetables, fruits, and whole grains. Although not a direct target for weight management, the program also includes (4) increasing dietary sources of vitamin D and calcium.
- The physical activity focus is to increase activity by (1) reducing screening time, (2) gradually increasing activity to 60 or more minutes/day and incorporating physical activity into daily activities, and (3) incorporating bone-strengthening activity 3 or more days/week [30,31].

Developing Behavioral Skills

The HEAL program is designed to increase behavioral skills through goal-setting, self-monitoring, and problem-solving. Goal-setting uses SMART planning to help parents set Specific, Measurable, Achievable, Relevant, and Time-bound goals and action items [32]. Parents are asked to set individual goals and action plans within the context of the overall HEAL program goals for parenting, nutrition, and physical activity. Table 1 describes the program goals. For self-monitoring, parents complete weekly online food and activity logs for their child and are provided with the opportunity to monitor progress online. Problem-solving is incorporated to address specific barriers experienced by childhood cancer survivors and families for making healthy food choices or being physical active. These sessions include overcoming food cravings, coping with food aversion and changes in taste preference, fatigue, curbing emotional eating, safety concern for physical activity, and stress and time management. The program also embeds a session that asks parents to identify barriers, list options to overcome barriers, and make plans for realizing options.

Table 1. Healthy Eating and Active Living program goals.

Goal	Action plan
Raise obesity awareness	Be aware of the importance of unhealthy weight gain in survivors' long-term health and how cancer treatment impacts eating, activity, and weight patterns.
Improve parenting style and practices	Increase authoritative parenting, establish healthy routines, offer choices, set expectations, reinforce positive behavior, improve family communication.
Reduce empty calories	Limit consumption of sugar-sweetened beverages and snacks and desserts high in empty calories to 1 or fewer servings/day.
Reduce sodium	Limit eating out at fast food restaurants to 1 or fewer times/week; choose low-sodium option.
Increase fruits, vegetables, and whole grains	Increase fruits and vegetables to 5 or more servings/day; make half of the grains whole grains.
Decrease sedentary behavior	Reduce recreational screen time such as TV, computer/tablet, and video games to fewer than 2 hours/day.
Increase physical activity	Gradually increase physical activity to 60 or more minutes/day
Increase bone-strengthening activity	Gradually increase bone-strengthening activity to 3 or more days/week
Set healthy home environment	Increase family meals to 3 or more times/week; Active together as a family to 3 or more times/week

Increasing Self-Efficacy

The HEAL program is designed to incrementally support and increase behavioral skills. As these are developed, participants acquire mastery experiences to increase self-efficacy.

Positive Reinforcement

The program uses positive reinforcement strategies to further promote self-efficacy by sending parents motivational messaging throughout the course of the program. The motivational messages were developed by the clinical psychologist and behavioral scientist on the research team. They serve to remind parents to set goals, track child's food intake and physical activity, and complete self-guided curriculum sessions and to provide recognition and encouragement after parents complete these activities. Some of the messages are also designed to promote 3 basic psychological needs: competence, autonomy, and relatedness, grounded in self-determination theory (SDT). The motivational messages are sent automatically to parents' email or through short message service (SMS) after parents enroll into the program, following predetermined algorithms based on program usage and completion status. Alternatively, motivational messages can be delivered by a lifestyle coach trained in motivational interviewing who can further provide feedback based on usage and completion. The use of a lifestyle coach as human contact to support the program is optional and is currently only available in research settings. Parents cannot opt out of motivational messages but can choose to receive messages through email or SMS. Some examples of motivational messages are presented in Table 2. The program also provides multiple digital rewards to reinforce attendance and encourage adherence.

Table 2. Examples of Healthy Eating and Active Living program motivational messages.

Type of messages	Examples
To remind parents to complete self-guided curriculum	"Welcome to Session 8! This week is about getting up and getting active. Encourage your child to do physical activity. Any activity counts! Click here to learn more."
To reinforce completion of self-guided sessions	"Congratulations! You have just completed Session 3. One step closer toward achieving your goal!"
SDT[a]-grounded motivational message promoting relatedness	"Try to get the whole family moving! Believe it or not, your child is watching, and your habits, both good and bad, have a strong influence on them."
SDT-grounded motivational message promoting competence	"As a parent, you are capable of using positive family communication to talk to your child about eating healthy and being active! Use RECIPE[b] strategies. Success is yours!"
SDT-grounded motivational message promoting autonomy	"Eat family meals together more often. How often? You decide. You are in charge!"

[a]SDT: self-determination theory.

[b]RECIPE: reflective listening, encouragement, compromise and cooperation, "I" message, practice, and engagement.

Results

The HEAL program website was created by an in-house facility, the Center for Engineering Education and Outreach, at Tufts University between January and June 2015. The website has incorporated 4 active modules: Curriculum, SMART Plans, Logs, and Rewards (Figure 3). Additional modules such as Resources and HEAL Forum are optional for providing additional resources when needed. Parents can access the Web-based program from any browser on a computer or mobile phone after registering a HEAL account with a username and password.

The curriculum includes 12 weekly sessions outlining topics on targeted behaviors and specific barriers (Figure 4). Each session takes approximately 30 minutes to complete. The curriculum was initially developed in the written format and went under revision following initial development. The revision was made by the research team based on findings from 4 focus groups conducted with 19 oncology care team members who were invited to provide their perceptions on the content, preferred delivery mode, and timing of weight management for pediatric ALL survivors (detailed results of the focus groups will be provided elsewhere). Specifically, the revision expanded the curriculum by including an audio format for each session created using Articulate to meet the needs of families with low literacy levels. Parents can access either format after they log into the curriculum, but they can only be accessed at the program's website (ie, not downloadable) so that the program can track usage. In addition, the curriculum contains expanded sessions on specific nutritional issues identified in childhood cancer survivors (eg, high intake of empty calories and sodium and low intake of fiber, whole grains, and vitamin D and calcium) and barriers experienced by the survivors (eg, food craving, change in taste preference, fatigue, stress, lack of time). The revision also includes a module called Kid's Corner embedded into each individual sessions (see Figure 4) for parents to involve children participating in activities that promote healthy eating (such as *Grocery Store Scavenger Hunt*, *Create Your Own MyPlate*, *Eat the Rainbow*, *Grow Your Own Veggies*, *Sugar Detectives*, *Cook from Scratch*, *Drinks for Strong Bones and Teeth*) and physical activity (such as *Body Sketch-Hopscotch* and *Fun and Fast Circuit Course*) for the whole family.

Parents enrolled in the HEAL program are asked to complete the weekly self-guided curriculum; set up behavioral goals on parenting, nutrition, and physical activity using SMART plans; and complete weekly food and activity logs online (for at least 2 weekdays and 1 weekend per week) for 12 weeks. All curriculum sessions are accessible by the participants after they log in, although instructions are provided in the first session that they are expected to complete one session per week. The HEAL program has built-in functions that monitor how many minutes a HEAL user spends daily on each session to track usage. Based on the usage, the program sends automated motivational messages to parents after completion of goal-setting, logs, and curriculum session. Parents achieve Bronze, Silver, and Gold status after completing each of the 4 sessions as rewards, and children receive a digital certificate after completing family activities. At the end of each curriculum session, parents are encouraged to complete an online evaluation that asks them to rate statements about their knowledge of session-specific topics before and after each session on a 5-point Likert scale and answer open-ended questions on their perceptions of session strengths and weakness. As part of the study end assessment, parents are asked to complete a usability assessment once they have finished the program.

Figure 3. Screenshot of the main Healthy Eating and Active Living component page after log-in.

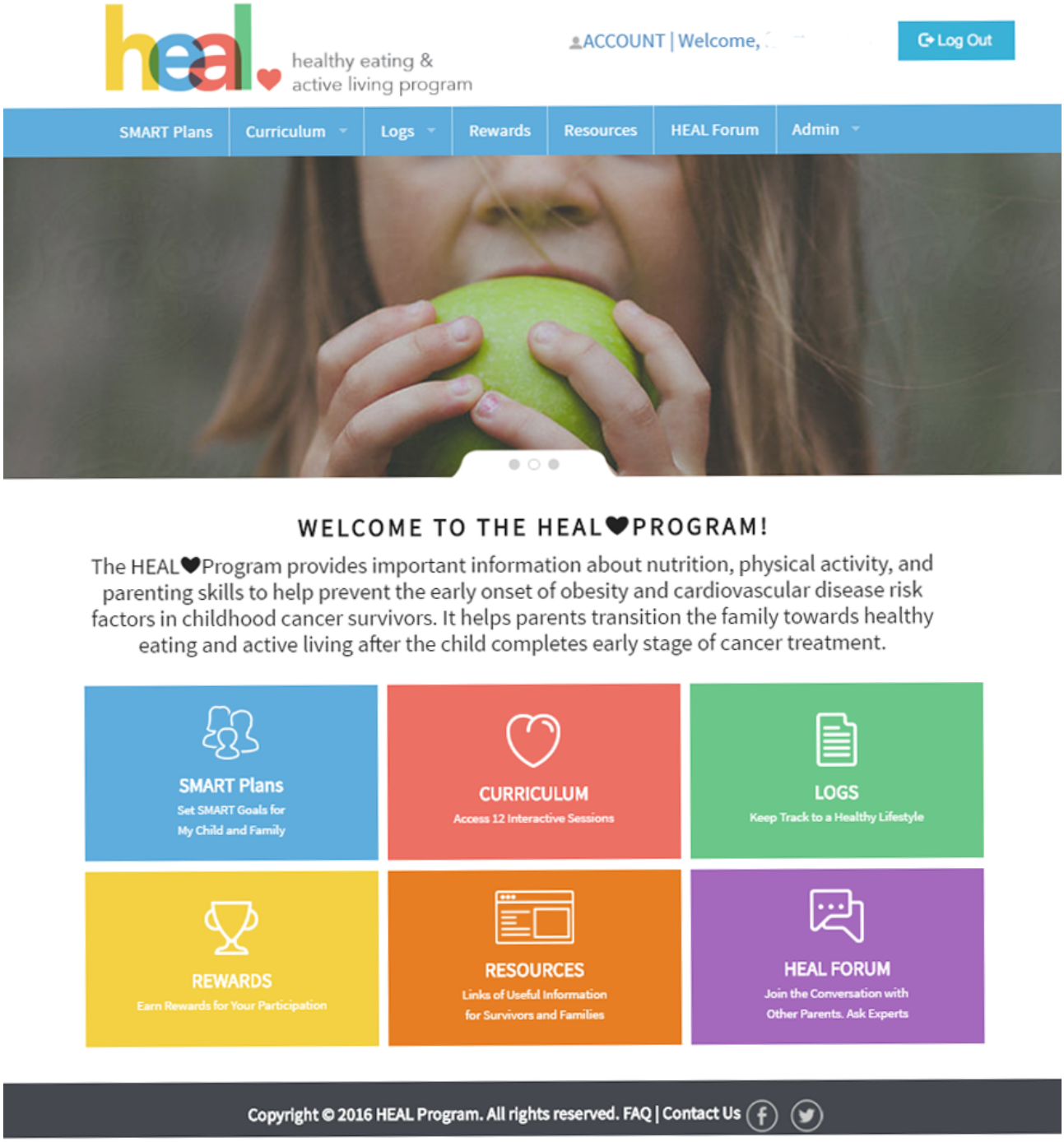


Figure 4. Healthy Eating and Active Living program 12-week curriculum.

Discussion

Childhood cancer survivors are at substantially increased risk of developing cardiometabolic conditions at a young age. Although treatment exposure, alone or in combination, contributes to elevated CVD risk in childhood cancer survivors, the attributable fraction was less than 50%, ranging from 9.3% for hypertension, 15.5% for dyslipidemia, 41.7% for diabetes, and 42.1% for obesity [2]. A large proportion of the CVD burden can be reduced through lifestyle interventions. Nevertheless, promotion of healthy eating, active living, and weight management is not routinely integrated into cancer care for childhood cancer survivors and families in many oncology clinics around the country. The HEAL program addresses this gap by empowering parents with knowledge and skills to facilitate healthy eating and active living as soon as the child completes intensive cancer treatment and is ready for transition. To our best knowledge, it is among the first to introduce the importance of healthy eating and active living early in cancer care (during maintenance therapy or within 2 years of treatment

completion) in order to capture a sensitive window of unhealthy weight gain and prevent the early onset of CVD risk factors in childhood ALL survivors.

Many survivorship programs for childhood cancer lack a focus on nutrition, or when nutrition is introduced, the priority is to satisfy caloric needs and prevent weight loss. Although malnutrition due to cancer-related anorexia and cachexia still represents an important concern in cancer care [33], overconsumption of calories through poor eating habits [12,15-17] and a high prevalence of obesity are increasingly recognized in childhood ALL survivors [2,34]. Weight management programs for childhood cancer survivors should respond to the growing need to curb early onset of obesity and CVD risk factors by reducing overconsumption of calories to achieve energy balance. It is also important to note that maintaining energy balance should focus on improving diet quality and healthy eating patterns rather than on calorie restriction alone [35]. The nutrition component of weight management must address survivors' targeted nutritional needs such as excessive intakes of empty calories and sodium and inadequate intakes of vegetables and whole grains identified in the survivors [12,15-17] in order to be effective. These nutritional targets are similar to those identified in the general population. However, childhood cancer survivors experience a substantially higher CVD burden than the general population. Interventions to improve these nutritional targets for a high-risk population can have a much larger impact on reducing the CVD burden than that in the general population. Similarly, a large proportion of childhood cancer survivors have low bone mineral density due to exposure to glucocorticoids treatment [30,31]. Having adequate vitamin D and calcium intake from dietary sources and increasing bone-strengthening activities are important targets for improving bone health in this population. It is equally important to recognize that cancer treatment can have a long-lasting impact on survivors' eating patterns or activity levels, such as food craving [36], change in taste preference [37], fatigue [38,39], and stress [40]. These barriers may prevent childhood cancer survivors from making healthy food choices and being physical activity. Therefore, the weight management program for childhood cancer survivors should meet their targeted nutrition needs and help survivors and parents identify options to overcome barriers.

Parenting styles and practices are important behavioral targets for weight management in childhood cancer survivors. For young survivors (aged 10 years or under) with limited autonomy and greater dependence on caregivers, family environment plays a highly influential role in facilitating a child's eating and activity behaviors. For families with childhood cancer survivors, family environment can be even more important, because a close parent-child relationship is often expected in this context [41]. Qualitative research suggests that parents tend to change parenting styles after a child's diagnosis and treatment of cancer [26]. Parents may practice permissive parenting, allowing their child to choose highly preferred, processed snack foods. Parents may also practice protective parenting, encouraging sedentary behavior because of concerns about the safety of exercise. Prior research provides convincing evidence that interventions targeting parents exclusively or targeting parents and children together yields greater success in preventing childhood obesity than those targeting children alone [42-44]. Therefore, weight management programs should engage parents as the agents of change, improve parenting style and practices, and emphasize the parents' roles in transitioning the family towards healthy eating and exercise through modifying family environment. Since these types of programs are more effective when based on behavioral theory [45], a strong theoretical framework underpins the HEAL program. A limitation of the program, however, is that it does not explicitly address the family structure of the intervention. Although the program can be accessible by any parent or caregiver after he or she registers for an account, it does not address behavioral issues that may arise when both parents or all caregivers enroll in the program.

An important characteristic of childhood cancer survivors is that they are geographically dispersed. As a consequence, they have transportation difficulties coming to interventions delivered at a central location. Intensive time commitment to cancer-related care adds an additional barrier for families to participate in interventions scheduled at fixed times [46]. On the other hand, 87% of the American adults have Internet access and 90% have a mobile phone [47,48]. Access to Internet and mobile phones is observed across all major ethnic groups and socioeconomic backgrounds. Interventions delivered remotely through Web- and mobile-based apps, combined with individualized feedback and motivational messages provided through emails and phones, can substantially increase reach and reduce cost. In addition, they provide a cost-effective option for integrating weight management into the survivorship care for childhood cancer survivors and families [49].

In summary, lifestyle interventions are becoming a priority in cancer care to prevent excessive weight gain and early onset of CVD risk factors in childhood cancer survivors. These interventions must meet the targeted behavioral needs of the survivors; address specific barriers; capture a sensitive window for behavioral change; and be convenient, cost-effective, and scalable. Future research is needed to evaluate the feasibility of engaging pediatric ALL survivors and families in early weight management either within or outside cancer clinics and to assess participation, adherence, and retention rates. Such findings will provide an important foundation to inform the design and implementation of a fully-powered randomized controlled trial to evaluate the effect of early weight management on preventing unhealthy weight gain and CVD risk in young survivors of childhood ALL and to identify effective strategies to integrate weight management into cancer care and adapt the program to survivors with other cancer diagnoses.

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Conflicts of Interest

None declared.

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Abbreviations

ALL: childhood acute lymphoblastic leukemia
BMI: body mass index
CVD: cardiovascular disease
HEAL: Healthy Eating and Active Living
SDT: self-determination theory
SMART: Specific, Measurable, Achievable, Relevant, and Time-bound
SSB: sugar-sweetened beverage

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Original Paper

Internet-Based Delivery of Evidence-Based Health Promotion Programs Among American Indian and Alaska Native Youth: A Case Study

Christine M Markham[1], PhD; Stephanie Craig Rushing[2], PhD, MPH; Cornelia Jessen[3], MA; Gwenda Gorman[4], BSc; Jennifer Torres[1], MPH; William E Lambert[5], PhD; Alexander V Prokhorov[6], MD, PhD; Leslie Miller[7], PhD; Kelly Allums-Featherston[8], PhD; Robert C Addy[1], PhD; Melissa F Peskin[1], PhD; Ross Shegog[1], PhD

[1]Department of Health Promotion and Behavioral Sciences, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, United States

[2]Northwest Portland Area Indian Health Board, Portland, OR, United States

[3]Alaska Native Tribal Health Consortium, Anchorage, AK, United States

[4]Inter Tribal Council of Arizona, Inc., Phoenix, AZ, United States

[5]Oregon Health & Science University, Portland, OR, United States

[6]The University of Texas MD Anderson Cancer Center, Houston, TX, United States

[7]Rice University, Houston, TX, United States

[8]The Cooper Institute, Dallas, TX, United States

Corresponding Author:
Christine M Markham, PhD
Department of Health Promotion and Behavioral Sciences
School of Public Health
University of Texas Health Science Center at Houston
7000 Fannin St., Rm 2622
Houston, TX, 77030
United States
Phone: 1 713 500 9646
Fax: 1 713 500 9602
Email: Christine.Markham@uth.tmc.edu

Abstract

Background: American Indian and Alaska Native (AI/AN) youth face multiple health challenges compared to other racial/ethnic groups, which could potentially be ameliorated by the dissemination of evidence-based adolescent health promotion programs. Previous studies have indicated that limited trained personnel, cultural barriers, and geographic isolation may hinder the reach and implementation of evidence-based health promotion programs among AI/AN youth. Although Internet access is variable in AI/AN communities across the United States, it is swiftly and steadily improving, and it may provide a viable strategy to disseminate evidence-based health promotion programs to this underserved population.

Objective: We explored the potential of using the Internet to disseminate evidence-based health promotion programs on multiple health topics to AI/AN youth living in diverse communities across 3 geographically dispersed regions of the United States. Specifically, we assessed the Internet's potential to increase the reach and implementation of evidence-based health promotion programs for AI/AN youth, and to engage AI/AN youth.

Methods: This randomized controlled trial was conducted in 25 participating sites in Alaska, Arizona, and the Pacific Northwest. Predominantly AI/AN youth, aged 12-14 years, accessed 6 evidence-based health promotion programs delivered via the Internet, which focused on sexual health, hearing loss, alcohol use, tobacco use, drug use, and nutrition and physical activity. Adult site coordinators completed computer-based education inventory surveys, connectivity and bandwidth testing to assess parameters related to program reach (computer access, connectivity, and bandwidth), and implementation logs to assess barriers to implementation (program errors and delivery issues). We assessed youths' perceptions of program engagement via ratings on ease of use, understandability, credibility, likeability, perceived impact, and motivational appeal, using previously established measures.

Results: Sites had sufficient computer access and Internet connectivity to implement the 6 programs with adequate fidelity; however, variable bandwidth (ranging from 0.24 to 93.5 megabits per second; mean 25.6) and technical issues led some sites to access programs via back-up modalities (eg, uploading the programs from a Universal Serial Bus drive). The number of youth providing engagement ratings varied by program (n=40-191; 48-60% female, 85-90% self-identified AI/AN). Across programs, youth rated the programs as easy to use (68-91%), trustworthy (61-89%), likeable (59-87%), and impactful (63-91%). Most youth understood the words in the programs (60-83%), although some needed hints to complete the programs (16-49%). Overall, 37-66% of the participants would recommend the programs to a classmate, and 62-87% found the programs enjoyable when compared to other school lessons.

Conclusions: Findings demonstrate the potential of the Internet to enhance the reach and implementation of evidence-based health promotion programs, and to engage AI/AN youth. Provision of back-up modalities is recommended to address possible connectivity or technical issues. The dissemination of Internet-based health promotion programs may be a promising strategy to address health disparities for this underserved population.

Trial Registration: Clinicaltrials.gov NCT01303575; https://clinicaltrials.gov/ct2/show/NCT01303575 (Archived by WebCite at http://www.webcitation.org/6m7DO4g7c)

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KEYWORDS

adolescents; American Indian; Alaska Native; health promotion; Internet

Introduction

As of 2012, an estimated 5.2 million individuals in the United States identified as American Indian and Alaska Native (AI/AN) alone or combined with other races, comprising 2% of the nation's population [1]. The AI/AN population is diverse, with 567 federally recognized tribes; 60% of AI/AN individuals live in metropolitan areas and 22% live on reservations or other trust lands [1]. The AI/AN population is younger and faster growing than other US racial groups, with 30% under 18 years of age, making adolescent health a major priority [1]. Nationally, AI/AN youth are more likely to engage in sexual risk and substance use behaviors than their racial/ethnic peers [2], contributing to health disparities in teen births, sexually transmitted infections, unintentional injuries, and suicide. In 2014, AI/AN females aged 15-19 years had the third highest teen birth rate in the United States (27.3 per 1000 vs 38.0 for Hispanics, 34.9 for blacks, and 17.3 for whites) [3]; however, AI/AN females represent the highest prevalence of repeat teen births (21.6% versus 20.9% for Hispanics, 20.4% for blacks, and 14.8% for whites) [4]. Furthermore, in 2011 AI/AN females aged 15-24 years reported the highest age-specific rates of chlamydial infections among US women [5]. Between 1999 and 2009, AI/AN youth aged 15-19 were more than twice as likely as white youth to be at risk for unintentional injuries, and three times as likely to be at risk for suicide [6].

AI/AN youth also face disparities related to obesity and diabetes. Previous studies have indicated that 20-30% of AI/AN children are obese [7], compared to 17% of children nationally [8]. Furthermore, in 2001 AI/AN youth aged 10-19 years were nine times more likely to be diagnosed with type 2 diabetes compared to non-Hispanic whites (1.74 per 1000 vs 0.19 per 1000) [9]. Sequela from these health conditions often carry over into adulthood, making heart disease and cancer the leading causes of death among AI/AN adults [10]. AI/AN adults also experience higher rates of hearing loss than other racial/ethnic groups [11].

These health disparities could potentially be ameliorated by the dissemination and implementation of evidence-based adolescent health promotion programs. The United States Department of Health and Human Services' Office of Adolescent Health, Substance Abuse and Mental Health Services Administration, and Centers for Disease Control and Prevention (CDC) have identified adolescent health promotion programs proven to impact behavior change across various health domains, including sexual health, violence and substance use prevention, physical activity, and nutrition [12-14]. However, the public health impact of health promotion programs depends both upon their efficacy and their reach [15]. To be impactful, evidence-based programs must have sufficient *reach* to their intended audience, be *implemented* as intended in the real world, and adequately *engage* their audience [16].

Limited data exist regarding the reach and implementation of evidence-based health promotion programs among AI/AN youth. The Bureau of Indian Education (BIE) supports 183 primary and secondary schools in 23 states, serving approximately 50,000 students. A school health assessment of BIE schools conducted in New Mexico in 2006 reported that 38 of 39 schools (97%) provided health education and/or health promotion activities, and 67% used a comprehensive health education curriculum [17]. Curriculum content centered predominantly on violence and substance use prevention, physical activity, and nutrition. Less than 50% of the schools provided education on pregnancy prevention, highlighting the sensitive nature of sexual health education in AI/AN communities. Ten of the 39 schools (26%) had certified health educators. No information was provided regarding whether curriculum content was evidence-based or culturally sensitive [17]; however, few culturally based or culturally sensitive behavioral health promotion programs exist for AI/AN youth [18]. Furthermore, data from the 2013 Youth Risk Behavior Surveillance Survey indicate that AI/AN students in Alaska and Montana (states with high proportions of rural and remote communities) were less likely to receive school-based human immunodeficiency virus/acquired immune deficiency syndrome education

compared to white students [19]. Although restricted in scope, these findings indicate that limited trained personnel, cultural barriers, and geographic isolation may hinder the reach and implementation of evidence-based health promotion programs among AI/AN youth [1,20].

Technology-based programs may offer a viable strategy to increase the reach and implementation of evidence-based health promotion programs in this underserved population [21]. Furthermore, AI/AN youth themselves have repeatedly voiced the need for technology-based health programs to address sensitive health topics [22,23]. Although Internet access is highly variable in tribal communities across the United States, it is swiftly and steadily improving [24]. For example, BIE-funded schools are part of the federal ConnectED initiative to increase Internet connectivity and educational technology in schools. Technology usage rates among AI/AN youth exceed national averages, and many use the Internet to access health information [25,26]. These factors suggest that utilizing the Internet could increase the reach of evidence-based health promotion to AI/AN communities. Internet-based programs can also improve the implementation of programs as intended, given the reduced need for specialized facilitator training and enhanced confidentiality to deliver sensitive topics, such as sexual health [21]. Internet-based programs may also increase student engagement with program activities [21,27], and provide the ability to tailor instructions to individual characteristics (eg, gender, risk factor, or stage of change) [28]. Most importantly, Internet-based health promotion programs have been shown to impact behavior change across multiple health domains, including sexual health, substance use, physical activity and nutrition, and hearing protection [26-31].

Recently, Internet-based sexual health promotion programs have been specifically developed or adapted for AI/AN youth, with high satisfaction ratings reported [21,24]. The purpose of this study was to examine the potential of using the Internet to increase the reach and implementation of evidence-based health promotion programs across a variety of health topics, and to engage early adolescent AI/AN youth in 3 geographically dispersed regions in the United States. The findings from this study have broader implications in understanding the degree to which Internet-based programs may increase the dissemination and utilization of evidence-based health promotion programs in tribal communities.

Methods

Study Design

This study presents a secondary analysis of data collected during the implementation phase of a randomized controlled trial (Clinicaltrials.gov NCT01303575) that assessed the effectiveness of Native It's Your Game (Native IYG; a Web-based sexual health education program adapted for AI/AN youth) relative to a comparison suite of 5 evidence-based Internet-based health promotion programs, across 3 geographically dispersed regions in the United States. A detailed description of the adaptation process for Native IYG is provided in a supplemental file [32]. Primary outcomes of the randomized controlled trial are forthcoming. Data presented here provide insight into the potential of using the Internet to increase the reach and implementation of evidence-based adolescent health promotion programs across a variety of health topics to AI/AN youth in diverse geographic regions, and the ability of Internet-based programs to engage AI/AN youth.

Participants

Participants were primarily self-identified AI/AN youth aged 12-14 years and adult site coordinators (teachers, counselors, nurses, wellness coordinators, and college students) that were recruited from 25 study sites. The sites were located in 13 urban and 12 rural/tribal settings in Alaska, Arizona, and the Pacific Northwest (Oregon, Idaho, and Washington), and comprised schools, tribal community centers, after school programs, and summer youth programs. Given the importance of confidentiality when partnering with AI/AN communities, specific tribal names have been withheld. The study was approved by the Alaska Area Institutional Review Board (IRB), the Portland Area Indian Health Service IRB, the University of Texas Health Science Center at Houston (UTHealth) IRB, and 16 tribal organizations (ie, tribal councils, tribal health boards, villages, and community agencies).

Procedure

Study activities were coordinated regionally by 3 organizations that collectively serve 295 federally recognized AI/AN tribes. Regional staff used convenience sampling to recruit tribal communities that were interested in participating in an early adolescent sexual health study. Regional staff sent flyers to schools, tribal community centers, after school programs, and summer camp programs, and advertised on organizational websites, social media outlets, and/or via newsletters. Participating sites were randomized to a treatment condition (Native IYG, n=14) or a comparison condition (n=11) featuring a suite of 5 evidence-based Internet-based health promotion programs that were not focused on sexual health.

Site Coordinator Training

Site coordinators at each study site completed the Collaborative Institutional Training Initiative Program's online certification in human subject research and a live webinar (tailored for treatment or control conditions) coordinated by UTHealth research staff, which explained intervention content and protocols for logging-in youth, documentation, and maintaining confidentiality.

Internet-Based Health Promotion Programs

Native IYG is a 13-lesson, multimedia sexual health education curriculum for AI/AN youth (aged 12-14 years). The curriculum was adapted from an Internet-based curriculum for urban middle schools titled *It's Your Game-Tech* (IYG-Tech) [32]. Lessons are approximately 35 minutes long. Adaption and formative development, guided by feedback from AI/AN youth and adults, comprised surface alterations (eg, changing the program logo) and deep cultural adaptations (eg, adding a blessing by AI elders and videos featuring AI/AN youth). A detailed description of the adaptation process has been published elsewhere [32].

The 5 evidence-based, Internet-based programs that comprised the comparison suite addressed hearing loss (Dangerous

Decibels), alcohol use (N-Squad), tobacco use (A Smoking Prevention Interactive Experience; ASPIRE), drug use (Reconstructors), and physical activity and nutrition (The Quest to Lava Mountain). Each program has undergone usability testing with non-AI/AN youth as part of its own formative development, and has demonstrated efficacy to positively impact health behaviors and/or related psychosocial factors in other adolescent populations. The Dangerous Decibels Virtual Exhibit was developed by the Oregon Museum of Science and Industry as an online component of a public health campaign to reduce the incidence and prevalence of noise-induced hearing loss and tinnitus (ringing in the ear) by improving knowledge, attitudes, and protective behaviors of school-aged children [33]. N-Squad and Reconstructors, developed by the Rice University Center for Technology in Teaching and Learning, are Internet-based adventures for middle school students to learn about alcohol's interaction in the digestive, circulatory, and nervous systems, and explore the science behind drugs of abuse [34,35]. ASPIRE is an online tobacco prevention and cessation curriculum, developed jointly by researchers at The University of Texas MD Anderson Cancer Center and UTHealth, with demonstrated efficacy in preventing smoking onset in high school youth [36]. The Quest to Lava Mountain, developed as part of the Texas Department of Agriculture NutriGram program by The Cooper Institute, is an educational game designed to raise awareness about healthy eating and physical activity [37].

Site coordinators logged participants onto the programs on desktop or laptop computers located in quiet locations (eg, a computer lab, empty classroom, or library). Sites with insufficient bandwidth to accommodate simultaneous Internet access by multiple users were provided with uploadable versions of their respective programs on a Universal Serial Bus (USB) drive or digital video disc (DVD).

Data Collection

Assessing Reach and Implementation

Prior to implementation, site coordinators completed a computer-based education inventory survey [32] and connectivity and bandwidth testing [38] to document access parameters related to program reach. The site coordinators used problem logs during implementation to document program errors and technical issues that impacted implementation.

Assessing Youth Engagement

We used Likert-type scales adapted from previous studies to assess youths' perceptions of engagement [39-42]. *Ease of use* was based on how easy it was to use the program, using a Likert-type 3-point scale (*very easy* to *kind of hard*). *Understandability* was based on whether youth understood the words used and if they needed hints from an adult to play the game, using a Likert-type 3-point scale (*yes*, *no*, and *don't know*). *Credibility* was based on youths' perceptions of content correctness, using a Likert-type 3-point scale (*right*, *wrong*, and *don't know*) and trustworthiness (*yes*, *no*, and *don't know*). *Likeability* was based on how much youth liked the program activities, using a Likert-type 5-point scale (*dislike a lot* to *like a lot*). *Perceived impact* was based on whether youth thought the program would help them make healthy decisions, using a Likert-type 3-point scale (*yes*, *no*, and *don't know*). *Motivational appeal* was based on whether youth would play more program lessons if available, if they would recommend the program to classmates, and whether the program was *as much or more fun* than other lessons at school, including other health lessons, computer-based lessons, and their favorite video game, using a Likert-type 3-point scale (*yes*, *no*, and *don't know*).

Ratings were collected via an Internet-based Qualtrics usability survey administered at the completion of each program. Demographic characteristics (gender, age, and self-identified race/ethnicity) were collected during the study's baseline survey, using an Internet-based Qualtrics self-report survey [43]. Upon entering the study, youth received a unique study identification number to link data across surveys. No names were associated with the surveys. All youth provided signed parental consent and youth assent prior to participating in the study. A detailed description of study procedures has been published elsewhere [43].

Data Analysis

We used descriptive statistics (frequencies, median/mean, and/or range) to summarize data on reach parameters (computer access, connectivity, and bandwidth) and implementation (program errors and technical issues). Regarding youth engagement, for each parameter we calculated the percent of youth who rated each program favorably, and the range of ratings across all 6 programs, from lowest to highest.

Results

Reach and Implementation

Twenty-four site coordinators (24/25, 96%) provided complete or partial information related to Internet reach parameters. Eighteen computer labs, one classroom, and one after school classroom across the 3 regions were primarily composed of personal computers (13/20, 65%) and Mac computers (6/20, 30%), were mostly wired (16/18, 89%), and most had access to the Internet (22/24, 92%). Primary Web browsers included Chrome (7/20, 35%), Safari (5/20, 25%), Internet Explorer (5/20, 25%), Firefox (2/20, 10%), and Mozilla (1/20, 5%). Download speeds ranged from 0.24 megabits per second (Mbps) to 93.5 Mbps (mean 25.6 Mbps, standard deviation 31.14; median 6.37 Mbps).

At some sites, the method of program delivery changed during implementation. Treatment sites commenced the study accessing Native IYG as an online streaming program (n=12) or as an uploadable program from a USB drive (n=2). During the study, several sites that initially accessed Native IYG as an online streaming program converted to uploading Native IYG from a USB drive (n=4) due to the inability of local bandwidth to accommodate larger Native IYG video files while providing simultaneous streaming for multiple youth.

Comparison condition sites commenced the study by accessing the suite of health promotion programs via online streaming (n=8) or a combination of online streaming and an uploadable program from DVDs (n=2). Information regarding program access was missing from one site. During the study, most sites

continued to access these programs via Internet connections (n=8).

The most commonly reported problems that were documented by site coordinators during implementation included frozen screens (4/6 programs), activities taking a long time to load (3/6 programs)—both of which were related to multiple simultaneous users—and trouble navigating the programs (3/6 programs).

Youth Engagement

During implementation, 387 youth received Native IYG, of whom 191 (49%) provided feedback; 136 youth received the comparison suite of programs, of whom 108 (79%) completed at least one feedback survey. Across programs, participants were 48-60% female, with a mean age of 13.1-13.3 years, and 85-90% self-identified as AI/AN (Table 1).

Table 1. Demographic characteristics for AI/AN youth who provided ratings for each program (n=40-191): Alaska, Arizona, and Pacific Northwest, 2012-2014.

	Native IYG (n=191)	Dangerous Decibels (n=62)	N-Squad (n=62)	ASPIRE (n=52)	Reconstructors (n=45)	Lava Mountain (n=40)
Gender, n (%)						
Female	114 (59.7)	30 (48.4)	34 (54.8)	25 (48.1)	24 (53.3)	21 (52.5)
Male	77 (40.3)	32 (51.6)	28 (45.2)	27 (51.9)	21 (46.7)	19 (47.5)
Self-identify as AI/AN, n (%)	164 (85.9)	54 (87.1)	56 (90.3)	46 (88.5)	40 (88.9)	34 (85.0)
Mean age (standard deviation)	13.1 (0.98)	13.2 (0.83)	13.3 (0.84)	13.3 (0.77)	13.2 (0.78)	13.3 (0.88)

Youth generally rated the programs as easy to use (68-91%) and the majority understood the words in the programs (60-83%). However, some participants needed adult assistance or hints to complete the programs (16-49%). Over half of the youth reported that the program content was credible, rating it *correct* (58-90%) and *trustworthy* (61-89%), and 63-91% reported that the programs would help them make better choices. Regarding likeability, 59-87% of youth liked the programs *a little* or *a lot*. In terms of motivational appeal, 35-63% of youth reported that they would play more lessons from each program, if available; 37-66% would recommend the programs to a classmate. Although fewer youth considered the programs *as much or more fun* than their favorite video game (25-61%), youth stated that the programs were *as much or more fun* than other lessons at school (62-87%), other health lessons at school (61-79%), and other computer-based lessons at school (57-85%; Multimedia Appendix 1).

Discussion

AI/AN youth face multiple health challenges compared to youth of other racial/ethnic groups. Viable program delivery strategies that overcome limited personnel with training in health education, cultural barriers, and geographic isolation (ie, the Internet) are needed to increase the reach and implementation fidelity of evidence-based adolescent health promotion programs in tribal communities. We examined the potential of using the Internet to deliver 6 evidence-based health promotion programs to AI/AN youth living in urban and rural settings in 3 geographically diverse regions of the United States. The health topics addressed included sexual health, hearing loss, substance use, physical activity, and nutrition. Despite variability in connectivity and bandwidth, most sites were able to access the programs via the Internet. However, technical and connectivity issues led some sites to access the programs via back-up modalities (ie, uploading the programs from a USB drive or DVD). Practitioners interested in implementing Internet-based programs in tribal communities are advised to provide contingency plans as back-ups to technical failures. We also recommend conducting bandwidth assessments, especially when dealing with multiple simultaneous users, prior to implementing an Internet-based program.

Adult site coordinators from each tribal community (including teachers, counselors, nurses, wellness coordinators, and college students) facilitated youths' access to the Internet-based programs. Regarding implementation fidelity and program errors, site coordinators reported issues with frozen screens (4/6 programs), activities taking a long time to load (3/6 programs), and trouble navigating the programs (3/6 programs). Given that 16-49% of youth needed assistance to complete the programs, some adult oversight is recommended when implementing Internet-based programs for youth. Although the site coordinators received webinar training prior to program implementation, the training focused primarily on research study-specific protocols (eg, logging students onto computers using study identification numbers and reporting technical issues). The training related to actual program implementation, such as reviewing specific program content, was limited to approximately one hour, indicating that a broad range of personnel (including those not certified in health education) may be able to implement Internet-based health promotion programs.

Overall, AI/AN youth rated the programs favorably. Although fewer youth rated the programs as being *as engaging as their favorite video game* (a lofty expectation for any educational program), over 60% stated that the programs were *as much or more fun* than other lessons at school. These findings indicate that Internet-based health promotion programs are engaging to AI/AN youth in the diverse settings of both rural (reservation and village) and urban locations. These results also support previous studies indicating that Internet-based health promotion programs provide an engaging educational format for Millennium learners. Internet-based programs are uniquely

positioned to allow for: the provision of motivational learning experiences delivered via video, animated characters, and gaming formats; the provision of role modeling activities that influence normative perceptions and skills; confidential and personalized presentation of sensitive and potentially embarrassing issues (eg, sexual health); and intervention messages that are tailored to specific user characteristics [27,28]. These features may help to engage and retain AI/AN youth in health promotion programs.

It is worth noting that youth rated Native IYG most favorably across all programs on 10 of the 13 usability parameters, possibly because this program was specifically adapted for AI/AN youth. This finding aligns with previous studies that point to the value of cultural tailoring [44]. Incorporating traditional AI/AN values and teaching methods into Internet-based health promotion programs may strengthen or reinforce a sense of cultural identity and belonging among AI/AN youth, better align with health epistemologies and learning styles, and help protect against engaging in early risk behaviors [24]. The evidence-based approach that we used to adapt IYG for AI/AN youth may provide a useful model for adapting other health promotion programs [32]. The favorable ratings for Native IYG are also noteworthy, given the sensitivity associated with sexual health education in AI/AN communities, and indicate that Internet-based programs may be an appropriate delivery channel for other sensitive health topics.

Across all programs, we experienced attrition in the number of youth who received the programs compared to those who completed a feedback survey. This attrition may have been due to respondent burden or fatigue in completing surveys after each program. However, the relatively high motivational appeal ratings across programs (eg, at least 60% of youth stated that the programs were *as much or more fun* than other lessons at school) suggest that the programs would be engaging for AI/AN youth in school, after school, or in community-based settings.

This study has several strengths. First, most feasibility studies for technology-based health promotion programs feature small numbers of participants (typically <30 users), as they do not require statistical significance to determine major usability problems [45]. In contrast, at least 40 AI/AN youth reviewed each program, with a relatively even mix of males and females in each program. Second, participants were recruited from a range of urban and rural settings across 3 geographic regions, thereby increasing the representation of youth from varied tribal communities that represent differing cultural perspectives, traditions, and values, as well as varied urbanicity and Internet access. Third, the study included Internet-based programs across a variety of health promotion topics that are important to AI/AN communities. Taken together, these factors may enhance the generalizability of findings to AI/AN communities beyond the study sample.

Despite these strengths, several limitations should be noted. First, the sample was restricted to early adolescent AI/AN youth, aged 12-14 years; thus, findings may not apply to older AI/AN youth. Second, social desirability may have biased youths' ratings of the programs; however, the fact that some items scored lower than others (eg, comparing programs to their favorite video game) suggests that youth answered honestly, based on their experience with each program. Third, the intervention program, Native IYG, was specifically adapted for AI/AN youth. In contrast, no attempt was made to adapt the comparison group programs for AI/AN youth; this factor may have negatively impacted program ratings relative to Native IYG. Finally, although the use of percent ranges to evaluate engagement is sufficient for this kind of exploratory trial, more thorough quantitative analyses, such as appropriately powered randomized pilot tests of the programs' impact on behavioral determinants or randomized controlled efficacy field trials, are needed to determine long-term behavioral impact.

Despite these limitations, this study demonstrates the potential of using the Internet to disseminate evidence-based health promotion programs to AI/AN youth across 3 separate geographic regions. These findings may have broader implications for understanding the degree to which Internet-based programs may enhance the reach and implementation of evidence-based health promotion programs in tribal communities, and provide an educational format that is engaging for AI/AN youth.

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Authors' Contributions

CMM served as joint Principal Investigator with RS on the conceptualization and design of the study, drafted the initial manuscript, and approved the final manuscript as submitted. SCR, CJ, and GG served as Regional Principal Investigators for the study, contributed to the intervention design, coordinated site recruitment in their respective regions, codesigned the data collection instrument, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. WEL, AVP, and LM were program developers for Dangerous Decibels, ASPIRE, N-Squad, and Reconstructors, respectively. These authors critically reviewed and revised the manuscript, and approved the final manuscript as submitted. KA-F served as a representative for The Cooper Institute (the program developer for The Quest to Lava Mountain), critically reviewed and revised the manuscript, and approved the final manuscript as submitted. JT coordinated intervention development and data collection across all 3 regions,

assisted in data cleaning and initial analyses, drafted sections of the initial manuscript, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. RCA conducted statistical analyses, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. MFP served as Co-Investigator for the study and codesigned the data collection instrument, study design, and analyses. She critically reviewed and revised the manuscript and approved the final manuscript as submitted. RS served as joint Principal Investigator with CMM on the conceptualization and design of the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Conflicts of Interest

None declared.

Multimedia Appendix 1

[PDF File (Adobe PDF File), 31KB - resprot_v5i4e225_app1.pdf]

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Abbreviations

AI/AN: American Indian and Alaska Native (AI/AN)
BIE: Bureau of Indian Education
CDC: Centers for Disease Control and Prevention
DVD: digital video disc
IRB: Institutional Review Board
IYG: It's Your Game
Mbps: megabits per second
USB: Universal Serial Bus
UTHealth: University of Texas Health Science Center at Houston

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Original Paper

Parent and Clinician Preferences for an Asthma App to Promote Adolescent Self-Management: A Formative Study

Lorie L Geryk[1], MPH, PhD; Courtney A Roberts[1], MSPH; Adam J Sage[1], MA; Tamera Coyne-Beasley[2], MPH, MD; Betsy L Sleath[1], PhD; Delesha M Carpenter[1], MSPH, PhD

[1]Division of Pharmaceutical Outcomes and Policy, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, United States
[2]Division of General Pediatrics and Adolescent Medicine, School of Medicine, University of North Carolina, Chapel Hill, NC, United States

Corresponding Author:
Lorie L Geryk, MPH, PhD
Division of Pharmaceutical Outcomes and Policy
Eshelman School of Pharmacy
University of North Carolina
301 Pharmacy Lane
Chapel Hill, NC, 27599
United States
Phone: 1 9198432278
Fax: 1 9199668486
Email: llgeryk@email.unc.edu

Abstract

Background: Most youth asthma apps are not designed with parent and clinician use in mind, and rarely is the app development process informed by parent or clinician input.

Objective: This study was conducted to generate formative data on the use, attitudes, and preferences for asthma mHealth app features among parents and clinicians, the important stakeholders who support adolescents with asthma and promote adolescent self-management skills.

Methods: We conducted a mixed-methods study from 2013 to 2014 employing a user-centered design philosophy to acquire feedback from a convenience sample of 20 parents and 6 clinicians. Participants were given an iPod Touch and asked to evaluate 10 features on 2 existing asthma apps. Participant experiences using the apps were collected from questionnaires and a thematic analysis of audio-recorded and transcribed (verbatim) interviews using MAXQDA. Descriptive statistics were calculated to characterize the study sample and app feature feedback. Independent samples *t* tests were performed to compare parent and clinician ratings of app feature usefulness (ratings: 1=not at all useful to 5=very useful).

Results: All parents were female (n=20), 45% were black, 20% had an income ≥US $50,000, and 45% had a bachelor's degree or higher education. The clinician sample included 2 nurses and 4 physicians with a mean practice time of 13 years. Three main themes provided an understanding of how participants perceived their roles and use of asthma app features to support adolescent asthma self-management: monitoring and supervision, education, and communication/information sharing. Parents rated the doctor report feature highest, and clinicians rated the doctor appointment reminder highest of all evaluated app features on usefulness. The peak flow monitoring feature was the lowest ranked feature by both parents and clinicians. Parents reported higher usefulness for the doctor report ($t_{(10)}$=2.7, P<.02), diary ($t_{(10)}$=2.7, P<.03), and self-check quiz ($t_{(14)}$=2.5, P<.02) features than clinicians. Specific participant suggestions for app enhancements (eg, a tutorial showing correct inhaler use, refill reminders, pop-up messages tied to a medication log, evidence-based management steps) were also provided.

Conclusions: Parent and clinician evaluations and recommendations can play an important role in the development of an asthma app designed to help support youth asthma management. Two-way asthma care communication between families and clinicians and components involving families and clinicians that support adolescent self-management should be incorporated into adolescent asthma apps.

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KEYWORDS

asthma; self-management; social support; mHealth; mobile apps; adolescents; parents; clinicians

Introduction

Youth with asthma often have complex self-management regimens that include responding to changes in symptoms, taking multiple medications, dealing with doctor consultations, and adjusting to treatment changes [1]. The asthma care process (eg, developing and implementing an asthma management plan) should involve collaboration between the clinician, the patient, and his/her parents [2,3]. Self-management support should be provided to families in between medical visits, using a style that reflects individual needs and with an understanding that youth with asthma generally take on greater self-care autonomy with age [1,4]. Better clinician and caregiver involvement and support for self-management is known to improve asthma control among children and adolescents [5-8], and, increasingly, digital technologies (eg, Internet and mHealth apps) are being used to deliver that support [9]. While asthma apps offer a promising method for providing self-management support [10], little is known about how parents and clinicians would prefer to use an asthma self-management app to promote adolescent self-management.

Internet interventions designed to facilitate adolescent asthma self-management often take a fragmentary approach by addressing information, decision support, or social support individually, and not as part of a comprehensive asthma management strategy [11]. In a review, Morrison et al [9] found that most digital asthma self-management interventions incorporated an average of 4 of the following common features: asthma self-care education, asthma action plan, self-monitoring, interactive/receiving immediate feedback from the device, alerts from device, alerts from health professionals, and games. Interventions rarely possessed features that encouraged two-way asthma care communication between families and clinicians or features to help families and clinicians facilitate adolescent self-management. In fact, in 2013, only 1% of available apps (3/209) targeted both children and their caregivers [12]. As of 2015, in a review of asthma-related apps by Wu et al [13], only 8% (9/209) of apps were child-focused, with only 2 including adolescents and neither having components for parents or clinicians.

Few studies have sought to assess clinician and parent perspectives on adolescent asthma self-management apps [14-16]. In a pilot study, Haze et al [14] found that nurses believed the use of smartphone apps improved their ability to contact adolescents and increased the accuracy of clinical assessment. In another study, parents suggested medication and refill reminders and alerts (eg, teen to call the doctor when peak flow readings are concerning) when asked what they would like to see in a digital asthma tool for teens with asthma [15]. Another study found that clinicians believed apps could assist patients in developing self-management skills and serve as a two-way channel for sharing accurate and credible information [16].

This study adds to the existing literature because it simultaneously considers clinician and parent perspectives related to a wider-ranging array of app self-management features (eg, diary, chart, self-check quiz, reminder alerts) than have previously been considered. This study is part of a larger exploratory pilot project proposing to develop a comprehensive mHealth adolescent-centered asthma self-management app. The overall goals of the parent study are to design and test a theory-based adolescent centered mHealth app and to examine adolescent patient satisfaction with and feasibility of the app prototype. The purpose of this study was to gather data relevant to designing future adolescent asthma self-management apps by having parents and clinicians evaluate features from 2 existing asthma apps. Specifically the goals were to obtain (1) general app and specific feature impressions, (2) suggestions for modifications and new features, and (3) to identify ways participants would like to be included in app use to more effectively support adolescent asthma self-management behaviors.

Methods

Recruitment

For this formative study, we gathered ideas for future adolescent asthma self-management app features by leveraging the opinions and feedback of a convenience sample of 20 caregivers and 6 clinicians (2 nurses and 4 physicians). Participants were recruited from 2 pediatric practices located in an urban area of North Carolina between 2013 and 2014. This study is part of a larger study that explored adolescent feedback and theoretical pathways through which asthma app features can promote adolescent self-management [17,18].

Study Procedures

A designated clinic liaison used the eHealth record to identify adolescents with asthma and informed parents about the study prior to the adolescent's regularly scheduled clinic appointment. Upon arriving for the adolescent's appointment, interested parents were introduced to the study research assistant (RA). Parents were eligible if they (1) were at least 18 years of age, (2) could read and understand English, and (3) were the biological parent or legal guardian of an adolescent (12-17 years of age) with persistent asthma, which was defined as experiencing asthma-related daytime symptoms more than twice a week, asthma-related nighttime symptoms more than twice a month, or receiving one or more long-term control therapies for asthma [19,20].

After providing consent and prior to the adolescent's appointment, parents completed a brief questionnaire that assessed demographics and technology use. After the appointment, the RA gave the parent an iPod Touch that contained 2 asthma self-management apps; one app targeted adults and one targeted children. The 2 apps were purposely selected from those that were available on the iOS platform in late 2012 because they had the combined characteristics of being user-friendly and having multiple self-management features. At the time, no app was targeted to adolescents or had components designed to incorporate caregiver or clinician use. The RA demonstrated how to use the 2 apps and then allowed parents to explore the apps on their own for approximately 10 minutes. Parents were then asked to explore and use features of both apps over the course of 1 week and completed a 20- to 30-minute semistructured telephone interview that assessed

their experience using the apps, perceived usefulness of app features, how app features could be improved, and suggestions for new features.

Three clinicians were recruited from each pediatric practice. Clinicians were eligible for a 30-minute in-person interview if they provided health care for adolescents with asthma. After providing consent and prior to being given the iPod Touch, clinicians answered demographic and technology use surveys. The RA then demonstrated how to use the 2 apps and then allowed clinicians to explore the apps on their own for approximately 10 minutes prior to completing a semistructured interview to obtain feedback on app use and usefulness of specific app features. Clinicians were not asked to evaluate the apps for a longer period due to professional time-constraints.

All interviews were digitally audio recorded. Parents and clinicians were allowed to keep their iPod Touches as incentives. The study was reviewed and approved by the University of North Carolina Institutional Review Board institutional review board and was conducted in accordance with the tenets of the Declaration of Helsinki.

Measures

Demographic and Clinical Characteristics

Parents and clinicians reported their gender, age, and ethnicity (Hispanic, Latino or Spanish origin). Race was measured as a categorical variable (White, Black or African American, American Indian or Alaskan Native, Asian, Native Hawaiian and Other Pacific Islander, or Other) and, for descriptive purposes, was recoded into the following categories: White, Black, and Other. Parents reported their highest level of education (less than high school; high school graduate or general education development; some college, no degree; associate's degree; bachelor's degree; more than bachelor's degree) and annual household income (<US $25,000, US $25,000 to US $34,999, US $35,000 to US $49,999, US $50,000 to US $74,999, and ≥US $75,000). Clinicians reported occupation and years in practice.

Technology Use

Parents and clinicians answered the following close-ended questions to report: owned a cell phone (yes/no), what type of cell phone they used (iPhone, android, other "basic"), owned another Internet-capable device (ie, computer, tablet, or iPad) (yes/no). Using a yes/no response format, we also asked parents and clinicians if they had (1) ever downloaded an app to a cell phone, tablet, or other handheld device, (2) ever downloaded a health-related app, (3) ever paid to download an app, or (4) ever avoided downloading an app due to privacy concerns. Parents were also asked about their interest in using an app to watch videos of correct inhaler technique, to take asthma quizzes, and to send information about the child's health to the doctor.

App Use Questions and App Feature Usefulness Ratings

Parents and clinicians were asked, "[w]hat did you think of (feature name here)?" The following 10 features were asked about: diary, chart, self-check quiz, allergies and emergency plan, doctor appointment reminder, medication reminder, asthma triggers, doctor report, school form, and peak flow. Parents and clinicians were asked additional open-ended questions about how the app or specific features could be changed and improved upon to make them better and if they had any ideas for new app features that they would like to see included in an app. Parents were asked which features they used the most and why, and which features they used the least and why. Parents and clinicians were also asked to rate the 10 app features on a scale from 1 to 5 (1=not at all useful to 5=very useful).

Parents were asked the following four questions: (1) After using the apps would you say that it helped you to better monitor your child's asthma? (2) Do you believe that using the apps helped you control your child's asthma better than you have in the past? (3) Do you feel more involved in managing your child's care after using the apps? (4) Would you say using an app helped you follow the doctor's advice better? Clinicians were asked if they thought that "using an app would help parents and adolescents…" (1) better monitor their child's/their asthma, (2) control their child's/their asthma better than they would without using an app, (3) feel more involved in asthma management, and (4) follow their advice better.

Data Analysis

Quantitative statistical analyses were conducted using IBM SPSS Version 21. Each interview was transcribed verbatim, de-identified, and analyzed thematically using MAXQDA software. Descriptive statistics were calculated to characterize the study sample. Independent samples *t* tests were performed to compare parent and clinician ratings of app feature usefulness. For qualitative data, 3 research team members engaged in an iterative process of reading and rereading the initial transcripts [21] in order to identify relevant themes and create a detailed codebook with code definitions and example quotations that was applied to all transcripts [22]. The codebook included codes for app features, facilitators and barriers to app use, asthma self-management (eg, medication management), and information related to improving app features. These codes were then placed within 3 major theme categories related to how clinicians and parents could use apps to support adolescent self-management: monitoring/supervision, communication/information sharing, and education. Monitoring and supervision related to using apps to oversee and be involved in various aspects of the adolescents' asthma care and management. Communication/information sharing related to using apps to give and receive information and discuss information effectively with social network members. Education concerned use of the app as a teaching and support tool to encourage learning about asthma. After the codebook was finalized, a primary coder coded all interview transcripts and a secondary coder coded 10% of the transcripts; inter-rater reliability was good (k=0.85).

Results

Sample Characteristics and Technology Use

Table 1 presents the demographic characteristics of parents (n=20) who participated in the study. The clinician sample included 2 nurses and 4 physicians with a mean practice time of 13 years. Clinicians were 83% female (5/6), 67% white (4/6), 17% Hispanic (1/6), and 40-years old on average. Table 2 shows reported technology use of both parents and clinicians. Of

parents 50% (10/20) reported often seeking out Web-based medical information about asthma, but 80% (16/20) had never used an asthma app before the study. Four parents did not complete their 1-week follow-up telephone interview, and these individuals were not demographically different from those who completed the study.

Table 1. Parent demographics.

Demographics	(n)/mean	%/(standard deviation)
Gender		
Male	(0)	0
Female	(20)	100
Age	44	(±8.4)
Highest level of education completed		
Less than high school	(2)	10
High school graduate or GED	(1)	5
Some college, no degree	(6)	30
Associate's degree	(2)	10
Bachelor's degree	(5)	25
More than bachelor's degree	(4)	20
Total household income before taxes during (last 12 months)		
Less than US $25,000	(7)	35
US $25,000-$34,999	(3)	15
US $35,000-$49,999	(2)	10
US $50,000-$74,999	(2)	10
US $75,000-$99,999	(1)	5
US $100,000-$149,999	(1)	5
US $150,000 or more	(2)	10
Refused	(2)	10
Race		
White	(9)	45
Black	(9)	45
Other (all options selected)	(1)	5
Missing	(1)	5
Ethnicity		
Hispanic/Latino/Spanish	(4)	20

Overall App Use Impressions

Monitoring and Supervision

Overall, parental opinions for using the apps to monitor and supervise their child's asthma were positive. One parent of a 14-year-old girl stated, “[i]t’s a very good digital record-keeper.” Clinicians generally had positive things to say about the apps as a self-management tool to help parents and adolescents including the following: “hands-on” and provides a “more interactive or fun way to check on their asthma.”

Of parents, 80% (16/20) said that using an app helped them better monitor their child's asthma, and 40% (8/20) believed that using an app helped them control their child's asthma better than they had in the past. Fifty percent (10/20) of parents felt more involved in managing their child's asthma after using an app, and half felt that using an app helped them follow their child's doctor's advice better.

Of clinicians, 50% (3/6) thought that using an app would help parents and adolescents better monitor their child's/their asthma, and 83% (5/6) believed that using an asthma app would help parents/adolescents control their child's/their asthma better than they would without using an app. All clinicians (6/6, 100%) thought that parents and adolescents would feel more involved in managing asthma by using an app, and 83% (5/6) thought that asthma apps would help parents and adolescents follow their advice better.

Communication/Information Sharing

Overall, parent and clinician opinions of using the apps for communication/information sharing purposes were positive. Of parents, 80% (16/20) said that they would use an app to send information about their child to their child's doctor. One parent pointed out the benefit of having asthma information in an app form, over paper, so that the information is in one place to be pulled up and easily shared. One clinician stated,

> *As a nurse, I would love to communicate with my patient through it. It's a better tracking device. Kids always have their phone in their hand.*

Clinicians felt that use of the app could lead to a better medical appointment both in terms of efficiency, patient-centered care, and decision making. Multiple clinicians expressed data security concerns (eg, insecure email) or differed in their preference for information delivery method; some preferred email, some preferred hand-delivery or hard copy print-outs, and others preferred the phone.

Table 2. Parent and clinician technology use.

Technology use	Parents	Clinicians
	n (%)	n (%)
Do you own a cell phone?		
Yes	18 (90)	6 (100)
Missing	2 (10)	-
Type of phone		
iPhone	9 (45)	6 (100)
Android	8 (40)	-
Other “basic”	1 (5)	-
Do you own any other Internet-capable device?[a]		
Computer	19 (95)	6 (100)
Tablet	7 (35)	5 (83)
iPad	4 (20)	4 (67)
Other (laptop)	1 (5)	1 (17)
Have you downloaded an app to a cell phone, tablet, or other handheld device?		
Yes	19 (95)	6 (100)
No	1 (5)	-
Have you ever downloaded a health-related app to a cell phone, tablet, or other handheld device?		
Yes	10 (50)	5 (83)
No	10 (50)	1 (17)
Have you ever paid to download an app?		
Yes	6 (30)	5 (83)
No	14 (70)	1 (17)
Have you ever avoided downloading an app due to concerns about sharing your personal information?		
Yes	11 (55)	2 (33)
No	9 (45)	4 (67)

[a]Participants could report owning more than one device.

Education

There were 75% of parents (15/20) who said that they would use an app to watch videos of correct inhaler technique, and 80% (16/20) would take asthma quizzes if they were part of the app. One clinician thought that the use of an app would serve to reinforce important concepts that they heard in the doctor’s office such as why daily controller medication is useful. Parents and clinicians thought an app would help reduce confusion about the difference between a rescue medication and maintenance medication. One clinician had this to say:

> *I think most of them engage in devices like this for entertainment, right? And so you want to have something that provides them an educational opportunity, um, but also something that they – they won’t get bored with.*

Table 3. App features and their relationship to self-management support.

App feature (major theme category)	Feature description	Parent and clinician example quotes
Diary (monitoring/supervision)	A place to review past asthma data entered for each day, including peak flows, selected symptoms and triggers (adult app).	Related theme: monitoring/supervision *Parent: I like the diary part because they can – I can see the days that they dipped, the days that were good. And then I can go back and see, okay, well, she was on a bad day on this day[….] You know, just kind of me being able to really see, you know, how she's doing, when, the how, when and where of how functions are actually doing.*
Chart (monitoring/supervision)	At-a-glance, graphical view of peak flow meter readings (adult app).	Related theme: monitoring/supervision *Clinician: So if you're utilizing peak flow, I think that's good, um, and if you don't have a sense of where you typically run, having this long, longer, um, snapshot of what. your peak flows typically are could be helpful.*
Self-check quiz (monitoring/supervision, education)	Seven questions that assess asthma control and output a numerical score telling the user how well-controlled their asthma is and to discuss the results of quiz with caregivers and physician (child app).	Related theme: education *Parent: I think it, it's a good teaching tool for him.*
Allergies and emergency plan (monitoring/supervision, education, communication/ information sharing)	A place to document emergency contact and doctor's phone number, best and recent peak flow records, allergy medications and dosage, and an allergic reaction plan (child app).	Related theme: education *Clinician: Um–, we give patients an asthma action plan, but if that's sitting at home on the refrigerator and they're out at the grocery store and they don't remember what they're supposed to do having something that's right there with them...I think, um, would be really useful.*
Doctor appointment reminder (monitoring/supervision)	Enter doctor's appointments in icalendar (ical) to receive a text reminder (child app).	Related theme: monitoring/supervision *Parent: That's good because – so I don't forget. I don't forget the, the appointment, that – that's good.*
Medication reminder (monitoring/supervision)	Allows user to enter daily and emergency medications, input times they take their medications in ical, and then request a daily text reminding them to take their medication. Alerts user when it is time to take their medications (adult app). Allows users to drag and drop the medication into the open mouth of a monster to verify that medication has been taken (child app).	Related theme: monitoring/supervision *Clinician: Um, I think tracking medications is critical, and reminding –having a feature within the app that you can remind patients to take their medications and also track when they actually took them. So, you know, like you – where they – the app feeds the med to the monster's mouth I think that's really useful.*
Asthma triggers (monitoring/supervision, education, communication/information sharing)	A place for selecting triggers from a preexisting list as well as a place to add custom asthma triggers [adult app].	Related theme: monitoring/supervision *Parent: It keeps the triggers of what triggers her asthma in front of us. Um, so we know what we're looking for and how she might turn out that day just because of the weather or because she had to do certain exercises, um, so that reminds us to keep her rescue inhaler with her during, um, those different times.*
Doctor report (monitoring/supervision, communication/information sharing)	Allows patient to share asthma record with care team by sending an email to them through the app to view record (adult app).	Related theme: communication/information sharing *Clinician: If I had a patient that could send me information on if they were doing...peak flow, what it's been and what your symptoms have been in the last two weeks, like...that would be really easy for me to, um, say, "You need a visit, we need to up your control or we need to,- whatever.*
School form (communication/information sharing)	Physician approval forms that allow students to possess and use an inhaler in school. Form can be emailed from the app to the physician. Physician can print form or fill it out electronically and email to child's school (child app).	Related theme: communication/information sharing *Clinician: That saves us some [time], and plus they have a copy and it goes straight to the school. And everyone is on the same page.*
Peak flow (Monitoring/supervision)	A place where one can enter their daily peak flow measurements. The information can be relayed to chart and visualized in graphical format (adult app).	Related theme: monitoring/supervision *Parent: That part's really not useful to us…cause she doesn't have to do peak flows on -- on a regular basis, so, um, we only do those when she's had an attack and then they want us to keep track of them for a week and then she doesn't have to do them anymore.*

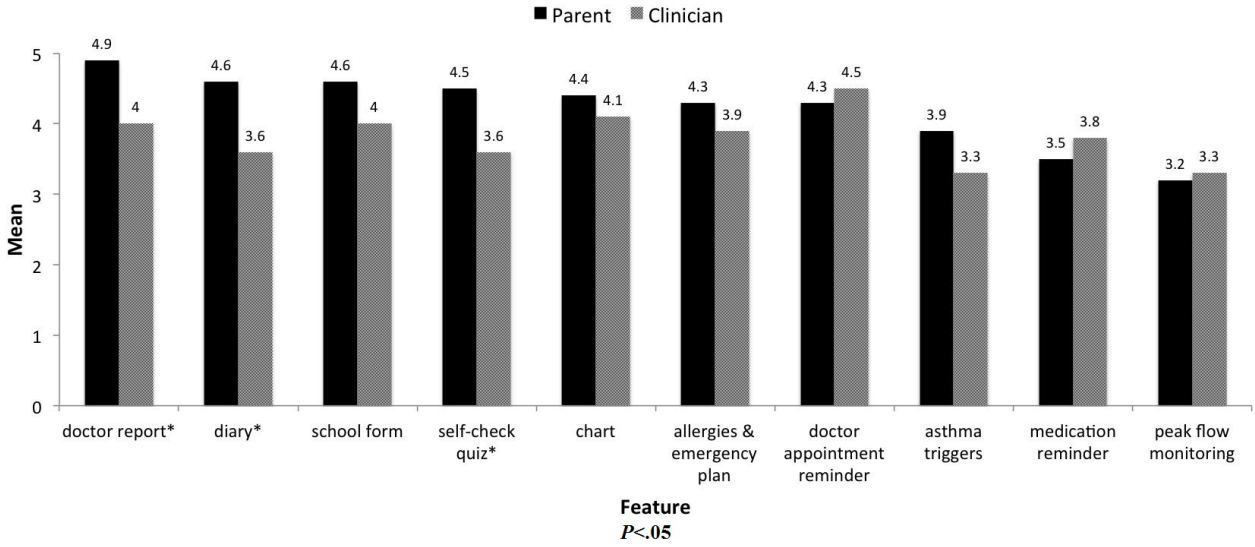
App Features

Table 3 provides a list of the app features that parents and clinicians evaluated. Feature descriptions are also provided as well as example quotes associated with major theme categories (monitoring/supervision, education, communication/information sharing) for each feature. Monitoring and supervision was discussed in relationship with 9 of 10 app features. Communication/information sharing was discussed in relationship with 4 of 10 app features. Education was discussed in relationship with 3 of 10 app features.

Perceived Usefulness of App Features

Figure 1 presents the usefulness of app features as ranked by parents (ordered highest to lowest) and clinicians. Parents rated the doctor report highest (4.9/5) and clinicians rated the doctor appointment reminder highest (4.5/5) of all app features on usefulness. The peak flow feature was the lowest ranked feature by both parents (3.2/5) and clinicians (3.3/5). Parents reported higher usefulness for the doctor report ($t_{(10)}$=2.7, P<.02), diary ($t_{(10)}$=2.7, P<.03), and self-check quiz ($t_{(14)}$=2.5, P<.02) features than clinicians.

Figure 1. Parent and clinician app feature usefulness rankings (note: mean feature usefulness ratings on a scale of one to five; 1=not at all useful to 5=very useful).



Impressions of App Features

Diary and chart feature. Most parents and clinicians believed the diary and chart were crucial features for management of the child's asthma. One parent suggested improving the diary and chart features by adding a tagging feature to identify problem times of the year, where greater vigilance may help avoid an emergency room visit. One clinician felt that the existing diary feature does not assist with management and "the ideal tool would take kind of what you're on, where you fall in your critical level, and give a re-, a recommendation."

Self-Check Quiz Feature

Regarding the self-check quiz feature, one clinician said that "[k]ids are involved. They are more willing to be self-advocates for themselves." One parent felt that the quiz was a helpful daily check to help her child better control his asthma. However, one parent said she didn't know how valuable the feedback from the feature was and didn't understand its purpose. Another parent felt it lacked long-term asthma monitoring capability because it didn't save the results after showing the rating. One clinician stated that they would love to see the self-check quiz replaced with a validated measure of asthma control such as the Asthma Control Test and to also have the test result linked with clinical management steps for the patient, for example, "[i]f it's low then you should call your doctor."

My Allergies and Emergency Plan Feature

Parents stated that my allergies and emergency plan was a feature that would be helpful especially in places outside the home such as school. One parent stated the plan would allow her to "feel a little more at ease" knowing that her child would "have his emergency contacts right there in front of him." In terms of communication, one parent liked that her child could show his basketball coach the plan so the coach would know what types of medicines he takes and when he takes them. One clinician brought up the benefits of using the feature for "engaging with them [patients]" including jointly inputting information into the plan and/or discussing what patients have previously input to ensure they are getting the correct guidance, especially regarding emergency situations.

Doctor Appointment Reminder Feature

Parents described the doctor appointment reminder feature as beneficial in helping them remember their child's medical appointments, which several parents said they sometimes forgot. The majority of clinicians saw it as crucial to ensure that their patients are staying on top of their asthma care. Multiple clinicians mentioned that appointment noncompliance is a problem, one stating that "[a]ny extra reminder that families have that they have an appointment I think is helpful." However, the feature was also criticized by parents for its lack of integration into the app. One nurse offered a suggestion for improvement when she said,

> *If there was a way that mom can put it on parental controls and schedule the appointment or cancel the appointment and talk to our systems that will be a good thing as well too.*

Medication Reminder Feature

Some parents saw value in the medication reminder feature in helping their child keep track of taking their asthma medicines. However, one parent stated that medication reminders would only be useful for adolescents who can't remember to take their medication. Some parents stated the medication reminder feature could be improved with an alarm. Most clinicians felt that the medication reminder feature would help their patients a lot, particularly with their controller medications, as they saw medication nonadherence as an important clinical issue.

Asthma Triggers Feature

Although one parent spoke positively about the trigger feature, this feature was more often criticized by parents and clinicians because of its lack of long-term monitoring and feedback capabilities. One clinician expressed the opinions of other participants when stating, “I don’t know what you’d [do] with it. Other than just be aware of it.” One parent suggested the asthma triggers feature be changed to provide trigger avoidance information when you click on each trigger. The inclusion of a global positioning system feature was also mentioned by one parent in order to track air quality by zip code. Related to communication, parents stated that the asthma triggers feature may prompt communication with the clinician and be beneficial in communicating a problem to others.

Doctor Report Feature

Parents expressed interest in being able to send updates to the doctor. Clinicians cited the feature as potentially good for monitoring their patients' asthma and determining next clinical steps. Related to communication, participants were generally supportive of the idea of using the doctor report feature as a way of collecting important clinical information, conveniently sending it to the doctor, and opening a communication channel. However, clinicians mentioned specific communication-related concerns including the Health Insurance Portability and Accountability Act (HIPAA) and security concerns, not wanting to be handed the report by families in clinic, or seeing the feature as impractical with difficulties getting it to interface well with office technology and to link to a patient chart.

Peak Flow Feature

Parents who did not find it useful said that they either did not use or rarely use a peak flow meter (a device used to measure how well air moves out of the lungs). Clinicians expressed some reservations to patient peak flow use, including worrying about the adolescent obtaining an accurate peak flow reading. One clinician would be interested in having patients blow into a device attached to the app to get an accurate peak flow.

School Form Feature

Some parents and clinicians felt that communicating asthma care between various entities using the school form feature would be very convenient. However, participants highlighted barriers to use including lack of applicability in which “not every school form is going to be the same” and “a lot of the schools want you to have–have the name of the school on it or the county on it.”

Suggestions for New App Features or Components

One parent suggested adding additional reminder features to the app that would let their child know when to clean their spacers and when their medications need to be refilled. One doctor suggested pop-up messages tied to a medication log that would prompt patients with tips to improve medication use as well as setting the app to push automatic messages each day asking the patient about medication adherence and symptom levels.

In terms of education, parents stated that it would be helpful to have a frequently asked questions section, a visual library or location to display helpful tips, a tutorial showing the correct way to use an inhaler, and more specific information regarding asthma and medications, such as causes and treatments. Clinicians suggested including education for adolescents and their parents about asthma and asthma management, such as a section with pictures showing disease and medication information.

Discussion

Principal Findings

This study provides wide-ranging insight into how parents and clinicians perceive asthma app self-management features. We specifically explored how apps can involve these individuals who play key roles in the development and support of adolescents’ self-management skills [23], an endeavor few studies have undertaken [14-16]. With only 1 in 5 parents reporting ever having used an asthma app prior to this study, and to our knowledge, no app existing for adolescents that have both parent and clinician support features [12,13], we were able to gather valuable potential end-user feedback. Parents and clinicians in this study saw potential in using an asthma app related to three main themes: asthma monitoring and supervision, communication and information sharing, and education.

Although parents felt that their use of the apps for 1 week helped them better monitor their child's asthma, our findings that less than half believed the apps helped them better control their child’s asthma or follow doctors’ advice better were not surprising given that they were tasked with simply exploring the various feature of 2 existing apps. Further, neither of the 2 evaluated apps contained doctors’ advice or were equipped with specific components designed to actively involve parents or clinicians. While participants saw value in various features, such as the self-check quiz and asthma triggers, several critical comments revealed that the purpose of some of the features was not clear and several features lacked long-term asthma control and feedback capabilities.

Parents and clinicians provided generally positive feedback in terms of the apps potential for enabling communication and information sharing (eg, between clinician, parent, adolescent, and other social network members). This finding is important because research shows that adherence to treatment among

adolescents with asthma is associated with adolescent's perceived support (including self-management encouragement) from doctors [24]. Additionally, increased parental perception of increased parent-doctor communication has been linked to fewer pediatric office visits [25].

While participants saw the app as a device that simplified storing and tracking information as well as promoting data sharing, clinicians expressed some concerns about data transfer and security. Schneider et al [16] found that doctors perceived similar benefits (eg, a channel for accurate and credible information, a way to promote communication to engage adolescents in disease care) and barriers (eg, protection of personal medical information and security risks) related to using an asthma app as a way to connect with patients. Apps are often designed without enough or appropriate security and privacy measures in place to protect users' health information [26]. There are numerous options for safeguarding health information and creating HIPAA compliant apps that allow for efficient and convenient data transfer [27] and these should be incorporated into new adolescent asthma app designs.

Regarding the theme of education, clinicians saw the app as a valuable forum through which to educate adolescents and a place to reinforce what was said in the doctor's office. Parents talked in terms of the app as a teaching tool for the child, to enhance their own knowledge as well as a utility to provide education to others in the child's social circle. Collectively, these findings plus theme findings related to monitoring/supervision and communication/information sharing offer support for integrating information, decision support, and social support components, a needed methodological app template [11].

The knowledge that their child would have an app with an emergency action plan available (when needed) eased parental concerns. This finding concurs with another study showing parents believed their own anxieties would be relieved with better asthma control on the part of their children [15]. An app may be a useful device to promote treatment planning during office visits, as doctors rarely discuss action plans with children and their caregivers [28].

Interestingly, neither parents nor clinicians talked about the medication reminder feature in relation to them using the feature to assist the youth in any way, likely in-part, because the youth were teenagers rather than younger children. Findings that clinicians rated the medication reminder as the most useful feature are supported by another study showing that physicians believed medication reminders would assist adolescents in following their asthma action plan [16]. Parents ranked the reminder feature lower than clinicians, and in this example, where usefulness ratings differ among parents and clinicians, incorporating both views may lead to a design decision to allow users to hide the medication reminder feature, based on user preference. These and other study findings based on different stakeholder perspectives support research suggesting the need for a team approach involving parents and health professionals in the design, development, and evaluation of adolescent-centered asthma self-management apps [23]. Adolescents' perspectives should also be considered in such design and development decisions [14,15,17,18,29-32]. Findings from our parent study show adolescents with asthma feel that asthma apps can positively influence their self-management behaviors and the majority of adolescents believed apps could enhance communication with their caregivers and medical providers [17,18].

Finally, parents and clinicians offered valuable suggestions for app improvements and new apps features. Participants thought that an app could be more useful if data entry was encouraged in a more consistent manner (eg, daily prompts encouraging specific input) and data output provided in a more useful and engaging way. Other studies have found that both parents and physicians think refill reminders would be helpful [15,16] and parents in one study embraced weather condition alerts that related to asthma trigger risk [15]. The need to ensure the use of validated measures was also suggested pointing to the need for evidence-based app content, something that is currently lacking in existing asthma apps [33,34]. Specific suggestions for new educational app components or features highlight valuable participant ideas that should be considered for incorporation into future adolescent asthma app designs.

Limitations

The use of a convenience sample of parents and clinicians, the different interview modalities, the small sample size, and exploratory nature of this study limits our ability to generalize results to the larger population, especially to families and providers in rural areas who may have less access to cellphones [35]. Parents used the 2 asthma apps for a 1-week period and clinicians used them for 10-15 minutes, so they had real-world experience with the apps to inform their opinions about the usefulness and effects of various features. It is possible that giving both groups a longer period of time to use the apps would have yielded additional insights related to using the asthma apps. Several participants discussed having technical difficulties with various features, which limited their ability to provide detailed information in some cases. Also, although the 4 parents that did not complete the 1-week follow-up interview did not appear demographically different from the parents who completed the study, selection bias could have affected our results. Lastly, parent and clinician ratings of feature usefulness could have been inflated due to social desirability bias.

Implications

An app that allows adolescents to optimally engage clinician and parent support could potentially improve adolescent self-management by allowing adolescents to obtain support in between doctors' appointments [36]. The current study identified several features that may enhance and improve the ability of parents and clinicians to support adolescents as they self-manage their asthma. Incorporating components and features informed by the socioecological model or other frameworks that increase attention to social factors influencing adolescent's engagement in asthma self-care (including two-way asthma care communication between families and clinicians and components involving families and clinicians that encourage adolescent self-management) will likely impact patient care and asthma outcomes, such as medication adherence and asthma control. Well-designed asthma apps have a great deal of potential to benefit adolescents with asthma and enhance asthma

service–delivery processes as they are cost-effective, convenient, easy to access, and can be tailored to individual needs. More research is needed to compare and evaluate various aspects of intervention use and efficacy (eg, patient management, usability, acceptability, adoption, clinical outcomes) of newly designed apps.

Conclusions

This study was conducted to inform the development of future asthma apps in order to engage important stakeholders who interact with adolescents to assist in asthma management and promote self-management skills. These findings provide valuable insight and revealed potential app and app feature requirements that were expressed as three main themes: monitoring/supervision, education, and communication/information sharing. Involving parents and clinicians in asthma app planning, development, and intervention activities is likely to result in more widely accepted, understood, and effective adolescent asthma self-management apps [23,36].

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Conflicts of Interest

None declared.

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Abbreviations

HIPAA: Health Insurance Portability and Accountability Act
RA: research assistant

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Protocol

Data-as-a-Service Platform for Delivering Healthy Lifestyle and Preventive Medicine: Concept and Structure of the DAPHNE Project

Catherine Gibbons[1], PhD; Gonzalo Bailador del Pozo[2], PhD; Javier Andrés[2], MSc; Tim Lobstein[3], PhD; Melania Manco[4], PhD, MD; Hadas Lewy[5], PhD; Einat Bergman[5], MSc; David O'Callaghan[6], PhD; Gavin Doherty[6], DPhil; Olga Kudrautseva[6], MA; Angel Palomares[7], BSc; Roni Ram[8], MSc; Alberto Olmo[9], PhD

[1]School of Psychology, University of Leeds, Leeds, United Kingdom
[2]CeDInt, Technical University of Madrid, Madrid, Spain
[3]World Obesity Federation, London, United Kingdom
[4]Bambino Gesù Children's Hospital, Rome, Italy
[5]Nevet Ltd, Tel-Aviv, Israel
[6]SilverCloud Health Ltd, Dublin, Ireland
[7]Atos Research and Innovation, Madrid, Spain
[8]IBM Research, Haifa, Israel
[9]Treelogic SL, Madrid, Spain

Corresponding Author:
Catherine Gibbons, PhD
School of Psychology
University of Leeds
Leeds,
United Kingdom
Phone: 44 1133435753
Fax: 44 113 343 6674
Email: c.gibbons@leeds.ac.uk

Abstract

Background: Overweight and obesity is related to many health problems and diseases. The current obesity epidemic, which is a major health problem, is closely related to a lack of physical activity, high levels of sedentary behavior, and increased energy intake; with evidence to show increasing incidence of these issues in the younger population. Tackling obesity and its comorbid conditions requires a holistic approach encompassing attention on physical activity, healthy diet, and behavioral activation in order to enable and maintain meaningful and long-term weight loss and weight maintenance.

Objective: The objective of the Data-as-a-Service Platform for Healthy Lifestyle and Preventive Medicine (DAPHNE) project is to develop a breakthrough information communications technology (ICT) platform for tracking health, weight, physical activity, diet, lifestyle, and psychological components within health care systems, whereby the platform and clinical support is linked.

Methods: The DAPHNE platform aims to deliver personalized guidance services for lifestyle management to the citizen/patient by means of (1) advanced sensors and mobile phone apps to acquire and store continuous/real-time data on lifestyle aspects, behavior, and surrounding environment; (2) individual models to monitor their health and fitness status; (3) intelligent data processing for the recognition of behavioral trends; and (4) specific services for personalized guidance on healthy lifestyle and disease prevention. It is well known that weight loss and maintenance of weight loss are particularly difficult. This tool will address some of the issues found with conventional treatment/advice in that it will collect data in real time, thereby reducing reliability issues known with recalling events once they have passed and will also allow adjustment of behavior through timely support and recommendations sent through the platform without the necessity of formal one-to-one visits between patient and clinician. Patient motivation/compliance is a particular issue with conventional weight loss regimes; DAPHNE aims to increase the individuals' awareness of their own behavior and fosters their accountability.

Results: The project has been funded and the research work has started. Results for the validation of the different components is due imminently.

Conclusions: In contrast with previous existing solutions, the DAPHNE project tackles the obesity problem from a clinical point of view, designing the different interfaces for its use by patients (adults and children), physicians, and caregivers. A specific design for children and adolescent patients treated for obesity has been followed, guided by pediatric physicians at hospitals in Europe. The final clinical validation of the DAPHNE platform will be carried out in different European hospitals, testing the platform in both adolescents and adults.

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KEYWORDS

information communications technology; clinical weight management; physician and patient portal; obesity; physical activity; advanced motion sensors; behavior change

Introduction

The DAPHNE Concept

The prevalence of overweight and obesity across Europe is high, with rates doubling during the last few decades in several countries. More than 50% of the total European adult population is now overweight (body mass index [BMI]>25 kg/m^2) and obesity levels (BMI>30 kg/m^2) of adults in many Member States on average exceed 20% [1]. Data from several studies suggest that childhood obesity has also increased steadily in Europe over the past two to three decades. In Europe, almost 20% of children are overweight or obese [2]. The highest prevalence levels are observed in southern European countries [3]. Both in young and adult populations, obesity is now therefore regarded as one of the most important determinants of avoidable burden of disease. From our knowledge, there are 2 commercially available products similar to the Data-as-a-Service Platform for Healthy Lifestyle and Preventive Medicine (DAPHNE) concept. “Retrofit” [4] is the provider of corporate weight loss programs and “Omada” [5] is designed to help individuals lose weight. Both are largely aimed at behavior change and the combination of exercise physiologists and dietitians. These 2 products have been successful and a number of characteristics are similar to those proposed by DAPHNE. However, the major difference is that DAPHNE is being designed as a system to be used between a physician/caregiver and the patient having taken into account the privacy and security aspects of this scenario.

The DAPHNE Approach

A holistic approach is required when investigating obesity, both energy expenditure and energy intake are important. There is irrefutable evidence of the effectiveness of regular physical activity in the primary (preventing disease in the first place) and secondary prevention (halting/slowing the progress of disease) of several chronic diseases (eg, cardiovascular disease [CVD], diabetes, cancer, hypertension, obesity, and osteoporosis) [6], and the more activity people partake in the more the risks of ill-health are reduced [7]. There is little doubt in the adult population that high levels of physical activity are associated with reduced risk of type 2 diabetes, CVD, and premature mortality [8-10]. There have been some longitudinal studies examining the effect of physical activity and fitness during the early years on CVD risk later in life. Overall, these studies agree that high levels of physical fitness during adolescence and young adulthood are related to healthy CVD risk profiles later in life; however, physical activity appears to have little influence later in life. Steinbeck et al [11] have shown cross-sectional evidence linking physical inactivity to the development of obesity in children, but as of yet there is little evidence showing physical inactivity preceding the weight gain. Exercise is likely to be most effective in controlling childhood obesity when it is combined with appropriate dietary changes [12]. Furthermore, there are a number of diets advocated in the literature to be successful for weight loss and weight maintenance [13,14]. Overall, the Mediterranean diet is often seen as the best diet to follow at population level [15,16]. All diets have an element of control, whether it be low fat, low carbohydrate, at least 5 pieces of fruit and vegetables, and so on. Governmental agencies across Europe have guidelines for dietary advice in place and it will be these that are followed within the DAPHNE project [15,16].

In addition to the metabolic and physiological benefits of exercise and physical activity, there is growing evidence that exercise can be effective in improving the mental wellbeing of the general public, largely through improved mood and self-perceptions. These are often major concerns in those with weight or obesity problems. Because the concept of the DAPHNE project is a holistic approach, we have decided to add the functionality to measure psychological wellbeing. It is generally assumed that exercise also exerts a positive effect on psychological functioning (ie, reduction in symptoms of depression, anxiety, stress, and negative mood states) and previous studies corroborate this assumption. It has been demonstrated that there is an inverse association between physical activity and likelihood of depression, mainly considering higher levels of physical activity (as recommended in physical activity guidelines), but also at lower doses [17,18]. There is evidence suggesting positive effects of exercise on depression in intervention [19,20], cross-sectional [21], population-based [22], and cohort studies [23-25], indicating that participation in exercise could be an important target of mental health treatments. Further to this, exercise has been shown to be effective as a treatment for clinical depression [26] and anxiety in both adults [27] and adolescents [28].

Both energy expenditure through exercise/physical activity and energy intake through food consumption are deemed important in the control of energy balance. There is a plethora of studies looking at the role of diet in obesity and advice doctors provide is typically based on the country’s policy in this area. Specific dietary guidelines of less fat, more fruit and vegetables, and so on are commonplace; the DAPHNE system and mobile apps will be built with these standards. Therefore, the aim of the

current project is to design and develop information communications technology (ICT) platforms that will enable the monitoring, intervention, and follow-up of health behavior using measurement and tracking of both energy expenditure and energy intake, along with anthropometric variables, health markers, and psychological status. Furthermore, a secondary aim of this project is to design the platforms for clinical use and to improve the link between physicians (and their care team of nutritionists, physiotherapists, etc) and their patients and have an additive effect to usual treatment.

The last decade has seen growing popularity and uptake of self-monitoring technology including wireless sensor devices and mobile apps for tracking physical activity, sedentary behavior, sleep patterns, diet, and stress. However, their application as a means of monitoring and motivating out patients in health service settings remains to be developed and the application and interaction between the care provider and the patient using innovative ICT tools for health behavior change is limited, and there is currently no system that enables involvement of both parties in the process of preventive medicine. Furthermore, the system will be developed for use by both adolescents and adults with input of physicians regarding the different requirements of both population groups. DAPHNE is a collaborative European research project. The objective of the project is to develop an innovative ICT platform toward a holistic approach for weight management through measurement and tracking of physical activity, diet, lifestyle, health, and weight over time and validate the use of this platform in clinical settings, assessing the acceptability of the proposed solutions and the benefits for physicians and patients. The present manuscript aims to identify and explain the structure of the DAPHNE platform including full details about the data input and output that will be provided.

Methods

Overview of the Architecture

The objective of the DAPHNE project is to provide the services for patients within health care systems, but also for the wellbeing of users who would not be linked to a health care physician. For the purpose of this manuscript, only the version developed for the health care system will be discussed because it is, to our knowledge, the only model to do so (Figure 1). The Personal Health Services (PHS) of the DAPHNE project are provided through 3 pathways: the PHS portal, the mobile phone apps, and the physician application in order to assist in the provision of continuous, quality-controlled, PHS (Textbox 1). These services can be implemented in a wide variety of environments, such as hospitals, clinics, sports teams, and ultimately, in any environments that have external health advisers/trainers/coaches and/or end users that need or decide to lead a healthy lifestyle.

Textbox 1. How the developed services are provided.

1. Personal Health Services (PHS) Portal:

This is the access point for patients and caregivers (Figure 2). It consists of a Web-based app where users can check and see their information in the platform. This tool allows users to control their health information, motion sensor analysis, and receive personalized recommendations. In order to facilitate the usability of the portal and aid the insertion of data, some PHS services will be based on information provided or collected through mobile phone apps.

2. Data-as-a-Service Platform for Healthy Lifestyle and Preventive Medicine (DAPHNE) mobile phone apps:

These apps allow users to enter their nutrition data (via mobile and Web interfaces, connected to the European Food Information Resource (EuroFIR) [29] nutritional database) and monitor their physical activity (through the DAPHNE sensors, aggregator app, mobile, and Web interfaces); the subjects can also fill in physical activity questionnaires (standardized questionnaires via the Web interface/mobile app) and answer psychological questionnaires (through standardized questionnaires, via mobile and Web interfaces).

3. Physician application:

This is a Web portal and is the interface between the physician and DAPHNE System. It allows physicians to follow-up with their patients in an efficient and innovative way. All the information on a particular patient is centralized in this portal and facilitates the analysis to be performed by the caregiver. This tool also provides options to allow settings for the patient's physical activity, goals, coaching messages, and so on. Furthermore, the physical activity module also enables sending the subjects educational material promoting a healthier lifestyle.

Figure 1. Overview of Data-as-a-Service Platform for Healthy Lifestyle and Preventive Medicine (DAPHNE) architecture.

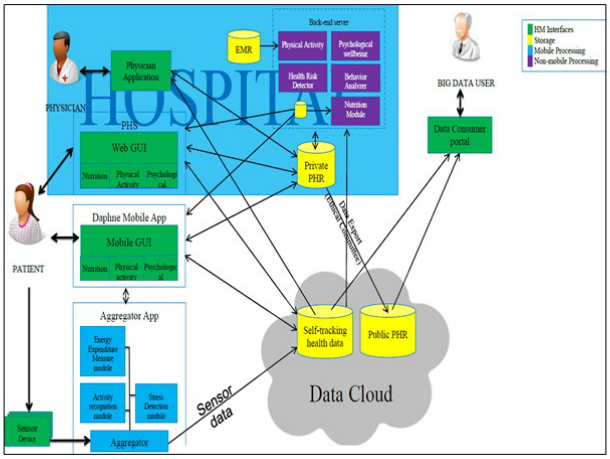
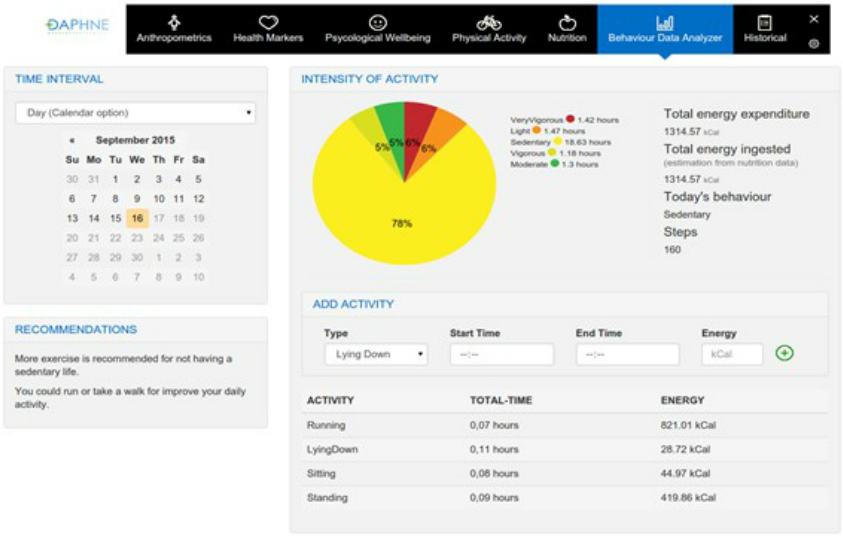


Figure 2. Screenshot of the Data-as-a-Service Platform for Healthy Lifestyle and Preventive Medicine (DAPHNE) personal health system.



DAPHNE Physical Activity and Physiological Sensors

Alongside the ICT platform within the DAPHNE project, there is also the development of an innovative physical activity and physiological sensor. There are a number of devices available on the market that measure physical activity behavior. At present, there are a number that would be considered commercial devices and only a few that would be considered “research grade” standard. One of these devices is “Empatica,” which is a wristband that provides raw data from sensors instead of processed signals. This device is able to capture the following parameters at a high acquisition rate: heart rate, skin conductance, temperature, heat flux, and movement. The DAPHNE sensor device is one of several main innovations of the DAPHNE project and it aims to go beyond what is already available. The sensor device pushes the implementation of sensor and communication technology beyond current state of the art technology, by combining many functions (it measures and classifies physical activity, heart rate, and galvanic skin response) within a very small device (Figure 3), for a more precise energy consumption and stress estimation, and by streaming raw measurement data at a very high data rate over low-energy Bluetooth. This enables data to be uploaded automatically and immediately visible in the PHS by both the user and the caregiver.

The sensor has implemented advanced algorithms for the detection of different activities (such as running, walking, lying, or sitting), estimating the energy consumption and measuring stress. The sensor has recently achieved the CE certification for its use in clinical environments. Initial validation studies have been implemented comparing this sensor with other research grade sensors, and also to gold standard measurements of energy expenditure. Results of the validation studies will be presented in further scientific manuscripts.

An aggregator app has also been developed for the connection of the sensor with the Daphne Data Cloud, allowing also the interoperability with other Continua Alliance physical activity sensors.

DAPHNE Data Cloud

The Daphne data could provide the storage of user data (1) in the cloud, which includes the Public Personal Health Record repository and the Self-Tracking Health Data Repository; and

(2) in the hospital facilities, which includes a Personal Health Record repository for each hospital. The separation into 2 different repositories intends to address privacy and security regulations that prevent the user data from leaving the care giver facility. The data cloud manages the data and provides access to user data only to authorized users.

In addition, the user data in the data cloud can be retrieved for secondary use in research as anonymized data sets subject to user consent policy and under preservation of intellectual property rights.

Figure 3. Activity sensor developed in Data-as-a-Service Platform for Healthy Lifestyle and Preventive Medicine (DAPHNE).

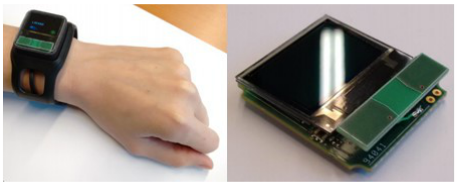
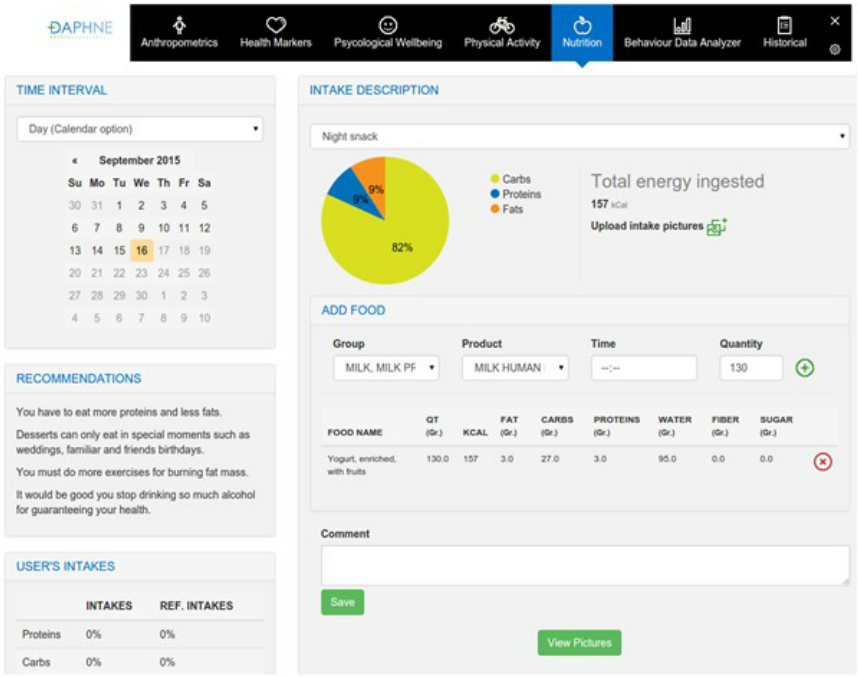


Figure 4. Screenshot of the nutrition section within the Data-as-a-Service Platform for Healthy Lifestyle and Preventive Medicine (DAPHNE) user portal.



Functional Requirements

The authentication procedures for patients are that they will only be able to register via their physician through the physician portal. On any occasion of use, the PHS will require login details (username and password) to ensure security of data (further details on security are explained later in the manuscript). All users of the system must opt-in and consent to anonymous data analysis (big data processing capabilities) before any data is uploaded to the cloud from the mobile or the user/physician portal; however, they will be able to opt-out at any time. The idea for the anonymous big data processing functionalities is to enable data analytics by the health care and research organizations involved, and perhaps in the long term to share these data with other organizations interested in public health, scientific research, health marketing, or pharmaceutical research.

Input and Output Data

To achieve semantic interoperability, uniform data representation has been taken into account within the formulation and planning of the DAPHNE system. Terminology systems are used to transform descriptions and values of medical data into universal medical code numbers to achieve an unambiguous understanding of the meaning while the data is transferred from one place to the other. These coding systems (ie, Systematized Nomenclature of Medicine—Clinical Terms, etc) are used for a variety of domains: for example, medicine, public health, and medical informatics.

There are country specific and international classification systems. Internationally endorsed classifications facilitate the storage, retrieval, analysis, and interpretation of data. They also permit the comparison of data within populations over time and between populations at the same point in time as well as the compilation of nationally consistent data.

To address the health information system interoperability needs, DAPHNE will use continuity of care documents (CCD) to export data. CCD is currently one of the most frequently used interoperability standards and it is human-readable using any standard Web browser.

Anthropometrics and Health Markers

In order to have the most comprehensive view of the user/patients health and behavior, there are a number of categories of input data within the DAPHNE system—anthropometrics, health markers, nutrition, physical activity, and psychological wellbeing. Not all input data will be available for each patient, therefore there is limited compulsory data required and the automatic analysis and recommendations will rely on as little data as possible. The DAPHNE system is configured to provide cut-points based on available clinical guidelines. Firstly, anthropometrics (age, gender, height, weight, waist and hip circumference, fat mass, and fat-free mass) and health markers (blood pressure, cardiovascular fitness, smoking status, fasting glucose, diabetic status, familial history of diabetes, HBA1c, triglyceride levels, medications, and cholesterol levels) can be entered into the PHS. Embedded within the analytics of the DAPHNE system will be the capability of calculating BMI, for example, and then the system will alert the user of their BMI compared with clinical cut points. The same is true for body fatness and a number of health markers. Data can be viewed as a single entry, but also tracked over time periods of 7 days, 14 days, 1 month, and 3 months.

Nutrition

The user/patients nutrition assessment will be entered and analyzed via the nutrition app designed within the DAPHNE project. An estimation of energy requirements will be calculated using validated equations [30] by the DAPHNE system based on the anthropometric information of the user plus the energy expenditure from the motion sensors. The app works with the European Food Information Resource (EuroFIR) Database [29]. EuroFIR is a member-based international nonprofit association of food composition data compilers, expert users, and stakeholders, based in Belgium. EuroFIR continues in activities established by a successfully completed EuroFIR project, a 5-year Network of Excellence funded by the European Commission's Research Directorate General under the "Food Quality and Safety Priority" of the Sixth Framework Programme for Research and Technological Development. The EuroFIR database contains food composition information, such as energy, macronutrients (eg, protein, carbohydrate, fat), and their components (eg, sugars, starch, fatty acids), minerals and vitamins of approximately 15,000 food items from different countries within Europe (United Kingdom, Italy, the Netherlands, Spain, Denmark, France, Norway, etc) and the United States. The app will learn from user preferences, facilitating the introduction of food intake to the system. The data required for input includes the food item in grams and the intake description (breakfast, morning snack, lunch, afternoon snack, dinner, evening snack). The app offers the possibility that users can personalize the type of food intake they generally have, adapting to the volumes usually eaten and mixing different foods in personalized meals. Users will be asked to input their food intake after each occasion of consumption of food or drinks. However, in some instances this may not be possible, therefore functionality within the system will enable the user to enter the information retrospectively. In the user portal, the user will then be able to see the analyzed data regarding their dietary intake. For each day, the user can see the nutritional information about his/her food intake. Then, a summary is presented by the system and a complete report is available. In this report, the good behaviors of the user are emphasized and recommendations about bad habits are given. The idea is that the physician and user can manage and track their nutritional behaviors. A special design has been followed for children and adolescents patients with the support of Ospedale Pediatrico Bambino Gesú; (eg, hiding calorie intake information to patients), in order to avoid possible psychological problems in the use of the platform and providing the right type of messages for children and adolescents.

Physical Activity

The Department of Health (UK) recommended levels of physical activity are at least 150 minutes of moderate intensity physical activity in bouts of 10 minutes or more per week (for example 30 minutes in 5 days or more) [31]. Sedentary behavior has traditionally been used to describe low levels of moderate to vigorous activity. However, the term sedentary behavior from the Latin "sedere" (to sit) has now been categorized as an independent behavior of interest. In this emerging field, sedentary behavior describes a class of activities that have both a low-energy expenditure typically ≤1.5 metabolic equivalent thresholds, and a sitting or reclining position [32-34]. "Inactivity," on the other hand, should be used to describe those who are not performing sufficient amounts of moderate to vigorous physical activity [35]. There is building evidence that this sedentary behavior is adversely associated with a number of health markers, some relationships seen across the lifespan. The types and amount of sedentary behavior engaged in may be different in children compared with adults due to differences in how time is spent and choices made about leisure time versus obligatory activity [36], therefore it is important to consider these separately. It has also been demonstrated that sedentary behaviors increase and that physical activity decreases during adolescence [37], and this development of early sedentary behaviors may form the foundation for such behaviors in the future [38]. In this input category, sedentary behavior, physical inactivity, and physical activity will be categorized. Input data will be automatically uploaded from the DAPHNE sensor and aggregator providing information on energy expenditure, time in different intensities of activity, mode of activity, and frequency of activity performed. Energy expenditure will be calculated for the whole day and also activity energy expenditure (ie, removing energy expended during sedentary behavior). Time in sedentary behavior, light, moderate, and vigorous intensity activities will be categorized during waking hours. The type of activity will also be recognized (lying, sitting, walking, running, etc). These input data will be compared with the recommended physical activity guidelines and users will be advised on their current status (meeting recommendations for physical activity or physically inactive) and also be provided

with recommendations on how to improve (eg, reducing periods of sedentary time). Both daily and 7-day average activity pattern will be inputted into the DAPHNE system as an indicator of time spent in sedentary behavior and physical activity. People do not always perform the same amount of activity every day and weekdays may differ markedly to weekend days. The 7-day average is therefore a better indicator of lifestyle than 1 day on its own. Furthermore, users will have the option to add activities manually into the user portal in the case that physical activity devices are not worn. The physical activity module will enable caregivers to devise treatments plans for their patients, which include type and intensity of activity, time of activity, scheduling of activities, setting reminders, goals for duration, intensity, target heart rate, and so on. These programs are accessible by either mobile app or Web interface, allowing the patients to make minor adjustments to the training program, for instance choosing between activity types of the same intensity level. The physical activity module will also provide the user with an indication of hisher performance compared with the goal set by the care provider. The patient will receive reports from the system of his/hers physical activity. Those reports will have the option to be filtered and sorted, in order to provide the patient a tool to see his/her progress in physical status. If motion sensors are not available, physical activity will be monitored using validated questionnaires within the DAPHNE project using the physical activity module of the system.

Psychological Wellbeing

The DAPHNE system will be designed to capture assessments of psychological wellbeing via an app, which will incorporate many validated questionnaires to assess constructs, such as anxiety, stress, depression, and quality of life, among others. The DAPHNE system will be set up so that the physician can choose from a large library of validated questionnaires; the user will then receive a notification that the physician has requested they fill in particular questionnaires, which they can do within the psychological wellbeing app. The scoring outcomes have been automatically incorporated into the DAPHNE system so that the physician will be alerted to unfavorable scores on the questionnaires and will be able to deal with those in the correct manner. Again, scores can be tracked over time, but due to the nature of the questionnaires measuring trait characteristics of the person, it is unlikely that the questionnaires will be completed more than once per month. Furthermore, there will be an added functionality within the psychological wellbeing app where the user can type in journal entries, which can be seen by the physician.

Behavior

The final segment of the user portal will allow the user/patient to see an overview of their behavior—in terms of the food consumption and physical activity. Here, they will be able to view their physical activity in amounts of sedentary, light, moderate, and vigorous physical activity segments that have accumulated across the day alongside the accumulation of calories, fat, carbohydrate, and protein. Recommendations to increase the levels and intensity of activities performed and decrease intake of unhealthy foods will be sent automatically. In the case of patients, recommendations will only be sent after the approval of the physician. Physicians will have the capacity to provide personalized recommendations to the patient through the DAPHNE system. Users will be able to view data for a single day, or accumulated over 7 days, 14 days, 1 month, and 3 months in order to track their behavior change over time.

Privacy and Security

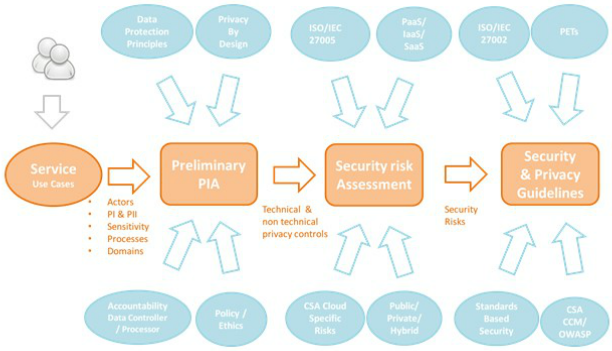
Due to the sensitive nature of the data used/processed by the DAPHNE project it was imperative to take into account the EU Data Protection and Electronic Communications Directives to comply with current EU data protection regulations; and further meet current General Data Protection Regulation principles.

Therefore, the Consortium adopted the use of the Privacy by Design (PbD) and Security by Design (SbD) paradigms into the development of the DAPHNE project. These paradigms incorporate privacy and security aspects from the earliest stage of the project and they can be defined as follows: (1) PbD is an approach to system engineering, which takes privacy into account throughout the whole engineering process; and (2) SbD is an approach to system engineering where measures to protect ICT assets have been designed throughout the whole engineering process.

The methodology used to achieve Privacy and Security by Default paradigms is shown in Figure 5.

There were 4 steps followed: (1) define the service and identify personal data collection, processing, and sharing; (2) early in the project, carry out a Preliminary Privacy Impact Assessment with respect to EU Data Protection Principles and the organization’s own data and ethical policies; (3) perform a risk assessment for the cloud architecture to be deployed; and (4) define the security controls and privacy guidelines for the system.

Figure 5. Methodology to be used to achieve privacy and security in the Data-as-a-Service Platform for Healthy Lifestyle and Preventive Medicine (DAPHNE) project.



Awareness

The majority of the security control mechanisms used within DAPHNE are imposed in order to comply with actual legislation. However, the awareness services go one step beyond the current legal constraints. The main aim of the awareness services is to keep the patient informed of the access made to their sensitive data. In order to do so, the system will track and audit every single access to the patient information. These services will provide them with a list of the different occasions of access, specifying who has made access, from which group or role, and the time of each access.

Results

The project has been funded and the research work has started. Results for the validation of the different components are due in March 2017.

Discussion

Overview of Progress

The aim of this paper was to describe and detail the structure of the DAPHNE ICT platform and fully describe the data that is required to be inputted into the system and the data that will be available to the user. The DAPHNE project will provide personalized ICT services for the prevention of overweight and obesity, taking into account anthropometry, health markers, food intake, physical activity, and psychological wellbeing. To our knowledge, this system will be the most holistic approach toward overweight and obesity in that it incorporates features from these different sections and allows them to be tracked and visualized simultaneously. Personalized sensors, models, and services will be developed, based on clinical requirements to increase physical activity, reduce sedentariness, and improve eating habits in order to initiate behavior change in a beneficial way for weight loss and maintenance. A particularly innovative feature of the DAPHNE system is that it is designed for use in clinical settings, providing an additional link between physicians and patients that does not require further appointments or face-to-face time. As a difference with previous existing solutions, the DAPHNE project tackles the obesity problem from a clinical point of view, designing the different interfaces for its use by patients (adults and children), physicians, and caregivers. Interoperability with existing medical systems and clinical standards has been taken into account, for its future deployment in public and private hospitals in Europe and worldwide.

Validation Procedures

There are several steps of validation that are planned as part of the DAPHNE project over the coming months and years. Firstly, the components of the system have to be validated to ensure they measure what they are supposed to. For example, the physical activity sensor will be validated against other highly validated devices and against gold standard indirect calorimetry measures of energy expenditure. Additionally, it must be ensured that all components of the system work together correctly, for example, the different mobile apps being developed must all link and show data consistently and correctly within the PHS part of the system. Initial feedback regarding the degree of motivation of the end users in the usability and feasibility of the system will be sought and evaluated at a primary endpoint of the DAPHNE project. Once the short-term studies are finalized in these areas and any problems are resolved by the technical partners in the project, the longer term objectives of DAPHNE will be studied. These include a clinical validation of the system in different European Hospitals (Ospedale Pediatrico Bambino Gesù [OPBG], Italy, and Maccabi Healthcare, Israel) with different end users in mind: (1) in OPBG, the system will be used by adolescents with obesity problems, under the supervision of their parents; and (2) in Maccabi, the system will be used by adults with obesity problems.

Both clinical trials will be conducted over 12 weeks and will compare the usual care provided to these obesity patients with the usual care plus the addition of the DAPHNE platform and physical activity sensor. Alongside comparison of the overall results in terms of clinical outcomes (markers of weight, body composition, and health), there will also be feasibility and usability questionnaires about the system in order to assess the patients' views of the platform. The planning for this project is detailed and strong with the consortium working hard in the funding process and planning stages of the project. We are looking forward to progressing through the different stages of the project and to publishing the details and results in the near future.

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Conflicts of Interest

None declared.

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Abbreviations

BMI: body mass index
CCD: continuity of care documents
CVD: cardiovascular disease
DAPHNE: Data-as-a-Service Platform for Healthy Lifestyle and Preventive Medicine
EuroFIR: European food information resource
OPBG: Ospedale Pediatrico Bambino Gesù
PbD: privacy by design
PHS: personal health services
SbD: security by design

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Protocol

Perivascular Adipose Tissue Inflammation and Coronary Artery Disease: An Autopsy Study Protocol

Daniela Souza Farias-Itao[1,2], BSN, MSc; Carlos Augusto Pasqualucci[1,2], MD, PhD; Aline Nishizawa[1,2], BNS, PhD; Luiz Fernando Ferraz Silva[3], MD, PhD; Fernanda Marinho Campos[1], B Pharm; Karen Cristina Souza da Silva[1,2], BS (Biology); Renata Elaine Paraizo Leite[2,4], BPT, PhD; Lea Tenenholz Grinberg[2,5], MD, PhD; Renata Eloah Lucena Ferretti-Rebustini[2,6], BNS, PhD; Wilson Jacob Filho[2,4], MD, PhD; Claudia Kimie Suemoto[1,2,4], MD, PhD, MSc

[1]Laboratory of Cardiovascular Pathology, Department of Pathology – LIM22, University of Sao Paulo Medical School, Sao Paulo, Brazil

[2]Physiopathology in Aging Lab/Brazilian Aging Brain Study Group – LIM22, University of Sao Paulo Medical School, Sao Paulo, Brazil

[3]Department of Pathology, University of Sao Paulo Medical School, Sao Paulo, Brazil

[4]Discipline of Geriatrics, University of Sao Paulo Medical School, Sao Paulo, Brazil

[5]Memory and Aging Center, Department of Neurology, University of California, San Francisco, CA, United States

[6]Medical-Surgical Nursing Department, University of Sao Paulo School of Nursing, Sao Paulo, Brazil

Corresponding Author:
Claudia Kimie Suemoto, MD, PhD, MSc
Physiopathology in Aging Lab/Brazilian Aging Brain Study Group – LIM22
University of Sao Paulo Medical School
Avenida Doutor Arnaldo, 455, room 1353
Sao Paulo, 01246903
Brazil
Phone: 55 1130618249
Fax: 55 1130618249
Email: cksuemoto@usp.br

Abstract

Background: Perivascular adipose tissue (PAT) inflammation may have a role in coronary artery disease (CAD) pathophysiology. However, most evidence has come from samples obtained during surgical procedures that may imply in some limitations. Moreover, the role of B lymphocytes and inflammation in PAT that is adjacent to unstable atheroma plaques has not been investigated in humans using morphometric measurements.

Objective: The objective of this study is to investigate the inflammation in PAT, subcutaneous, and perirenal adipose tissues (SAT and PrAT) among chronic CAD, acute CAD, and control groups in an autopsy study.

Methods: Heart, SAT, and PrAT samples are collected from autopsied subjects in a general autopsy service, with the written informed consent of the next-of-kin (NOK). Sociodemographic and clinical data are obtained from a semistructure interview with the NOK. Coronary arteries are dissected and PAT are removed. Sections with the greatest arterial obstruction or unstable plaques, and the local with absence of atherosclerosis in all coronary arteries are sampled. PAT are represented adjacent to these fragments. Adipose tissues are fixed in 4% buffered paraformaldehyde solution and analyzed immunohistochemically for macrophages (CD68), macrophage polarization (CD11c for proinflammatory and CD206 for anti-inflammatory), B lymphocytes (CD20), and T lymphocytes (CD3). Slides will be scanned, and inflammatory cells will be quantified in 20 random fields. Participants will be categorized in CAD groups, after morphometric measurement of arterial obstruction and plaque composition analysis in accordance with American Heart Association classification. Three study groups will be investigated: acute CAD (at least one unstable plaque); chronic CAD (≥50% arterial obstruction); and controls (<50% arterial obstruction). Inflammatory cells in PAT, SAT, and PrAT will be counted and compared between groups using multivariate linear regression, adjusted for age, body mass index, hypertension, diabetes, alcohol use, and smoking.

Results: We present the methods of our study that was developed from 2 pilots. Currently, data collection and tissue processing are ongoing. Data collection, histology and immunochemistry procedures, and quantification of all inflammatory cells are expected to be concluded within 1 year.

Conclusions: This study will contribute for the understanding of the mechanisms of CAD pathophysiology because it will help to clarify the role of inflammation both in chronic and acute CAD.

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KEYWORDS

coronary artery disease; atherosclerosis; inflammation; adipose tissue; macrophages; B lymphocytes; T lymphocytes

Introduction

Cardiovascular disease is the leading global cause of death, accounting for 17.3 million deaths per year worldwide, and its prevalence is expected to grow to 23.6 million by 2030 [1,2]. Moreover, ischemic heart disease was the most frequent cause of disability-adjusted life years in 2012 [3]. Atherosclerosis is the main cause of cardiovascular disease deaths [4], and it is a chronic disease that can evolve into acute events related to vasospasm, thrombosis of advanced plaques, and embolism. The progression of atherosclerosis may be accelerated by inflammation [5]. Inflammation of the epicardial adipose tissue (EAT) has been linked to coronary artery disease (CAD) pathophysiology. The EAT has been reported to show high levels of inflammatory cytokines [6] and infiltration of leukocytes [7], particularly macrophages and T lymphocytes [6,8]. These changes appear to reflect a chronic proinflammatory response that is mediated by polarized macrophages [9] and is restricted to the heart [6,8,9].

Perivascular adipose tissue (PAT) surrounds most systemic blood vessels, except for the cerebral circulation; this may be a specialized type of adipose tissue related to inflammation and CAD severity [10]. PAT adipocytes have been found in the lamina adventitia of coronary arteries and the aorta [11,12]. Inflammatory cells, such as macrophages and T lymphocytes, were found between the PAT and the aorta adventitia [11]. PAT thickness has been associated with coronary artery calcification, cardiovascular risk factors [13], CAD burden [14], and the degree of atheroma plaque stenosis [15]. The number of macrophages in PAT has been related to the size and characteristics of the atheroma plaque (lipid core, calcification, collagen, and smooth muscle cell content), and to the degree of plaque infiltration by macrophages and lymphocytes. However, some limitations of previous studies should be considered. First, the location of PAT was not defined by its proximity to the atheroma plaque, but by its distance from the coronary artery ostium [15]. Moreover, the dissection of EAT was not conducted adjacent to the most relevant atherosclerotic plaque (periplaque PAT) in most studies, and no comparison was performed with a control area far from the atheroma plaque in the same individual. Second, the association between PAT inflammation and acute CAD was only investigated by imaging studies and no autopsy studies have been conducted to corroborate this association [16]. Third, although previous evidence suggested an association between PAT inflammation and CAD, most studies were conducted using samples collected during surgical procedures, which could had initiated the inflammatory process; the observed changes may therefore be unrelated to the chronic inflammation associated with atherosclerosis [17]. Finally, infiltration of B lymphocytes in PAT has not been investigated using autopsy studies.

The present manuscript aimed to describe standardized methods that were developed to investigate the association between inflammation of PAT and CAD in an autopsy study. The specifics aims of our study are to (1) investigate the association of macrophages, T and B lymphocytes with chronic CAD, acute CAD, and controls, (2) investigate the correlation between number of inflammatory cells in periplaque PAT and percentage of arterial obstruction, (3) investigate the association between number of inflammatory cells in periplaque PAT and atheroma plaque composition, and (4) compare the number of macrophages, polarized macrophages, T and B lymphocytes in periplaque PAT with the number of the same inflammatory cells in a control area far from the atheroma plaque, in SAT and in PrAT in the same individual.

Methods

Study Design and Setting

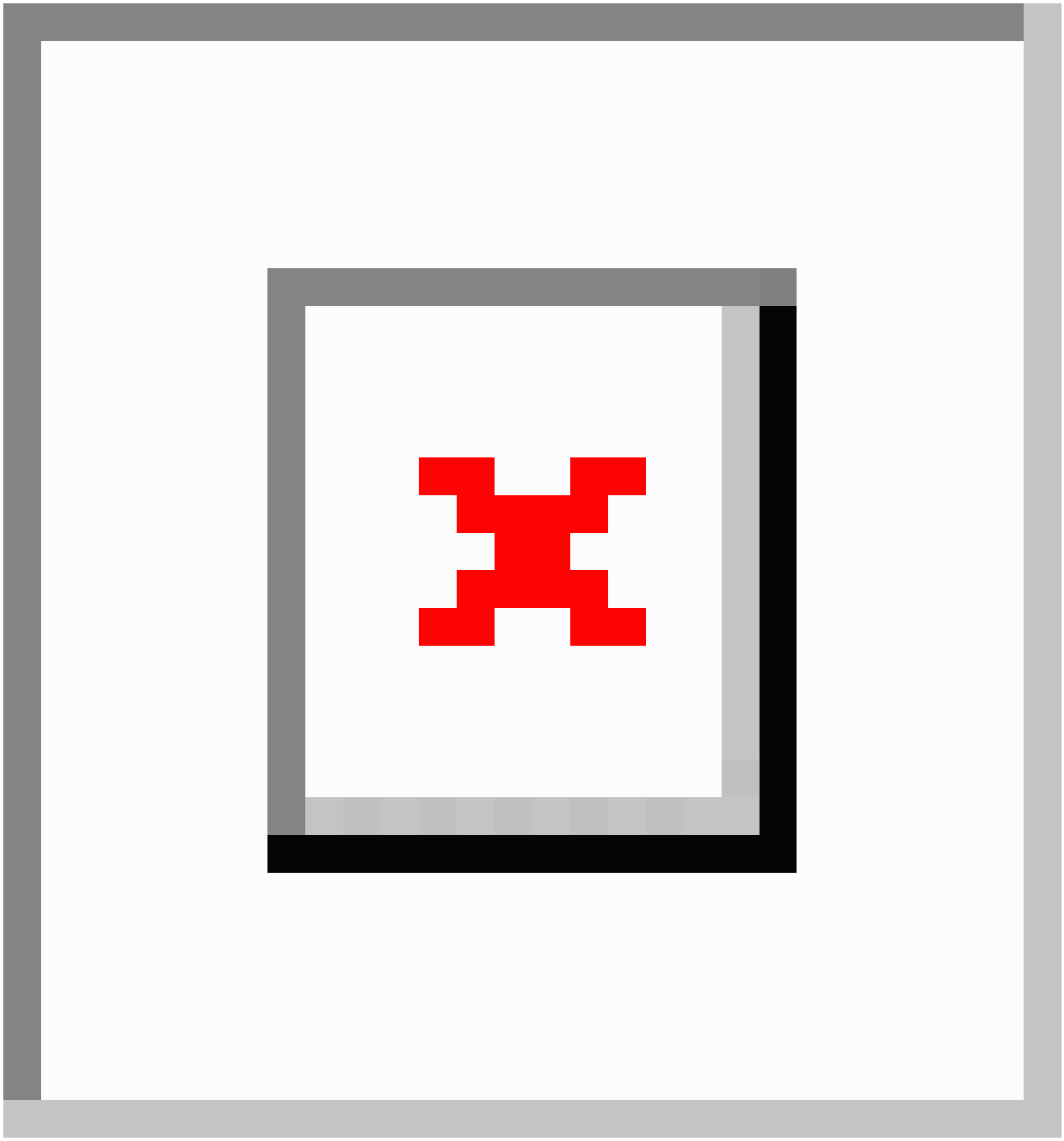
This observational cross-sectional autopsy study was approved by the local ethics committee. Written informed consent is obtained from the next-of-kin (NOK) of all participants before starting any study procedure.

The Sao Paulo Autopsy Service (SPAS) is a general autopsy service based at the University of Sao Paulo that performs approximately 13,000 autopsies per year. In Sao Paulo city, autopsy is mandatory when an individual dies from a natural cause, and where the cause of death is unclear or the individual did not have medical assistance. Since 2004, the Brazilian Aging Brain Study Group has sourced autopsy material from SPAS to investigate the normal and pathological aging brain [18]. The present study employed the same approach to collect adipose tissue samples and hearts.

Recruitment

While the NOK waits for the autopsy of their deceased family member, they are invited to participate in this study. Nurses explain the aim of the study to the NOK and ask for their signature on an informed consent form. For all subjects to be included in this study, the NOK needs to have at least weekly interactions with the deceased and can therefore provide reliable information. A semistructured interview relating to sociodemographic and clinical information is conducted with each NOK prior to the collection of tissue samples (Figure 1).

Figure 1. Study outline. SPAS: Sao Paulo Autopsy Service; ICF: informed consent form; SAT: subcutaneous adipose tissue; PrAT: perirenal adipose tissue; PAT: perivascular adipose tissue.



Study Population

The inclusion criteria for this study are: individuals of age ≥30 years at the time of death; a post mortem interval of ≤24 hours; a NOK with at least weekly contact with the deceased in the 6 months prior to death; and the availability of heart, SAT, and PrAT tissues from the medical pathologist. We included participants aged 30 years or older because advanced atherosclerotic plaques could be found in individuals with at least 30-years old at death [19].

The exclusion criteria employed in this study include: inconsistent clinical data provided by the NOK; adipose tissue fixation >72 hours; the use of corticosteroids or immunosuppressants, the presence of autoimmune disease, pericarditis, pericardial effusion, myocarditis, endocarditis, Chagas' disease, hemopericardium, cardiac tamponade, coronary artery stent, or previous cardiac surgery. Patients with these conditions are excluded because they could induce or suppress inflammation in an atheroma plaque-independent manner. During the autopsy, samples of the major organs (heart, lung, spleen, kidney, and liver) are collected, processed, and stained with hematoxylin and eosin. Individuals that have an infection and show 2 or more criteria associated with sepsis in these samples, as defined previously [20,21], are also excluded from this study.

Clinical Evaluation

The cause of death is determined by certified pathologists, based on the autopsy. In addition to the semistructured interview relating to the deceased's sociodemographic information (including age, race, and education in years completed) [19,22]. The NOK provide clinical information relating to diagnosis (hypertension, diabetes, CAD, heart failure, dyslipidemia, or stroke) and lifestyle (physical activity, alcohol use, and smoking). Body mass index is calculated using the weight and height measured in a supine position, while the deceased have no clothes or shoes before the autopsy exam.

Tissue Sampling

The heart is collected to obtain PAT and coronary arteries. SAT is removed from the region of the umbilical scar and PrAT from the kidney. The heart, SAT, and PrAT is washed in running water to remove blood and clots.

Pilot Studies for Tissue Fixation

Two processes were compared for heart fixation. The first involved fixation of the heart (with EAT) by immersion in 70% alcohol for at least 24 hours. After this period, we dissected the right coronary artery, left coronary artery trunk, anterior descending coronary artery, and circumflex coronary artery, together with 1 cm of the adjacent PAT and all EAT was removed from myocardium. PAT was removed systematically and cut into 1.5 cm sections, starting from the ostium (Figure 2). After these dissections, PAT and EAT were weighted using an electronic scale. Subsequently, agar was injected into the lumen of each coronary artery, which was then stored in 10% formaldehyde solution for 5 days. However, we observed flattening of the coronary arteries (Figures 3 D, 3 E), even with agar injection.

Therefore, we changed our fixation protocol. The second fixation process involved the coronary artery dissection with the adjacent PAT immediately after heart collection to test whether the dissection of fresh coronary arteries and PAT would be more effective. The heart was incubated at −20°C for 2 minutes prior to injecting agar inside each coronary artery, and then the heart was placed at −20°C for another 2 minutes to solidify the agar. The coronary arteries were then dissected as described above and PAT was removed. The second fixation protocol has two advantages. First, the injection of agar before artery dissection allows agar infiltration until minor branches. Second, when we dissect the coronary arteries, there are already solidified agar inside the arterial lumen, facilitating arterial opening after repeated injections of agar (Figures 2 B, 2 C). The problem of injecting agar only after heart fixation is that coronary arteries are already hardened by alcohol. Moreover, when we injected agar after coronary dissection, most of the agar did not stay inside the lumen, preventing arterial opening (Figures 3 D, 3 E).

We also investigated whether the 10% formaldehyde solution and 4% buffered paraformaldehyde solution (pH 7.2-7.4) influenced coronary artery fixation. Coronary arteries samples were identified and then fixed for 5 days. We used the same fragment of coronary artery divided in 3 to compare agar injection procedures and fixatives. Agar prevented artery flattening (Figures 3 B, 3 C), which could interfere with the measurement of arterial stenosis. Moreover, the presence of the agar protected the intima layer from 10% formaldehyde solution damage (Figure 3 A, 3 B). In addition, the 4% buffered paraformaldehyde solution was less aggressive to the tissue than 10% unbuffered formaldehyde solution (Figure 3 C). Therefore, we chose to dissect fresh coronary arteries and PAT and used 4% buffered paraformaldehyde solution as the fixative.

We compared adipose tissue fixation times of 24, 48, and 72 hours in 4% buffered paraformaldehyde solution. Fixation times >72 hours were not tested because they can lead to a loss of antigenicity or the production of formic acid, which can impair identification of immune cells [23,24]. All primary antibodies were tested in positive control tissue sections (lung, tonsil, and lymph node) to facilitate standardization (Table 1). No difference in inflammatory cell staining was found using the 3 different fixation times (Figure 4). Thus, although 24 hours was chosen as the fixation time for subsequent analyses, this could be extended for up to 72 hours if necessary.

Table 1. Primary antibodies used to identify inflammatory cells.

Target	Specification	Dilution	Inflammatory cell
CD3	Polyclonal rabbit anti-human	1:1500	T lymphocytes [6]
CD20	Monoclonal mouse anti-human clone L26	1:12,000	B lymphocytes
CD68	Monoclonal mouse anti-human clone KP-1	1:5000	Macrophages [6,8,15]
CD11c	Monoclonal rabbit anti-human clone EP1347Y	1:400	Macrophages polarized M1 [9]
CD206	Monoclonal mouse anti-human clone 5C11	1:1500	Macrophages polarized M2 [9]

Figure 2. Perivascular adipose tissue (PAT) and coronary artery preparation of pilot 2. A: Agar was initially injected in the ostium of right coronary artery, the heart was cooled, and PAT was sampled at 1.5 cm intervals from the ostium until the final trajectory of the coronary artery. B: After PAT removal, the coronary artery was flat partially. C: The revised fixation procedure included at least two agar injections, and the coronary arteries were effectively open.

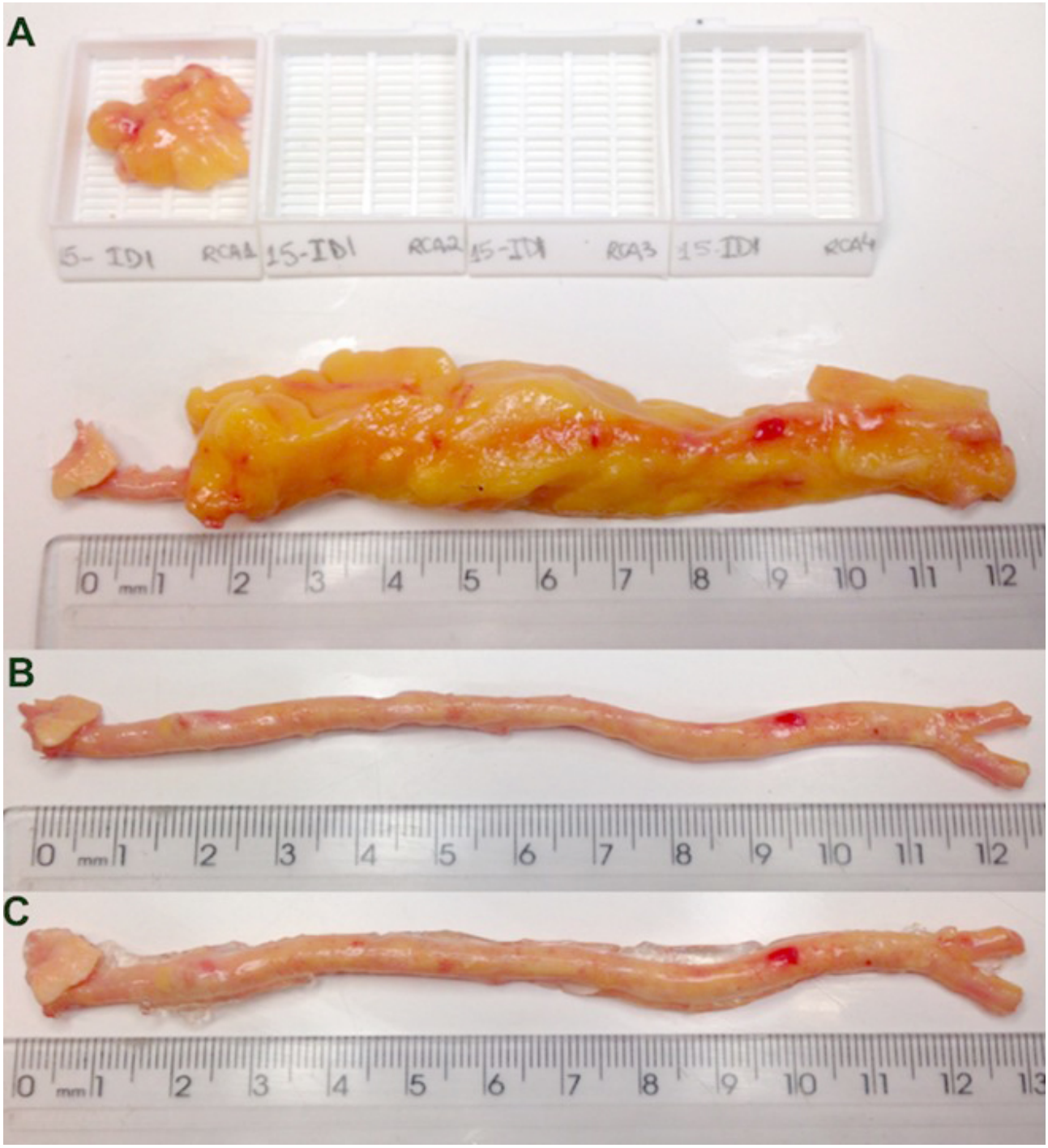


Figure 3. Fixation of the coronary artery. A: Coronary artery without agar injection and fixation in 10% formaldehyde solution. B: Coronary artery with agar injection and fixation in 10% formaldehyde solution. C: Coronary artery with agar injection and fixation in 4% buffered paraformaldehyde solution. D: Coronary artery flattening observed following heart fixation by immersion in alcohol prior to dissection of the coronary arteries (photographed macroscopically). E: Section of the same tissue shown in panel D, photographed microscopically after staining.

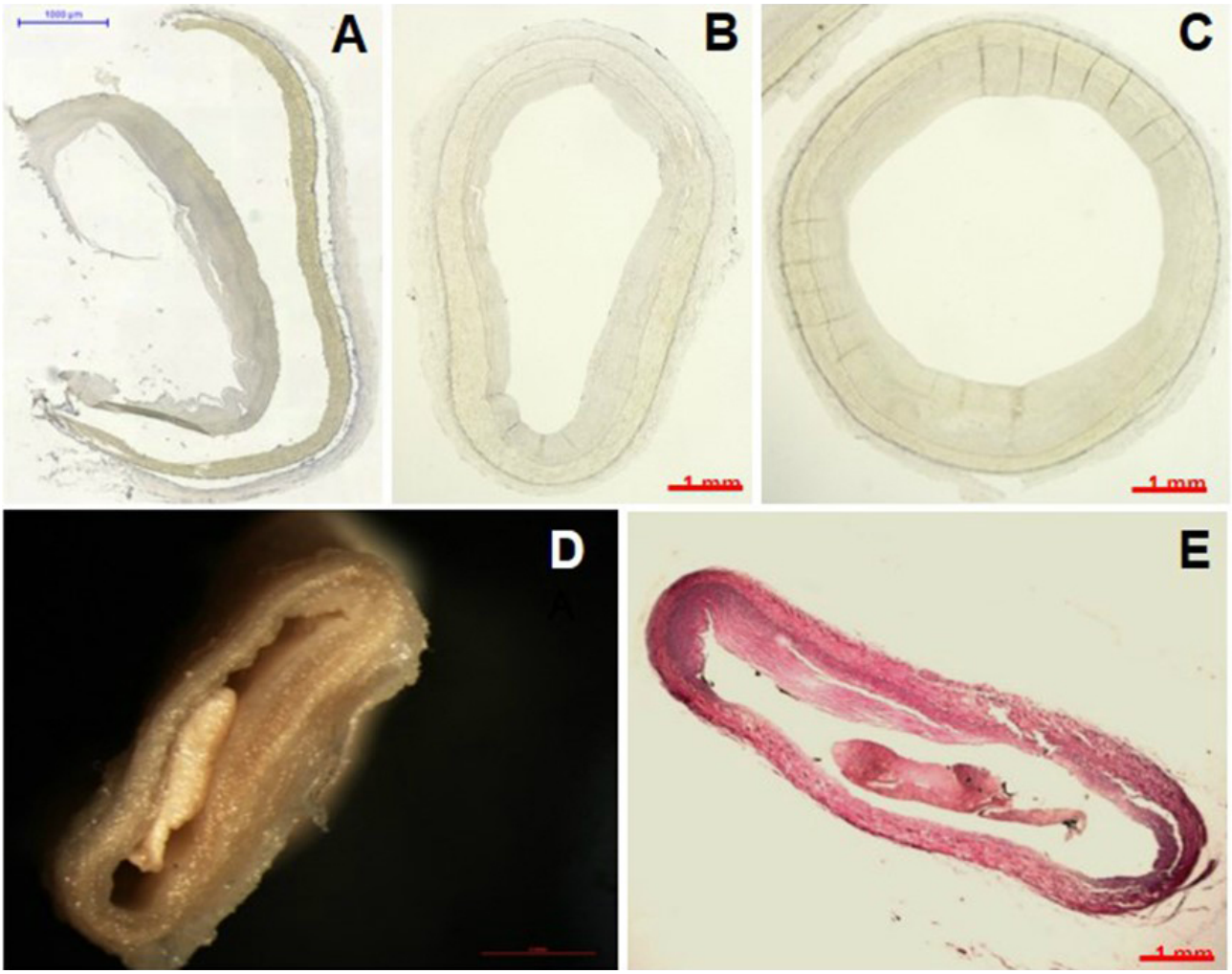


Figure 4. Immunochemistry of perivascular adipose tissue (PAT) using an anti-CD3 primary antibody. PAT was fixed for A: 24 hours; B: 48 hours; and C: 72 hours. Red arrows indicate CD3-positive T lymphocytes. All images were obtained using a microscope at 20× magnification.

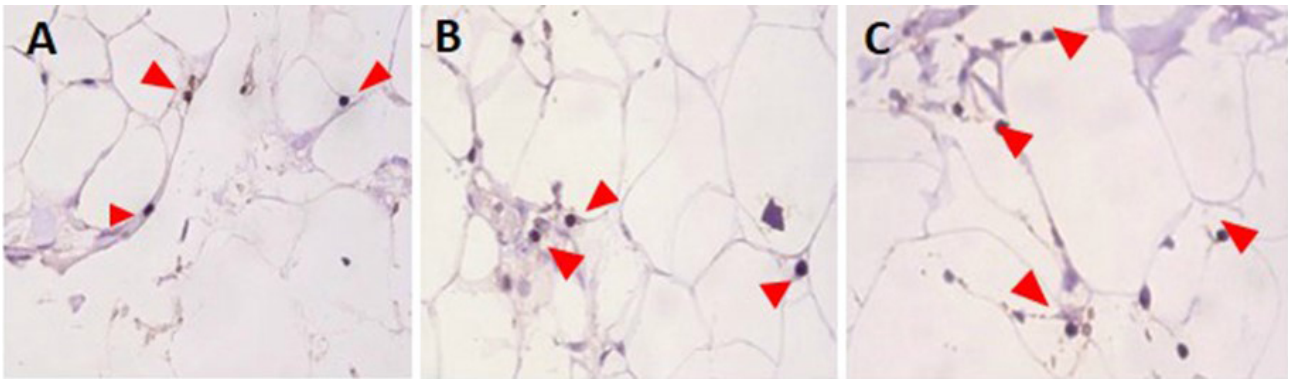
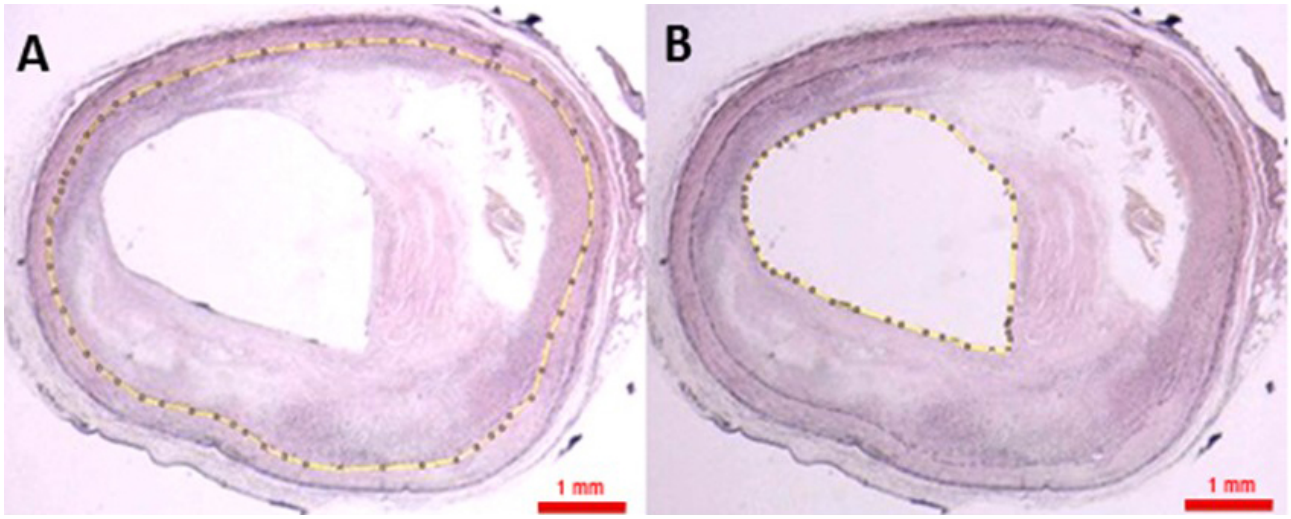


Figure 5. Area measurements: the internal elastic lamina (IEL) and lumen. A: Area delineated by the IEL. B: Area of the lumen.



Evaluation of Coronary Artery Atherosclerosis

Macroscopic Evaluation

After fixation, coronary arteries are washed in running water for 30 minutes to remove excess paraformaldehyde solution. All coronary arteries are cut in 5-mm sections to identify the section with the largest obstruction or unstable plaques (eg, hemorrhage or thrombus), using a magnifying glass (Emporionet LP 500). An area without atherosclerosis that is distal to the section with the largest degree of arterial stenosis is also sampled. The number of atherosclerotic plaques is counted along the artery, as a measure of the extent of atherosclerosis. The agar is removed from inside the arterial lumen and the sections are photographed using a stereomicroscope (Nikon SMZ 1000).

Microscopic Evaluation

The coronary arteries are decalcified, dehydrated, diaphonized, and immersed in paraffin prior to cutting 4 µm sections, using a microtome and staining with Verhoeff's stain, as well as hematoxylin and eosin. The sections are then photographed using a stereomicroscope. The percentage of arterial obstruction is measured by morphometric methods using an image processing software (ImageJ). We measure the area of the lumen and the area delineated by the internal elastic lamina (IEL) (Figure 5). To calculate the percentage of arterial obstruction, we divide the difference between the area within the IEL and the area of the lumen by the area within the IEL, and multiplied the result by 100 [25]. Moreover, we classify the atheroma plaque in accordance with the American Heart Association (AHA) criteria [19].

CAD Classification

After we complete the tissue processing, participants will be classified into 3 groups: chronic CAD, with ≥50% obstruction in at least one artery [7], and an AHA classification different than VI [25]; acute CAD, with at least one atheroma plaque with an AHA classification of VI (unstable plaque) [19]; with no meaningful CAD [7], and an AHA classification different than VI [19]. If the sample size allows, we will perform a subanalysis with participants without arterial obstruction as the control group.

Histological and Immunochemical Procedures in Adipose Tissues

PAT, SAT, and PrAT are cut into 4 µm sections, applied to silanized slides (3-aminopropyltriethoxysilane), and immersed in paraffin. Prior to immunochemistry, the sections of PAT that correspond with sampled coronary artery fragments, SAT, and PrAT are deparaffinized by placing the slides in hot xylene in an oven at 60°C to 65°C for 5 minutes and then dipping in 3 baths of cold xylene. The sections are then hydrated in 95% alcohol, followed by 70% alcohol, washed in tap water and deionized water, and placed in phosphate buffer, pH 7.4. Antigen recovery is performed in 10 mM citric acid, pH 6, at a high temperature in a pressure cooker. Endogenous peroxidase is blocked using 3% hydrogen peroxide prior to incubating the slides with the indicated primary antibodies in the presence of 1% bovine serum albumin for 24 hours at 4°C. The slides are then incubated with the appropriate horseradish peroxidase-conjugated secondary antibody and EasyLink One and the signal is generated using the chromogen, diaminobenzidine. The sections are counterstained using Harris hematoxylin.

Inflammatory Cell Counting

The slides are scanned and analyzed at 40× magnification using the Pannoramic Viewer software. This program hides the slide identification so that the operator is blinded to the subject's diagnosis, the source and type of adipose tissue, and hotspots (ie, accumulation of inflammatory cells). Twenty random fields with 600 µm of diameter were also analyzed with no magnification (cells can only be observed with precision at 20× magnification). This process is systematic and large cell agglomerates (identified in >20× magnification) are avoided. Inflammatory cells are counted per the primary antibody staining and these results were expressed as the number of cells per micrometers squared.

Statistical Analyses

To calculate the sample size, we used a previous study that found an effect size of 0.93, with a mean standard deviation of

44 (SD 21) inflammatory cells/μm² in a CAD group and 24 (SD 22) inflammatory cells/μm² in a control group [7]. Assuming an alpha of 5% and a power of 90%, we estimated that 26 subjects would be needed in each group, giving a total sample size of 78. The independent variable of our study is CAD and the dependent variables are the numbers of macrophages, polarized macrophages, and lymphocytes (B and T) in PAT, PrAT, and SAT. The groups will be compared regarding demographic and clinical variables, using chi-square test for categorical variables and one-way analysis of the variance (ANOVA) for continuous ones. The weight of EAT will be compared among groups using one-way ANOVA. A multivariate linear regression model will be used to compare the dependent and independent variables, adjusted for age, hypertension, diabetes mellitus, body mass index, alcohol use, and smoking. The significance level for all tests will be set at 5% in two-tailed tests. We will use STATA 13.0 to perform these analyses.

Results

Currently, data collection and tissue processing are ongoing. The data collection, histology and immunochemistry procedures, and quantification of inflammatory cells are expected to be concluded by May 2017.

Discussion

Clinical Implications

Although EAT thickness and volume can be evaluated using imaging methods [26], the number and type of inflammatory cells in PAT can only be determined by pathological examination. In addition, autopsy studies can employ morphometric methods to calculate the degree of plaque stenosis and plaque composition. Finally, they can exclude other inflammatory diseases, which could bias the results. Here, we describe a protocol for sample processing, immunochemical analyses, and morphometric measurements of coronary artery stenosis and inflammatory cells in adipose tissues.

Although the association of CAD with macrophages and T lymphocytes has been investigated previously [6,8,9,15], a study of this association using a range of controls, including the analysis of SAT, PrAT, and EAT distal from the atheroma plaque will help to determine the extent of the inflammatory process. Moreover, the contribution of B lymphocytes in PAT to the atherosclerotic process has not yet been investigated, and the association between EAT inflammation and acute CAD has only been investigated using imaging methods, thus precluding the direct quantification of inflammatory cells [6].

It is possible that inflammation in PAT could contribute locally to the development of the atherosclerotic plaque, as suggested by previous imaging [7,6] and autopsy studies [15]. The mechanism underlying these findings is not yet established, but it is biologically plausible. Infiltration of adipocytes in the PAT was found in the adventitial layer, which could have direct influence on the inflammation in coronary arteries [12,27]. In addition, the vasa vasorum, which is in close contact with the PAT [10,26], grows in the direction of the intimal layer [28] when intima media thickness is present. The infiltration of inflammatory cells in adventitial layer may contribute to this angiogenesis.

PAT inflammation may be a measurable and modifiable risk factor that could be used in clinical practice. Some studies have investigated interventions that aim to reduce the inflammatory burden, for example by reducing the EAT volume via a reduction of the total body weight or by promoting the conversion of white adipose tissue into brown adipose tissue, which is associated with a decreased risk of obesity-related disorders. Other studies have investigated drugs that modulate immune receptors to reduce inflammation [29,30].

However, while inflammation and PAT thickness have been suggested to show positive associations with the degree of arterial stenosis [31], a paradox has been observed in clinical practice, whereby a low EAT volume was associated with a reduced myocardial salvage area and a larger infarct size in patients with a first ST-segment elevation myocardial infarction [32]. Therefore, studies of the roles of different inflammatory cells in PAT are important to elucidate CAD pathophysiology and identify new therapeutic targets.

Strengths and Limitations

Nevertheless, one limitation of the present study is that the sociodemographic and clinical information are collected after death from the NOK. To improve the accuracy of this information, we only include NOK with daily or weekly interactions with the deceased. Moreover, the reliability of the post mortem interview had been demonstrated by a previous study from our group, which showed a high sensitivity (87%) and specificity (94%) using this approach [33]. In addition, the main variables analyzed in the present study (atherosclerotic burden and inflammatory cell numbers) are measured objectively.

Here, we described the protocol that we are using to investigate the association between CAD and inflammation in adipose tissues. Particularly, we described in details the pilot studies that we performed to fixate and process the arteries and adipose tissues. These measures are important to allow for unbiased morphometric measures of atherosclerosis and inflammatory cell counting.

Acknowledgments

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Authors' Contributions

DSFI, CAP, and CKS were responsible for study design. DSFI and CKS contributed to manuscript writing. AN contributed to the method design of pilot 1. DSFI, CAP, and CKS were responsible for data analysis and interpretation. LFFS helped with standardization of the immunochemistry protocols and will evaluates signs of sepsis. FMC and KCSS helped to collect the samples. DSFI and FMC performed dissections. DSFI will evaluate coronaries and count immune cells. REPL, LTG, RELFR, and WJF contributed resources and tissue bank support. All authors reviewed the paper.

Conflicts of Interest

None declared.

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Abbreviations

AHA: American Heart Association
ANOVA: analysis of the variance
CAD: coronary artery disease
CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
EAT: epicardial adipose tissue
FAPESP: Fundação de Amparo à Pesquisa do Estado de São Paulo
ICF: informed consent
IEL: internal elastic lamina
NOK: next-of-kin
PAT: perivascular adipose tissue
PrAT: perirenal adipose tissue
SAT: subcutaneous adipose tissue
SPAS: Sao Paulo Autopsy Service

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Protocol

An Observational Registry of Carotid Endarterectomy and Carotid Artery Stenting in Brazil: Study Protocol

Edwaldo Edner Joviliano[1], MD, PhD; Winston Bonetti Yoshida[2], MD, PhD; Marcone Lima Sobreira[2], MD, PhD; Regina Moura[2], MD, PhD; Ana Terezinha Guillaumon[3], MD, PhD; Selma Regina De Oliveira Raymundo[4], MD, PhD; Daniel Gustavo Miquelin[4], MD, PhD; Ludvig Hafner[5], MD, PhD; Marcelo Jose Almeida[5], MD, PhD

[1]Department of Surgery and Anatomy, Ribeirao Preto Medical School, University of São Paulo, Ribeirao Preto, Brazil

[2]Department of Surgery, Botucatu Medical School, University Julio de Mesquita Filho UNESP, Botucatu, Brazil

[3]Department of Surgery, School of Medical Sciences, University of Campinas, Campinas, Brazil

[4]Department of Surgery, São Jose do Rio Preto Medical School FAMERP, Sao Jose do Rio Preto, Brazil

[5]Department of Surgery, Marilia Medical School FAMEMA, Marilia, Brazil

Corresponding Author:
Edwaldo Edner Joviliano, MD, PhD
Department of Surgery and Anatomy
Ribeirao Preto Medical School
University of São Paulo
Avenida dos bandeirantes 3900
Ribeirao Preto, 14048900
Brazil
Phone: 55 1636022406
Fax: 55 1536022593
Email: eejoviliano@gmail.com

Abstract

Background: Carotid artery stenting (CAS) and carotid endarterectomy (CEA) are alternative strategies for stroke prevention in patients with atherosclerotic carotid disease. CEA has been considered the first-line treatment for carotid stenosis worldwide, and the safety and efficacy of CAS compared to CEA remains in question.

Objective: The purpose of this study is to compare the practice and outcomes of CAS and CEA in a real-world setting within public university hospitals in Brazil.

Methods: This study will be a prospective 5-year analysis of treatment for atherosclerotic carotid stenosis with CEA and CAS performed at 5 centers affiliated with the Vascular Study Group at public university hospitals in Brazil. The indications for the procedures will be determined by each surgeon's individual discretion, in accordance with preoperative risk evaluation. The primary outcome measures will be (1) any in-hospital stroke or death, and (2) any per-procedural stroke, death, or myocardial infarction (MI). Patients undergoing CEA in conjunction with cardiac surgery will be excluded from the study. Multivariate logistic regression will be performed to identify predictors of stroke or death in patients undergoing CEA and CAS. All tests of significance will be performed at the .05 level. This study was approved by the Committee of Ethics in Research at the University Hospital of Ribeirao Preto Medical School, and in all other participating institutions linked to National Research System and National Board of Health in Brazil (Process 15695/2011).

Results: This study is currently in the recruitment phase, and the final patient is expected to be enrolled by the end of 2018. We hope to recruit approximately 800 patients to the study. Analyses will focus on primary end points for patients that are allocated to each treatment group. During the per-procedural period, the occurrence of the primary end point components (stroke, MI, or death) for CAS and CEA will be analyzed for symptomatic or asymptomatic subjects.

Conclusions: The analyses of the primary endpoints (and all others variables of the study) are expected to be published in 2019 in a peer reviewed journal, and results will be presented at scientific meetings, with summary results published online. This study will obtain new data related to the quality of treatment for carotid disease in Brazil at the primary training centers of future vascular surgeons, but the initial data that will be obtained and published (with the outcomes and complications) are restricted to the first 30 days postprocedure. This time restriction limits the comparison of the results that relate to the main goal of treatment, which is to decrease the risk of stroke over 5 years. The purpose of the study group is to continue the monitoring of patient records, and

evaluate the follow-up data in the 5 years following the initial evaluation. This study protocol will contribute very significantly to improving the care of patients with carotid disease, in addition to qualifying the level of assistance provided in public university hospitals in the state of São Paulo, Brazil.

Trial Registration: Clinicaltrials.gov NCT02538276; https://www.clinicaltrials.gov/ct2/show/NCT02538276 (Archived by WebCite at http://www.webcitation.org/6m7APnFLD)

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KEYWORDS

carotid artery diseases; carotid endarterectomy; carotid stenosis; carotid stenting; medical record linkage

Introduction

Cerebrovascular disease is a leading cause of serious long-term disability and death [1,2]. A significant proportion of ischemic strokes originate from the atherosclerosis of extracranial arteries. In most cases, carotid endarterectomy (CEA) or stent angioplasty of the carotid bifurcation is considered when color duplex ultrasound detects clinically significant extracranial internal carotid artery stenosis. However, several clinical situations exist in which other imaging techniques are needed to provide greater anatomical detail and resolution.

Revascularization of severely atherosclerotic carotid arteries has been shown to be safe and effective in the prevention of stroke [2-5]. Carotid artery stenting (CAS) and CEA are two alternative methods of revascularization, and these techniques have been compared in small randomized clinical trials [6-10]. In the 2010 International Carotid Stenting Study (ICSS), 1713 symptomatic patients from 50 centers in Europe, Australia, New Zealand, and Canada were prospectively randomized to a CAS or CEA condition. The 30-day results showed a combined stroke, death, and myocardial infarction (MI) rate of 7.4% for CAS and 4.0% for CEA (P<.006). This effect was primarily driven by an increased stroke rate of 7.0% for CAS versus 3.3% for CEA [1].

Although randomized trials provide the most scientifically valid comparisons between treatments, they do not reflect the diversity of patients or technical proficiency present in broad contemporary clinical practice. CEA has been considered the first-line treatment for carotid stenosis worldwide, and the safety and efficacy of CAS compared to CEA remains in question. CAS is officially approved for use in multiple countries, and the number of patients undergoing CAS has been increasing due to its less-invasive nature. The present study aims to demonstrate the real-world status of the treatment of carotid artery disease with CAS and CEA using the prospective registry of vascular diseases of university hospitals in the state of Sao Paulo, Brazil, called the RHEUNI (Registry Project of Vascular Disease in the Public University Hospitals of São Paulo). It is well known that no prospective studies with a significant number of cases concerning the treatment of carotid disease exist in Brazil; all available data were derived from studies conducted in other countries. Thus, the main objective of this study is to evaluate the quality of treatment for carotid disease in Brazil by analyzing the two main techniques currently available. The data will be derived from the vascular surgery centers that bear primary responsibility for the training of future vascular surgeons.

Methods

Patient Population and Setting

The CEA and CAS registry in Brazil (part of RHEUNI) is being used as a prospective observational study in Brazil, and has been conducted since July 2013. Final data analyses are expected in July 2018 from the 5 public university hospitals of the São Paulo state that provide vascular therapy. Several consecutive procedures will be registered as CEA or CAS by certified vascular surgeons from 5 centers (University Hospital of Ribeirão Preto Medical School of University of São Paulo, University Hospital of School of Medical Sciences of University of Campinas, University Hospital of Marilia Medical School, University Hospital of Botucatu Medical School, and University Hospital of São Jose do Rio Preto Medical School). All participating vascular surgical centers have extensive experience in the treatment of carotid disease, and they are all training centers of reference in Brazil. The ethical committee of each hospital has approved this project.

Inclusion criteria are as follows: patients with carotid atherosclerotic stenosis >70% who underwent CEA or CAS for the treatment of carotid stenosis at any of the 5 hospitals involved in the study, male or female, and >18 years of age. Carotid stenosis is defined as (1) stenosis >70% by catheter angiography (North American Symptomatic Carotid Endarterectomy Trial criteria) or (2) by Doppler ultrasound with >70% stenosis defined by a peak systolic velocity of at least 230 cm/second, plus at least one of the following: an end diastolic velocity >100 cm/second, or internal carotid/common carotid artery peak systolic velocity ratio >4.0, or computer tomography with >70% stenosis, or magnetic resonance with >70% stenosis. Exclusion criteria include cases of concomitant cardiac surgery, carotid dissection, fibromuscular dysplasia, or trauma.

RHEUNI data have been validated for completeness by quarterly audits of discharge claims data from each participating institution. These audits ensure complete inclusion of all consecutive procedures performed at the participating hospitals.

Data Collection

The recorded characteristics and backgrounds of patients who undergo CAS and CEA will include: age, gender, and high-risk CEA characteristics (according to the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial [6]). In addition, symptom presentation and the degree of stenosis will be analyzed. Procedural success, antiplatelet use,

embolic protection device (EPD) use, and the type of stent strut (open-cell or closed-cell) or patch used for CEA will be recorded, and the execution of prior post balloon dilatation at CAS (and procedure-related complications) will be analyzed to clarify the current strategy and the treatment results of both techniques. The degrees of stenosis will be measured using the method employed by the North American Symptomatic Carotid Endarterectomy Trial [2].

Data Source and Measurement

Outcomes will be stratified by symptomatic and asymptomatic status. Symptomatic patients will be defined as having a neurological event, including any hemispheric or ocular transient ischemic attack, or major or minor stroke, that precedes the intervention ipsilateral to the treated lesion. Our definition of a symptomatic patient is the occurrence of symptoms for up to 180 days. This definition is similar to that of the Carotid Revascularization Stent Trial (CREST), although ICSS trial lesions were considered symptomatic for up to one year [1,11,12].

Technical success pertains to per-procedural events from the initiation of the procedure through the first 24-hour post operative period. Primary technical success will require the successful excision of the carotid plaque by surgical or interventional means. Technical success will be assessed by the outcomes and complications related to preoperative carotid angiograms, whenever these imaging studies are obtained prior to the carotid intervention. For CEA, primary technical success implies the successful removal of the carotid plaque and closure of the artery, with or without a patch, with less than 30% residual stenosis in the absence of stroke, MI, and death. For CAS, the introduction and deployment of the EPD and carotid stent in the absence of stroke, MI, death, surgical conversion, and vascular obstruction constitute primary technical success [13]. Secondary endpoints of interest include procedure time, blood loss, blood transfusion, clamping and shunting time, fluoroscopy time, contrast load, recovery time, range and average number of days in an intensive care unit, and length of hospital stay.

All complications will be categorized as local vascular, local nonvascular, or systemic. Complications after carotid interventions will be reported in a systematic and standardized manner with a description of the degrees of severity. Although assigning a degree of severity to all complications arising from different treatment methods may be difficult, severity scales should be provided whenever possible to allow for the assessment and comparison of adverse events. The following severity scale has been modified from the reporting standards for lower extremity ischemia established by Rutherford et al [14]: *Mild* (level 1) refers to a complication that resolves spontaneously or with minimal intervention, does not increase the length of hospital stay, and does not cause permanent disability. *Moderate* (level 2) refers to the need for significant intervention, an extension of hospitalization beyond 24 hours, and, at most, minor permanent disability that does not interfere with normal daily activity. A *severe* complication (level 3) requires major surgical, endovascular, or medical intervention, may be associated with prolonged convalescence, is usually accompanied by prolonged or permanent disability, and may result in death. Prehospital discharge data related to stroke/death will be recorded, as applicable.

When obtaining patient consent, the patient will first be approached by a doctor who is a member of the treatment team at the same hospital in which the patient will be receiving treatment. Upon obtaining patient consent, we will record the patient name, patient signature, date of signature, and the name of the doctor who introduced the study to the patient, as well as his/her professional number and signature.

Researcher Responsibilities, Institutions, and Sponsors

The principal investigators are committed to continuing the project over time while ensuring the accuracy of the information. Data will be collected from the routine diagnostic tests and specific treatment at each institution. There will be no project sponsor external to the universities.

The recruitment information will be available from the participating hospitals via an online document available to participants. In addition, the analytical procedure will include bimonthly meetings of the group of doctors responsible for the study, along with the respective principal investigators, to observe the progress of the project and evaluate the partial and total data, in addition to writing the manuscript.

Statistical Analyses

Initial analyses will include sociodemographic characteristics of patients undergoing CAS, and those referred for CEA. The projected number of cases during the study period is approximately 800. Categorical variables will be compared and presented as percentages. Continuous variables will be compared using analysis of variance and will be presented as means with standard deviations. To identify patient characteristics that are independently associated with a referral for CAS versus CEA, no parsimonious multivariate logistic regression analysis of the probability of undergoing CAS will be performed. All analyses will be conducted using Microsoft Excel (Redmond, WA, USA) and Epi-Info (Atlanta, GA, USA). All significance tests will be performed at the .05 level.

Results

The study is in the recruitment phase, and we are enrolling patients at 5 centers in Brazil. It is anticipated that 800 patients will be recruited to the study by the end of 2018. Analyses will focus on primary end points for patients that are allocated to each treatment group. During the per-procedural period, the occurrence of the primary end point components (stroke, MI, or death) for CAS and CEA will be analyzed for symptomatic or asymptomatic subjects. The median time from randomization to the procedure will be compared for CAS and CEA. Stenting with embolic protection of patients will be assigned to the CAS group. General or local anesthesia of patients will be assigned to the CEA group. The median duration of follow-up will be determined. During that time, the level or prevalence of selected risk factors will be analyzed to determine if they remained similar between the two treatment groups.

Discussion

Clinical studies that evaluate carotid interventions, particularly those that compare different treatment modalities, may be difficult to interpret when differences in demographics, comorbid conditions, and perioperative risk factors are not identified and characterized [13,15].

The primary objective of the treatment for carotid stenosis is the reduction of risks related to stroke and death. Therefore, the primary outcome criteria for any carotid intervention include the prevention of the following: (1) all per-procedural strokes and death; (2) subsequent ipsilateral stroke; and (3) stroke or death that may result from primary or secondary treatment. There is agreement among health professionals that adequate training and experience of vascular surgeons is an important factor in maintaining the quality and outcomes of CAS or CEA, and this issue has been discussed in many reports following the results of European randomized controlled trials [16]. It has been suggested that CAS and CEA surgeons select an optimal strategy for each case, especially regarding protection methods, in accordance with preoperative risk evaluation. One of the major concerns associated with CAS is the potential for embolic infarction during the procedure. Among other causes of plaque components at the stenotic site, lipid core and plaque hemorrhaging are highly associated with increasing incidents of embolic infarction after CAS [17]. Multiple randomized trials have compared CAS with CEA, with varying results. Variability among the trials complicates efforts to make direct comparisons; thus, determining the best treatment strategy for symptomatic or asymptomatic patients is difficult.

One meta-analysis pooled data from 13 prospective, randomized, or controlled clinical trials that compared CEA with CAS [18]. With combined data from all trials, over 7000 patients were included, the majority of whom (79%) were symptomatic. The post operative risk of stroke and death over the subsequent 30 days was higher in the CAS group compared with the CEA group (odds ratio [OR] 1.57, P=.01) and was highest in symptomatic patients (OR 1.89, P=.01). EPDs used with CAS did not significantly reduce the 30-day per-procedural risk of stroke/death related to CEA, but they did decrease the 30-day risk of stroke/death compared to that associated with CAS without an EPD (2.7% vs 7.5%, OR 0.34, P<.01). In contrast, CAS was associated with a lower risk of cranial neuropathy (OR 0.06, P<.01) and a lower risk of post operative MI (OR 0.43, P<.01). Based on these findings, the authors advocated reserving CAS for revascularization in patients with anatomical conditions that make CEA difficult or place patients at higher risk for cranial nerve injury (such as restenosis after prior CEA), or in patients with concomitant significant carotid artery disease. The limitation of CAS to specific patient groups is outlined in both the Society of Vascular Surgery and European Society of Vascular Surgery guidelines, particularly for those at high risk for CEA and in, “high-volume centers with documented low per-procedural stroke and death rates or inside a randomized clinical trial” [19,20].

Some other important studies are underway. In response to the growing uncertainty regarding clinical management of asymptomatic patients with carotid artery disease, the National Institutes of Health is financing the CREST-2 trial. This multicenter, randomized study has two arms related to intervention: CEA versus best medical therapy (BMT) and CAS versus BMT. Patients can opt to enroll in either the CEA or CAS arm. Randomization, therefore, determines whether a patient undergoes an intervention or BMT, rather than the type of intervention (CEA or CAS). Patients allocated to CEA or CAS treatments will also receive the same BMT as those randomized to medical treatments. The study is expected to take approximately 10 years to complete randomization, and produce results for at least 4 years of follow-up [21].

The hospitals participating in this proposed study have a common characteristic: specifically, each is a large public university hospital involved in the training of new vascular surgeons within the most densely populated state of Brazil. This study, therefore, will represent a significant and ecologically valid sample for the treatment of carotid atherosclerosis in Brazil. Despite the existence of countless studies and international records pertaining to treatment for carotid artery disease, our study aims to obtain relevant data in the real-world of medical care in public university hospitals that are training future Brazilian vascular surgeons. Interactions between professionals who specialize in treating neurovascular diseases and vascular surgeons has become increasingly important in the ongoing search for the best approach to treating carotid disease, so the increased knowledge regarding the therapeutic results that are obtained in each region or country is of fundamental importance [22]. This knowledge will contribute very significantly to improving care for patients with carotid disease, in addition to qualifying the level of assistance provided in public university hospitals in the state of São Paulo, Brazil.

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Authors' Contributions

All authors had a fundamental role in conducting the study: EEJ conceived and interpreted the data; WBY designed the study; MLS, RM, ATG, SRO, DGM, and LH undertook data acquisition and analyses; MJA undertook data acquisition and analyses, and interpreted the data. All authors have approved the final version of the paper.

Conflicts of Interest

None declared.

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Abbreviations

BMT: best medical therapy
CAS: carotid artery stenting
CEA: carotid endarterectomy
CREST: Carotid Revascularization Stent Trial
EPD: embolic protection device
ICSS: International Carotid Stenting Study
MI: myocardial infarction
OR: odds ratio
RHEUNI: Registry Project of Vascular Disease in the Public University Hospitals of São Paulo

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Original Paper

Spinal Cord Injury—Assessing Tolerability and Use of Combined Rehabilitation and NeuroAiD (SATURN Study): Protocol of An Exploratory Study In Assessing the Safety and Efficacy of NeuroAiD Amongst People Who Sustain Severe Spinal Cord Injury

Ramesh Kumar[1], FRCS (Neurosurgery); Ohnmar Htwe[2], M Med Sc (Rehab Med); Azmi Baharudin[2], MS (Ortho); Mohammad Hisam Ariffin[2], MS (Ortho); Shaharuddin Abdul Rhani[2], MS (Ortho); Kamalnizat Ibrahim[2], MS (Ortho); Aishah Rustam[3], MD; Robert Gan[3], MD

[1]Department of Neurosurgery, Faculty of Medicine, University Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia
[2]Department of Orthopaedics and Traumatology, Faculty of Medicine, University Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia
[3]Medical Affairs, Moleac, Biopolis Way, Singapore

Corresponding Author:
Ramesh Kumar, FRCS (Neurosurgery)
Department of Neurosurgery
Faculty of Medicine
University Kebangsaan Malaysia Medical Centre
Jalan Yaacob Latif
Kuala Lumpur,
Malaysia
Phone: 60 391455555
Fax: 60 391456684
Email: rameshkumar71@hotmail.com

Abstract

Background: Spinal cord injury (SCI) is a devastating condition with limited therapeutic options despite decades of research. Current treatment options include use of steroids, surgery, and rehabilitation. Nevertheless, many patients with SCI remain disabled. MLC601 (NeuroAiD), a combination of natural products, has been shown to be safe and to aid neurological recovery after brain injuries and may have a potential role in improving recovery after SCI.

Objective: The aim of this study is to evaluate the safety and efficacy of NeuroAiD amongst people who sustain SCI in the study setting.

Methods: Spinal Cord Injury—Assessing Tolerability and Use of Combined Rehabilitation and NeuroAiD (SATURN) is a prospective cohort study of patients with moderately severe to severe SCI, defined as American Spinal Injury Association (ASIA) Impairment Scale (AIS) A and B. These patients will be treated with open-label NeuroAiD for 6 months in addition to standard care and followed for 24 months. Anonymized data will be prospectively collected at baseline and months 1, 3, 6, 12, 18, and 24 and will include information on demographics; main diagnostics; and neurological and functional state assessed by the Spinal Cord Independence Measure, ASIA—International Standard for Neurological Classification Spinal Cord Injury, and Short Form (SF-8) Health Survey. In addition, NeuroAiD treatment, compliance, concomitant therapies, and side effects, if any, will be collected. Investigators will use a secured online system for data entry. The study is approved by the ethics committee of Hospital University Kebangsaan Malaysia.

Results: The coprimary endpoints are safety, AIS grade, and improvement in ASIA motor score at 6 months. Secondary endpoints are AIS grade, ASIA motor scores and sensory scores, Spinal Cord Independence Measure (SCIM), SF-8 Health Survey, and compliance at other time points.

Conclusions: SATURN investigates the promising role of NeuroAiD in SCI especially given its excellent safety profile. We described here the protocol and online data collection tool we will use for this prospective cohort study. The selection of moderately severe to severe SCI provides an opportunity to investigate the role of NeuroAiD in addition to standard rehabilitation in patients with poor prognosis. The results will provide important information on the feasibility of conducting larger controlled trials to improve long-term outcome of patients with SCI.

Trial Registration: Clinicaltrials.gov NCT02537899; https://clinicaltrials.gov/ct2/show/NCT02537899 (Archived by WebCite at http://www.webcitation.org/6m2pncVTG)

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KEYWORDS

spinal cord injury; NeuroAiD; MLC601; MLC901; safety; recovery; efficacy

Introduction

Background

Spinal cord injury (SCI) is a devastating neurological disorder that affects thousands of individuals each year. Global incidence rate of traumatic SCI in 2007 was estimated at 23 cases per million (133,000 to 226,000 cases per annum) and prevalence was between 236 to 4187 per million [1].

Over the past decades, much progress has been made in our understanding of the molecular and cellular events in SCI, providing insights into important mechanisms of tissue damage and failure of regeneration of injured neurons. Current treatment options for SCI include the use of high-dose methylprednisolone and surgical interventions to stabilize and decompress the spinal cord in the acute period, while rehabilitation is provided as long-term management. There is currently no treatment that enhances recovery after the injury, and SCI remains to be a devastating condition for which therapeutic options are still limited [2].

Three decades of clinical research on interventions to improve neurological outcomes in persons with SCI has not translated the promise of preclinical discovery into a consensus standard of care treatment. Nonetheless, SCI researchers remain hopeful that advances in preclinical discovery coupled with improved clinical trial performance will yield effective restorative treatment [3].

There have been many lessons learned from past failures in clinical trials, including patient selection based on knowledge of prognosis for spontaneous natural recovery and other eligibility criteria, clinical trial design, and outcome measures [4-7]. By taking the lessons into consideration in selecting a series of cases to be treated, important insights may be gained into the potential role of NeuroAiD as a therapy for SCI.

MLC601 (NeuroAiD, Nu-rAiD) is a combination of 14 natural ingredients indicated as treatment for poststroke recovery widely used in China and in many countries in Asia [8,9]. In Europe, a simplified formulation of the product, MLC901 (NeuroAid II, NurAiD II), consisting of 9 herbal components is available and will soon be available in Asian countries as well. Both formulations shall collectively be referred to as “NeuroAiD” in this study.

NeuroAiD efficacy and safety are supported by preclinical and clinical studies. The neuroprotective and neuroproliferative properties of NeuroAiD have been extensively elucidated during in vitro and in vivo experiments using animal and cellular models of focal and global ischemia [8-11]. In addition, research on its positive effects in traumatic brain injury (TBI) has recently been published [12,13]. What are remarkable are the effects of NeuroAiD on neurogenesis and neurorestoration beyond mere neuroprotection.

Case series reports of the use of NeuroAiD in neurosurgical conditions have been the subject of publications and presentations in international neurosurgical congresses [14-16]. In addition, there are several ongoing studies on the use of NeuroAiD in poststroke cognitive impairment and TBI [17-19].

The clinical data on NeuroAiD, however, are most well-reported in stroke. A systematic review of randomized clinical trials on NeuroAiD showed its benefits in improving functional outcomes and neurological deficits with 3 months treatment among patients with ischemic stroke in the preceding 1 week to 6 months [20-25]. Subsequently, NeuroAiD was investigated in acute ischemic stroke within 72 hours of onset which demonstrated the treatment effect to be larger in postacute and relatively more severe stroke at 3 months [26-29]. The updated meta-analysis showed a pooled odds ratio in favor of NeuroAiD [27]. Furthermore, treatment with NeuroAiD was associated with a reduction in risk of early vascular events after a stroke [30]. More recently, the extension study of this randomized, placebo-controlled, double blind trial has provided evidence of its benefit on long-term functional outcome persisting over time up to 18 months after a stroke with an excellent safety profile [31].

Since 2001 when it was marketed in China, there have been minimal serious side effects reported to date with the use of NeuroAiD. The common side effects reported from NeuroAiD were mostly mild and transient. Excellent clinical safety has been demonstrated in published clinical trials which reported the more common adverse events being gastrointestinal (nausea, vomiting, discomfort, diarrhea, dry mouth) and headache [20-34]. Safety studies in humans have shown that NeuroAiD, given alone or combined with aspirin, had no effect on clotting and coagulation [35]. Furthermore, there was no effect on hematological, hemostatic, and biochemical parameters or electrocardiogram in normal and stroke patients, even when started within 48 hours of stroke onset [35-37].

Study Objectives

The primary objective of this cases series is to evaluate the safety and potential role of NeuroAiD in SCI.

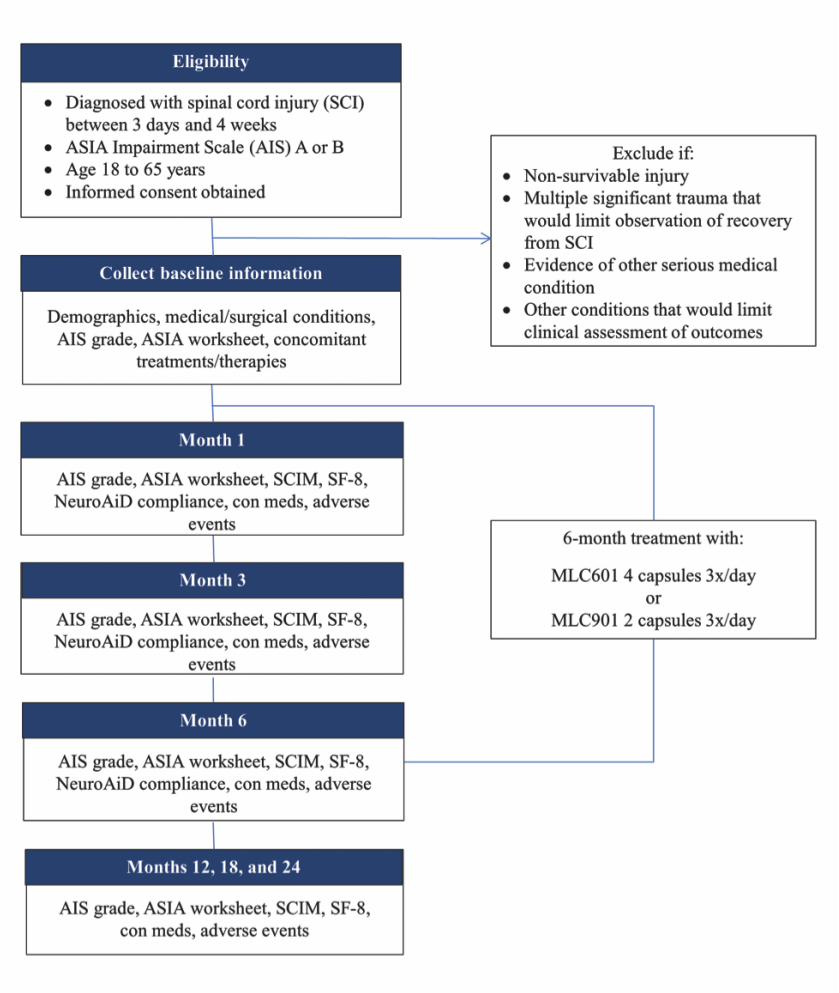
Methods

Study Design and Subject Eligibility

Spinal Cord Injury—Assessing Tolerability and Use of Combined Rehabilitation and NeuroAiD (SATURN) is a prospective cohort study of patients with moderately severe to severe SCI treated with open-label NeuroAiD in addition to standard care (Figure 1).

As this is an open-label study, inclusion of patients with SCI who are likely to spontaneously recover may confound the results of the study. Potential prognostic factors are severity of SCI and time from injury to assessment [4]. Therefore, patients are included in the study if they meet all of the following inclusion and none of the exclusion criteria (see Textbox 1).

Figure 1. Spinal Cord Injury—Assessing Tolerability and Use of Combined Rehabilitation and NeuroAiD (SATURN) study flowchart.



Textbox 1. Selection criteria for the study.

Inclusion criteria:

- Male or female
- Age 18 to 65 years
- Diagnosed with SCI between 3 days and 4 weeks
- American Spinal Injury Association (ASIA) Impairment Scale (AIS) A or B
- Informed consent obtained

Exclusion criteria:

- Nonsurvivable injury
- Multiple significant trauma (ie, significant intracranial and extracranial injuries including limb fractures) that would limit observation of recovery from spinal cord injury
- Other conditions that would limit clinical assessment of outcomes (eg, dementia, demyelinating disease, autoimmune disease)
- Refusal of treatment or contraindication to NeuroAiD

Study Setting and Recruitment of Participants

Information about the study will be disseminated to the hospital and department staff. Any potential subject referred to the study team will be prescreened for potential eligibility. Permission to approach the patient or their legal representative will be obtained from the primary physician. Participants who fulfil the eligibility criteria will be recruited while still in the hospital for treatment or rehabilitation within the specified time window from injury. Informed consent will be obtained from all participants after discussion of the nature, purpose, and potential risks of the study.

Treatment

Each 400 mg capsule of MLC601 contains 9 herbal ingredients (extracts of *Radix astragali*, *Radix salviae miltiorrhizae*, *Radix paeoniae rubra*, *Rhizoma chuanxiong*, *Radix angelicae sinensis*, *Carthamus tinctorius*, *Prunus persica*, *Radix polygalae*, and *Rhizoma acori tatarinowii*) and 5 nonherbal components (Hirudo, *Eupolyphaga seu steleophaga*, *Calculus bovisartifactus*, *Buthus martensii*, and *Cornu saigae tataricae*). MLC901 contains only the 9 herbal extracts.

The product is available in capsule form and administered orally or the contents may be diluted in water and administrated via gastric tube. The dosage is 4 capsules 3 times a day for MLC601 and 2 capsules 3 times a day for MLC901. The treatment duration is 6 months.

The capsules should be kept sealed until opened for administration and stored below 30°C in a dry place. NeuroAiD is manufactured according to applicable control measures that ensure the consistency and quality of the product from batch to batch and adhere to good manufacturing practice. The active ingredients and finished product are subjected to full quality control testing for safety.

All participants are allowed to receive standard care and other therapies and treatments including, but not limited to, surgery, rehabilitation, and other types of care deemed appropriate and as prescribed by their physician. There is no restriction to the use of any other treatment as recommended by the treating physician although other treatments should be recorded in the database.

Variables Collected

Subjects will undergo assessments at baseline and at months 1 (±7 days), 3 (±14 days), 6 (±14 days), 12 (±30 days), 18 (±30 days), and 24 (±30 days) (see Table 1). Information collected is meant to specifically address the objectives of the study.

Table 1. Schedule of Spinal Cord Injury—Assessing Tolerability and Use of Combined Rehabilitation and NeuroAiD (SATURN) study procedures.

Information collected	Base-line	Month 1 ±7d	Month 3 ±14d	Month 6 ±14d	Month 12 ±30d	Month 18 ±30d	Month 24 ±30d
Demographics	X						
Diagnosis and medical condition	X						
Surgical history	X						
AIS[a] grade	X	X	X	X	X	X	X
ASIA ISNCSCI[b] worksheet	X	X	X	X	X	X	X
NeuroAiD treatment/compliance	X	X	X	X			
SCIM[c]		X	X	X	X	X	X
SF-8[d] Health Survey	X	X	X	X	X	X	X
Concomitant treatments/therapies	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X

[a]AIS: American Spinal Injury Association Impairment Scale.

[b]ASIA ISNCSCI: American Spinal Injury Association International Standard for Neurological Classification Spinal Cord Injury.

[c]SCIM: Spinal Cord Independence Measure.

[d]SF: Short Form.

Data collected at baseline immediately prior to or at the start of NeuroAiD treatment will include

- Demographics data: date of birth, gender, ethnicity
- Details of diagnosis of SCI: date of occurrence; spinal cord level; cause of spinal cord injury; magnetic resonance imaging, computed tomography, or x-ray results; presence of specific sequelae of SCI (eg, respiratory failure, pneumonia, circulatory problems, spasticity and muscle tone, autonomic dysreflexia, pain, bladder and bowel dysfunctions, sexual dysfunction)
- AIS grade (pre- and postsurgery if patient undergoes surgery)
- ASIA International Standard for Neurological Classification Spinal Cord Injury (ISNCSCI) worksheet (pre- and postsurgery if patient undergoes surgery)
  - Motor subscores for each limb and total motor score based on ASIA
  - Sensory subscores based on ASIA
  - Other items in the ASIA ISNCSCI worksheet
- NeuroAiD use: date started and dose

- Concomitant medications and treatments including any surgical intervention (date performed), treatments administered (start date and stop date), and rehabilitation (ie, physical and occupational therapies [start date, stop date, location—rehabilitation center, home-based]).

Data collected from month 1 to month 24 will include compliance with intake of NeuroAiD, occurrence of any adverse event, Spinal Cord Independence Measure (SCIM), and Short Form (SF)-8 Health Survey, in addition to the other clinical assessments performed at baseline.

Data Collection

The investigators or designated personnel must record all required participant data in their entirety to ensure accurate interpretation of data. An explanation must be documented for any missing data. Data will be collected through an online data entry system [38] which is compliant with the Health Information Privacy and Security Act. Contributors to the study will be provided secured access accounts with username and password. Paper report forms are available if online submission is not possible (eg, Internet downtime, computer malfunction, power outage) but online entry is the preferred mode of data collection. If paper forms are used, data must be written in a neat and legible manner using black or blue ballpoint pen to ensure the clarity of the reproduced copy of all completed forms which are signed and dated. The completed online or paper forms shall serve as the source documents. No other medical record or source document will be required for this study.

Study Endpoints

The primary endpoints for this study are the AIS grade at 6 months, the improvement in ASIA total motor score at 6 months compared to baseline, and safety.

The secondary endpoint measures will be the neurological recovery of the subjects as assessed by

- AIS grade at 1, 3, 12, 18, and 24 months
- ASIA motor scores at 1, 3, 12, 18, and 24 months
- ASIA sensory scores at 1, 3, 6, 12, 18, and 24 months
- SCIM at 1, 3, 6, 12, 18, and 24 months
- SF-8 Health Survey at 1, 3, 6, 12, 18, and 24 months
- Compliance to NeuroAiD at 1, 3, and 6 months

Safety Considerations

Definition of Adverse Event and Serious Adverse Event

An adverse event is defined as any untoward medical occurrence in a person administered a product which does not necessarily have a causal relationship with this treatment. An adverse event is considered a serious adverse event if it results in death, persistent or significant disability, abortion, congenital anomaly, or birth defect; is life-threatening; or requires inpatient hospitalization or prolongation of existing hospitalization.

Side Effect (or Adverse Drug Reaction)

A side effect is an effect, whether therapeutic or adverse, that is secondary to the one intended. It can also apply to beneficial, but unintended, consequences of the use of a treatment. For the purpose of this study, a side effect (or adverse drug reaction) is any unintended adverse event that is related to the use of the treatment, NeuroAiD. Based on causality as defined by the World Health Organization–Uppsala Monitoring System [39], any adverse event that is considered by the treating physician as being possibly, probably, or definitely related to NeuroAiD would be considered as a side effect.

Reporting of Adverse Events and Side Effects

All adverse events or laboratory abnormalities that develop during the course of the participant's treatment will have to be reported in the study. Adverse events should be reported as a diagnosis or syndrome. If this is not possible, the specific symptom or abnormality may be entered. The start date of first onset of any sign or symptom of the event and stop date (date the event is considered to have resolved, if resolved) should be entered. Seriousness should be classified according to the definition of a serious adverse event.

Side effects that are reported in the study, especially those categorized as serious, will trigger a request for more medical information to ascertain details and need for reporting as serious adverse reaction to local regulatory authorities, if required.

Follow-Up of Adverse Events

Any adverse event must be followed until resolution, the condition stabilizes, the event is explained, or the participant is lost to follow-up. The physician is responsible to ensure that standard medical diagnostic or therapeutic management, if any, is performed.

Common Side Effects Reported From NeuroAiD

The common side effects reported from NeuroAiD use were mostly mild and transient. These include dry mouth, nausea, vomiting, abdominal discomfort, diarrhea, and headache. In many cases, the side effect resolved with reduction of the dose by half for one week, resumed at the usual dose after resolution of the symptom.

Ethical Considerations

Approval from the ethics committee of the Hospital University Kebangsaan Malaysia has been obtained for this study. Patient information sheet and informed consent form as approved by the ethics committee will be used to explain to the subjects the nature and purpose of their participation prior to performing any study-related procedures.

The potential risks involved in participating in the study will be explained to the patient. The medical judgement regarding the use of NeuroAiD as treatment for SCI is a joint decision of the physician and the patient or legal representative. This decision must be arrived at prior to and without consideration of the patient's potential participation in the study registry. Possible common side effects of the treatment and in very rare cases severe allergic reaction or unexpected life-threatening events will be explained.

Statistical Consideration

The target number of participants for this exploratory cohort study is set at 30. Descriptive statistics will be used to summarize data. Outcome assessments will be compared to baseline and previous observations. Comparison with appropriate historical controls with the same AIS grading and

timeframe will be performed [4]. Multiple variable analyses will be used to identify predictors of better outcome, when appropriate. Other analyses deemed appropriate by the investigators and statistical consultant will also be performed.

Study Administration and Oversight

The study shall be carried out in the Hospital University Kebangsaan Malaysia, Kuala Lumpur, Malaysia, led by the principal investigator (RK) and assisted by coinvestigators (OH, AB, MHA, SAR, KI).

Data Management

The online data entry system is compliant with the Health Information Privacy and Security Act. Data will be maintained in a secured database in Moleac (Singapore) accessible only to relevant personnel. Subjects' identities will be recorded only as initials with identification numbers. Specific individual information in the study will not be shared with other persons, entities, or companies unless required by legal authorities. Collective anonymized information will be summarized and reviewed. These summaries may be presented to stakeholders (eg, physicians, regulatory authorities, attendees in a conference) and/or published in scientific journals.

Adherence and Amendments to Protocol

Study investigators must adhere to the protocol and ensure that it is strictly followed. If necessary, an amendment may be implemented only after approval is obtained for the amendment from the ethics committee, except where necessary to eliminate an immediate hazard to participants or when changes involve any logistical or administrative aspects of the study (eg, change of personnel, change of telephone number). Amendments may not remove any of the basic data elements as described in this protocol.

Closure of Study

The study shall be closed when the number of study participants has been reached and the investigators agree that further inclusion of participants is no longer relevant or necessary. The closure will occur in steps, starting with informing investigators of the plan to discontinue inclusion of more participants and until after the follow-up of the last participant has been completed. The database will subsequently be locked upon an agreed timeframe with the principal investigator.

Results

The study is currently recruiting patients and is expected to complete in June 2018.

Discussion

The treatment options for SCI are limited. The reasons for the failure of earlier clinical trials to find new therapies in SCI have been extensively discussed [3-7]. Exploring new therapeutic strategies from natural substances is attractive and has gained much attention recently. The SATURN study investigates the promising role of NeuroAiD in SCI using an open-label cohort study design which is appropriate for a first-ever safety and efficacy study of a new treatment in this condition. Nevertheless, the design of the study takes much of past learnings into consideration. SATURN would include more severe and less acute patients among whom true treatment effect may be better demonstrated by reducing spontaneous recovery as a confounder. Neurological, functional, and quality of life outcomes are measured. As recovery and neuroplasticity may take time to accrue, the period of treatment and observation is extended to detect any delayed benefits which may not be apparent during the first few months of SCI. Published cohorts of patients with the same severity and timeframe may serve as historical controls. The knowledge gained from SATURN will certainly provide important insights on safety and efficacy in planning future clinical trials.

Acknowledgments

Saiful Najaib (Moleac Singapore) programmed and maintains the online data collection system for the study.

Authors' Contributions

RK is the principal investigator of this study. RK, OH, AB, MHA, SAR, KI, AR, and RG have contributed substantially to the conceptualization and design of the study. RK, OH, AB, MHA, and SAR will have equal contributions in patient recruitment, treatment, follow-up, data analysis, and writing of the manuscript reporting the results of the study.

Conflicts of Interest

This study is supported in part by Moleac Singapore Pte Ltd, 11 Biopolis Way #09-08 Helios, Singapore 138667. RK has received support for clinical trials and presentations at scientific meetings from Moleac Singapore. AR and RG are employees of Moleac Singapore. Other than support for this study, the other authors have no other competing interests to declare.

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Abbreviations

AIS: American Spinal Injury Association Impairment Scale
ASIA: American Spinal Injury Association
ISNCSCI: International Standard for Neurological Classification Spinal Cord Injury
SATURN: Spinal Cord Injury—Assessing Tolerability and Use of Combined Rehabilitation and NeuroAiD
SCI: spinal cord injury
SCIM: Spinal Cord Independence Measure
SF-8: Short Form 8-Item Health Survey
TBI: traumatic brain injury

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Protocol

A Multidisciplinary Model to Guide Employment Outcomes Among People Living With Spinal Cord Injuries in South Africa: A Mixed Methods Study Protocol

Ntsikelelo Pefile[1*], BSc (Physio), PGDip (PH), MScMedSc (Rehab); Joyce Mothabeng[2*], BSc (Physio), MSc (Physio), PhD (Physio); Saloshni Naidoo[3], MBChB, MMed, FCPHM, PhD (PH)

[1]School of Health Sciences, Division of Physiotherapy, University of KwaZulu-Natal, Durban, South Africa

[2]Department of Physiotherapy, School of Health Sciences, Univeristy of Pretoria, Pretoria, South Africa

[3]Department of Public Health Medicine, School of Nursing and Public Health, University of KwaZulu-Natal, Durban, South Africa

[*]these authors contributed equally

Corresponding Author:
Ntsikelelo Pefile, BSc (Physio), PGDip (PH), MScMedSc (Rehab)
School of Health Sciences
Division of Physiotherapy
University of KwaZulu-Natal
Private bag x54001
Durban,
South Africa
Phone: 27 0312607181 ext 7181
Fax: 27 0312608106
Email: pefilen@ukzn.ac.za

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Abstract

Background: Spinal cord injury (SCI) often results in complete or partial loss of functioning of the upper and/or lower limbs, leading to the affected individual experiencing difficulties in performing activities of daily living. This results in reduced participation in social, religious, recreational, and economic activities (employment). The South Africa legal framework promotes the employment and assistance of people with disabilities. However, rehabilitation interventions focus mainly on impairments and activity limitations, with few attempts to prepare those with SCI to return to gainful employment. There is therefore a need for a well-coordinated, multidisciplinary rehabilitation initiative that will promote the employment of people living with spinal cord injuries (PLWSCI) in South Africa.

Objective: This study aims to develop a multidisciplinary model to guide employment outcomes amongst PLWSCI in South Africa.

Methods: This study will utilize explanatory mixed methods during 3 phases. The first phase will explore the current rehabilitation practices, and the second will establish the factors that influence employment outcomes among PLWSCI. A multidisciplinary team consisting of health care professionals, representatives from the departments of Labour, Education, Social Development, and Health, and nongovernment organizations representing PLWSCI will provide feedback for the model development of phase 3, along with results from the previous 2 phases, using a multistage Delphi technique.

Results: It is estimated that the results of phases 1 and 2 will be completed 11 months after data collection commencement (November 2015). Phase 3 results will be finalized 4 months after phases 1 and 2.

Conclusions: Developing a multidisciplinary model to guide the employment outcomes of PLWSCI will ensure a coordinated response to integrate them into a productive life and will assist them to achieve economic self-sufficiency, personal growth, social integration, life satisfaction, and an improved quality of life. This can be achieved by active inclusion of PLWSCI to ensure that their concerns and recommendations are addressed.

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KEYWORDS

employment; spinal cord injury; vocational rehabilitation

Introduction

Overview

A spinal cord injury (SCI) is a life-transforming condition of sudden onset that can have devastating consequences [1]. It often results in complete or partial loss of functioning of the upper and/or lower limbs, and the affected individuals have difficulties in performing activities of daily living, which reduces their participation in social, recreational, and economic activities. An important activity for adults is the participation in productive work, as most societies expect people to work, with employment being regarded as a key indicator of social integration [2]. Employment provides people living with spinal cord injuries (PLWSCI) with economic and intrinsic rewards and enables greater life satisfaction and an improved quality of life. Globally, it is estimated that the employment rate of PLWSCI, following rehabilitation, ranges between 21% to 67% depending on age, gender, level of education, race, marital status, cause of injury, neurological level and classification, health status, degree of functional independence, time since injury and internal locus of control, access (including transport), and accommodation [2]. There is a paucity of information on the unemployment rate of people with disabilities (especially PLWSCI) in South Africa, which is estimated to be 25.2% [3]. However, this is compounded by a lack of information on the factors influencing employment and the absence of a rehabilitation framework aimed at improving employment outcomes among PLWSCI in South Africa.

In South Africa, a legal framework exists that promotes the employment as well as assistance of people with disabilities in the workplace. The Constitution of the Republic of South Africa 108 (1996) [4] clearly stipulates that all South African citizens (including PLWSCI) are equally entitled to the rights, privileges, and benefits (including employment) of citizenship [5]. Furthermore, chapter 2 of the constitution states that no citizen may be unfairly discriminated against (directly or indirectly) on one or more grounds (including disability). In addition, the Promotion of Equality and Prevention of Unfair Discrimination Act 4 (2000) [6] and the Employment Equity Act 55 (1998) [7] were promulgated to prevent unfair discrimination of people with disabilities and to promote their employment. The Labour Relations Act 66 (1995) [8], Skills Development Act 97 (1998) [9], Public Service Act 103 (1994) [10], and Basic Conditions of Employment Act 11 (1997) [11] were also enacted to guide employers (in private and public sector) in employing people with disabilities (including PLWSCI). The Integrated National Disability Strategy [12] and the South African National Rehabilitation Policy (2000) identified vocational rehabilitation as one of the key components of providing services to those affected. Rehabilitating individuals with SCI is intended to maximize their physical functioning and gainful employment so as to integrate them into their communities [13-15] and is often achieved through coordinated efforts in a multidisciplinary setting that includes physiotherapy.

There are 24 private and government-funded rehabilitation facilities in South Africa, none of which offers comprehensive rehabilitation programs that are multisectorial and multidisciplinary and facilitates employment of PLWSCI. Rehabilitation interventions provided in such institutions are mainly medical, with limited attempts to prepare those with SCI to return to gainful employment [16]. There is therefore a need for a well-coordinated, multisectorial, multidisciplinary, and multifactorial rehabilitation intervention that will promote the employment of PLWSCI in South Africa. Data on vocational rehabilitation practices, employment status, and factors influencing employment outcomes among PLWSCI are therefore required in order to develop a model that will guide the employment outcomes for affected individuals. Consequently, the aim of this study is to develop a multidisciplinary model to guide employment among people living with SCI in South Africa.

The objectives are to

1. Systematically review the literature on international vocational rehabilitation interventions for PLWSCI

2. Identify gaps in vocational rehabilitation practices by retrospectively analyzing the medical files of SCI patients

3. Explore vocational rehabilitation practices used by rehabilitation professionals among people who sustain SCI in KwaZulu-Natal, South Africa

4. Explore employment and its influencing factors amongst PLWSCI in KwaZulu-Natal

5. Determine the barriers and facilitators of employment among PLWSCI in KwaZulu-Natal

6. Triangulate information from phase 1 and 2 of the study and create aspects and structure of the proposed model

7. Validate and refine the model through consensus among stakeholders

8. Disseminate the model to stakeholders and relevant industry players in South Africa.

Theoretical Framework

The conceptualization and development of this study is based on a combination of social justice theory, the social model of disability, international classification of functioning, disability and health. These are the guiding lenses to identify the variables to be assessed and the manner of their assessment and analysis.

Social justice is about declaring the protection of equal access to liberties, rights, and opportunities, as well as taking care of the least advantaged members of society (including individuals living with SCI) [17]. Social justice is concerned with human well-being, which is described with 6 dimensions (related to each other) being identified as health, personal security, reasoning, respect, attachment, and self-determination [18]. For the purpose of this study, health, reasoning, respect, attachment, and self-determination will be explored.

Health is expressed as crucial to sustaining human existence across the full life span. Health in this context is described as more than the absence of biological malfunctioning or impairment and includes functional ability such as mobility, sight or hearing, pain, sexual dysfunction, infertility, and occupation [18,19]. Poor health is positively associated with poor employment outcomes in PLWSCI, often due to secondary complications such as pressure sores, depression, spasms, pneumonia, and heterotrophic ossification [20]. These and other conditions will be explored in this study to determine their impact on employment outcomes among PLWSCI using the International Classification of Diseases and Function (ICF). The ICF is a framework that is used to holistically assess the impairments, activity limitations, and participation restrictions in an individual with a disease or injury [21-24]. It assists professionals to establish the interactions of these domains with the environment to develop appropriate rehabilitation interventions.

It is further argued that reasoning includes analytical ability, imagination, the ability to form beliefs based on evidence (or experience), the ability to reflect on what counts as relevant evidence for those beliefs, and the ability to weigh the probative value of each [18]. In this study, this dimension will be explored by investigating the perspectives of PLWSCI regarding the impact of rehabilitation on their preparedness to participate in employment activities once discharged and by describing the factors that influence their participation in employment activities. PLWSCI will form an integral part of the team developing the proposed model to improve their employment outcomes.

Respect is an essential element of human flourishing and is an important concern of justice, being linked to self-respect [18]. The authors perceive respect as involving treatment of others as dignified moral beings, deserving of equal moral concern, which requires an ability to see people as independent sources of moral worth and dignity and view them as appropriate objects of sympathetic identification. Throughout the 3 phases of this study, this dimension will be achieved through the active participation of PLWSCI, which will be guided by the social model of disability.

The social model of disability is a paradigm that redefines disability in terms of the disabling environment and repositions disabled people as citizens with rights [25]. This model contends that society fails to provide appropriate services for PLWSCI and that barriers in society have to be removed for people with disabilities to fully participate in life situations (especially employment) [25-28]. Furthermore, the model stipulates that the programs or approaches developed to remove those barriers should be developed in consultation with people living with disabilities.

Attachment is the fourth dimension of Powers and Faden's social justice theory [18]. They argue that forming bonds of attachment is one of the most central dimensions of human well-being. These bonds include friendship, love, solidarity, or fellow-feeling with others within their home, work, and social communities. In this study, the impact of employment on these relationships will be explored for PLWSCI and will give clarity on how they perceive their social role in interacting with fellow coworkers.

The last dimension put forward by Powers and Faden is self-determination, which is argued to be the ability to make decisions about one's life plan [18]. While many PLWSCI are unable to control their physical mobility and their interaction with their physical environment, this does not mean that they should be excluded from being involved in making decisions about their lives. Therefore, developing a model that will attempt to improve employment outcomes in PLWSCI needs their active participation, this being in line with the principles enshrined in the social model of disability.

Methods

Overview

This explanatory mixed methods study will entail the collection and analysis of both quantitative and qualitative data [29-31]. An explanatory sequential approach will be used as described by Cresswell [30]. This study is divided into 3 phases, each of which consists of a number of stages to address the study objectives (see Figure 1).

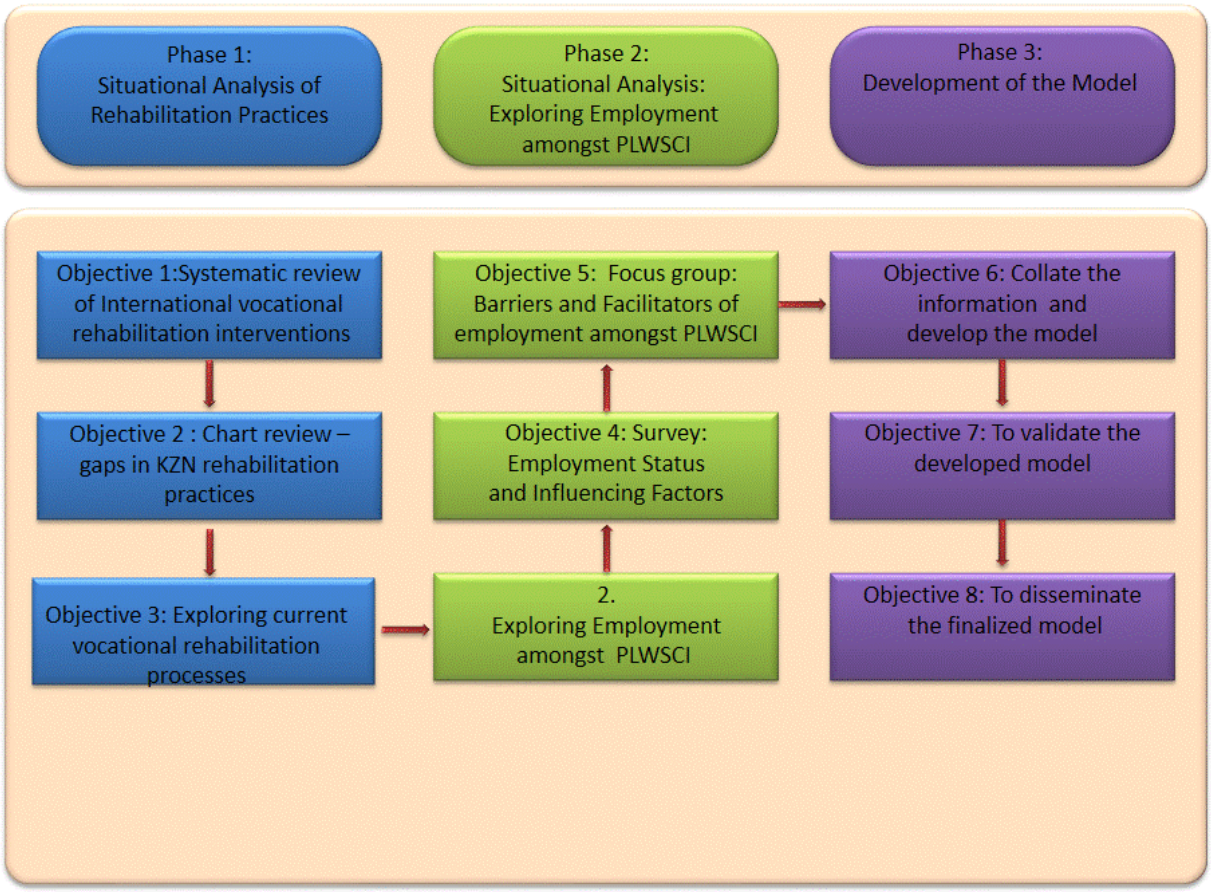
Phase 1 of this study will address objectives 1 through 3 and will provide the background to current international and local practices regarding vocational rehabilitation strategies. This phase will also enable questionnaires and focus group schedules to be developed for discussion with stakeholders (rehabilitation professions, academics, nonprofit organizations, PLWSCI, insurers, and government representatives) for subsequent phases. Objective 1 will entail a systematic review of literature to identify the current best practices for vocational rehabilitation interventions. Objective 2 will identify gaps in vocational rehabilitation practices through retrospective review of the medical files of SCI patients at 2 regional spinal units in KwaZulu-Natal Province, South Africa [32]. Objective 3 will consist of semistructured interviews and focus groups with rehabilitation professionals and PLWSCI to establish the vocational rehabilitation services currently being rendered to SCI patients in KwaZulu-Natal Province.

Phase 2 will provide opportunities to engage with relevant stakeholders (PLWSCI, rehabilitation professionals, medical insures, and representatives from the KwaZulu Natal provincial departments of Education, Health, Social Development, Transport, and Labour) to determine the employment rate and associated factors of affected persons in postrehabilitation. Objective 4 will consist of structured interviews with PLWSCI to establish the contributing factors to their employment status since their injury. Objective 5 will explore the barriers and

facilitators of employment among PLWSCI focus groups. The inclusion of several stakeholders will enable a range of perspectives to be explored, this being important for developing the model.

The results obtained from phases 1 and 2 will be used to develop and validate a model in phase 3. Objective 6 will entail triangulating information from phases 1 and 2 to create the aspects and processes of the proposed model. Objective 7 will consist of a focus group with the stakeholders who participated in phase 2 to validate the content of the proposed model and will entail obtaining consensus (after 3 rounds) among the rehabilitation professionals and academics regarding the structure and the content of the proposed model and using the modified Delphi technique [33-35]. The model will then be made available to relevant organizations, institutions, and publications for dissemination (objective 8).

Figure 1. Methodology schematic diagram.



Data Collection Tools

Data collection tools for phase 1 (objectives 2 and 3) were developed using the International Spinal Cord Injury Core Data Sets [36,37] and the ICF checklists for individuals who sustained SCI [21,38,39]. The tool is divided into 5 sections: sections A and B contain information relating to the demographic profile (gender, age, marital status, population group, etc) of individuals who sustains SCI. Sections C and D contain information related to the injury and type of rehabilitation received in an acute or subacute setting. The last section of the tool contains information regarding the outcomes of rehabilitation and circumstances related to the discharge process. The interview schedule to be used to collect data to realize objective 3 contains questions relating to current rehabilitation practices and perceived barriers and facilitators of employment among PLWSCI from the perspective of the health care team (directly involved in caring for individuals who sustain SCI in the study setting). During the quantitative stage of phase 2 (objective 4), a data collection tool developed by the researcher using the literature [40-44] will be used. This tool is divided into 12 sections: sections A and B contain information relating to demographic information and employment history; sections C and D contain information relating to the attitudes toward employment and environment; sections E and F contain information relating to medical complications and social support; section G, H, and I contain attendance and bowel and bladder management information, and sections K, L, M, and N contain information relating to the injury, functional abilities, and quality of life. The tool will be assessed for validity and reliability in the study setting. The interview guide to realize objective 5 will be developed using the information obtained in objective 4. This tool will also be validated. Data collections tools for phase 3 will be developed once the data of phases 1 and 2 are analyzed. Moreover, SurveyMonkey (SurveyMonkey.com LLC) will be used to develop the questionnaire and undertake each Delphi round

[35]. A 4-point Likert scale will be used to avoid neutral responses: agree, strongly agree, disagree, and strongly disagree). Each questionnaire will also have open-ended questions for participants to support their quantitative choices.

Ethical Considerations

The study protocol received full ethical clearance from the University of KwaZulu-Natal (UKZN) Biomedical Research Ethics Committee (BE499/14) and the KwaZulu-Natal Provincial Department of Health (KZ_2015RP38_59) and is registered at ClinicalTrials.gov [NCT02582619]. Informed consent will be sought from all participants before they participate in the study.

Study Setting and Participants

Objectives 2 and 3 of phase 1 will take place at 2 public sector hospitals that provide acute care services and the only public sector spinal rehabilitation unit in KwaZulu-Natal; the participants will consist of patients receiving care in these facilities and rehabilitation and health care professionals. Phase 2 will entail working with relevant nonprofit organizations to be able to access PLWSCI postrehabilitation as well as other stakeholders such as representatives from the private and public insurers, representatives from the state departments (Education, Health, Social Development, Transport, and Labour), and academics (who have a special interest in vocational rehabilitation and SCI care) invited to participate due to their expertise or role in providing services to people with SCI. The focus group discussions for objectives 7 and 8 (phase 3) will take place at the Physiotherapy Department, UKZN, Westville Campus, Durban, and will consist of rehabilitation specialists and PLWSCI, who will be provided with transport to and from the venue.

Multistage sampling technique will be used throughout the various phases of the study. A random sampling technique will be used to select participants during the quantitative parts of the study and purposive sampling during the qualitative (interviews and focus groups) parts. The sample size was calculated using the formula, $n=Z^2(1-\alpha/2)\ pq/d^2$ where $Z(1-\alpha/2)=1.96$ at 95% confidence interval (p=proportion of individuals with SCI admitted, q=1−p, and d=absolute allowable error). For this study, we presumed that $P=.5$ yields the largest possible sample size (maximum variability) if better approximation is not known, q=0.5, and precision (d)=±5%. This yielded a required size of 384 participants for phase 1.

Based on the finite population correction for estimated number of individuals who sustain a spinal cord injury previously seen in each facility over the last 5 years, the overall required sample size can be reduced to 295 for phase 1 (objective 2). Proportional sampling of each facility will be done based on the annual numbers of patients seen in each facility. Within each facility, files will be randomly selected to achieve the expected number of participants in each facility. The same formula was used to calculate the sample size for the quantitative phase 2 (objective 4) and yielded 123 participants. During the qualitative stages of phases 1 and 2 purposive sampling (representation of all study identified stakeholders) will be used to select participants. In phase 3, participants will be purposively selected with a representation from each group of the stakeholders for both the focus group and the Delphi rounds. Therefore, 18 participants will form part of the focus group and 30 participants will be identified in the subsequent Delphi rounds. During the interviews and focus group discussions, participants will be recruited in person and telephonically, after which they will be sent an email with a formal invitation to participate in the study and will also be requested to provide informed consent.

Data Analysis

Throughout the phases, the quantitative data will be captured and analyzed using SPSS version 23 (IBM Corp). For objective 1, exploratory data analysis will be performed using a leaf and box plot to determine the distribution of the data to select the appropriate statistical tests. For objectives 1, 2, and 4 measures of central tendency and frequency distributions will be used to describe continuous and categorical data respectively. Depending on the distribution of the data, parametric and nonparametric tests will be used for bivariate analysis. Correlation efficient tests (Pearson correlation coefficient or Spearman rank correlation efficient) will be used to determine the relationship between the functional scores and the level of injury, the level of injury versus the length of stay, etc. Multiple linear regression and multiple logistic regression tests will be used to establish a relationship between demographic information and level of injury with the functional scores. The accepted level of significance will be less than .05. Analysis of data for objective 7 will include central tendencies such as median, mean, and mode and percentage score for each statement calculated to determine the level of dispersion and agreement respectively. The level of dispersion will be calculated for each statement using the interquartile range and standard deviation. Consensus will be defined as 70% or more of the participants being in agreement with a statement (that is participants scoring 4 (agree) or 5 (strongly agree), mean rating of more or equal than 3.5, and a coefficient of variation of less or equal to 30%. Kendall coefficient of concordance (W) will be calculated to measure consensus across participants. In consequent rounds (3) consensus will be acceptance of ratings higher than previously determined number by at least 51% of the participants and the elimination of topics that are vigorously opposed.

Qualitative data from objective 3 and 5 and part of objective 7 will be transcribed. To ensure accuracy, the research team will separately transcribe the information and compare and discuss discrepancies to reach a consensus using grounded theory. The written information will be checked for validity by the research team. Data will be uploaded to Nvivo version 10 (QSR International). This will be followed by content analysis during which the data from the interviews will be analyzed according to the following distinct but interconnected stages: Familiarizing (through reading and rereading transcripts as well as through listening to tapes over and over), identifying a thematic framework, indexing, charting and mapping, and interpretating the data as described by Raibee [45].

Attention will also be given to the nonverbal communication of interviewees. This will be noted on the interview schedule during the interview, and where nonverbal means of

communication is evident on recordings (eg, lengthy silences, laughter), it will be added to transcripts. Data will be presented according to identified themes, with narrative examples being used to highlight each. Verification of data will be done through member checking and will continue with interviews and discussions until data saturation has occurred [46].

Results

Phase 1 results will be triangulated and used to develop a guideline to integrate vocational rehabilitation during acute care and inpatient rehabilitation in the 2 public facilities that service people who sustain spinal cord injuries in KwaZulu-Natal. This phase will take 8 months to complete. The results from phase 2 will assist in describing the employment status, factors that influence employment, and barriers and facilitators of employment among PLWSCI. This phase will last for 3 months. The results from phases 1 and 2 will be integrated and used to develop the aspects and process of vocational rehabilitation model to improve employment outcomes. Once developed, the model will be validated through Delphi rounds. The last phase will last for 4 to 6 months.

Discussion

Despite the existence of a good legal and policy framework that promotes the employment of people living with disabilities in South Africa, there is a scarcity of literature addressing the employment outcomes in affected persons during rehabilitation. Vocational rehabilitation is a broad term that includes a variety of services to assist an individual following an illness or disability [43]. It is also a multidisciplinary rehabilitation strategy that aims at enabling a disabled person to secure, retain, and advance in suitable employment [47,48]. It is concerned with supporting efforts made by a person with a disability to return to and maintain employment and includes vocational guidance and training, placement, employment, and other related services [47]. Vocational rehabilitation has been proven to be effective in improving employment outcomes in PLWSCI in developed and some developing countries [43,49-52]. However, there are no studies that have been done in Africa and South Africa on PLWSCI. This study will therefore develop a multidisciplinary and multisectorial model that will facilitate and guide employment outcomes for PLWSCI. This model will be developed in collaboration with affected persons, rehabilitation professionals, public service, private sector, and the insurance industry. It will propose and advocate strategies to implement policy imperatives that promote the employment of people living with spinal cord injuries in South Africa in an endeavor to improve their quality of life and sense of self-worth as contributing members of society. Further studies will be proposed that will assess the cost effectiveness and general effectiveness of various vocational rehabilitation approaches amongst PLWSCI, as this is beyond the scope of this study.

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Conflicts of Interest

None declared.

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Abbreviations

ICF: International Classification of Disease and Function
PLWSCI: people living with spinal cord injury
SCI: spinal cord injury
UKZN: University of KwaZulu-Natal

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Original Paper

The e-EPIDEMIOLOGY Mobile Phone App for Dietary Intake Assessment: Comparison with a Food Frequency Questionnaire

Luis Maria Bejar[1], PhD; Brett Northrop Sharp[2], MD; María Dolores García-Perea[3], PhD

[1]Department of Preventive Medicine and Public Health, University of Seville, Seville, Spain

[2]Virgen Rocio University Hospital, Seville, Spain

[3]Virgen Macarena University Hospital, Seville, Spain

Corresponding Author:
Luis Maria Bejar, PhD
Department of Preventive Medicine and Public Health
University of Seville
Institute of Anatomy, 3rd floor
Sánchez-Pizjuán Avenue
Seville, 41009
Spain
Phone: 34 954551771
Fax: 34 954556481
Email: lmbprado@us.es

Abstract

Background: There is a great necessity for new methods of evaluation of dietary intake that overcome the limitations of traditional self-reporting methods.

Objective: The objective of this study was to develop a new method, based on an app for mobile phones called e-EPIDEMIOLOGY, which was designed to collect individual consumption data for a series of foods/drinks, and to compare this app with a previously validated paper food frequency questionnaire (FFQ).

Methods: University students >18 years of age recorded the consumption of certain foods/drinks using e-EPIDEMIOLOGY during 28 consecutive days and then filled out a paper FFQ at the end of the study period. To evaluate the agreement between the categories of habitual consumption for each of the foods/drinks included in the study, cross-classification analysis and a weighted kappa statistic were used.

Results: A total of 119 participants completed the study (71% female, 85/119; 29% male, 34/119). Cross-classification analysis showed that 79.8% of the participants were correctly classified into the same category and just 1.1% were misclassified into opposite categories. The average weighted kappa statistic was good (κ=.64).

Conclusions: The results indicate that e-EPIDEMIOLOGY generated ranks of dietary intakes that were highly comparable with the previously validated paper FFQ. However, it was noted that further testing of e-EPIDEMIOLOGY is required to establish its wider utility.

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KEYWORDS

dietary assessment; mobile phone application; food frequency questionnaire; epidemiological methods

Introduction

Traditional self-reporting methods that evaluate dietary intake, such as dietary registries and 24-hour recall questionnaires (short-term methods), and food frequency questionnaires (FFQs; long-term instruments) present important limitations [1-4]. Short-term tools allow for the collection of data that include quantities of all foods/drinks consumed by a person during a certain number of days. Dietary registries that require weighing of foods are time-consuming and create a great deal of work for study participants, which can lead to deviations from normal food intake (especially underestimation of quantities), as well as low rates of participation and compliance. The use of 24-hour recall questionnaires requires trained personnel and are short-term memory dependent. In order to determine habitual dietetic intake (the long-term mean consumption of foods/drinks)

using these short-term tools, it would also be necessary to repeat these measures multiple times, which would only worsen the problems inherent to these procedures. Long-term recall methods such as FFQs allow information to be collected regarding the consumption of a series of foods/drinks over prolonged periods of time (weeks or months), classifying a person according to the consumption category applied to each of the foods/drinks considered. FFQs depend mostly on the memory of the subject being interviewed, and these questionnaires do not take into account intrapersonal variation in the recording of daily food consumption during the time period of the study, nor do they allow precise estimation of food portion size. Despite these limitations, FFQs are the most practical, accessible, and commonly utilized tools in research to determine habitual dietary intake [2,5,6]. One inherent limitation to most FFQs is that they are paper-based. As a result, errors such as skipped questions or multiple marks are common, and incorporating complex skip patterns, a broad and varying number of portions size options, and extensive food and portion-size graphics is challenging [7]. Both long-term and short-term tools employ traditional techniques (paper and pen) to collect information, with posterior manual introduction for statistical analyses, which increases research costs and time consumption considerably [3,8]. For these reasons, improvement upon traditional methods for the determination of dietary intake remains one of the most important challenges in nutritional epidemiology [5,8-10]. Improvement of self-reporting that contributes to greater precision in the measurement of habitual dietary intake would represent a considerable boon for researchers, as well as for society as a whole, considering the important repercussions that the results and conclusions of these studies can have on the general population.

Traditional self-reporting techniques that evaluate dietary intake need to be replaced by new solutions, or nutritional research and treatments for nutritional problems will remain restricted and deficient [11]. Web-based FFQs offer straightforward solutions to the limitations of paper FFQs, and several examples of computer-administered FFQs exist in the published literature [12-16]. Additionally, certain dietary registries and 24-hour recall mobile phone apps have been developed recently that could reduce the limitations of these methods, with promising results [8-10,17,18].

The use of the Internet on mobile phones is widespread in Spain, with 83% of all Spaniards having accessed the Internet using their mobile phones within the last three months. This usage is even more extended in Spaniards between the ages of 16 and 24, with 92.6% accessing the Internet via their mobile phones in this same time period [19]. This broad usage facilitates the introduction of new methods of evaluation of dietary intake that include mobile technology. These new technologies need to be developed according to different local conditions, and evaluated with objective measures [10].

The objective of this study was to develop a new method, based on an application for mobile phones called e-EPIDEMIOLOGY, that was designed to collect individual consumption data about a series of foods/drinks, and to compare data recorded using this tool with that obtained through a previously validated paper FFQ.

Methods

Study Sample

This study was performed among medical and pharmaceutical students at the University of Seville (Andalusia, Spain, Southern Europe). Different events were organized at both faculties, during which the research team personally presented the project to the students. At the end of each presentation, interested students and those that fit inclusion criteria signed up for a personal interview. Of the 183 students that were interested, 136 were eligible and were signed up for the interview, in which the study protocol was explained. A total of 120 students decided to participate in the study. Of these, 119 completed both the e-EPIDEMIOLOGY app and the paper FFQ. The period of participant recruitment spanned from October, 2014 to June, 2016. The inclusion criteria were the following: (1) being a University of Seville student from the Medical or Pharmaceutical Schools; (2) being over 18 years of age; and (3) owning a mobile phone with access to the Internet and an Android operating system. As an incentive, all participants were entered into a raffle for a tablet at the conclusion of the study. The study was performed according to directives established in the Helsinki Declaration and the Biomedical Research Law [20], and all procedures on human beings were approved by the Research Ethics Committee at the University of Seville. Written informed consent was obtained from all participants.

The e-EPIDEMIOLOGY Mobile Phone App

Participants downloaded the e-EPIDEMIOLOGY app to their personal mobile phones. This app permitted the recording of each participant's daily consumption of a series of the foods/drinks selected for the study. At the end of each day, a notice would appear on the participant's mobile phone, informing them that it was time to use the app. At that time, the participant could access the app and register the number of standard portions that had been consumed during that day, for each of the foods/drinks included in the study. The list of foods/drinks appeared every day in the same order to facilitate completion of the app. This list consisted of 12 items which referred to 10 different foods/drinks: fruit, vegetables, legumes, chicken/turkey, fish, red meat (lamb, beef, and pork), soft drinks, sweets, prepared foods, and alcoholic beverages (Multimedia Appendix 1).

These items were selected for the study because they provide a wide range of consumption patterns, from *daily* to *sporadic*, for the population [5]. These foods were also considered to be markers for healthy (fruits, vegetables, legumes, and fish) and unhealthy (soft drinks, sweets, and prepared foods) dietary habits [21]. When accessing the first food/drink on the list, the number of standard portions of this food/drink consumed throughout the day was introduced. The *Next* button was then pressed to go on to the following item, in order to record all foods/drinks consumed that day (Multimedia Appendix 2). After finishing the task on e-EPIDEMIOLOGY, the data was automatically saved and sent to the research administrator's website via Wi-Fi or 3G/4G, after which time the user could not access or change answers on the questionnaire.

The app used to register daily consumption of selected foods/drinks was based on a questionnaire elaborated upon using the FFQ from the European Health Survey (Multimedia Appendix 1) [22]. Standardized portions were added after testing a previous prototype of e-EPIDEMIOLOGY (results not published) and were obtained from an FFQ validated for the Spanish population [23]. The app also allows for registry of other lifestyle habits (hours of sleep, oral hygiene, physical activity, and tobacco consumption). The app recorded this information using a different questionnaire with 11 items, which were also based on validated instruments from the European Health Survey [22].

Anthropomorphic Measurements

Researchers used the personal interview to both explain the study protocol and collect anthropomorphic data using a standard procedure. Height was measured in centimeters (cm), with a precision of 0.5 cm, and weight was measured in kilograms (kg), with a precision of 0.1 kg (wearing lightweight clothing, with shoes off and pockets empty). Using these data, body mass index (BMI; kg/m^2) was calculated using categories defined by the World Health Organization [24].

Procedure

All participants completed a questionnaire during the personal interview, in which demographic data was collected (date of birth, gender, birthplace, current place of residence, and employment). Participants were instructed in the use of e-EPIDEMIOLOGY with a personal demonstration of how to use the app, as well as an estimation of standardized portion sizes, and were reminded to maintain their habitual diet. The recording of food/drink intake was to be completed during 28 consecutive days using the app. Participants were recruited to the study during the entire period of research, so that all seasons, as well as days of the month and week, were included in the sample. As a reference, a paper FFQ was filled out at the end of the study period, through personal interviews and at the convenience of the participants. During the personal interviews, the participants were also asked how much time, on average, was necessary to complete the task each day. Participants could choose from one of the following options: *approximately 1 minute per day*, *approximately 2 minutes per day*, *approximately 3 minutes per day*, *approximately 4 minutes per day*, or *approximately 5 minutes or more per day*. Almost all (94.1%; 112/119) of the participants selected the option *approximately 1 minute per day* and the remaining 5.9% (7/119) chose *approximately 2 minutes per day*. Thus, the time necessary to complete e-EPIDEMIOLOGY was approximately one minute per day. Both methods asked about food/drink intake over a period of 28 days, and in order to make comparisons about the usefulness of each tool, it was desirable to keep food/drink records during the same period of time with each method [25]. The paper FFQ was based on a previously validated questionnaire used in the European Health Survey (Multimedia Appendix 3) [22]. Standardized portion sizes were obtained from an FFQ validated for the Spanish population [23]. Both of the questionnaires used in the app and the paper FFQ had the same items (Multimedia Appendices 1 and 3); the only difference being that the e-EPIDEMIOLOGY questionnaire refers to daily consumption while the paper FFQ refers to consumption during the previous 28 days.

All of the personal data collected in this study remained anonymous and confidential, and were treated according to current Spanish legislation [26]. To that end, each participant was assigned a personal alphanumeric code, so that no one (including the researchers) could link personal information to the results obtained. The code was introduced the first time the participant accessed the app, and when completing the demographic questionnaire and paper FFQ, for organizational purposes.

Codification and Revision of Data

For each participant, the data collected from the paper FFQ for each of the 10 foods/drinks were categorized. The frequency of consumption of food/drink items was categorized into six subgroups, ranging from *Less than once a week* to *3 times or more a day* (Multimedia Appendix 3). For the same foods/drinks, the data from the 28 days using e-EPIDEMIOLOGY were recorded as daily consumption. These data were transformed in order to include them in one of the same categories of habitual consumption included in the FFQ. This analysis was made possible because both the paper FFQ and e-EPIDEMIOLOGY used the same standardized portion sizes. For example, a participant consumed an average of 0.25 standard rations of fish daily during 28 days using e-EPIDEMIOLOGY; this average consumption represents 1.75 standard portions per week (0.25x7=1.75), which would be classified in the category *Once or twice a week*.

The data collected from the paper FFQ were manually introduced into the database by the research team. These results were then reviewed in order to avoid data entry errors. Data collected from e-EPIDEMIOLOGY were saved without modifications in a separate database. Subsequently, one set of data was removed due to an obvious inconsistency: one participant had registered the consumption of 200 standardized portions of legumes in one day.

Statistical Analyses

Due to the lack of agreement on the best way to present results from comparison studies, it is necessary to use more than one statistical method, in order to give credence to the results. In this study, cross-classification analysis and the weighted kappa statistic were used. To assess agreement, subjects were classified into categories of intake by e-EPIDEMIOLOGY and the reference method, and the percentage of subjects correctly classified into the same category, and misclassified into different categories, was calculated. Using cross-classification, the percentages misclassified clearly illustrate the likely impact of measurement error; however, the percentage of agreement will include agreement that can be accounted for by chance. The weighted kappa statistic is a summary measure of cross-classification that takes into account the agreement expected by chance, and has the added advantage over the kappa statistic in that it also takes into account the degree of misclassification. However, both the cross-classification analysis and the weighted kappa statistic are still dependent on the number of categories used [27]. In order to limit this

dependence, the six original categories were reorganized into three (Category 1: *Less than once a week* and *Once or twice a week*; Category 2: *3-4 times a week* and *5-6 times a week*; Category 3: Once or twice a day and *3 times or more a day*), in order to apply criteria defined by Masson et al [27] to evaluate agreement and misclassification. The interrater agreement of two assessment methods was analyzed by weighted kappa statistic [28], assigning partial credit to scores using the Stata prerecorded weights. If there was complete agreement, a weight of 1.00 was assigned. Slight disagreements (off by one) were given a weight of .50, and a weight of .00 was assigned if there was a complete disagreement. Values of kappa >.80 indicate very good agreement; between .61 and .80 indicate good agreement; .41 to .60 indicate moderate agreement; .21 to .40 indicate fair agreement; and <.20 indicate poor agreement [27]. All statistical analyses were performed using STATA version MP 13.1 (Stata Corp LP, Texas, USA) and a *P* value <.05 was considered statistically significant [29].

Results

A total of 120 individuals participated in the study, but one participant did not complete the app and the FFQ. This individual's data were not used for posterior analyses. Of the 119 participants who completed the study, 93 individuals completed the app every day, 15 completed the app 26 days, 1 completed the app 25 days, 9 completed the app 24 days, and 1 completed the app 20 days (Table 1).

Among the participants, the mean age was 21.9 years (standard deviation [SD] 3.2). The sample was 71.4% (85/119) female and 28.6% (34/119) male, and a minority (15.1%, 18/119) of participants were smokers. Less than one third (29.4%, 35/119) of respondents performed 150 minutes or more of moderate-intensity physical activities per week. The mean BMI was 22.3 kg/m^2 (SD 3.1), with 72.3% of participants in the healthy weight range (86/119; BMI 18.5-24.9), 16.8% being overweight (20/119; BMI 25.0-29.9), 2.5% obese (3/119; BMI >30.0), and 8.4% underweight (10/119; BMI <18.5) (Table 1).

The mean percentage of individuals correctly classified into the same category was 79.8% (ranging from 73.9% for vegetables to 84.9% for prepared foods), the mean percentage of individuals misclassified into an adjacent category was 19.1% (ranging from 15.1% for prepared foods to 26.1% for vegetables), and the mean percentage of individuals misclassified into an opposite category was 1.1% (ranging from 0% for vegetables, fish, and prepared foods to 3.4% for sweets; Table 2).

Table 1. Characteristics of participants in the study.

Characteristics	n (%)	mean (SD)
Participants who completed the study	119	
Number of days completed through the app		
28 days	93 (78.2)	
26 days	15 (12.6)	
25 days	1 (0.8)	
24 days	9 (7.6)	
20 days	1 (0.8)	
Age in years		21.9 (3.2)
Gender		
Female	85 (71.4)	
Male	34 (28.6)	
Smoking status		
No	101 (84.9)	
Yes	18 (15.1)	
Physical activity status		
150 minutes or more/week	35 (29.4)	
Less than 150 minutes/week	84 (70.6)	
BMI in kg/m^2		22.3 (3.1)
Underweight	10 (8.4)	
Normal range	86 (72.3)	
Overweight	20 (16.8)	
Obesity	3 (2.5)	

Table 2. Cross-classification analysis derived from e-EPIDEMIOLOGY and the paper FFQ.

Comparison	Agreement (%)		
	Same category	Adjacent category	Extreme category
Fruit	79.8	18.5	1.7
Vegetables	73.9	26.1	0.0
Legumes	83.2	16.0	0.8
Chicken/turkey	80.7	16.8	2.5
Fish	76.5	23.5	0.0
Red meat	79.8	19.3	0.8
Soft drinks	79.0	20.2	0.8
Sweets	79.8	16.8	3.4
Prepared foods	84.9	15.1	0.0
Alcoholic beverages	80.7	18.5	0.8
Average	79.8	19.1	1.1

The average weighted kappa statistic was good (κ=.64). The weighted kappa statistic values showed good agreement for fruit, vegetables, chicken/turkey, red meat, soft drinks, sweets, and alcoholic beverages (κ=.61 to .70) and moderate agreement for legumes, fish, and prepared foods (κ=.52 to .55; Table 3).

Table 3. Percentage agreement, percentage expected agreement, and weighted kappa statistic derived from e-EPIDEMIOLOGY and the paper FFQ.

Comparison	Agreement (%)	Expected agreement (%)	Weighted kappa	*P* value
Fruit	89.1	63.2	0.70	<.001
Vegetables	87.0	59.8	0.68	<.001
Legumes	91.2	81.7	0.52	<.001
Chicken/turkey	89.1	66.3	0.68	<.001
Fish	88.2	73.9	0.55	<.001
Red meat	89.5	72.7	0.61	<.001
Soft drinks	89.1	64.8	0.69	<.001
Sweets	88.2	60.9	0.70	<.001
Prepared foods	92.4	83.8	0.53	<.001
Alcoholic beverages	89.9	67.1	0.69	<.001
Average	-	-	0.64	-

Discussion

Principal Findings

The present study puts forth the development of a new method for the determination of habitual dietary intake using mobile technologies, and its comparison with a previously validated paper FFQ. Recently, certain short-term methods that use mobile technologies have been developed [8-10,17,18]. However, until now, no long-term instruments had been developed for evaluating habitual dietary intake, benefitting from mobile technologies and serving as an alternative to traditional FFQs. This new method, based on an app for mobile phones called e-EPIDEMIOLOGY, is not intended to determine the total food consumption of an individual nor the exact quantity consumed of a selected food/beverage. There are different tools, such as dietary registries or 24-hour recalls, which serve that purpose [1-4]. This method using e-EPIDEMIOLOGY was designed to record the amount of selected foods/drinks consumed throughout each day during the study period; data which can later be used to calculate the average consumption of said items in that period. This process then allows for classification of participants into distinct categories of habitual consumption of selected foods/drinks. The app can also be used to identify potential deficits in nutrient consumption, to analyze possible associations with risks for chronic diseases, and to evaluate the effectiveness of personalized measures that promote healthy lifestyle changes [7]. Although this method allows for the classification of individuals into categories (much like an FFQ), it is basically a simplified 24-hour food recall, repeated many times (once per day) during the study period of 28 days. Ultimately both methods (e-EPIDEMIOLOGY and FFQ) are very different and therefore present different measurement errors, due, for example, to the fact that dependence on the memory of participants in both methods is different (e-EPIDEMIOLOGY data collection is performed daily, while the collection of data with paper FFQs

refers to the last 28 days), or that e-EPIDEMIOLOGY allows for daily intrapersonal variability in the collection of data regarding the consumption of foods/drinks (which is not possible with a paper FFQ).

Cross-classification analysis showed that 79.8% of the participants were correctly classified into the same category and just 1.1% were misclassified into an opposite category. The average weighted kappa statistic was good (κ=.64), with values >.55 for 8 of the 10 foods/drinks selected for the study. These results indicate that e-EPIDEMIOLOGY generates ranks of dietary intakes that are highly comparable with the previously validated paper FFQ [13], according to Masson's criteria [27]. However, it was noted that further testing of e-EPIDEMIOLOGY is required to establish its wider utility [13,30]. While e-EPIDEMIOLOGY demonstrated good agreement with the paper FFQ, some disagreement was observed between the two instruments (cross-classification analysis showed that 19.1% of the participants were incorrectly classified into an adjacent category and 1.1% were misclassified into an opposite category). Multiple factors could have contributed to the discrepancies observed between the two methods. For each of the foods/drinks considered, both methods used the same question to measure the frequency of consumption. For example, both ask, *"How many portions of fish have you eaten? (1 portion = approx. 150 g)"*. Consequently, both methods present the same difficulties in the precise estimation of portion size, given that standardized serving sizes are used in both.

The difference between the methods lies in the timing of responses: e-EPIDEMIOLOGY requires that questions are answered at the end of each day during the study period, while the paper FFQ is completed at the end of 28 days. For this reason, e-EPIDEMIOLOGY permits daily collection of information, while an FFQ only allows for the collection of information at the end of the study period. This shortened time frame minimizes the dependence on the memory of the participant using e-EPIDEMIOLOGY in comparison to the FFQ, considering the fact that the recollection of past consumption of foods can be influenced by more recent food consumption [3]. Additionally, e-EPIDEMIOLOGY allows for daily intrapersonal variability in the collection of data on the consumption of foods/drinks. Among university students, who comprised the study sample, dietary intake is variable from day to day, with sporadic changes in food intake (skipping meals, snacking, school events that interfere with meal times), as well as frequent dining out. These aspects interfere with the precise determination of habitual dietary intake [17], especially in the case of FFQs, when data is collected only once at the end of an extended time period. Repeated applications of traditional short-term instruments, such as dietary registries and 24-hour recalls, can modify habitual intake due to the excessive workload for participants. Any tool that provides a simple method that facilitates the collection of data regarding dietary intake, without changing behavior, is an important advancement in nutritional epidemiology [17]. Despite repeated use, the modification of habitual intake seems unlikely via the use of e-EPIDEMIOLOGY, due to the reduced workload that using this app presents (one minute per day).

Interviewer-administration of 24-hour recall questionnaires or FFQs, versus self-administration, may decrease the accuracy of dietary intake reporting [31,32]. Psychological factors, among others, may have contributed to this underreporting, such as social desirability and a fear of negative evaluation [32]. If the data collection method was administered by an interviewer, participants with a high drive for social desirability were provided with an opportunity to please the interviewer. Conversely, the interviewer may have provoked underreporting of the consumption of food in those with a fear of negative evaluation [32]. Several studies suggest that underreporters are more likely to estimate low intake of foods perceived as unhealthy or undesirable (eg, sweets, fats, and snacks) than those perceived as healthy (eg, fruits, vegetables, and reduced fat products) [30,33,34]. Some of the characteristics of e-EPIDEMIOLOGY, such as asynchrony [35-38] and the ease with which privacy can be maintained [39], have made it possible to collect data anonymously on the Internet. This factor could contribute to reducing the problem of underestimation, mainly with those foods/drinks that are socially considered unhealthy, as this would minimize the effect of the psychological factors previously mentioned.

In their most simple applications, paper FFQs match Web-based FFQs; this allows for the flexibility of using either a paper or computerized questionnaire interchangeably, but the benefits of computer administration are limited to direct data entry, real-time error checking, and rapid analysis [40]. Other advantages include reducing paper waste and postage costs, and optimizing the space, security, and organization required for paper file storage [12]. In this study, it was considered that the potential disadvantages of developing a Web-based FFQ (in comparison with a paper-based FFQ) outweighed its potential benefits, keeping in mind two inherent characteristics of this study: the paper FFQ used was very short and simple (containing only 12 items), and the sample was comprised of students from the Medical and Pharmacy Schools of the University of Seville. The simplicity of the paper FFQ reduced the chance for errors, the amount of paper consumed, and storage space issues. Relatively easy access to the sample population made it possible to complete the paper FFQ in person, making it unnecessary to send it via mail. In this case, the costs associated with data entry were minimal compared with the potential costs of developing a Web-based FFQ.

For research, clinical practice, and policy determination, a great need exists for accurately determining dietary intake. However, current methods of self-reporting present limitations that are amply described in the scientific literature [1-4]. Due to these limitations, results obtained from these inaccurate scientific methods can lead to inaccurate conclusions and decision-making. Emerging alternatives for the determination of dietary intake include digital photography, chewing and swallowing monitors, and wrist motion detectors that count plate-to-mouth motion [41-44]. Some authors argue that more research is needed to develop these and other more objective and accurate tools. In addition, long-term funding should be made available for the measurement of dietary intake, whereby consumption can be measured over long periods of time. Meanwhile, the use of decidedly inaccurate instruments to

measure dietary intake needs to be discontinued [45]. A necessity exists for the development of better methods that can eventually replace current long-term self-reporting methods, and more resources should be directed to that end. Until these long-term alternatives are available, new technologies for self-reporting methods can, and should, be developed and utilized. Thus, further research to improve both short-term and long-term self-reporting methods (not only for clinical applications, but also for investigations) is well motivated [7]. These new tools, developed using new technologies such as e-EPIDEMIOLOGY, should be validated with objective studies that allow for the confirmation of an improvement over the traditional methods upon which they are based.

Limitations

The main limitation of this study is the fact that e-EPIDEMIOLOGY was compared to an FFQ (not validated). Another limitation of this study is the possible rate of nonresponse. Some of the characteristics of these types of mobile technologies, such as asynchrony [35-38], the ease with which privacy can be maintained [39], and the light workload for the participants (1 minute per day), helped to increase participation and could have contributed to the minimization of nonresponse rates. Young people have expressed their preference for methods of dietary intake evaluation that utilize new technologies, as they can easily be incorporated into their lifestyles, and are more amenable than traditional paper-based methods [9,17]. The possible limitation presented by the rate of nonresponse was minimized, as no statistically significant differences were found in any of the variables studied (age, gender, tobacco consumption, physical activity, and BMI), after analyzing the basic characteristics of responders and nonresponders.

Another possible limitation of the current study is that the participants involved were students. The majority of participants were also women (which is a reflection of the proportion of male and female students enrolled in the Schools of Medicine and Pharmacy at the University of Seville) and were, therefore, representative of a convenient sample rather than a nationally representative sample.

Another possible limitation lies in the fact that access to these technologies is not universal, excluding especially vulnerable groups, such as students from poorer social strata. In the environment in which this study was performed, the percentage of students with mobile phones with Internet access was very high, which minimized this possible limitation [19].

Future Studies

A validation study has been planned in which both methods (e-EPIDEMIOLOGY and paper FFQs), will be compared to a 3-7 day weighed food record. This approach will help to more thoroughly evaluate the potential validity of e-EPIDEMIOLOGY as a research tool for the determination of habitual dietary intake. Evaluation of e-EPIDEMIOLOGY is also planned in different sociodemographic groups, and will entail modifying the follow-up time, reducing from daily data input to input 2-3 times per week, and varying the foods/drinks selected. Another line of study would be to analyze the impact of factors that can affect the validity of data collected with e-EPIDEMIOLOGY, such as age, gender, employment, and health-related behavior (tobacco consumption, physical activity, and BMI). In future validation studies of e-EPIDEMIOLOGY, a third version of the app will be used (the second version is currently in use) which includes several improvements, such as an adaptation to iOS (which will help increase the sample size), and the inclusion of photographs to help participants estimate portion size.

Conclusions

In conclusion, this study of young adults generated good agreement with a previously validated paper-based FFQ. A variety of analyses, combined with the ease of use of e-EPIDEMIOLOGY, indicated the utility of the method based on this app for classifying individuals according to their consumption of the foods/drinks selected for the study, and is potentially valuable for use in other epidemiological studies as an alternative to paper FFQs [13]. Due to the growing popularity of mobile phones among young adults, the e-EPIDEMIOLOGY app is likely to be accepted by this population, and could reduce some of the inherent limitations present in paper FFQs, such as dependence on the memory of participants and the impossibility of reflecting intrapersonal variability in daily consumption of foods/drinks. However, it was noted that further testing of e-EPIDEMIOLOGY is required to establish its wider utility [13,30].

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Authors' Contributions

LMB performed the conception and design of the study, developed the app, analyzed and interpreted data, and wrote the paper. BS and MDG were involved in data collection and interpretation of the data, and contributed in drafting the article. All authors were involved in the editing, critical revision, and approval of the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Questionnaire used in e-EPIDEMIOLOGY, with weights/measurements of standardized portions of selected foods/drinks.

[PDF File (Adobe PDF File), 23KB - resprot_v5i4e208_app1.pdf]

Multimedia Appendix 2

Twelve screen captures of the e-EPIDEMIOLOGY app.

[PDF File (Adobe PDF File), 1MB - resprot_v5i4e208_app2.pdf]

Multimedia Appendix 3

Questionnaire utilized for paper FFQ, with weights/measurements of standardized portions of selected foods/drinks.

[PDF File (Adobe PDF File), 17KB - resprot_v5i4e208_app3.pdf]

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Abbreviations

BMI: body mass index
cm: centimeter
FFQ: food frequency questionnaire
kg: kilogram
SD: standard deviation

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Original Paper

A Comparison of Mobile and Fixed Device Access on User Engagement Associated With Women, Infants, and Children (WIC) Online Nutrition Education

John J Brusk[1*], MPH; Robert J Bensley[1*], PhD

Western Michigan University, Department of Human Performance and Health Education, Kalamazoo, MI, United States

[*]all authors contributed equally

Corresponding Author:
Robert J Bensley, PhD
Western Michigan University
Department of Human Performance and Health Education
1903 W. Michigan Ave.
Kalamazoo, MI, 49008
United States
Phone: 1 269 387 3081
Fax: 1 269 387 2704
Email: bensley@wmich.edu

Abstract

Background: Online health education has expanded its reach due to cost-effective implementation and demonstrated effectiveness. However, a limitation exists with the evaluation of online health education implementations and how the impact of the system is attenuated by the extent to which a user engages with it. Moreover, the current online health education research does not consider how this engagement has been affected by the transition from fixed to mobile user access over the last decade.

Objective: This paper focuses on comparing the impact mobile versus fixed devices have on user engagement key performance indicators (KPI) associated with the wichealth website (.org), an Internet-based parent-child feeding intervention offered to clients associated with the US Department of Agriculture's Special Supplemental Nutrition Program for Women, Infants, and Children (WIC).

Methods: Data were collected from 612,201 nutrition education lessons completed by 305,735 unique WIC participants in 21 states over a 1-year period. Data consisted of system-collected measures, profile items, and items from an exit survey administered at the conclusion of each lesson. User engagement was defined based on 3 KPIs associated with usage of the wichealth website: number of link views, link view time, and progression in stage of readiness to change. Independent samples *t* tests were used to compare KPIs between fixed only and mobile only device users and paired samples *t* tests were used to compare KPIs within users who completed at least one lesson each on both a fixed and mobile device. A logistic regression was performed to estimate the odds of KPI performance thresholds in the independent samples study group given access device type while controlling for confounding of user characteristics associated with these KPIs.

Results: Analysis of 8 user characteristics (lessons completed, race, ethnicity, language, state of residence, pregnancy status, beginning stage of change, and preferred nutrition education method) were significantly (P<.001) related to various KPI differences between mobile and fixed device access. Non-mobile users were significantly (P<.001) more likely to engage based on all 3 KPIs, even after logistic regression control for the potential confounding related to the strongly associated user characteristics identified.

Conclusions: The findings of this study support the idea that online health education developers need to seriously consider access device when creating programs. Online health education developers need to take extra effort to truly understand access patterns of populations being served, and whether or not access device will influence user engagement performance indicators.

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KEYWORDS

Internet; mobile phone; mHealth; eHealth

Introduction

Online health education, often referred to as electronic health (eHealth) and now mobile health (mHealth) education, has experienced tremendous growth over the last several years, primarily due to its cost-effectiveness [1]. The rapid growth of mobile broadband technology has expanded access to online health education among individuals with lower socioeconomic status whom may have had less access to fixed devices, such as a personal computer or laptop [2,3]. Not only has mobile broadband technology significantly extended the reach of the Internet, it has become the primary access method worldwide [4].

A recent systematic literature review of mobile nutrition apps concluded that effectiveness of mobile phone and tablet apps for online health education need additional research, as mobile platforms now allow consumers to access information on the go [5,6]. Mobile access to online health education represents a major shift in how users interact with information, resulting in differences in usage patterns and levels of engagement [7]. Many online health sites, including the wichealth website (.org), an online nutrition education and parent-child feeding behavior change system currently being implemented for use by the US Department of Agriculture's (USDA) Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) programs in 28 states and the platform of focus in this paper, began development when most access was fixed via device locations, such as personal computers at home, work, clinics, or libraries. Wichealth applies the eHealth Behavior Management Model in triaging a client through a series of response-dependent dialogue between the user and a virtual educator toward an initial stage of readiness to change a specific parent-child feeding behavior [8]. It is at this point where intervention content and resources are presented to the user. The client is then presented with the opportunity to engage in further stage-based resources based on intent to move toward active change. Further discussions of the model and features inherent within the wichealth system have been thoroughly described elsewhere [8,9]. However, mobile technology has made impressive gains in just the last several years. Ownership of cellular phones by US adults increased to 92% and mobile phones with app capabilities from 35% to 68% between 2011 and 2015 [10]. Even though mobile phone owners are more likely to be young, affluent, and highly educated, access is not restricted, as 52% of US adults earning less than US $30,000 per year own a mobile phone and mobile technology interest is high among WIC clients [10,11].

It is undeniable that the Internet has become a widely used resource for people seeking health information [12]. Online health education strategies can provide users with more flexibility and an opportunity to become more involved in the management of their health [13]. This increase in consumer knowledge may then lead to improved health outcomes, as online resources offer users greater interactivity and potential for engagement, which should enhance their learning and understanding [14-18]. Mobile access to health education, in particular, may at first appear beneficial for improving user engagement because people tend to be more proximally associated with their mobile devices, frequently keeping them close at hand. However, the quality of the engagement may actually suffer even though the impedance to engage is reduced and the frequency of engagement is increased. The manner in which mobile device users interact with Internet content is sufficiently different from those that access the media from a fixed device [19]. As a result, some evaluation researchers have called for alternative models to assess user impact as, despite the increase in usefulness that accompanies mobile access, this benefit has come at the expense of their usability in some contexts [20].

Over a decade ago, Zhang and Adipat [21] highlighted a number of usability challenges that occurred as a result of the advent of mobile devices, including the ability of users to access the Internet in multiple locations while doing multiple activities, smaller screen size, variable screen resolutions, more restricted user input, and limited processing power. More recent studies have demonstrated these challenges, especially with regard to user interaction. Harrison and colleagues [20] indicated that most usability research does not consider the impact of the mobile transition and its consequences. Their research addressed how mobile devices increase an individual's cognitive load capacity. The increased ability for users to "multi-task" through mobile device use may come at a cost of user engagement with the content of interest, which is often a critical factor to the success or failure of an application [22]. In addition, mobile access changes the quality of user interaction with health and personal information. A study of data quality in Web surveys found mobile access generally produced lower item completion rates and shorter length of answers [23]. Similarly, a study comparing the differences in survey response completion quality and time found data collection via a mobile device was associated with longer user input time and lower quality and quantity responses. This may suggest that mobile device users either find it more difficult to input data into the online health education system or they may be accessing the system while performing multiple tasks, giving less than their full attention to the task at hand [24]. Furthermore, the effect of primacy is stronger in a mobile setting. Users are significantly more likely to select the top sorted link on a mobile device compared to a computer [25]. Even though it has been clear that Internet interaction differs depending on access device, a systematic review of 8 mobile technologies including mobile phones, personal digital assistants (PDA), PDA phones, enterprise digital assistants (EDA), portable media players, handheld video gaming consoles, and tablets screened from over 26,000 possible studies for inclusion concluded that the overall impact and effectiveness of the applications did not address mobile access as a potential barrier and critical design consideration for online health interventions [26].

More research is needed to determine the extent to which mobile access to Web applications may engage the user differently than fixed access devices and how to design applications to ensure this impact does not affect quality of the intervention. Few studies have been conducted that differentiate fixed eHealth and mHealth education, which is slowly becoming ubiquitous health (uHealth), as devices such as watches, eyeglasses, and home appliances will all soon be tapped into the Internet

[2,3,5,13,27,28]. The purpose of this study was to expand the body of research exploring the differences between eHealth and mHealth engagement by exploring the usage pattern differences and impact on key performance indicators (KPI) between fixed and mobile device completion of parent-child feeding lessons associated with the wichealth website.

Methods

Participants

The population of interest for this study consisted of clients of the WIC program from 21 states who completed a lesson on the wichealth website during the government fiscal year period October 1, 2014 through September 30, 2015. Participants self-selected to complete a wichealth lesson as a means of meeting secondary contact requirements associated with the WIC program. Data collection protocols using wichealth have been approved for use by the Western Michigan University Human Subjects Institutional Review Board. Online informed consent was available prior to completion of the online survey.

Data Collection

Data utilized in this study was garnered from 305,735 unique WIC clients who completed 612,201 wichealth lessons over the 1-year period of study. Participants were divided into 2 study groups. The first study group consisted of 280,845 unique WIC clients whose interaction with the wichealth website during the study period consisted of either fixed (desktop computer, laptop, or kiosk) or mobile (phone or tablet) device access, but not both. The second study group consisted of 24,890 unique WIC clients who completed both at least one lesson using fixed access and at least one lesson using a mobile device during the study period. All lessons were completed using the wichealth website, which consists of a responsive design that adjusts based on screen size of device. Data consisted of 6 system-collected measures (links viewed, link view time, device type, beginning and ending stages of change, lessons completed), 5 profile items (ethnicity, race, language, pregnancy status, state of residence), and 1 item focused on nutrition education method ("How do you prefer to get your nutrition education") from an exit survey administered at the conclusion of each lesson. User engagement was defined based on 3 KPIs associated with wichealth usage, including number of link views, link view time, and progression in stage of change. Link visits are a central component of the behavior change theory inherent within the wichealth system, as it is at the link level where stage-based content and skills are delivered. Links consist of static and interactive webpages, downloadable Portable Document Folders (PDFs), and videos where content and skills relevant to the behavioral focus of the lesson are presented. All links are selected and developed based on learning and behavior change skills relevant to the priority population. Reliability of the exit survey was previously established using Cronbach alpha, and the staging algorithms used to identify beginning and ending stages were based on criteria previously used to determine stages of change and have been described in detail elsewhere [8,9,29]. Separate studies to determine current stage of change associated with parent-child feeding behaviors among a sample of WIC participants from Michigan and Washington found similar trends as the staging algorithms used in the wichealth website, further increasing confidence in the validity of data collection procedures used in the current study [30].

Statistical Analysis

The purpose of this study was to determine how wichealth KPIs varied between fixed and mobile device access. First, user characteristics were evaluated to identify whether they were independently associated with either the KPI outcomes or device type. Independent samples *t* tests were used to compare KPIs between fixed only and mobile only device users and paired samples *t* tests were used to compare KPIs within users who completed at least one lesson each on both a fixed and mobile device. A logistic regression was performed to estimate the odds of KPI performance thresholds in the independent samples study group given access device type while controlling for confounding of user characteristics associated with these KPIs. Odds ratios (OR) with significance determined using chi-square were calculated for both study groups using the general linear models package in R. Per the American Statistical Association [31], using a *P* value by convention, such as achieving statistical significance when $P<.05$, does not ensure a material effect and is likely to generate a number of false and weak claims about a relationship. Given this and the very large sample size available for this research, only levels of significance below .001 were reported for *P* values obtained from results of Student *t* tests and chi-square. This was to ensure differences that are not practically important or relevant were not considered as such.

Results

Mobile access made up 43.66% (267,317/612,201) of all wichealth lessons completed during the study period. Access to the wichealth website by a mobile device was inversely associated with user engagement, in particular the number of educational links viewed within a wichealth lesson and progression of stage of readiness to change. Individuals who accessed wichealth using a mobile device were more than 2 times less likely to visit any educational links that are part of the wichealth lesson. Those who did access a link via a mobile device accessed, on average, fewer links and spent fewer minutes viewing those links than non-mobile device users. With regard to intent to change the parent-child feeding behavior associated with the lesson, mobile device users who began a lesson in an early stage of readiness to change (precontemplation, contemplation, or preparation) were significantly less likely to progress in stage of change than users who accessed wichealth via a personal computer or kiosk (Table 1).

Although these differences in wichealth KPIs appear to be statistically significant ($P<.001$) between fixed and mobile usage, several user characteristics were also found to be associated with the wichealth KPIs. The paired sample study group of individuals who completed lessons via both fixed and mobile access should control for this confounding; however, this group of users is not defensibly generalizable to the group of individuals that only completed lessons via either fixed or mobile access, but not both. Number of lessons was not used

as a measure of KPI because the typical user only completed a single lesson. Within the group that completed lessons only on a fixed or mobile device but not both, 56.56% (158,835/280,845) completed only 1 lesson. Both fixed and mobile access users in this group averaged close to 1.9 lessons per user, which was not significantly different. Users who completed lessons via both fixed and mobile access represented individuals that were likely more engaged, as they completed at least 2 lessons, whereas the typical user completed less than 2 lessons. Further, observed differences between some KPIs of users that completed at least 2 lessons via either fixed or mobile access and users that completed at least 2 lessons via a combination of fixed and mobile access were significantly different (P<.001) indicating that these groups are not representative of each other (Table 2).

Table 1. Key performance indicators by device type.

Performance indicator	Independent samples		Paired samples	
	Fixed	Mobile	Fixed	Mobile
Unique users, n	161,356	119,489	12,445	12,445
Lessons completed, n	303,815	227,273	41,069	40,044
LLV[a], %	75.23	32.56[c]	74.95	40.66[c]
Link views per LLV, n	2.18	1.76[c]	2.25	2.01[c]
Link view minutes per LLV, n	1.46	0.84[c]	1.61	1.32[c]
ESOC[b], n	98,777	67,221[c]	13,327	12,468
ESOC with stage progression, %	85.55	80.89[c]	84.95	84.41

[a]LLV: lessons completed that had at least one link view.

[b]Lessons beginning in an early stage of change (ESOC).

[c]P<.001.

Table 2. Key performance indicators by lessons completed.

Performance indicator	Independent samples		Paired samples: 2 or more lessons completed
	1 lesson completed	2 or more lessons completed	
Unique users, n	158,835	122,010	24,890
Lessons completed, n	158,835	372,253	81,113
LLV[a], %	55.71[c]	57.51	58.02
Link views per LLV, n	1.89[c]	2.15	2.17
Link view minutes per LLV, n	2.46	0.83[c]	1.51
ESOC[b], n	54,098	111,900	25,795
ESOC with stage progression, %	85.20	82.86[c]	84.69

[a]LLV: lessons completed that had at least one link view.

[b]Lessons beginning in an early stage of change (ESOC).

[c]P<.001.

Other user characteristics associated with wichealth KPIs included race, Hispanic ethnicity, language, state, pregnancy status, early beginning readiness to change status, and preferred method for receiving nutrition education. Lessons with link views, links viewed per lesson, and link view time demonstrated some significant differences by race (Table 3). Although black users had a similar proportion of completed lessons with link views as white users, those who did have link views, had fewer on average than other users. They were also less likely to advance in stage of change. Users who did not report being either white or black were less likely to view a link during their lesson, but more likely to spend more time on the links that were accessed. Similarly, users of Hispanic ethnicity were less likely to access a link during their lesson compared to other users, but those who did access links also viewed them for longer. Hispanic users were also more likely to advance in stage of change (Table 4). These findings raise the suspicion that users who either did not report race or reported themselves as "other" may have actually considered their race to be Hispanic, as has been found elsewhere [32]. Hispanic engagement in KPI is further demonstrated as users of the Spanish language version of wichealth consistently had more link views and link view time among individuals who used at least one link during their lesson compared to English version users (Table 5).

Table 3. Key performance indicators by race.

Performance indicator	Independent samples			Paired samples		
	White	Black	Other/missing	White	Black	Other/missing
Unique users, n	145,853	36,201	98,791	12,676	2730	9484
Lessons completed, n	274,624	65,535	190,929	40,274	9154	31,685
LLV[a], %	58.99	59.38	53.23[c]	58.80	62.67[c]	55.72
Link views per LLV, n	2.08	1.86[c]	2.14	2.17	1.92	2.25
Link view minutes per LLV	1.28	1.23	1.38[c]	1.47[c]	1.33	1.62[c]
ESOC[b]	86,123	20,467	59,408	12,916	2907	9972
ESOC with stage progression, %	84.49	78.28[c]	84.29	85.44	79.86[c]	85.09

[a]LLV: lessons completed that had at least one link view.

[b]Lessons beginning in an early stage of change (ESOC).

[c]*P*<.001.

Table 4. Key performance indicators by ethnicity.

Performance indicator	Independent samples		Paired samples	
	Non-Hispanic	Hispanic	Non-Hispanic	Hispanic
Unique users, n	184,023	96,822	15,190	9700
Lessons completed, n	348,018	183,070	48,871	32,242
LLV[a], %	59.45	52.25[c]	59.77	55.36[c]
Link views per LLV, n	2.06	2.10	2.12	2.25[c]
Link view minutes per LLV	1.25	1.44[c]	1.42	1.67[c]
ESOC[b]	109,474	56,524	15,544	10,251
ESOC with stage progression, %	82.98	85.04[c]	84.16	85.53[c]

[a]LLV: lessons completed that had at least one link view.

[b]Lessons beginning in an early stage of change (ESOC).

[c]*P*<.001.

Table 5. Key performance indicators by language.

Performance indicator	Independent samples		Paired samples	
	English	Spanish	English	Spanish
Unique users, n	268,655	12,189	24,074	816
Lessons completed, n	508,050	23,038	78,053	3060
LLV[a], %	57.13	53.52[c]	57.84[c]	62.58
Link views per LLV, n	2.06	2.46[c]	2.12	3.40[c]
Link view minutes per LLV	1.29	1.83	1.49	1.87[c]
ESOC[b]	158,140	7858	24,704	1091
ESOC with stage progression, %	83.47[c]	86.42	84.86	80.73[c]

[a]LLV: lessons completed that had at least one link view.

[b]Lessons beginning in an early stage of change (ESOC, precontemplation, contemplation, preparation).

[c]*P*<.001.

Table 6. Key performance indicators by state mobile access level.

Performance indicator	Independent samples		Paired samples	
	High	Low	High	Low
Unique users, n	206,274	74,571	20,156	4734
Lessons completed, n	392,614	138,474	66,161	14,952
LLV[a], %	55.15	62.13[c]	57.38	60.83[c]
Link views per LLV, n	2.05	2.14	2.18	2.11
Link view minutes per LLV	1.31	1.32	1.51	1.50
ESOC[b]	121,628	44,370	20,882	4913
ESOC with stage progression, %	82.96	82.65	84.22	84.14

[a]LLV: lessons completed that had at least one link view.

[b]Lessons beginning in an early stage of change (ESOC).

[c]*P*<.001.

Table 7. Key performance indicators by pregnancy status.

Performance indicator	Independent samples		Paired samples	
	Not pregnant	Pregnant	Not pregnant	Pregnant
Unique users, n	237,117	43,728	19,891	4999
Lessons completed, n	439,654	91,434	63,046	18,067
LLV[a], %	57.47	54.54[c]	58.56	56.11[c]
Link views per LLV, n	2.06	2.15	2.09	2.46[c]
Link view minutes per LLV	1.33	1.19[c]	1.54	1.41[c]
ESOC[b]	139,199	26,799	20,223	5572
ESOC with stage progression, %	85.06	76.28[c]	87.42	74.82[c]

[a]LLV: lessons completed that had at least one link view.

[b]Lessons beginning in an early stage of change (ESOC).

[c]*P*<.001.

User state of residence was grouped based on whether mobile access rates in that state were high or low given the relative extent of usage in the state compared to other participating states. Alabama, California, Iowa, Louisiana, Michigan, and South Dakota all had mobile access rates that significantly exceeded the overall average of 43.66%. These states were assigned a high level of mobile access, while the remaining were classified as low. States that tended to have lower mobile access levels were more likely to have users that used at least one link view during their lesson (Table 6).

Pregnancy status was strongly associated with wichealth KPIs, with pregnant users significantly less likely to complete lessons with at least one link view, spend time on links accessed, and progress in stage of change than non-pregnant users (Table 7). These findings may be related to the fact that users completed pregnancy-specific lessons at a greater rate than other lessons. This set of lessons address behaviors that are often more difficult for users to progress along the stage of change continuum, and therefore the cause of the lower level of progression is likely related to the lesson, rather than the user.

User beginning stage status is another characteristic associated with wichealth KPI performance. Specifically, early stage of readiness to change users were more likely to use a link during their lesson, and they accessed about one link more on average than non-early stage of readiness to change users (Table 8). This makes sense because when users progress, they are provided the opportunity to continue their learning with an additional pool of links from which to select in order to help them progress further.

Finally, user preference for wichealth as a means for receiving future nutrition education was assessed for its association with wichealth KPIs in each study group. Users who preferred the wichealth website were more likely to view more links during their lesson and to progress in stage of readiness to change than users who preferred another nutrition education method, such as counseling, group classes, or other onsite learning activities (Table 9).

Table 8. Key performance indicators by early begin stage user.

Performance indicator	Independent samples		Paired samples	
	Non-ESOC[a]	ESOC	Non-ESOC	ESOC
Unique users, n	153,862	126,983	14,408	10,482
Lessons completed, n	233,647	297,441	39,721	41,392
LLV[b], %	53.19	59.94[c]	54.21	61.67[c]
Link views per LLV, n	1.49	2.48[c]	1.59	2.65[c]
Link view minutes per LLV	1.36	1.27	1.54	1.48
ESOC	N/A	165,998	N/A	25,942
ESOC with stage progression, %	N/A	83.66	N/A	84.69

[a]Lessons beginning in an early stage of change (ESOC).

[b]LLV: lessons completed that had at least one link view.

[c]*P*<.001.

Table 9. Key performance indicators by preferred nutrition education method.

Performance indicator	Independent samples		Paired samples	
	Other	wichealth	Other	wichealth
Unique users, n	54,478	226,367	4015	20,875
Lessons completed, n	85,380	445,708	11,794	69,319
LLV[a], %	56.36	57.09	57.38	58.13
Link views per LLV, n	1.86	2.11[c]	2.00	2.20[c]
Link view minutes per LLV	1.41[c]	1.29	1.53	1.51
ESOC[b]	25,664	140,334	3617	22,178
ESOC with stage progression, %	77.43	84.83[c]	80.45	85.38[c]

[a]LLV: lessons completed that had at least one link view.

[b]Lessons beginning in an early stage of change (ESOC).

[c]*P*<.001.

Given the paired sample study group of individuals having completed a lesson via both fixed and mobile access, control of confounding user characteristics on the association of lower KPIs with mobile access was essentially achieved. Within this group, there was still significant differences between KPIs for lessons completed via fixed compared to mobile access, such as the percent of lessons completed using a link and the link view minutes per lesson; however, the main outcome of stage of change progression was not significant (see Table 1). This suggests that the effect of mobile device on user engagement was still significant in that there was a mobile-specific reason for lower engagement; however, mobile use did not appear to impact progression in stage of readiness to change. Yet as indicated, because this paired sample study group was not representative of the typical user, control for the user characteristics associated with wichealth KPIs is warranted to evaluate the effect on the observed difference in stage progression between typical fixed access and mobile access users. To achieve this, a logistic regression model was developed to include all of the user characteristics previously presented in order to determine if the associations observed of stage progression and lower wichealth KPIs among mobile users was a product of confounding or effect modification. The results of the logistic regression model set up with device access as the dependent outcome variable (fixed or mobile) and the wichealth KPIs as predictors along with all of the associated user characteristics is presented in Table 10. In this manner, the association of the wichealth KPIs and mobile access type could be evaluated controlling for any potential confounding or effect modification of user characteristics found to be related to the KPIs. Table 10 contains the regression coefficients and their standard errors, the *z* statistic, ORs, and confidence intervals (CIs). Supporting the univariate comparisons made above, all of the model predictors were statistically significant in their association with device type. The logistic regression coefficients can be interpreted as the change in the log odds of whether a mobile device was used for a 1-unit increase in the wichealth KPIs or user characteristic variable.

Table 10. Independent samples study group logistic regression model results.

Model feature	beta[a]	SE[b]	z [c]	OR[d]	95% CI[e] (upper-lower)
Intercept	.159	0.205	6.13[g]	1.17	1.11-1.23
Race (black)	.695	0.013	52.16[g]	2.00	1.95-2.06
Race (other)	.064	0.011	6.15[g]	1.07	1.04-1.09
Hispanic	.286	0.011	26.52[g]	1.33	1.30-1.36
Language	.184	0.022	8.39[g]	1.20	1.15-1.25
State mobile access	.306	0.010	30.18[g]	1.36	1.33-1.38
Pregnancy status	.030	0.012	2.39	1.03	1.01-1.05
Preferred nutrition education	.026	0.011	1.90	1.02	1.00-1.04
ESOC[f]	–.093	0.016	–5.31[g]	0.92	0.89-0.95
Link view	–1.719	0.010	–178.19[g]	0.18	0.17-0.18
Link view minutes	–.205	0.005	–36.54[g]	0.82	0.81-0.82
Stages progressed	–.201	0.038	–5.35[g]	0.82	0.76-0.88

[a]beta: regression coefficient.

[b]SE: standard error.

[c]z: z statistic.

[d]OR: odds ratio.

[e]CI: confidence interval.

[f]Lessons beginning in an early stage of change (ESOC).

[g]$P<.001$.

After controlling for user characteristics associated with mobile device use, users of mobile devices were over 5 times less likely to access any links during their lesson (OR = 0.18, $P<.001$, 95% CI [.17, .18]). Further, mobile device users were less likely to spend as many minutes viewing links when they did use them (OR = 0.82, $P<.001$, 95% CI [.81, .82]). Finally, even with all potential confounders accounted for in the model, the stages progressed among early beginning stage of change users was significantly lower among those accessing wichealth via mobile rather than fixed access (OR = 0.82, $P<.001$, 95% CI [.76, .88]).

Discussion

Principal Findings

The advent and expansion of mobile devices has clear implications for Internet intervention designers. As demonstrated in this study, the expansion of mHealth use in the wichealth website, which was originally designed for completion on a fixed device, resulted in lower KPIs. Based on the findings presented, it is clear that a difference exists between mobile and fixed device users in how they interact with this online nutrition education and behavior change system.

Although the review of literature previously presented indicates a number of reasons why mobile devices often achieve lower levels of performance associated with measures of engagement, strategies for how to address these issues, especially with respect to wichealth, are not clear. The observation that user engagement is impeded by mobile device use across many user characteristics such as age, race, language, state of residence, and preference for the learning modality, demonstrates how strong this impact is and underlines the significance of implementing design features to diminish it. In fact, all key wichealth performance measures were significantly lower for mobile device users.

The findings of this study support the idea that online health education developers need to seriously consider access device when creating programs. Over the next year it is likely wichealth will transition to become accessed primarily by mobile devices, as personal computers and kiosks become a less frequent option for individuals to retrieve online content. Mobile access of wichealth lessons has been increasing by 15% every 6 months, which has now made wichealth predominately accessed via mobile device. This transition has important implications, especially as users who access wichealth via a mobile device behave in a significantly different manner than users accessing a lesson by a computer, laptop, or kiosk. To address the findings presented in this study, the developers of wichealth recently redesigned the experience to ensure it is appropriate for the growing percentage of mobile users. A mobile first design strategy was used to ensure the responsive nature of the website did not deteriorate on mobile devices. Specific design changes with wichealth will be described elsewhere, as the purpose of this study was to present findings that would raise awareness in developers to ensure mobile user engagement characteristics are not automatically lumped together with fixed device users, but rather design focuses on both methods of access in order to create the most likely positive user experience. It is important for developers to consider the nature of the mobile access

environment. Mobile phones and tablets are indicative of "on the go" usage, whereas access from a fixed device may be associated with users having more time and a better environment for focusing on the intervention. Further, mobile devices have less screen viewing real estate, which may increase the likelihood that users will not be as engaged. Finally, mobile devices may be less likely to be fully compatible with the internet content presented, lowering measures of user engagement.

Limitations

Results should be interpreted realizing limitations existed. Wichealth was originally conceived as a fixed device intervention although it incorporated a responsive design appropriate for a mobile experience. As such, generalizability of results should be considered with this in mind. Another potential limitation is that participation in wichealth was through self-selection versus assignment, reducing the ability to generalize findings to all WIC populations. In addition, historically approximately 40% of wichealth lessons tended to have been completed by repeat users, which may have influenced findings. However, it is not conclusive whether repeat users always used the same access device for more than one lesson. Even so, the large number of users and lessons completed within this study mitigate any extreme influence a few users may have had on findings.

Recommendations

There are many opportunities for further study, as this description of wichealth use has generated many questions and areas of speculation. First it is interesting that some key user characteristics such as Spanish language, black race, and user state of residence in Alabama were all associated with a higher likelihood that the user completed their lesson using a mobile device. Future research could attempt to address how this may be related to whether mobile device Internet access was the initial means for these users to gain access to the Internet on a regular basis. Also, these users appeared to be less impacted in terms of wichealth KPIs compared to fixed and mobile access users.

Additional investigation into whether the device operating system has any impact on measures of user engagement is warranted. For example, is there a difference in how these measures are affected if the user has an Android or iOS platform? Also, many of the reasons speculated for why mobile device access may have lower levels of user engagement could be evaluated by comparing mobile phone and tablet access, both of which were considered mHealth devices. As more users completed their lessons using a mobile device, additional investigation of these subcategories of mobile device usage should be completed.

Conclusions

Online health education developers need to take extra effort to truly understand access patterns of populations being served, and whether or not access device will influence user engagement performance indicators. As mobile access continues to increase, especially among younger populations, application managers need to consider what changes in design and functionality needs to occur to ensure the intervention being delivered is appropriate for the user.

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Conflicts of Interest

RB is director and JB is evaluator of the wichealth website. Neither of these should be considered conflict of interest, as the entire study was only with regard to comparing access to the wichealth website from different devices rather than compared to other websites.

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Abbreviations

CI: confidence interval
EDA: enterprise digital assistant
ESOC: early beginning stage of readiness to change
eHealth: electronic health
KPI: key performance indicators
LLV: lessons completed that had at least one link view.
mHealth: mobile health
OR: odds ratio
PDA: personal digital assistant
uHealth: ubiquitous health
USDA: US Department of Agriculture
WIC: Special Supplemental Nutrition Program for Women, Infants, and Children

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Original Paper

Can a Free Wearable Activity Tracker Change Behavior? The Impact of Trackers on Adults in a Physician-Led Wellness Group

Lisa Gualtieri[1], PhD, ScM; Sandra Rosenbluth[1], MS; Jeffrey Phillips[2], MD

[1]Tufts University School of Medicine, Department of Public Health and Community Medicine, Boston, MA, United States

[2]Family Doctors, LLC, Swampscott, MA, United States

Corresponding Author:
Lisa Gualtieri, PhD, ScM
Department of Public Health and Community Medicine
Tufts University School of Medicine
136 Harrison Avenue
Boston, MA, 02111
United States
Phone: 1 617 636 0438
Fax: 1 617 636 4017
Email: lisa.gualtieri@tufts.edu

Abstract

Background: Wearable activity trackers (trackers) are increasingly popular devices used to track step count and other health indicators. Trackers have the potential to benefit those in need of increased physical activity, such as adults who are older and face significant health challenges. These populations are least likely to purchase trackers and most likely to face challenges in using them, yet may derive educational, motivational, and health benefits from their use once these barriers are removed.

Objective: The aim of this pilot research is to investigate the use of trackers by adults with chronic medical conditions who have never used trackers previously. Specifically, we aim to determine (1) if participants would accept and use trackers to increase their physical activity; (2) if there were barriers to use besides cost and training; (3) if trackers would educate participants on their baseline and ongoing activity levels and support behavior change; and (4) if clinical outcomes would show improvements in participants' health.

Methods: This study was conducted with patients (N=10) in a 12-week physician-led wellness group offered by Family Doctors, LLC. Patients were given trackers in the second week of The Wellness Group and were interviewed 2 to 4 weeks after it ended. The study investigators analyzed the interview notes to extract themes about the participants' attitudes and behavior changes and collected and analyzed participants' clinical data, including weight and low-density lipoprotein (LDL) cholesterol over the course of the study.

Results: Over the 12 to 14 weeks of tracker use, improvements were seen in clinical outcomes, attitudes towards the trackers, and physical activity behaviors. Participants lost an average of 0.5 lbs per week (SD 0.4), with a mean total weight loss of 5.97 lbs (P=.004). Other short-term clinical outcomes included a 9.2% decrease in LDL levels (P=.038). All participants reported an increase in well-being and confidence in their ability to lead more active lives. We identified the following 6 major attitudinal themes from our qualitative analysis of the interview notes: (1) barriers to tracker purchase included cost, perceived value, and choice confusion; (2) attitudes towards the trackers shifted for many, from half of the participants expressing excitement and hope and half expressing hesitation or trepidation, to all participants feeling positive towards their tracker at the time of the interviews; (3) trackers served as educational tools for baseline activity levels; (4) trackers provided concrete feedback on physical activity, which motivated behavior change; (5) tracker use reinforced wellness group activities and goals; and (6) although commitment to tracker use did not waver, external circumstances influenced some participants' ongoing use.

Conclusions: Our findings suggest that adding trackers to wellness groups comprising primarily older adults with chronic medical conditions can support education and behavior change to be more physically active. The trackers increased participant self-efficacy by providing a tangible, visible reminder of a commitment to increasing activity and immediate feedback on step count and progress towards a daily step goal. While acceptance was high and attitudes ultimately positive, training and support are needed and short-term drop-off in participant use is to be expected. Future research will further consider the potential of trackers in older adults with chronic medical conditions who are unlikely to purchase them, and studies will use larger samples, continue over a longer period of time, and evaluate outcomes independent of a wellness group.

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KEYWORDS

wearable activity trackers; fitness trackers; trackers; physical activity; chronic disease; behavior change; wellness group; wellness; older adults; digital health

Introduction

The aim of this pilot research is to investigate the use of wearable activity trackers (trackers) by primarily older adults with chronic medical conditions who have never used trackers previously. This population is among the least likely to purchase trackers and the most likely to face challenges in using them, yet may derive educational, motivational, and health benefits from their use once these barriers are removed. Our study provided free trackers, with training on their setup and use, to patients enrolled in a 12-week physician-led wellness group. Our primary research aims are to determine (1) if participants would accept and use trackers to increase their physical activity; (2) if there were barriers to use besides cost and training; (3) if trackers would educate participants on their baseline and ongoing activity levels and support behavior change in conjunction with the education participants received through the wellness group; and (4) if clinical outcomes would show improvements in participant health.

Physical Activity

"Regular physical activity is one of the most powerful health promoting practices that physicians and other health care professionals can recommend for patients" [1]. The Physical Activity Guidelines for Americans recommend 150 minutes of moderate-intensity aerobic activity every week, in addition to muscle-strengthening activities at least twice a week, to improve health and lower the risk of chronic conditions [2]. Yet fewer than half of all American adults meet the minimum requirement for physical activity. In some groups, this rate is even lower; only 17.8% of adults aged 45 to 64 and 14.7% of adults aged 65 to 74 meet the aerobic and muscle strengthening physical activity recommendations for their age group, compared to the 25.7% of adults aged 18 to 44 [3].

Trackers

Trackers are devices that measure health indicators; the most common tracker feature, step count, is set to a default goal of 10,000 steps per day, which is more than the 7000 to 8000 steps per day recommended by the Physical Activity Guidelines [2] and greater than many people can achieve [4]. Tracker sales are growing, with 16.4 million trackers shipped worldwide in the first quarter of 2016 [5]. In the United States, 16% of adults 18 years of age and older who have health insurance have purchased trackers [6]. Almost half of tracker owners are under the age of 35: 42% are 18 to 34 years old, 19% are 35 to 44 years old, 16% are 45 to 54 years old, 16% are 55 to 64 years old, and 7% are 65 and older [7]. Nearly one third of those who buy trackers earn more than US $100,000 a year [8]. Trackers range in price from about US $60 to US $250 for popular brands like Fitbit and Withings, making cost a barrier for many people who may benefit the most from these technologies [9].

Currently, 64% of trackers are purchased for personal use, while 35% of people with trackers received them as a gift or from their employer [10]. In one study, 65% of respondents expressed excitement about their doctors providing trackers [11]. In another study, 48.2% of US adults who do not use a tracker said they would use a free one provided by their physician [12], and 81% of respondents said they would be more likely to monitor health indicators with a device if it was recommended by their health care professional [13].

Behavior Change

Most people know they should exercise more. In one study, 49.4% of respondents said they tried to increase their exercise in the previous year [14]; however, initiating and maintaining this behavior change is difficult. Self-efficacy, the belief in one's ability to complete tasks and reach goals, is one of the most consistent predictors of physical activity in adults of all ages, and a lack of self-efficacy is a barrier for many [15]. Other barriers that reduce adherence to behavior change include cost and time [16].

Use of Trackers to Support Behavior Change

There is a substantial gap between recording information, such as step count, and changing behavior, and limited data exists about the efficacy of trackers in enacting change in physical activity behaviors in any population [17]. Trackers may support behavior change through education and feedback about baseline and ongoing physical activity levels and the ensuing increase in accountability. One study showed that patients dramatically underestimated the number of hours they were sedentary in a day [18], and another found that 69% of tracker users reported that their device improved personal accountability [11].

Use of Trackers With Older Adults

Several studies have examined the perception and use of trackers in older populations although not in the context of a wellness group setting. One such study found that 58% of 18 to 35 year olds judged trackers as effective, versus 20% of those 56 and older [19]. One study examined the usability and usefulness of trackers as perceived by adults 50 years of age and older with chronic illnesses, and found that trackers helped increase physical activity self-awareness and goal setting [20]. Another study examined how overweight or obese postmenopausal women used trackers and found that, while physical activity levels initially rose, they plateaued after 3 weeks [21]. This study raised the question of how to motivate individuals to achieve further gains after initial success. Finally, another study suggested that new tracker designs and features may be needed for increasing physical activity in people 70 years of age and older [22].

Although those who are older, less affluent, and face significant health challenges are less likely to adopt new technologies, they are more likely to accrue greater benefits from an increase in

physical activity, as compared to younger and healthier demographics, once the barriers of cost and training are removed [23]. In one study where adults aged 50 and older tested different trackers for at least 3 days, 73% of the participants felt they would purchase one; however, a lack of instruction manuals and limited familiarity with terminology, such as "link with Bluetooth," erected barriers to use in this age group [20]. Finally, another study found that adults aged 50 and older were 76% adherent with tracker use in a 6-week pilot study and that 45% reported increased motivation for healthier living, while 46% reported being more active, sleeping better, or eating more healthfully [24]. In addition to removing barriers, increasing physician involvement may also serve to increase tracker effectiveness in changing behaviors. There is an opportunity for health care providers to recommend trackers to patients using data on the risks, benefits, and effectiveness [25], and to assist patients in developing behavior change strategies around tracker use [17].

Methods

Setting

Family Doctors, LLC is a private practice in a suburban community north of Boston, MA serving patients of all ages. Two of their physicians, Jeffrey Phillips (JP) and Lisa Ceplikas (LC) cofounded the Family Doctors Wellness Group in 2015 with a nurse practitioner, Wendy Beaumier, and a registered dietitian, Diane Dube. They believed that the "traditional" model of seeing patients in a 15 minute office visit was incompatible with their goal of helping patients develop positive health habits and lifestyle changes. Furthermore, they felt that offering additional wellness coaching in a group setting would take advantage of built-in support from a cohort of patients facing similar challenges. The Wellness Group was designed as a 12-week program with 2 hour meetings every week, during which patients received guidance and teaching from JP and other health experts on physical activity, nutrition, mental health, mindfulness, and sleep.

To be considered for inclusion into the group, patients had to be part of the practice, have at least one chronic medical condition, and be over 18 years of age. Patients were excluded if they didn't comprehend and speak English or if they had advanced dementia. Recruitment was done through the Family Doctors Facebook page, brochures in the office, and word of mouth. Cost to patients was a US $150 program fee, plus insurance co-payments. Two wellness groups met in 2015, each with an average of 10 participants, and the third started in January 2016. For the third group, which is the focus of this study, recruitment of patients included informal mentions from Family Doctors, LLC staff that patients would receive a free wearable activity tracker. Other than the addition of the tracker, the structure and the demographics of the group were similar to those of the previous wellness groups.

Participant Demographics

Of the 11 patients who participated in the wellness group from the start, 1 left after eight weeks for personal reasons unrelated to health and is not included in any reported results. For the 10 who completed the program, ages ranged from 39 to 77 years old with a mean age of 61 and a median age of 63. Patients included 2 (20%, 2/10) males and 8 (80%, 8/10) females. Of the 10 primarily lower-income patients, 5 (50%, 5/10) worked full-time, 1 (10%, 1/10) worked part-time, and 4 (40%, 4/10) were retired. All patients suffered from at least one of the following chronic medical problems: overweight and obesity, hypertension, type 2 diabetes, hyperlipidemia, and joint pain. All but 1 of the patients was overweight or obese. Baseline levels of physical activity, as assessed by JP through patient interviews and group counseling, ranged from almost entirely sedentary to moderately active. All patients stated that they were first-time tracker users at the onset of the group.

Study Structure

At week 2 of the 12-week wellness group, all participants were given a new Withings Pulse, a wearable activity tracker that measures step count, calories burned, distance walked, heart rate, and sleep. Withings Pulse devices were selected for this study because of their availability, to maintain consistency between participants and avoid errors from device variation. Participants were given instructions developed by the research team on the setup and use of the tracker, and JP assisted 7 participants in setting up their devices, while the remaining 3 felt confident in setting up their devices independently. Participants were given guidance on how to select their daily step count goal. Some used the default step goal of 10,000 steps per day, while those with significant physical limitations used a goal personalized to their needs by JP, with instructions to slowly increase their daily and weekly step count as their health permitted.

In alignment with the philosophy of the wellness group, the use of trackers was discussed with participants as a way to build better health habits and create lifestyle change. To generate discussion and provide support, JP used anecdotes from his own tracker use to encourage participants, such as trying to "get in some steps" by taking short walks when possible. In addition, JP helped to troubleshoot or answer participant questions about the trackers during weekly meetings, by phone, and by email.

The study received approval from the Tufts University Health Sciences Institutional Review Board. All 10 who completed the 12-week program consented to participate in semi-structured phone interviews, consisting of 18 open-ended questions with potential follow-up statements to encourage further responsiveness from the interviewees. Lisa Gualtieri (LG) conducted the interviews, which ran for approximately 30 minutes each, and Sandra Rosenbluth (SR) acted as scribe, taking notes to supplement LG's notes. Interviews took place during a 3-week period to accommodate participants' schedules. The interviews occurred at weeks 14, 15, and 16; thus participants had used the trackers for 12 to 14 weeks at the time of the interviews. In addition, JP recorded age, systolic blood pressure (SBP), diastolic blood pressure (DBP), low-density lipoprotein (LDL), and body weight at the start and end of the intervention.

Analysis

Once all interviews were completed, LG and SR independently conducted thematic analysis through reviews of the interview

notes to identify underlying themes in participant experiences. Transcripts were manually reviewed for common language and word choice, followed by multiple discussion sessions to determine significance and prevalence of themes. Clinical data recorded by JP were documented in a spreadsheet and analyzed with GraphPad QuickCalcs [26], shown in Table 1. Paired *t* tests and *P* values were calculated, and *P* values less than .05 were considered as significant.

Table 1. Changes in systolic blood pressure, diastolic blood pressure, low-density lipoprotein, and body weight after 12 weeks of wearable activity tracker use.

Characteristic	Before	After	Mean change	*P* value
Mean SBP[a], mmHg	129.8	130.0	0.2	.920
Mean DBP[b], mmHg	78.0	73.7	–4.3	.113
Mean LDL[c], mg/dL	105.1	95.4	–9.7	.038
Mean weight, lbs	236.4	230.4	–6.0	.004

[a]SBP: systolic blood pressure.

[b]DBP: diastolic blood pressure.

[c]LDL: low-density lipoprotein.

Results

Clinical Outcomes

Participants lost an average of 0.5 lbs per week (SD 0.4), with a mean total weight loss of 5.97 lbs (*P*=.004). Other short-term clinical outcomes included a 9.2% decrease in LDL levels (*P*=.038). Changes in blood pressure were non-significant. These results cannot separate the impact of the wellness group education and support from that of the tracker use.

Themes

From the interviews following the end of the wellness group, we identified 6 major themes related to the acceptability of, use of, and attitudes towards the trackers by participants.

Theme 1: Purchase Barriers

All participants were aware of trackers before receiving one, but none had purchased or used one prior to participation in the wellness group. Half had considered purchasing a device for themselves. For many, the cost of the trackers was an impediment to purchase, but for some the cost was coupled with the lack of perceived value of trackers.

> *I didn't want to invest money and then just put it aside. Studies show people fade away from these devices.*
>
> *I had friends who did it but didn't seem to get into physical shape, so I thought 'why bother?' Also, it was really expensive.*

Many participants expressed choice confusion due to the number of brands, models, and features on the market. However, all participants were willing to try a tracker, since being given a tracker removed the barriers of cost, perceived value, and choice confusion.

Theme 2: Attitudes Towards the Trackers

When participants were asked to use one word to retrospectively describe how they felt about their tracker when they initially received it, the language varied considerably. Half of the participants, many of whom were individuals who had previously considered purchasing a tracker, expressed excitement and hopeful feelings, such as "grateful" and "thrilled." In contrast, the other half of the participants expressed negative or neutral feelings, including that they viewed trackers as something for athletes, "a fashion trend," "a gimmick," or what "snobby people wore" to maintain "an air of superiority." Words like "skeptical," "overwhelmed," and "unsure" were also used.

Comparatively, when participants described how they felt about their tracker at the time of the interview, all responses were positive. Specific words used include "fantastic," "helpful," "optimistic," "very happy," "healthy," "very satisfied," and "elation."

A further indication of attitudes towards trackers was that all participants said they would recommend a wearable activity tracker to others. In addition, 8 (80%, 8/10) said they would purchase one as gift for someone else, although 2 (20%, 2/10) expressed concern about the cost. The remaining 2 (20%, 2/10) participants were hesitant about giving a tracker as a gift since they thought it could convey a negative message to the receiver.

Theme 3: Trackers as Educational Tools

With initial use, 8 (80%, 8/10) of the participants were surprised by what the tracker reported about their baseline activity level. For example, 40% (4/10 of the participants knew their activity levels were low due to being retired or working in sedentary jobs, but were disappointed to see how low the trackers reported their step counts to be and 2 (20%, 2/10) of the participants reported they were walking more than they thought. In addition, one participant who had low initial numbers expressed that it was important to avoid "doing nothing."

Theme 4: Trackers Provide Feedback on Physical Activity

All participants found it beneficial to have a tangible, visible reminder of a commitment to increasing activity and immediate feedback on step count and progress towards a daily step goal.

> *...[immediate feedback from the tracker] made me feel like I was making some progress. Before, I would*

> *go to the gym and get sweaty, but I didn't see any changes in the scale or the mirror right away, whereas the tracker was instant gratification.*

Another participant described increasing physical activity as something that became "unconscious," while others mentioned that the tracker served as a trigger to increase their physical activity by adding a walk or increasing the duration of a walk. Some participants expressed frustration that the tracker didn't register activities such as yoga, standing, or the use of some exercise machines.

> *Because of the way the machine was, the tracker wasn't tracking my exercise. I try to use my arms a little when I use that machine.*

When describing their tracker use, participants talked about how they felt accountable to it or were kept honest by it.

> *I don't have to report to anyone, but I kind of have to report to my tracker. I'm accountable to it in some way.*
>
> *It's indisputable. I can't argue with the numbers that are showing up.*
>
> *[It] keeps you honest about how much you're actually exercising.*
>
> *The tracker has become a part of me.*

Participants said they were less likely to make excuses for not being physically active and a few mentioned that they competed with themselves by trying to beat the previous day's step count, or, if they had a low step count one day, making sure the next day was better. As one said,

> *It's a great motivator without making you feel guilty that you didn't do it.*

Participants noted the satisfaction of reaching a goal, exceeding a goal, or setting a new goal.

> *If I really put my mind to it, it wasn't that difficult to achieve 7000 or 8000 steps.*
>
> *It was a real sense of accomplishment to be upping the steps [after increasing the goal from 8000 to 10,000 steps].*
>
> *[There were] days where I was walking more than expected and I felt good, I wanted to keep that feeling.*

Theme 5: Tracker Use Reinforced Wellness Group Activities and Goals

Receiving trackers through the wellness group appeared to amplify participants' positive experiences. Though speculative, participants were asked to consider how they thought their experience would have differed had they used the tracker without the group. Of the participants, 70% (7/10) strongly believed their tracker use would have been less positive without the informal discussion about the tracker and the support from other members during each session. One participant found inspiration from another participant who had a similar work situation, who "helped me figure out how to work on getting out and getting my walks in, especially on days where I felt I couldn't make the time." All participants expressed positive sentiments about the wellness group, noting the lack of competition in the group, and that the weekly meetings were "supportive" and provided a sense of "camaraderie."

Theme 6: External Circumstances and Ongoing Use

Participants noted external factors that influenced their tracker use or their ability to incorporate fitness in their lives. Weather was cited by a number of participants, and the constraints of jobs and retirement were also mentioned. Many participants mentioned fluctuations in routine between weekdays and weekends and how the tracker helped them identify and change that.

In the time between receiving the tracker and being interviewed, 40% (4/10) of the participants' use of the trackers or adherence to their fitness routine was temporarily derailed due to external circumstances. One individual stopped walking due to a fall. Another brought the tracker on a trip but didn't immediately unpack it after returning. A third had trouble fitting exercise into her schedule when a family member was hospitalized. A fourth participant's tracker stopped working. In all these cases, despite cessation, the intention to continue physical activity remained and was emphasized during the interview process.

Use of the tracker itself varied as well. Only 50% (5/10) of the participants used the wristband with the Withings Pulse. Of the others, 1 (10%, 1/10) alternated between wearing it with the wristband and clipping it to clothing, 2 (20%, 2/10) wore it solely clipped, and 1 (10%, 1/10) kept the device in a pocket. The reasons for solely clipping the device included poor fit and discomfort: in one case due to the circumference of the band and in the other the feel of the band when sweating during menopause. In addition, 1 (10%, 1/10) participant was unable to use the device due to incompatibility with her mobile phone operating system, but used the corresponding Withings app to track step count and thus answered interview questions referring to the impact of tracking on physical activity.

Discussion

Principal Findings

Our study findings suggest that adults with chronic medical conditions, when given free trackers in a physician-led group setting, are motivated to increase physical activity behaviors, regardless of their initial attitudes towards trackers. While attitudes were mixed in the beginning, by the end of the study all participants expressed positive attitudes in the interviews, further demonstrated by their commitment to the use of their trackers.

Since, many barriers exist to the purchase and use of trackers, our study was designed to remove cost and training as barriers. We identified perceived value and choice confusion as additional barriers to purchase that our study also removed. We identified ongoing support, in addition to training, as a barrier to use, which was also removed as part of the wellness group. These findings suggest that trackers can have an impact beyond the current consumer base, including with older adults with chronic medical conditions, when support is provided for selecting, purchasing, setting up, and using trackers. Additional potential barriers to use existed on a more individual basis, such as wristband size and material discomfort, which should be

considered in larger-scale studies. In this pilot, these barriers were overcome by the tracker brand's wearability options.

The trackers increased participant self-efficacy by providing a tangible, visible reminder of a commitment to increasing activity and immediate feedback on step count and progress towards a daily step goal (ie, by providing instant gratification when reaching said goal and feedback on the effect of changes to daily routines). Delayed benefits through a lack of feedback or sense of accomplishment can cause physical activity drop-off, a concept known as present-biased preferences. However, the trackers provided feedback that otherwise was only obtainable more slowly through observed changes in clothing sizes or weight on a scale. Having positive emotions associated with physical activity can further increase self-efficacy and is an important motivator for behavior maintenance, which trackers may foster. Identifying barriers and potential methods of increasing self-efficacy in pilot research can support the selection and use of specific theories of behavior change to guide the methodology of future studies. Based on these results from this pilot study, the Transtheoretical Model and Self-Determination Theory may serve as theories that could potentially lead to the development of effective intervention strategies.

Participant's felt accountable to the trackers, and, when competitive, participants were competing with themselves. The integration of trackers into the wellness group did not foster competitiveness; group discussions focused on sharing tips to increase physical activity and on tracker successes, and lapses were viewed as opportunities for learning. Participants had the same individual goal of creating a healthier lifestyle. The value of this non-competitive atmosphere was emphasized by one participant, who favorably contrasted it to the bullying that took place in a workplace wellness program that incorporated trackers. Trackers may have particular value as impartial aids to increasing physical activity for people who are wary of being judged, are not incented by group competition, or use the tracker feedback to compete with themselves.

In addition to the positive impact that trackers had on participants' self-efficacy, clinical measures of health improved as well. By the conclusion of the 12-week program, a significant amount of weight was lost. More importantly, the rate of weight loss was consistent with long-term true fat loss [27], thus suggesting that the healthy habits developed over the course of the wellness group were ones that could be maintained over the long-term. In addition, all participants reported an increase in well-being, health education, physical activity, and confidence in their ability to lead more active lives. The success of the wellness group is largely attributable to its multifaceted approach to health and wellness. Nutritional changes, increased physical activity, emotional health, improved sleep, and wellness coaching were all utilized in conjunction with one another to encourage participants to incorporate gradual, evidence-based changes into their lives, promoting true lifestyle change rather than "dieting" or being on an "exercise program" for a limited amount of time. Such wellness group programs can be enhanced by the integration of trackers to serve as reminders during the bulk of the week when not in the wellness group and in the time following the conclusion of the supportive group setting.

Limitations

Our study possesses several limitations which must be considered in interpreting the results. The most significant limitation was the lack of a control group comprised of an identically structured wellness group that did not provide patients with trackers. As such, some observed results cannot be directly attributed to the trackers. Instead, the results from this small pilot serve to inform the feasibility of research revolving around trackers in physician-guided settings; are trackers accepted and engaged with by participants, when these participants belong to a demographic that does not normally purchase wearable activity trackers? A future study with 3 arms (a wellness group without trackers, an un-enrolled but matched group with trackers, and a wellness group with trackers) would help determine the degree to which certain results can be attributed to certain inputs.

In addition, the small sample size and single study site provide encouraging results but should be replicated and reproduced with more participants and more study sites. Finally, study interviews were conducted between 14 to 16 weeks after the wellness group started and do not provide data on how participants' motivation to be physically active may change in the longer term.

Conclusion and Implications

Our findings suggest that adding trackers to wellness groups comprising older participants with chronic medical conditions can increase their self-efficacy and motivation to be more physically active. Barriers need to be identified and removed; in our study, the barriers to purchase included cost, perceived value, and choice confusion were removed by providing participants with free trackers and the barriers to use were removed by providing participants with initial training and ongoing support. Overall, our study demonstrated the educational benefits to individuals of learning their baseline activity levels, the increased self-efficacy arising from concrete feedback on physical activity that motivated behavior change, the positive attitudes that developed towards trackers, and improvements in clinical outcomes.

Other group programs may want to add trackers based on the benefits our study found to adding them in this setting. Furthermore, our findings suggest that it may be cost-effective for physicians and other health care providers to provide free or heavily subsidized trackers, along with training and support, to their patients, especially those who may most benefit from increasing their physical activity. A US $60 activity tracker that lowers the risk of chronic conditions or ameliorates their severity by facilitating changes in health behaviors would be greatly beneficial compared to the health care, medication, or intervention costs required to treat illnesses after they develop. Future research will further consider the potential of trackers in older adults with chronic medical conditions who are unlikely to purchase them, and studies will use larger samples, continue over a longer period of time, and evaluate outcomes independent of a wellness group.

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Conflicts of Interest

None declared.

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Abbreviations

DBP: diastolic blood pressure
LDL: low-density lipoprotein
SBP: systolic blood pressure

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Original Paper

Design, Response Rates, and Population Characteristics of a Cross-Sectional Study in Zanzibar, Tanzania

Maria Adam Nyangasa[1], MSc; Soerge Kelm[2], PhD; Mohammed Ali Sheikh[3], PhD; Antje Hebestreit[1], PhD

[1]Leibniz Institute for Prevention Research and Epidemiology-BIPS, Bremen, Germany

[2]Center for Biomolecular Interactions Bremen, University of Bremen, Bremen, Germany

[3]Environmental Analytical Chemistry and Eco-toxicology Lab, State University of Zanzibar, Zanzibar, United Republic of Tanzania

Corresponding Author:
Antje Hebestreit, PhD
Leibniz Institute for Prevention Research and Epidemiology-BIPS
Achterstrasse 30
Bremen, 28359
Germany
Phone: 49 421218 56849
Fax: 49 421218 56821
Email: hebestr@leibniz-bips.de

Abstract

Background: Data on nutritional status and correlates of noncommunicable diseases are scarce for resource-poor settings in sub-Saharan countries. With the scope of a project, "Access to Food and Nutrition Status of the Zanzibari Population," data for investigating public health questions were collected using proven measurement and laboratory standards.

Objective: The present study aims at providing a descriptive overview of recruitment approaches, standardization, quality control measures, and data collection, with special attention to the design, responses, and participant characteristics of the overall project.

Methods: A cross-sectional study across 80 randomly selected Shehias (wards) was conducted in 2013 in Unguja Island, Zanzibar. Examinations included all members living in 1 household, face-to-face interviews and anthropometric measurements (weight, height, mid-upper arm circumference, waist and hip circumference, and body composition) were assessed for all household members, blood pressure was taken from participants older than 2 years, and biosamples (urine and blood) from eligible household members were collected. Data collected from the core sample included sociodemographic data, nutritional status, and medical history (hypertension). Physical activity data was collected from a subsample of children between 3 and 16 years of age.

Results: A total of 1314 participants (mean age 23.6 ± 18.9 years, 54.54% female) completed all anthropometric measurements and were included in the analysis. Out of which, 98.40% (1293/1314) completed the household member's questionnaire, 93.32% (1229/1314) participants older than 2 years completed blood pressure measurements, and 64.31% (845/1314) blood samples were collected from participants older than 5 years. Underweight prevalence for the total study population was 36.53% (480/1314) with the highest prevalence in children under 14 years. Overweight and obesity was highest among females with the prevalence of 7.61% (100/1314) and 6.62% (87/1314), respectively; obesity was rare among male participants.

Conclusions: The study provides valuable data to investigate the interplay of socioeconomic, demographic, environmental, physiological, and behavioral factors in the development of diet-related disorders in a representative sample of the Zanzibari population.

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KEYWORDS

cross-sectional study; anthropometric measures; blood pressure; biosamples; response rates; sub-Saharan Africa

Introduction

Food and nutrition insecurity is defined as the uncertain or limited access to safe, sufficient, and adequate food that is supported by an environment of adequate sanitation and health services to allow a healthy and active life [1]; it is a leading cause of morbidity and mortality worldwide. The United Nations Food and Agriculture Organization (FAO) estimates that

approximately, 1 in 9 people was suffering from chronic undernourishment in 2012-2014, with a high prevalence in sub-Saharan African countries with low income [2]. Although some of these countries report to have adequate food at the national level, this does not guarantee food security at the household level [3]. Access to food in Zanzibar is one of the foremost food security problems for many Zanzibar households in both rural and urban areas. Access to food means individuals have adequate income or other sources to purchase or obtain levels of appropriate foods needed to maintain consumption of an adequate diet/nutrition level and are able to obtain these foods in socially acceptable ways [4].

Food insecurity has been linked to poor diet quality and has been found to have multiple negative health impacts beyond under nutrition, such as hypertension, obesity, and increased rates of gestational diabetes mellitus [5,6]. Also, data from mainland Tanzania show an increasing prevalence of overweight and obesity in urban, peri-urban, and rural areas [7-9]. In Zanzibar, education, food production, globalization, and sedentary lifestyle have noticeable effects on the health and nutrition status of the people. Like other developing countries, Zanzibar is undergoing a double burden of underweight and overweight/obesity [10] with a rapidly increasing number of noncommunicable diseases and associated risk factors. Data on nutrition and lifestyle factors and related determinants to assess the prevalence of cardiometabolic risk factors are scarce for resource-poor settings in sub-Saharan countries.

The project “Access to Food and Nutrition Status of the Zanzibari Population” comprises a population-based, cross-sectional survey in order to collect data for addressing these public health questions using proven measurement and laboratory standards [11,12]. The present study aims to describe the study design, field methods, and examination modules that were used to collect data in this representative study population. The present study will also present response proportions for all survey modules, prevalence estimates for underweight, overweight, and obesity for all study participants, and measures for data quality as well as giving a first glance on estimates of metabolic and nutritional markers of malnutrition for the study population. Further results on nutrition and health outcomes related to food access and food insecurity, diet, and biochemical indicators, as well as the potential determinants of nutritional status of the study participants are the subject of forthcoming publications.

Methods

Study Area

Zanzibar Island is located approximately 25 km off the coast of Mainland Tanzania. Zanzibar is comprised of 2 main Islands, Unguja and Pemba, with a projected population of 1.3 million people; almost 63% living in Unguja and 37% in Pemba [13]. Zanzibar Island has 2650 km^2 of land area, of which two-thirds is coral-derived and one-third, where the population is concentrated, is good for agricultural production. Based on the food security situational analysis of 2006, Zanzibar produces 59% of its needs and the rest is from imports. The major foods produced are rice, cassava, bananas, sweet potatoes, maize, yams, and fish, while major imports includes rice, wheat flour, maize flour, and sugar [14].

Administratively, Zanzibar is divided into 5 regions, 3 in Unguja, and 2 in Pemba. Each region has 2 districts under the District Commissioner; each district is also subdivided into several smaller administrative units known as Shehias (equivalent to wards).

Sampling

This baseline survey was carried out in 80 Shehias in Unguja. A two-staged sampling technique was used: (1) from a list of all 213 Shehias from the Tanzania population and housing Census 2010 [15], 80 Shehias were randomly selected using a Statistical Software procedure PROC SURVEYSELCT; and (2) participating households were randomly selected within each Shehia through the official Sheha’s (the Shehia’s administrative authority) registration where all members of each Shehia were registered according to household number and/or street name.

Households were defined as a group that shared meals and slept under the same roof [16], all members in a household constituted the target study population. The overall aim of the study was to estimate the prevalence of malnutrition in the Zanzibari population including possible correlates. As published prevalence estimates for malnutrition in the overall population are scarce, malnutrition prevalence among children under the age of 5 years (30% prevalence of chronic malnutrition in children <5 years) was taken from the Tanzanian Demographic and Health Survey 2010 [13]. Assuming a prevalence of approximately 30% malnutrition in children <5 years of age, a sample size of 323 children <5 years of age was needed to estimate 95% confidence interval with a precision of ±5%. The estimated sample size was determined based on the formula discussed by Lemeshow [17]. Given that each household takes care of 1 child <5 years of age and the reported average household size is 4.8 members [15], we estimated a final sample size of 1453 subjects when 4 households per Shehia were enrolled.

Recruitment

Eligible households/participants were visited twice for recruitment and examination: during an evening visit, members of selected households were asked for agreement in participation, and on the subsequent morning they were examined. The field team randomly selected participating households by choosing any number from the household registration book. With the Sheha’s assistance, the selected households were visited for further information about the survey and enrollment, and to receive informed consent for all household members. Morning visits were for conducting all measurements, questionnaires, collection of morning spot urine and venous blood, distribution of accelerometers to eligible members, and providing feedback to all participants. Blood drawing and anthropometric measurements were carried out in fasting status.

All members of the selected households living together and eating from 1 pot were considered eligible. The main respondent was the head of household (father/mother). However, in the

absence of the head of household, a guardian/caretaker of the house became the main respondent. In the case of polygamous families, all wives and their household members were also eligible for participation regardless of area of residence. One consent form was available per household; all participating members were given an anonymized identification number. Prior to the data collection process, all participants were verbally informed in Swahili on the study goals, purpose, target study group, contents, the amount of examinations involved, and that participation in the study was voluntary and consent could be withdrawn at any time without specifying any reason. Besides the verbal information given, all participants older than 16 years gave written consent and parents/guardians gave written consent on behalf of their children younger than 16 years. Participants signed 2 copies of the consent form, whereby 1 remained with them and the second was kept in the investigator's file on site. The study was approved by the Ethics Committees of the University of Bremen and of the Zanzibar Ministry of Health and the Zanzibar Medical Research and Ethics Committee in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments. The consent forms were approved by the Institutional Ethics Committee.

As an incentive, every participating household received a Swahili feedback sheet with information on anthropometric measurements, body composition, blood pressure, and urine dip stick test results (for feedback purposes only).

Anthropometric Measurements and Physical Examinations

The survey covered standard anthropometric measurements taken by trained fieldworkers following standardized procedures for anthropometric measurements, physical examination [11,18], and biosample collection and procession [12].

The measurement of body composition and body weight was carried out using an electronic scale (TANITA BC-420 SMA, Germany) to the nearest 0.1 kg. The surveyed area was a strict Muslim community; participants were covered with light clothing (“Kanga”). Like many similar studies [19,20], the weighing scale was tared with 1-kg clothing to give a zero reading before weighing the participant. At each instance, the actual weight of the participant was measured in fasting status and barefooted.

Height of participants who could stand alone was measured in accordance with international standards for anthropometric assessment and weight (kg) [11]. Recumbent length of young children under 2 years was measured using a measuring board (Seca 417 measuring board, UK); all measurements taken were recorded to the nearest 0.1 cm. Body mass index (BMI) was calculated by dividing weight in kilograms by height squared in meters (kg/m^2) and then transformed to age- and sex-specific z-score. According to World Health Organization (WHO) [21] recommendations, BMI (adults) and BMI z-score (children) were used to define individuals who are underweight, normal weight, overweight, and obese.

Mid-upper arm circumference (MUAC) was measured at the mid-point of the left arm. Waist circumference (WC) was measured at the midway point between the lower rib margin and the iliac crest, and hip circumference (HC) was measured at the widest portion of the buttocks. Waist-to-hip ratio was obtained by dividing WC by HC. All circumferences were measured in standing position and while wearing light clothing using an inelastic measuring tape (SECA 201) to the nearest 0.1 cm.

A digital automatic blood pressure (BP) monitor (Omron T3) was used by trained fieldworkers to measure the systolic and diastolic BP according to a standardized procedure. Cuff length for BP measurement was determined according to the arm circumference, which was measured to the nearest 0.1 cm using an inelastic measuring tape. Participants were asked to rest for at least 15 minutes before measurements. Two measurements were taken at an interval of 5 minutes apart, plus a third measurement in case of a >5% difference in BP between the previous 2 readings. Use of antihypertensive medication and name(s) of medication were also recorded. For statistical analysis the lowest reading was considered. Hypertension was defined as a sustained high BP (systolic BP≥140 mm Hg or diastolic BP≥90 mm Hg) [22], or reported regular use of antihypertensive medication.

Questionnaires

All forms and questionnaires were administered and well explained by trained fieldworkers in Swahili. Three main questionnaires (ie, head of household questionnaire, household members’ questionnaires, and young children questionnaire) were developed to collect data needed for the assessment. The questionnaires used were partly adapted from the Tanzania Demographic Survey 2010 [13] and Food and Nutrition Technical Assistance [23]. A partly validated head of household questionnaire was developed and administered to the head of the household (man/woman/guardian). This was used in collecting data on social, demographic, and economic indicators of the household: the ownership of livestock and other assets, sanitation, as well as information on household dietary behavior including expenditure and consumption. The household questionnaire also included a Swahili-translated version of Food Insecurity Experience questions [3], adapted from the original FAO 2007 [24]. Another tool used to measure food security was the Food Consumption Score, which was a composite score based on dietary diversity, food frequency, and relative nutritional importance of different food groups [25]. To measure nutritional quality and micronutrients adequacy of individual’s diets, an Individual Dietary Diversity Score was calculated based on the 14 food groups’ classification recommended by FAO (2007) [24]. Data derived with these instruments will be investigated in depth later and go beyond the scope of this study.

A (parental) proxy questionnaire was used to assess dietary diversity and consumption frequency of young children (0-24 months) addressing in particular breast-feeding habits, introduction to complimentary food, and a 24-hour dietary recall with food frequency questions adopted from the WHO [26].

Biosamples

The study collected venous blood and morning urine samples from eligible participants in an overnight fasting status, all participants were informed during the evening visits to avoid

eating or drinking anything (apart from water) prior to sample collection. According to several identified studies and guidelines [27], pediatric blood sample volume limits ranging from 1% to 5% of total blood volume within 24 hours is within the limits of minimal risks. In this study, venous blood was drawn from participants older than 5 years and the collection was restricted to 1% of the estimated total blood volume corresponding to approximately 8 mL in a child weighing 10 kg. Children between 5 and 10 years received an eutectic mixture of local anesthetics patch prior to the blood drawing. For healthy, nonpregnant adults weighing at least 50 kg, a maximum of 20.5-mL venous blood was drawn, this corresponds with other research guidelines for human blood drawing. Instructions and urine collection cups labelled with the identification number of the participants were given to each member of the household for morning urine collection. Morning urine of younger children was collected by the parents.

A 6-mL tube (4 mL for children) of ethylenediamine tetraacetic acid (EDTA) blood was collected from each participant and kept at 4°C and fractioning was done the same day in the laboratory. First, 0.5-mL whole EDTA blood was transferred into a 2-mL cryotube for glycated hemoglobin (HbA1c) analysis. Second, the EDTA blood was further separated after centrifugation for 10 minutes at 2500 *g*: this includes partitioning of the sample in 2 aliquots of plasma (0.5-1 mL) and 2 aliquots of red blood cells (RBC), as well as the isolation of 0.5-mL buffy coat white blood cells (WBC). Plasma, WBC, and RBC aliquots were sorted into separate cryoboxes and immediately stored at −80°C. From each participant, a 25-mL sample of urine was collected. Of the collected urine, 4 aliquots (5 mL) were transferred to a 5-mL vial. The urine samples were sorted into a separate cryobox for later analysis and stored in an upright position at −80°C. Blood and urine samples were analyzed for indicators of metabolic disorders and other health- and diet-related outcomes like blood glucose, HbA1c, cholesterol, triglycerides, low-density lipoprotein (LDL), insulin, leptin, C-reactive protein, urine albumin, and cytokines like tumour necrosis factor-α, inducible protein-10, interleukin (IL)-6, IL-8, IL-15, and IL-1 receptor antagonist.

Physical Activity

To measure objective physical activity data, a subsample of 102 children and adolescents, aged between 3 and 16 years, were randomly selected from the participated households in 20 Shehias covering the rural, urban, and peri-urban areas. Participants wore a uniaxial accelerometer on the right side of the hip for 3-7 consecutive days. Raw data collected by the accelerometer were integrated into 15-second epochs using ActiLife software. Wear time and nonwear time were determined using the algorithms developed by Choi et al [28]. Nonwear time was defined as 90-consecutive minutes of 0 cpm, allowing up to a 2-minute interval of non-zero cpm. Information regarding the correct wearing of the accelerometer was explained to the parents and the participants prior to the initial wear. Both parents and participants were instructed to remove the accelerometer during sleeping, bathing, swimming, or at any point where they had full body contact with water. Parents checked and corrected the accelerometer on regular basis and used a diary to document the times and durations when the accelerometer was not worn or removed for specific reasons. These diaries were returned to the survey team mostly incomplete, and thus were not yet considered for analysis. Accelerometer measurements were included from children who wore the accelerometer for at least 3 days, including 1 weekend day, and for at least 6 hours per day. The duration of moderate-to-vigorous physical activity was determined according to the cut-offs of Evenson [29,30].

Quality Control and Management

All measurements and methods followed standard operation procedures and were adopted from the Identification and prevention of the Dietary- and lifestyle-induced health EFfects in Children and InfantS study (IDEFICS) [11,12]. All instruments were developed in English and translated to Swahili and then back-translated to check for translation errors. The quality of translation and the relevance of the study and instruments were discussed with the team of experts from the Ministry of Agriculture under the department of Food and Nutrition and the United Nations Children's Fund in Unguja.

Field workers participated in local training in Zanzibar prior to the pretest; the fieldworkers were trained from basic interview techniques to the specific anthropometric measurements data collection as well as field methodology and sampling. Further training on laboratory procedures (ie, collection, processing, and storage of biosamples) and analysis were provided to laboratory technicians according to the IDEFICS study standards [12].

Prior to field work, a pretest was conducted in a convenience sample to test the wording flow, comprehension of the questions, and interviewing and anthropometric measurements techniques; the instruments were then modified accordingly. All instruments were finalized after the pretest of all measurements.

Fieldworkers were divided into 2 teams who used the same technical equipment and instruments for data collection to maximize comparability of data. Reliability measurement results were assessed by repeated measurements and swapping of the field team members on a regular basis. Quality control was applied daily during the field phase and included completeness, quality of documentation, and adherence to the study procedures. All numerical variables were entered twice, independently during data entry. In order to decrease measurement errors, subsamples of the study subjects were examined repeatedly to calculate the inter- and intraobserver reliability of anthropometric measurements. The protocol of the reliability measurements proposed that the manual set of anthropometric measurements (excluding those that were measured with an electronic and automated device) be taken in at least 20 children (10 girls and 10 boys, all primary school). Every observer measured each child 3 consecutive times within 1 hour in an extra sample. Analysis was performed according to Stromfai et al [11].

Quality control during biosample analysis comprised double analysis in most parameters where feasible (HbA1c, glucose, total cholesterol, triglycerides, LDL), and a third scan when the difference between the first 2 values was >10%. Other parameters were measured once, and reference samples (n=6) were scanned randomly in an independent laboratory in

Germany controlling for interassay reproducibility of values. Interclass coefficient correlation between the 2 sets was calculated for the measurements of cholesterol, glucose NaF, HbA1c, HDL-cholesterol, LDL-cholesterol, LDL-HDL-quotient, and triglycerides.

Results

Household Characteristics

The household characteristic was comprised of the number of households that participated in the survey, household size, sex, marital status, highest head of household's education level, source of income, as well as occupation (Table 1). A total of 239 households participated in the survey, more than half (131/239, 54.8%) were from rural areas with an average household size of 6 persons per household. Of the participated households, 62.8% (150/239) were headed by a male. Over half (124/226, 54.9%) were married in monogamy with the highest percentage from rural areas (69/124, 55.7%). The results further showed that more than three-quarters (184/224, 82.1%) of the household heads had attained some level of education, which means they could read and write; 17.9% (40/224) had no education. Of the respondents, 49.0% (117/239) had no regular income, and 45.6% (109/239) had at least 1 source of income to ensure stability of household food supplies, with a majority (73/109, 55.7%) of the respondents being from a rural area, and 5.4% (13/239) with more than 1 source of income. Primary sector (farmer, livestock, fishing, daily ages) was the main occupation group for the majority (73/215, 30.7%) of the household heads.

Table 1. General characteristics of head of households.

Characteristics	Rural	Urban	Peri-urban	Total
	n (%)	n (%)	n (%)	n (%)
Number of households	131 (54.8)	53 (22.2)	55 (23.0)	239
Average number of household members	6.0	8.1	7.1	6.7
Gender of household head (n=239)				
Male	81 (61.8)	37 (69.8)	32 (58.2)	150 (62.8)
Female	50 (38.2)	16 (30.2)	23 (41.8)	89 (37.2)
Matrimonial status (n=226)				
Other[a]	20 (16.1)	13 (26.5)	10 (18.9)	43 (19.0)
Monogamous	69 (55.7)	27 (55.1)	28 (52.8)	124 (54.9)
Polygamous	35 (28.2)	9 (18.4)	15 (28.3)	59 (26.1)
Education of the household head (n=224)				
None	28 (22.8)	5 (10.4)	7 (13.2)	40 (17.9)
Primary	38 (30.9)	19 (39.6)	16 (30.2)	73 (32.6)
Secondary	56 (45.5)	23 (48.0)	29 (54.7)	108 (48.2)
Tertiary	1 (0.8)	1 (2.1)	1 (1.9)	3 (1.3)
Source of income (n=239)				
None	50 (38.2)	35 (66.4)	32 (58.2)	117 (49.0)
One	73 (55.7)	18 (34.0)	18 (32.8)	109 (45.6)
More than one	8 (6.1)	0 (0)	5 (9.1)	13 (5.4)
Occupation sector (n=215)				
None	40 (33.1)	27 (60.0)	26 (53.1)	93 (43.3)
Primary[b]	52 (43.0)	5 (11.1)	9 (18.4)	66 (30.7)
Secondary[c]	3 (2.5)	1 (2.2)	3 (6.1)	7 (3.3)
Tertiary[d]	26 (21.5)	12 (26.7)	11 (22.5)	49 (22.8)

[a]Other includes single, divorced, widow, and cohabitation.

[b]Primary sector includes agriculture, fishing, mining, and forestry.

[c]Secondary sector includes craftsman and industry and construction work.

[d]Tertiary sector includes services and trade.

Age and Gender Distribution of the Study Population

Table 2 represents age distribution of the study population by gender. The sample consisted of 1314 participants; age ranging from 0 to 95 years with a mean (SD) of 23.6 (SD 18.9) years. Participants were predominantly women (715/1314, 54.41%), of which 54.0% (386/715) were between 15 and 59 years. Working and reproductive age adults (15-59 years) comprised 50.15% (659/1314) of the total study participants, 15.60% (205/1314) of the population were children younger than 5 years, 28.01% (368/1314) were school-age children between 6 ad 14 years, and 6.62% (87/1314) were elderly participants.

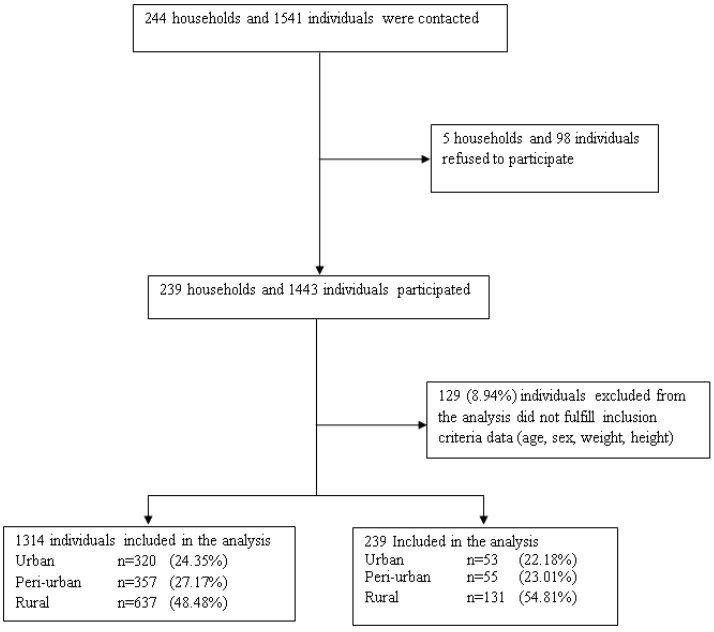
Table 2. Age distribution of the study population stratified by gender.

Age group in years	Male	Female	Total
	n=599 (45.59%)	n=715 (54.41%)	N=1314 (100.00%)
0-2	27 (4.51)	36 (5.03)	63 (4.79)
3-5	67 (11.19)	75 (10.49)	142 (10.81)
6-14	192 (32.05)	171 (23.92)	363 (27.62)
15-59	273 (45.58)	386 (53.99)	659 (50.15)
60+	40 (6.68)	47 (6.57)	87 (6.62)

Participation and Responses

Out of 323 targeted households, 244 households were contacted, of which 97.9% (239/244) were included in the analysis and 2.1% (5/239) of households refused to participate. There were 1453 individuals targeted; however, due to high number of household members 1541 subjects were contacted, of which 1443 took part in 1 or more examination and questionnaire. Overall, 1314 participants fulfilled all inclusion criteria (weight, height/length, age, and gender) and were included in the analysis (Figure 1).

Figure 1. Flow diagram of participants from recruitment to analysis.



Biomarkers in Urine and Blood

Table 3 presents proportions of analyzed biomarkers in urine and venous blood (≥5 years) stratified by age group. Approximately 63.5% (389/613) of the biosamples collected were from 15- to 59-year olds and the lowest proportion (8/585, 1.4%) was from children younger than 5 years, followed by elderly participants older than 60 years (58/613, 9.5%).

Table 3. Bio markers in urine and venous blood samples.

Biosample	Biomarker	<5 years n (%)	6-14 years n (%)	15-59 years n (%)	>60 years n (%)	Total n
Urine						
	Urine albumin-to-creatinine ratio[a]	85 (12.2)	202 (29.1)	353 (50.8)	55 (8.0)	695
Blood						
	Cholesterol[b]	6 (1.1)	152 (26.0)	372 (63.6)	55 (9.4)	585
	Glucose[b]	6 (1.0)	15.2 (26.0)	373 (63.7)	55 (9.4)	586
	Low-density lipoprotein[b]	7 (1.2)	15.2 (26.0)	372 (63.5)	55 (9.4)	586
	Triglycerides[b]	7 (1.2)	152 (26.0)	373 (63.5)	55 (9.4)	587
	C-reactive protein[c]	7 (1.2)	152 (26.0)	373 (63.5)	55 (9.4)	587
	Insulin[c]	8 (1.3)	158 (25.8)	389 (63.5)	58 (9.5)	613
	Leptin[c]	8 (1.3)	159 (25.9)	389 (63.5)	57 (9.3)	613
	IL[d]-1Ra[c]	8 (1.3)	158 (25.8)	389 (63.5)	58 (9.5)	613
	IL-6[c]	8 (1.3)	158 (25.8)	389 (63.5)	58 (9.5)	613
	IL-8[c]	8 (1.3)	159 (25.9)	389 (63.5)	57 (9.3)	613
	IL-15[c]	8 (1.3)	158 (25.8)	389 (63.5)	58 (9.5)	613
	Inducible protein-10[c]	8 (1.3)	158 (25.8)	389 (63.5)	58 (9.5)	613
	Tumor necrosis factor-α[c]	8 (1.3)	158 (25.8)	389 (63.5)	58 (9.5)	613
	HbA1c[e,f]	7 (0.9	219 (26.9)	524 (64.3)	65 (8.0)	815
	Homeostatic model assessment-insulin resistance[g]	6 (1.0)	151 (26.1)	369 (63.6)	54 (9.3)	580

[a]Data available for some of the urine samples collected (at date of publication of manuscript).

[b]Measured in NaF plasma.

[c]Measured in blood serum.

[d]IL: interleukin.

[e]HbA1c: glycated haemoglobin.

[f]Measured in ethylenediamine tetraacetic acid blood (n=870).

[g]Homeostatic model assessment index = insulin (fasting, µU/mL) × blood glucose (fasting, mmol/L)/22.5.

Individual Response for All Survey Modules

Core survey modules listed in Table 4 included questionnaires, anthropometric measurements, venous blood, BP, and a subsample for accelerometer use with children between 3 and 16 years. Besides the anthropometric measurement that had the minimum requirement inclusion for analysis (age, sex, height, weight), 100% response was not reached for other modules. The overall response rate for completing questionnaires was 98.40% (1293/1314); 64.31% (845/1314) for venous blood (restricted to participants ≥5 years), and 93.53% (1229/1314) for BP (participants ≥2 years). The use of an accelerometer was planned in a small subsample group of children between 3 and 16 years and was assessed in 95 children.

Table 4. Response of participants for all survey modules by age group.

Measurements/ examinations	Age group in years					Total	Overall response rate
	0-2	3-5	6-14	15-59	≥60		
	n (%)	n (%)	n (%)	n (%)	n (%)	n	%
Anthropometric measurements	63 (4.79)	142 (10.78)	364 (27.70)	659 (50.15)	86 (6.54)	1314	100
Household members questionnaire	60 (4.64)	142 (10.98)	358 (27.69)	648 (50.12)	85 (6.57)	1293	98.40
Venous blood[a]	-	8 (0.95)	233 (27.57)	537 (63.55)	67 (7.93)	845	64.31
Blood pressure[b]	-	124 (10.09)	364 (29.62)	655 (53.30)	86 (7.00)	1229	93.53
Accelerometer[c]	-	10 (10.53)	79 (83.16)	6 (6.32)	-	95	7.23

[a]Not measured in children below 5 years.

[b]Not measured in young children below 2 years.

[c]Measured only in a subsample of children and adolescents between 3 and 16 years (n=95).

Prevalence of Malnutrition

Table 5 represents the prevalence of nutritional status according to gender and age group of the entire study population. The overall prevalence of underweight, overweight, and obesity was 36.45% (479/1314), 13.09% (172/1314), and 8.14% (107/1314), respectively; 42.31% (556/1314) of participants had normal weight. A higher proportion 70.24% (144/205) of children below the age of 5 years were underweight, more boys were underweight compared with girls. Adult females ages 15-59 years were more obese (71/386, 18.39%) compared with males of the same age group. One-third (28/87, 32.18%) of the elderly participants, both male and female and 60+ years, were overweight, and 16.09% (14/87) were obese.

Table 5. Prevalence of nutritional status stratified by gender and age group.

Gender/age group	Underweight	Normal weight	Overweight	Obese	Total
	n (%)	n (%)	n (%)	n (%)	n
Male					
0-5 years	69 (73.40)	22 (23.40)	2 (2.12)	1 (1.06)	94
6-14 years	120 (62.18)	69 (35.75)	1 (0.52)	3 (1.55)	193
15-59 years	56 (20.51)	149 (54.58)	56 (20.5)	12 (4.40)	273
60+ years	7 (17.95)	14 (35.90)	13 (33.33)	5 (12.82)	39
Total male	252 (42.07)	254 (42.40)	72 (12.02)	21 (3.51)	599
Female					
0-5 years	75 (67.57)	27 (24.32)	4 (3.60)	5 (4.50)	111
6-14 years	93 (54.39)	63 (36.84)	13 (7.60)	2 (1.17)	171
15-59 years	53 (13.73)	194 (50.26)	68 (17.62)	71 (18.39)	386
60+ years	6 (12.77)	17 (36.17)	15 (31.91)	9 (19.15)	47
Total female	227 (31.75)	301 (42.10)	100 (13.16)	87 (12.17)	715
Total					
0-5 years	144 (70.24)	49 (23.90)	6 (2.93)	6 (2.93)	205
6-14 years	213 (58.68)	132 (36.36)	14 (3.86)	4 (1.10)	363
15-59 years	109 (16.54)	343 (52.15)	124 (18.82)	83 (12.59)	659
60+ years	13 (14.94)	32 (36.78)	28 (32.18)	14 (16.10)	87
Overall	479 (36.45)	556 (42.31)	172 (13.10)	107 (8.14)	1314

Quality Indicators

Results of inter- and intraobserver technical error of measurements (TEM) were generally low. Interobserver reliability as assessed by the R for repeated measurements of height, MUAC, WC, and HC was above 99% for all participants (Table 6). TEM% provides comparability of quality between measurements.

Table 6. Inter- and intraobserver technical error of height and circumferences of the arm, waist, and hip in an extra sample.

	Interobserver				Intraobserver (n=30)			
	Mean	TEM[a]	TEM%	R%	Mean	TEM	TEM%	R%
Height	1.36507	0.003524036	0.25816	99.98	1.27973	0.003570410	0.27900	99.99
MUAC[b]	0.21628	0.001305582	0.60365	99.95	0.20203	0.004684696	2.31877	99.35
WC[c]	0.66582	0.001857418	0.27897	99.98	0.59423	0.007834197	1.31837	99.73
HC[d]	0.76888	0.007254823	0.94356	99.86	0.70237	0.004697209	0.66877	99.94

[a]TEM: technical error of measurements.

[b]MUAC: mid upper arm circumference.

[c]WC: waist circumference.

[d]HC: hip circumference

Discussion

Participation and Response

Currently, there are no existing studies that collected anthropometric, biological, socioeconomic, and nutritional data in a representative study sample in randomly selected households in Zanzibar following standardized procedures. This study was successful in setting up a cross-sectional survey of over 1400 participants in 80 Shehias across Unguja. The study included young children to elderly participants ages 0-95 years. The response rate was higher than expected. This is most probably due to multiple reasons: (1) a good training of the field workers in giving out information to participants, (2) feedback on results that are normally not affordable if requested by a physician, and (3) support through the Shehas who clearly had an interest in the results of the study. Prior to the start of the survey, all Shehas were invited to a presentation of the aims and content of the study (examinations) and to request official approval and support by the Shehas. Information on this meeting was disseminated in the local media, describing the aims of the study, which led to an overall high acceptance among participating families. Further, all the measurements and examinations were conducted at the participant's homes and at their convenient time, having the advantage that all eligible individuals could be enrolled regardless of child care or (home) work. Our finding of an average household size of 6.7 compared with the officially reported average household size of 4.8 [15] supports that an official dissemination of study aims and measurements is a useful strategy to enhance response proportions for complete households. Also, the feedback sheets on personal measurements were appreciated and were useful to enhance response rates at family and community level. A feedback on all parameters of interest was promised to all Shehas, researchers, politicians, and stakeholders of health services prior to the survey and was presented 1 year after survey termination at a 2-day workshop in Zanzibar. Also, this workshop and the results were disseminated through the local media (television, newspaper) in order to give feedback to the general population.

However, approximately 11.29% (129/1443) of participants were excluded from the study for not fulfilling all criteria (weight, height/length, age, and sex) needed for analysis. This was due to respondents not knowing their exact date of birth and/or not having any records. Comparable to our results, Korkalo et al [31] encountered a similar problem in their study. Reasons for refusing anthropometric measurements were: pregnancy, illness/weakness, or fear in young children <2 years; a similar challenge was discussed in a previous study [32].

Quality Control

Anthropometric measurement error is unavoidable and should be minimized by high-quality standards regarding every aspect of the data collection process. In all cases intra- and interobserver reliability for all measurements was greater than 99%, these results are very similar and even better than other reported studies [11,33,34]. Comparison of results from this study to previous investigated TEM and R values indicated that height and MUAC were similar and within the range with the reference values recommended for intraobserver values by Ulijaszek and Kerr [33]. Interobserver reliability for all circumferences was above 99%, other researchers reported ranges for MUAC 94%-100% , WC 86%-99%, and HC 68%-99% [33]. Compared with above results, the present data prove a high degree of accuracy during examination. We conclude that the local training and using the rigorous standardization approach facilitated the collection of accurate and comparable data.

For quality control of the biosamples, data collection, processing, and storage, protocol was adapted from IDEFICS study [32] that applied a quality management system for the collection of biological sample in epidemiology study; the system was developed and introduced by Peplies et al [12]. The results of the validation study and the very high level of agreement we observed underlines the need for standardizing biosample collection, procession, storage, and analysis, as well

as for controlling the reliability of values obtained in order to repeat analysis if needed.

Anthropometry and Nutritional Status

This study provides information on the anthropometry and nutritional status of all members of household included in the survey. The comparison across Shehia, age groups, and gender facilitate focused nutrition interventions in these aspects. Although the mean BMI for both male and female was within the normal range (18.5-24.9 kg/m^2), both problems of underweight and overweight/obese were prevalent for both male and female. Among all study participants, 36.37% (479/1314) were considered to be underweight with a slightly higher prevalence in males (252/1314, 19.13%) compared with their female counterpart (227/1314, 17.28%). Of the 479 underweight participants, the highest proportion (213/479, 44.5%) was among school age children between 6 and 14 years. This result is almost similar to a study conducted in Nigeria (43.5%) for children between 9 and 12 years [35], and higher than studies conducted in India (38.4%) for children between 5 and 15 years [36], Mauritius (37.0%) for children between 8 and 12 years [37], and Uganda (13.0%) for children between 9 and 15 years [38]. The prevalence of underweight among young children <5 years was 70.1% (144/204), which is higher than reported in other studies conducted in sub-Saharan Africa for children <5 years in Tanzania Mainland (16%), Zanzibar (19%), Kenya (11.8%), and Cameroon (12.9%), respectively [13,39-41]. Although there are differences in sampling and target age groups, but nevertheless, the prevalence of underweight in our population-based survey among children <5 years and school age children 6-14 years is clearly higher than the above mentioned studies.

Overall prevalence of overweight and obesity is 13.1% and 8.1%, respectively, with the highest proportion in adult female participants ≥15-years old compared with their male counterparts. Prevalence of overweight and obesity for females 15- to 59-years old is 17.6% and 18.4%, respectively, and for elderly people above 60 years is 31.9% and 19.1%, respectively. This is found to be higher than that of the male participants, but lower than several studies conducted in Africa [42-45]. A higher prevalence of overweight and obesity among women has also been reported in other studies [13,44,45].

Strengths and Limitations

Age and gender are the primary basis for demographic classification and also very important variables in the study of mortality, fertility, and marriage [13]. As reported in the comprehensive food security and vulnerability analysis [46], Tanzania overall has a very young population due to its fertility rate in the past. The present study shows a similar trend for Unguja Island with approximately 43% of the population being <15 years, of which approximately 15% are <5 years of age. Unfortunately, the response rate for children <5 years is less than the expected sample size; this is due to the higher household size and that the priority of enrollment was given to entire families rather than on age. Nevertheless, we are confident that the overall sample size of 1314 individuals will enable us to investigate the aimed research question with sufficient statistical power.

A strong cooperation and support by the Shehas of the study Shehias facilitated an easy and problem-free collection of data. Standardized approaches and clear documentation of the field information made it easy and required less time for data editing and entry. This was possible due to a successful training of the survey team prior the field trips. Feedback results of the anthropometric measurements, urine test results, and BP were well appreciated incentives, which not only motivated the participants to take part, but also provided them with information on their health status immediately after the measurements and free of charge. One of the methodological challenges was taking anthropometric measurements from women and young children. Women wore several layers of light clothing during measurements, might have affected the measurements taken, and children were mostly playful and unstable during measurements. However, these challenges are unlikely to change the findings and prevalence because 1 kg for clothing was deducted from weight measurements for all participants. Another challenge encountered was that most of the participants did not know or could not remember their precise date, month, and/or year of birth; however, this problem was solved with the help of an event calendar developed by the field team prior to the field work. Despite these limitations in the method and data collection, recruitment and participation was very successful and data collected was a good representative of the population studied.

Conclusions

We can conclude that a rigorous standardization process and comprehensive training facilitated the collection of accurate and comparable anthropometric and biodata. The study provides valuable data to investigate the interplay of socioeconomic, demographic, environmental, physiological, and behavioral factors in the development of diet-related disorders in a representative sample of the Zanzibari population.

Further, investing time and endeavouring into a dissemination strategy involving important gatekeepers is a useful strategy to enhance response rates and acceptance in the study population. Transparency of population-based survey results at the individual, community, and governmental level are recommended at any time.

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We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. Approval by the Ethics Committees of the University of Bremen in Germany with a reference number 06-3 and of the Zanzibar Ministry of Health and the Zanzibar Medical Research and Ethics Committee in Zanzibar, Tanzania with a reference number ZAMREC/0001/AUGUST/013. Study participants did not undergo any procedures unless both children and their parents had given written informed consent for examinations, collection of samples, subsequent analysis, and storage of personal data and collected samples. Study subjects could consent to single components of the study while abstaining from others.

Authors' Contributions

This manuscript represents original work that has not been published previously and is currently not considered by another journal. The authors' responsibilities were as follows: AH and MAN had the idea of the analysis; MAN did the analysis, data interpretation, and wrote the manuscript, and had primary responsibility for final content and submitting the manuscript for publication; MAN, SK, MS, and AH were responsible for critical revisions and final approval of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BMI: body mass index
BP: blood pressure
EDTA: ethylenediamine tetraacetic acid
FAO: Food and Agriculture Organization
HbA1c: glycated hemoglobin
HC: hip circumference
IDEFICS: Identification and prevention of the Dietary- and lifestyle-induced health EFfects in Children and InfantS study
IL: interleukin
LDL: low-density lipoprotein
MUAC: mid upper arm circumference
RBC: red blood cells
TEM: technical error of measurements
WBC: white blood cells
WC: waist circumference
WHO: World Health Organization

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Original Paper

Pixel or Paper? Validation of a Mobile Technology for Collecting Patient-Reported Outcomes in Rheumatoid Arthritis

Oscar Massimiliano Epis[1], MD; Cinzia Casu[1], MD; Laura Belloli[1], MD; Emanuela Schito[1], MD; Davide Filippini[1], MD; Marina Muscarà[1], MD; Maria Giovanna Gentile[1], LPN; Paula Carina Perez Cagnone[2], MPharm; Chiara Venerelli[2], BSBME; Massimo Sonnati[2], CBDO; Irene Schiavetti[3], PhD; Eleonora Bruschi[1], MD

[1]Rheumatology Unit, Azienda Socio-Sanitaria Territoriale Grande Ospedale Metropolitano Niguarda, Milano, Italy

[2]Hippocrates Sintech Srl, Genova, Italy

[3]Hippocrates Research Srl, Genova, Italy

Corresponding Author:
Paula Carina Perez Cagnone, MPharm
Hippocrates Sintech Srl
via XX Settembre 30/4
Genova, 16121
Italy
Phone: 39 3491720506
Fax: 39 0108936856
Email: p.perez@hippocrates-sintech.it

Abstract

Background: In the management of chronic disease, new models for telemonitoring of patients combined with the choice of electronic patient-reported outcomes (ePRO) are being encouraged, with a clear improvement of both patients' and parents' quality of life. An Italian study demonstrated that ePRO were welcome in patients with rheumatoid arthritis (RA), with excellent matching data.

Objective: The aim of this study is to evaluate the level of agreement between electronic and paper-and-pencil questionnaire responses.

Methods: This is an observational prospective study. Patients were randomly assigned to first complete the questionnaire by paper and pencil and then by tablet or in the opposite order. The questionnaire consisted of 3 independent self-assessment visual rating scales (Visual Analog Scale, Global Health score, Patient Global Assessment of Disease Activity) commonly used in different adult patients, including those with rheumatic diseases.

Results: A total of 185 consecutive RA patients were admitted to hospital and were enrolled and completed the questionnaire both on paper and on electronic versions. For all the evaluated items, the intrarater degree of agreement between 2 approaches was found to be excellent (intraclass correlation coefficient>0.75, P<.001).

Conclusions: An electronic questionnaire is uploaded in a dedicated Web-based tool that could implement a telemonitoring system aimed at improving the follow-up of RA patients. High intrarater reliability between paper and electronic methods of data collection encourage the use of a new digital app with consequent benefit for the overall health care system.

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KEYWORDS

validation; rheumatoid arthritis; PROs; monitoring; electronic device; tablet; questionnaire; paper

Introduction

Patient-reported outcomes (PROs), defined by the US Food and Drug Administration as "any report of the status of a patient's health condition that comes directly from the patient," are becoming more and more common in the medical field, with an increasing improvement of dedicated software solutions for electronic capturing of data [1]. Furthermore, general advantages of using online formats compared to paper ones were already highlighted in the early 90s [2] and confirmed by further studies [3,4].

At present, the long-term disease monitoring of patients at home exemplifies the most promising application of telemonitoring technology for supplying cost-effective quality care [5]. Therefore, especially in the management of chronic disease, new models for telemonitoring of patients combined with the choice of electronic PRO (ePRO) are being encouraged, allowing a self-managing of patient care during all treatment phases, with a clear improvement not only of patients' but also of parents' quality of life, as reported in a recent pediatric study [6].

In the field of rheumatoid arthritis (RA), the validity and effectiveness of PRO data in addition to the standard clinical practice for the intensive care of the patients is well documented [7,8]. A recent systematic review from Johns Hopkins University assesses the frequency and the analyzed domains of PRO used in recent RA studies by collecting and summarizing data from 250 articles [9]. The first Italian study demonstrated that ePRO were welcome in patients with RA, with high levels of agreement between paper and electronic data and good reliability findings [10].

In 2010, the rheumatology unit of Azienda Socio-Sanitaria Territoriale Grande Ospedale Metropolitano Niguarda introduced a computer touch screen–based technology with the aim to collect and manage clinical data during the examinations of RA patients. In recent years, the daily medical practice has implemented this system and the assessment of PROs [11].

According to the outcome research guidelines proposed by the International Society for Pharmacoeconomics and Outcomes Research, ePRO questionnaires should provide comparable or better data than a paper questionnaire, and measurement of the difference between the 2 data-gathering approaches is a necessary validation method [12].

The task of this study is to compare electronic and paper-and-pencil questionnaire responses and verify that the ePRO supported by the use of innovative mobile technologies can be widely used in a program of tailored telemonitoring of RA patients.

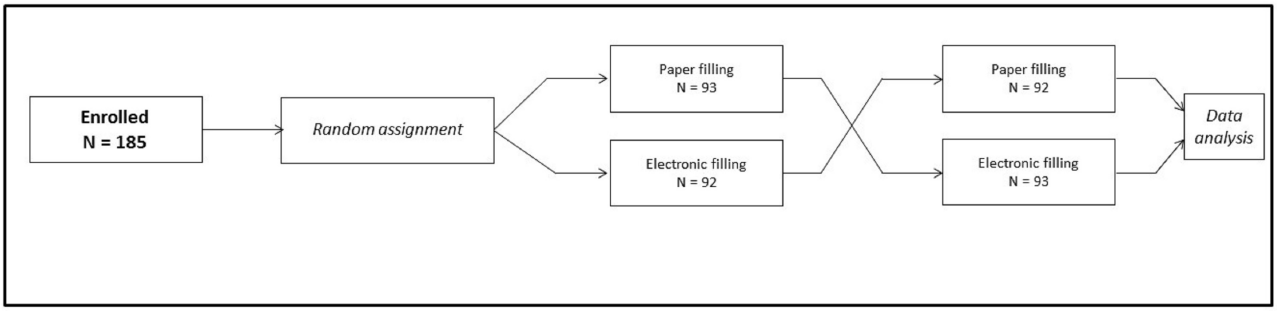
Methods

Study Design and Sample Size Calculation

This is an observational prospective study. All the patients in the study were randomly assigned to first complete the questionnaire by paper and pencil and then by tablet or in the opposite order (Figure 1). After both questionnaires were completed, physicians asked the patients to indicate their preferred version and comment on the accuracy of the paper in terms of it being easy to read and interpret. These additional data were collected together with demographics in a dedicated database.

Sample size was calculated basing on the literature regarding the estimates for sample size requirements for reliability studies using an intraclass correlation coefficient (ICC) [13]. In particular, assuming a possible 25% dropout rate [14], 185 patients were sufficient to detect an expected reliability of 0.8 against an acceptable reliability of 0.7, with an 85% power and a significance level of .05.

Figure 1. Study design.



Ethics, Consent, and Permissions

There was no need for ethical approval for this study. All the patients signed an informed consent form.

Recruitment

All patients aged 18 to 90 years who attended the Azienda Socio-Sanitaria Territoriale Grande Ospedale Metropolitano Niguarda between July and September 2013 and met the American College of Rheumatology criteria for RA [15] were considered for enrollment.

Questionnaire

The questionnaire consisted of 3 independent self-assessment visual rating scales, commonly used in different adult patients including those with rheumatic diseases [16].

1. Visual Analog Scale (VAS) pain [17]: RA patients reported the degree of their pain in a scale ranging from 0 (no pain) to 100 mm (worst imaginable pain).

2. Global Health (GH) score: patients reported the level of impact of the RA disease on their global health with a value ranging from 0 (no effect) to 100 mm (maximum effect).

3. Patient Global Assessment of Disease Activity (PGA) [18]: patients answered the question "In the last week, how active would you define your rheumatic condition?" on a 0 to 100 mm scale ranging from "not active at all" to "extremely active" as anchors.

Patients received both a device with an app version and a paper version. In the first case, they had to touch the visual scale on the screen of the electronic device at the same point corresponding with the status of their response; once the selected

questionnaire was completed and saved, the relative score was automatically calculated. For the paper version, patients were asked to place a perpendicular line in each scale at the point which best matched with the status of their response. The score was determined by measuring with a ruler the distance (mm) between the "0" dash and the patient's mark.

App Details

Electronic questionnaires are part of a dedicated Web-based tool that helps physicians managing patients affected by RA. Every piece of information is sent to a cloud system, and the security of the communication is ensured by authentication routines.

Therefore, the platform is accessible both through a link on the Web and through a dedicated app for the tablet. The Web form, accessible through a link, represents the core of the app and includes "entry," "search," and "edit" data functions. All data input from the tablet or Web are stored in a dedicated database in the main repository of the system.

At first, the physicians can create detailed and accurate patient profiles by filling in demographic and clinical assessments. Once the profile is created, patients receive a username and password to access the self-examination module and fill in the PROs.

The tool allows real-time data gathering, with data displayed in various ways including pictograms, balloon chart, and chromatic scales. All information is accessible both through the Web site and tablet app, which allow full access to the patients' data as well as direct access to the report printing functionalities.

Statistical Analysis

The normality of continuous variables was checked by the examination of histograms and confirmed by the Kolmogorov-Smirnov test. All nonnormally distributed data were ranked before further analysis. Demographic characteristics were summarized as count and percentage, mean and standard deviation, and median with range. Any difference between the orders of the questionnaire administration was assessed by using a chi-square test or Fisher's exact test for categorical data and independent sample *t* test for continuous data.

To evaluate possible order and format effects, any difference between paper and electronic results of each evaluated item was analyzed by an analysis of variance test for repeated measures with format as repeats and order of administration as factor.

For all the items, the level of agreement between the responses of electronic and paper formats was estimated with the ICC, expressed with 95% confidence interval. Fleiss recommendations [19] were followed to identify ICC cut-offs.

A Bland-Altman plot [20] was used to graphically confirm the results and visualize the concordance degree. This chart, for each subject, plots the difference between the 2 measurements (the *y* axis) as a function of the mean of the same values (the *x* axis). All statistical tests were 2-sided and the significance level (alpha error) was set at .05.

Results

A total of 185 consecutively admitted patients to hospital (100% recruitment rate), aged between 26 and 83 years, with a diagnosis of RA were invited to participate in the study.

All enrolled patients completed the questionnaire both on paper and on electronic versions. Randomization process was conducted without any statistically significant difference in the baseline characteristics between 2 groups (Table 1).

Likewise, no difference concerning the information on the quality of the questionnaire was revealed (Table 2).

For all the items, no significant main effects of order, format, or the interaction effect of both was observed, indicating that the order of completion did not matter (Table 3).

For all the evaluated items, the intrarater degree of agreement between paper and electronic responses was found to be excellent (ICC>0.75, P<.001) (Table 4).

The same results were graphically confirmed by the Bland-Altman plots (Figure 2).

Table 1. Baseline characteristics of the sample.

Demographic data	Total N=185	First paper then electronic version n=93	First electronic then paper version n=92	*P* value
Age (years), mean (SD)	59.5 (12.1)	59.5 (11.0)	59.4 (13.1)	.96
Sex, n (%)				
Female	155 (83.8)	82 (88.2)	73 (79.3)	
Male	30 (16.2)	11 (11.8)	19 (20.7)	.15
Nationality, n (%)				
Italian	166 (89.7)	83 (89.2)	83 (90.2)	
Foreign	19 (10.3)	10 (10.8)	9 (9.8)	>.99
Employment, n (%)				
Retired	52 (28.1)	26 (28.0)	26 (28.3)	
Workman	25 (13.5)	13 (14.0)	12 (13.0)	
Employee	55 (29.7)	28 (30.1)	27 (29.3)	
Housewife	53 (28.6)	26 (28.0)	27 (29.3)	.99
Education level, n (%)				
Lower school	32 (17.3)	16 (17.2)	16 (17.4)	
Middle school	60 (32.4)	30 (32.3)	30 (32.6)	
High school	75 (40.5)	39 (41.9)	36 (39.1)	
Degree	18 (9.7)	8 (8.6)	10 (10.9)	.95

Table 2. Data regarding the quality of the questionnaires.

Quality of the questionnaires	Total N=185 n (%)	First paper then electronic version n=93 n (%)	First electronic then paper version n=92 n (%)	*P* value
Accuracy of the paper version				
No	34 (18.4)	13 (14.0)	21 (22.8)	
Yes	151 (81.6)	80 (86.0)	71 (77.2)	.17
Preferred version				
Electronic	176 (95.1)	88 (94.6)	88 (95.7)	
Paper	9 (4.9)	5 (5.4)	4 (4.3)	>.99

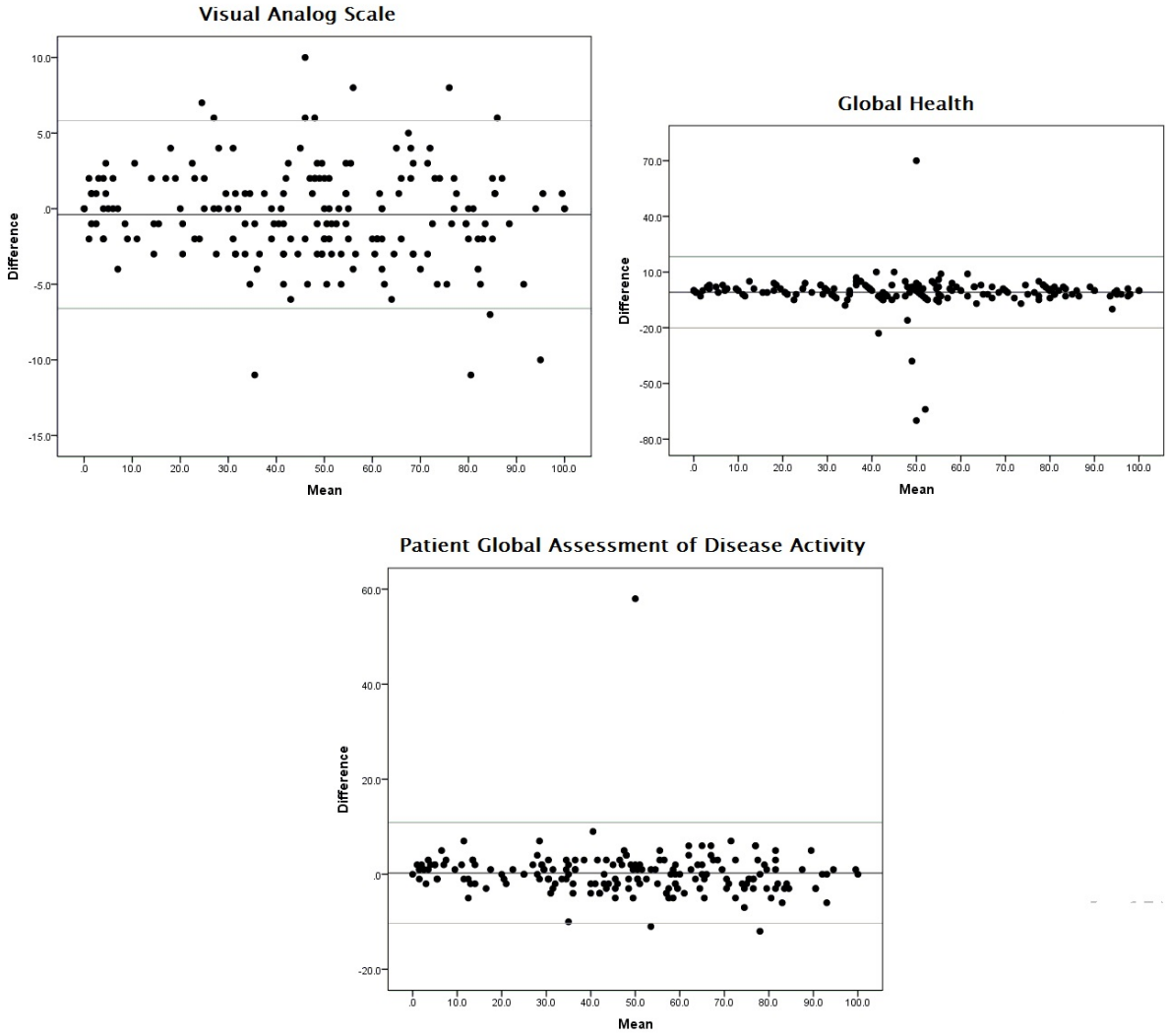
Table 3. Summary of *F* values from 2-way analyses of variance for format and order effect (N=185).

ANOVA	*F* values	*P* value
Visual Analog Scale	0.93	.34
Global Health Scale	0.08	.78
Patient Global Assessment	1.59	.21

Table 4. Agreement degree in the response questionnaires between 2 formats (N=185).

Visual Rating Scales	Paper version Mean (SD) Median (min-max)	Electronic version Mean (SD) Median (min-max)	ICC (95% CI)	*P* value
Visual Analog Scale	46.7 (25.9) 49.0 (0.0-100.0)	47.1 (26.3) 48.0 (0.0-100.0)	0.996 (0.995-0.997)	<.001
Global Health	48.8 (26.3) 50.0 (0.0-100.0)	49.7 (26.7) 50.0 (0.0-100.0)	0.959 (0.945-0.969)	<.001
Patient Global Assessment	47.8 (25.7) 50.0 (0.0-100.0)	47.5 (26.1) 49.0 (0.0-100.0)	0.988 (0.984-0.991)	<.001

Figure 2. Bland Altman plots.



Discussion

Principal Findings

In the modern clinical practice, fast and reliable collection of clinical data is an important need. The widespread use of mobile technologies throughout the world has also involved the medical field, where the use of information technology products and services allows access to health care, both containing costs and improving the quality of data and clinical outcomes.

As reported by the World Health Organization, mHealth or mobile health is a “medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices” [21].

This study proved that a new approach for telemonitoring, where desktop applications are fully integrated with external mobile devices, could play an important role in the patient follow-up. Response rate was 100% for both methods, Internet-based electronic questionnaires comply with the traditional paper formats, and the app is considered easy to use (electronic version is defined as the preferred choice by most patients).

In particular, for all the investigated items, no significant differences (by considering also any order effects) between the 2 approaches were found, and these findings are in agreement with previous studies reporting none or very few differences between computerized and paper-and-pencil assessments [22,23].

Furthermore, it is important to stress that ePRO can provide a valuable source of information. Data can be collected at any time of the day according to the wishes of the patient. In this way, the database can be fed continuously over time, providing the physicians useful tools for better defining strategies to deal with a long-lasting (chronic) disease. These findings have shed some light on the significant value to the patient, but they mostly highlight the benefit that the overall health care system can enjoy from this new digital app.

Limitations

These first results are applicable to RA patients, but further studies are recommended because the comparison between 2 approaches in other populations and settings has not yet been studied.

Furthermore, performed comparisons should be weighted by considering the low amount of collected data, in this case 3 independent single items. It would be interesting to gather data in order to study more complex measures of outcomes.

Sufficient privacy and security should be guaranteed: data transferred to a health care provider may be subject to hacking. A disaster recovery system should be ready at all times, and technical support for corrupted or erased data must be set up.

Finally, it is important to point out that rheumatology specialist care should never be substituted: telemonitoring systems are to be considered as an important challenge in the modern times, but they are complementary tools and not alternatives in the routine medical practice.

Acknowledgments

All authors have actively contributed to the study and read and approved the final manuscript. The authors thank the team for administering the questionnaires and the patients for filling out them.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Visual Analog, Global Health, and Patient Global Assessment scales.

[PNG File, 131KB - resprot_v5i4e219_app1.png]

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Abbreviations

ePRO: electronic patient-reported outcome
GH: Global Health
ICC: intraclass correlation coefficient
PGA: Patient Global Assessment of Disease Activity
PRO: patient-reported outcome
RA: rheumatoid arthritis
VAS: Visual Analog Scale

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Original Paper

Testing the Feasibility of Remote Patient Monitoring in Prenatal Care Using a Mobile App and Connected Devices: A Prospective Observational Trial

Kathryn I Marko[1*], MD; Jill M Krapf[2*], MD; Andrew C Meltzer[3*], MSc, MD; Julia Oh[4*], PhD; Nihar Ganju[1*], MD; Anjali G Martinez[1], MSc, PhD; Sheetal G Sheth[1*], MD; Nancy D Gaba[1*], MD

[1]George Washington University School of Medicine and Health Sciences, Washington, DC, United States

[2]OB Hospitalist Group, Baylor All-Saints Medical Center, Dallas, TX, United States

[3]Center for Healthcare Innovation and Policy Research, George Washington University School of Medicine and Health Sciences, Washington, DC, United States

[4]The Jackson Laboratory, Farmington, CT, United States

[*]these authors contributed equally

Corresponding Author:
Andrew C Meltzer, MSc, MD
Center for Healthcare Innovation and Policy Research
George Washington University School of Medicine and Health Sciences
2120 L Street NW
Suite 450
Washington, DC, 20037
United States
Phone: 1 2024457044
Fax: 1 2027412921
Email: ameltzer@mfa.gwu.edu

Abstract

Background: Excessive weight gain and elevated blood pressure are significant risk factors for adverse pregnancy outcomes such as gestational diabetes, premature birth, and preeclampsia. More effective strategies to facilitate adherence to gestational weight gain goals and monitor blood pressure may have a positive health benefit for pregnant women and their babies. The impact of utilizing a remote patient monitoring system to monitor blood pressure and weight gain as a component of prenatal care has not been previously assessed.

Objective: The objective of this study is to determine the feasibility of monitoring patients remotely in prenatal care using a mobile phone app and connected digital devices.

Methods: In this prospective observational study, 8 women with low risk pregnancy in the first trimester were recruited at an urban academic medical center. Participants received a mobile phone app with a connected digital weight scale and blood pressure cuff for at-home data collection for the duration of pregnancy. At-home data was assessed for abnormal values of blood pressure or weight to generate clinical alerts to the patient and provider. As measures of the feasibility of the system, participants were studied for engagement with the app, accuracy of remote data, efficacy of alert system, and patient satisfaction.

Results: Patient engagement with the mobile app averaged 5.5 times per week over the 6-month study period. Weight data collection and blood pressure data collection averaged 1.5 times and 1.1 times per week, respectively. At-home measurements of weight and blood pressure were highly accurate compared to in-office measurements. Automatic clinical alerts identified two episodes of abnormal weight gain with no false triggers. Patients demonstrated high satisfaction with the system.

Conclusions: In this pilot study, we demonstrated that a system using a mobile phone app coupled to remote monitoring devices is feasible for prenatal care.

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KEYWORDS

prenatal care; pregnancy; mobile app; remote pateint monitoring

Introduction

Excessive weight gain and elevated blood pressure are significant risk factors for adverse pregnancy outcomes such as gestational diabetes, premature birth, and preeclampsia [1-4]. The impact of utilizing a remote patient monitoring system to monitor blood pressure and weight gain as a component of prenatal care has not been previously assessed. Given current technology, tools to measure weight gain and blood pressure are generally affordable, readily available, and may be connected to mobile devices for data transfer to medical providers. In addition, the utilization of these technologies may promote self-care and improve overall engagement with prenatal care [5]. Mobile phone technology has been previously shown to improve disease management for diabetes self-care activities, HIV infection medication adherence, and sickle cell anemia medication adherence [6-8]. We hypothesize that using digital health tools (a mobile app and connected monitoring devices) may enhance prenatal care.

The purpose of this study is to determine the *feasibility* of using digital health tools to manage prenatal care. Feasibility was determined by studying the following specific outcomes: (1) patient engagement with the app and the remote monitoring tools, (2) accuracy of the remotely collected data, (3) efficacy of the alert systems, and (4) patient satisfaction.

Methods

Setting and Subject Selection

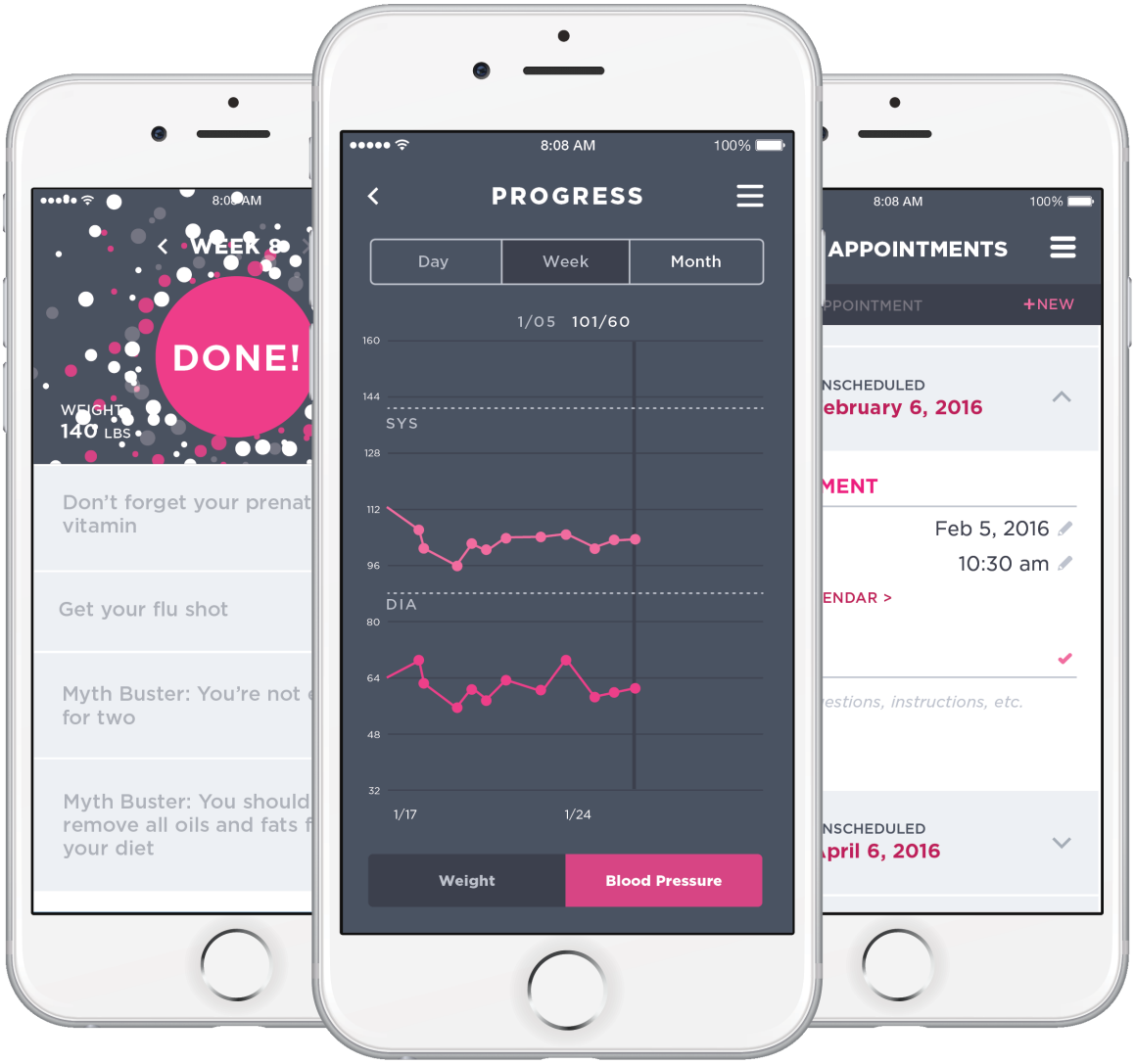
This prospective observational study was conducted between July 2014 and January 2015 in the Department of Obstetrics & Gynecology at the George Washington University Hospital, an urban academic medical center that delivers approximately 2900 babies per year. Pregnant women between the ages of 18 to 40 years old presenting for routine prenatal care in the first trimester were asked to participate in the study over the course of a recruitment period of one month. Inclusion criteria included self-reported regular usage of an iPhone and low-risk pregnancy status per established guidelines [9]. In total, 8 participants were enrolled in the study and were followed until their delivery.

There was no cost to the patients or provider for participation. Once consented, participants were given access to the Babyscripts (Washington, DC) mobile prenatal care platform consisting of a mobile phone app and connected devices. Patients received training on how to use the app and the devices as part of the enrollment process. All patients signed an end-user licensing agreement to use the app, permitting Babyscripts to access non-identifiable data collected by the app. Institutional review board (IRB) approval was granted prior to commencing the study (IRB# 051422).

Description of the Digital Health Platform

The Babyscripts platform was designed through a collaboration between the George Washington University Medical Faculty Associates and 1Eq Inc., the manufacturer of Babyscripts. The platform consists of a mobile phone app connected to a wireless weight scale and sphygmomanometer. The Babyscripts app contains evidence-based educational information related to prenatal care delivered at gestational age-specific times during pregnancy in the form of a to-do list (Figure 1). This information encompasses material covering pregnancy progression, modifiable risks such as alcohol intake, smoking or drug abuse, and information regarding nutrition, breastfeeding, appropriate weight gain, and pregnancy warning signs. This content was developed and validated in partnership with a committee of 3 board-certified obstetrician-gynecologists at the George Washington University Medical Faculty Associates. All items were derived from evidence-based standards supported by American Congress of Obstetrics and Gynecology (ACOG) and then further reviewed by each member of the committee.

Figure 1. Screenshots of the Babyscripts app.



Connected Devices

In addition to the Babyscripts app, participants received connected devices including a weight scale (Smart Body Analyzer, Withings) and a sphygmomanometer (Wireless Blood Pressure Monitor, Withings). As part of participation, patients collected weight and blood pressure data on a weekly basis.

Data Analysis and Alerts

Data points generated by the use of connected devices automatically populated the Babyscripts app for review by the patient as well as the provider. Patients were provided automated feedback about their individual weight and blood pressure goals. Abnormal values activated alerts to the patient and physician to communicate more urgently. For example, elevated blood pressure or abnormal weight gain or weight loss generated an automated alert to the clinician. The alert system consisted of an email to the office's triage nurse as well as an email and an in-app notification to the patient. If the alert was not addressed in 15 minutes, an automated phone call was placed to the triage nurse to alert the provider of the abnormality. The alert remained active until it was acknowledged by the provider.

Outcomes

Patient Engagement

Engagement with app and remote monitoring devices was measured by recording the number of times that a patient interacted with the app or recorded an at-home weight or blood pressure reading.

Accuracy of Remote Patient Monitoring

To measure the accuracy of remote monitoring, remote measurements were compared to in-office measurements. For in-office data, 2 trained abstractors reviewed the electronic medical record and then compared the data for discrepancies. Abstractors were not blinded to the study purpose. Standardized data collection sheets were used for data collection and all patient data was stored in a server compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Efficacy of Automatic Alerts

To measure the efficacy of the alert system, each patient's home measurements were reviewed and abnormal values were cross-checked with the report of clinical alerts. If there were any discrepancies, a more detailed review was performed.

Patient Satisfaction

Patient satisfaction was measured using a 12-question survey that was completed by participants after 20 weeks of platform usage. Questions were based on established satisfaction surveys that measure patient-centered outcomes [10]. Survey creation was based on the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [11].

Analysis

Statistical analysis was used to compare trends in the patient data collected remotely versus collected in-office. All statistical analyses were performed in the R programming environment (R Core Team, 2013) [12]. Standard statistical measures including *P* values and confidence intervals were calculated.

Results

For this feasibility study, 8 patients were recruited and consented to participate at 8 to 10 weeks gestation, and were followed through delivery. Most patients were primiparous, married, with private insurance, and no major pregnancy risk factors. The age range of the participants was from 25 to 33 years with body mass indexes (BMIs) of 17.3 to 33.8 (Table 1). One patient (#313) was identified to have fetal intrauterine growth restriction, while another (#278) was identified to have preeclampsia during labor. Of the patients, 5 delivered via normal spontaneous vaginal delivery, 2 required primary cesarean deliveries at term for non-reassuring fetal heart tracing and arrest of dilation, while 1 requested a repeat cesarean delivery.

Table 1. Demographics, history, and delivery outcomes of each patient in the study.

Characteristic	Patient number							
	265	271	273	274	275	278	313	323
Age, years	31	29	30	33	28	30	31	25
Gravida/para	1/000	1/0000	1/0000	3/1011	1/0000	1/0000	1/0000	2/1001
Race	Caucasian	Caucasian	Caucasian	African American/ Hispanic	African	Hispanic	Asian	African American
Education	Graduate	N/A	Graduate	N/A	Graduate	Graduate	Undergraduate	N/A
Marital status	Married	Married	Married	Married	Married	Married	Married	Single
Payer	Private	Private	Private	Private	Private	Private	Private	Private
Tobacco use	No	No	No	No	No	No	No	No
Alcohol use	Occasional	No	No	No	No	No	First trimester	No
BMI	17.3	23.5	25.9	28.0	20.6	33.8	23.0	24.0
Past medical history	None	Anxiety, ADD[a]	None	LEEP[b] x3; cesarean deliveryx1, HSV[c]	Sickle cell trait	None	None	None
Pregnancy complications	None	None	Marginal previa resolved in second trimester	None	None	Preeclampsia at term	IUGR diagnosed in second trimester	None
Delivery	NSVD[d] at 37.5 weeks	NSVD by induction of labor for macrosomia prevention at 40.6 weeks	Primary cesarean delivery for NRFHT[e] in labor at 38 weeks	Elective repeat cesarean delivery at 40.1 weeks	NSVD at 41.4 weeks	Primary cesarean delivery for arrest of dilation at 39.2 weeks	NSVD at 39.6 weeks	NSVD at 36.6 weeks

[a]ADD: attention deficit disorder

[b]LEEP: loop electrosurgical excision procedure

[c]HSV: herpes simplex virus

[d]NSVD: normal spontaneous vaginal delivery

[e]NRFHT: non reassuring fetal heart tracing

Figure 2. Comparison of average total number of measurements per individual over the course of pregnancy for patients with remote data collection versus in-office only. BRX: Babyscripts; BP: blood pressure.

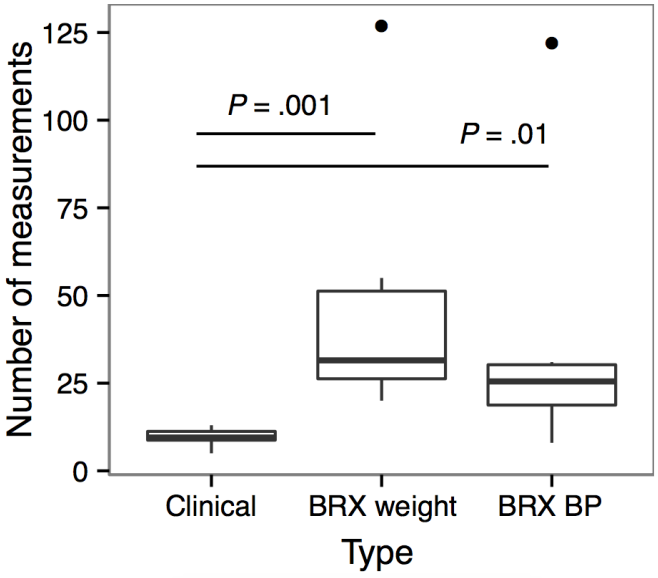


Figure 3. Comparison of weight values measured in office versus with remote digital device monitoring. Each box represents data points from an individual patient. BRX: Babyscripts.

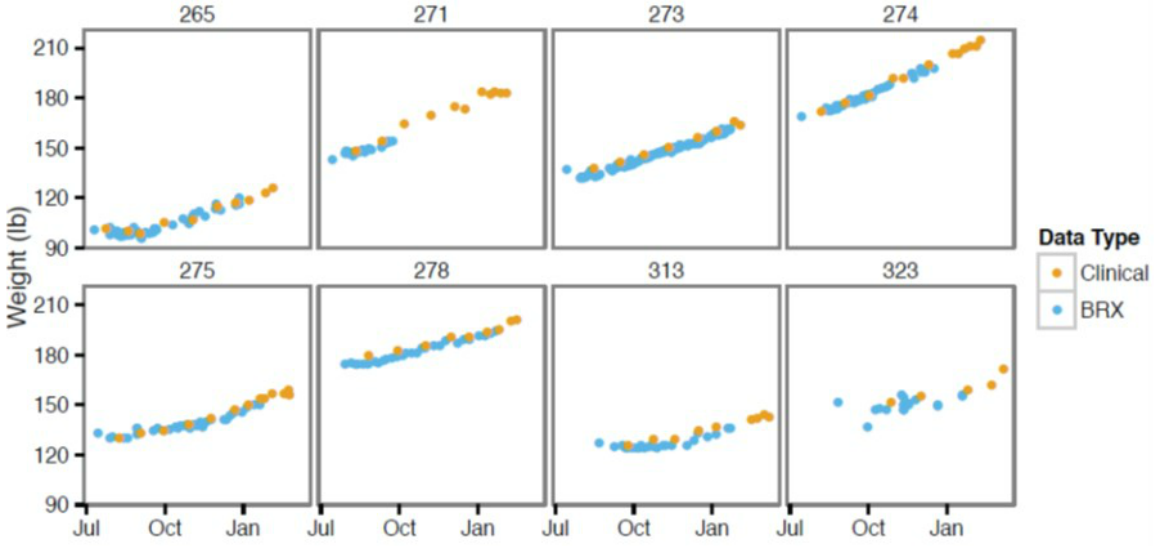


Figure 4. Weight gain for patient 313, who generated a clinical alert for poor weight gain.

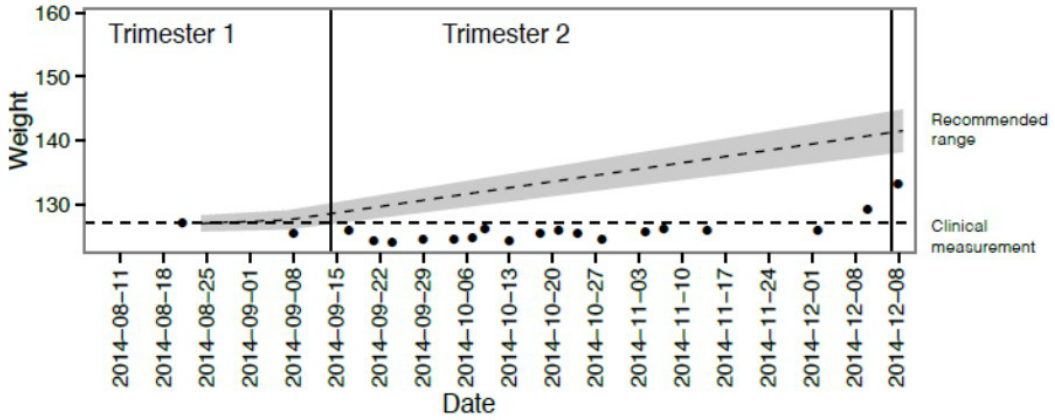
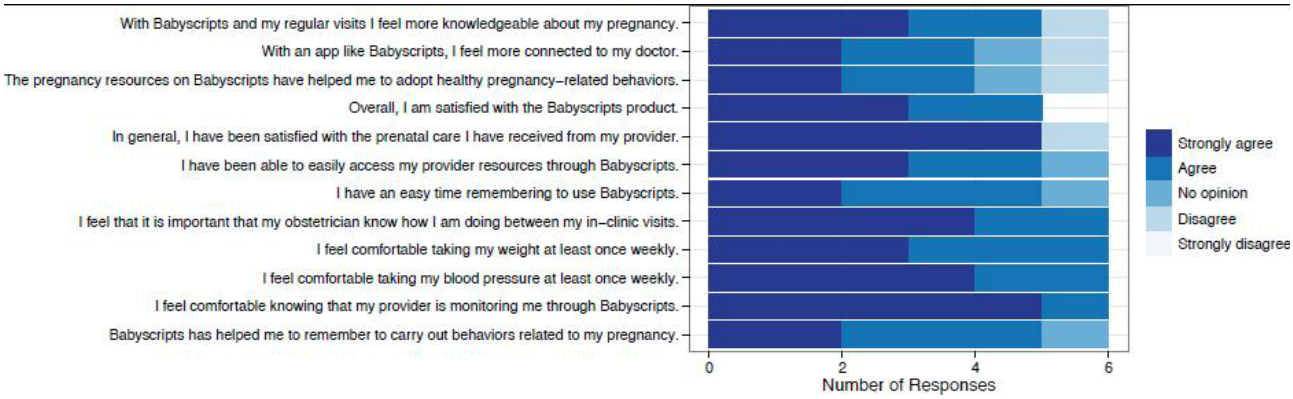


Figure 5. Distribution of survey responses for satisfaction with the Babyscripts experience.



Patient Engagement

Patient interaction with the mobile app averaged 5.5 times per week over the 6-month study period. Weight data collection averaged 1.5 times per week and blood pressure data collection averaged 1.1 times per week. One patient (#323) stopped collecting data after 29 weeks gestational age due to residence change. Remote patient monitoring increased the total number of data points collected throughout pregnancy compared to routine office measurements during prenatal care visits (Figure 2). The mean number of weight measurements collected by the connected devices (46, $P<.001$) and mean number of blood pressure measurements (34, $P=.01$) exceeded the number of data points collected in the office (10).

Accuracy of Remote Patient Monitoring

Weight measurements acquired by remote digital devices did not differ from in-office measurements ($P>.05$ for all patients) (Figure 3). The differences in the slope of gestational weight gain were determined by the F-statistic and resulting P values were Bonferroni-corrected. For all comparisons, adjusted is $P>.05$. For our cohort, mean blood pressure measurements remained consistent over the course of the pregnancy with a mild elevation (<10%) of in-office systolic blood pressure values compared to home measurement. Diastolic measurements tracked very closely with systolic measurements.

Efficacy of Automatic Alerts and Alerts

After reviewing data sets of all clinical variables and all organized alerts, no incidences of inappropriate alerts or unaddressed alerts were discovered. There was a total of 2 alerts fired during the study, both related to inappropriate weight gain (patient 313 and 323). Patient 313 did not gain weight over a 4-week interval, which generated an automatic clinical alert. As a result of this alert, the patient's obstetrician was notified and subsequently scheduled a more urgent office visit and closer monitoring (Figure 4). For patient 323, an automatic alert was generated at 15 weeks gestation for weight loss of 6 pounds in one week. The provider established contact with this patient and addressed any possible warning signs and monitored weight more closely until the patient was seen for her routine follow-up visit.

Patient Satisfaction

The patient satisfaction survey assessed themes of patient-provider relationship, engagement, patient education, and patient satisfaction and had a completion rate of 75% (6/8) (Figure 5). We attempted multiple times to reach the 2 participants who did not complete the survey.

All 6 participants who completed the survey felt comfortable with the concept and technical aspects of remote monitoring, were able to easily access provider resources through Babyscripts, and had an easy time remembering to use Babyscripts. Most (83%, 5/6) of the participants felt that the app assisted with healthy pregnancy-related behaviors, were satisfied with prenatal care, felt more connected with their provider, and felt more knowledgeable about their pregnancy.

Discussion

Principal Findings

The main finding of this study was that the use of a novel pregnancy platform, which incorporates remote monitoring and a clinical alert system, is feasible as evidenced by high patient-app engagement, accurate at-home measurements of weight and blood pressure, efficacy of the alert system, and high patient satisfaction scores.

Interaction with the app met expectations and collection goals. The app was designed to provide regular educational information regarding pregnancy and prenatal care. Patient interaction with the mobile app averaged 5.5 times per week over the 6-month study period demonstrating that patients are visiting the app almost daily. The app was also designed to prompt patients to record weight and blood pressure at least weekly. Given these collection goals, the average interaction per week was chosen as a metric for engagement. Weight data collection averaged 1.5 times per week and blood pressure data collection averaged 1.1 times per week, which is a significant increase from the current standard of only recording blood pressure and weight during office visits. Based on discussions with experts, we concluded that more frequent readings were unlikely to add additional clinical information.

Accuracy of remote measurements are essential to make appropriate clinical management decisions. Remotely collected data tracked closely with in-office data demonstrating the accuracy of the remote devices. Blood pressure values measured in the office were mildly (<10%) elevated compared to the remote measurements, which has been previously described in

the literature comparing at home blood pressure measurements to office measurements [13].

In addition, this platform demonstrated that automated alerts may be an effective way to notify the patient and provider regarding abnormal change in weight or blood pressure. The goal of the alert system is to facilitate earlier identification of pregnancy complications and optimize timely intervention. The described monitoring system has the ability to collect data more frequently than office visits alone, allowing for the potential to develop predictive models to screen normal pregnancies and identify pregnancy risk earlier.

Limitations

The major limitations to this study include the small sample size and the threat of selection bias due to a convenience sample. It is possible that our results will not be reproduced in a different population or larger population. There are a number of possible biases within the participant population that limit our ability to demonstrate feasibility. The limitations based on the breadth of the study population include a mostly married cohort with private insurance, and 75% (6/8) patients were experiencing their first pregnancy. The fact that this was their first pregnancy makes it difficult for them to compare mobile prenatal care with other models of prenatal care. None of the women had significant past medical history nor used tobacco. Despite the attempt to choose a healthy cohort of women, 25% (2/8) of the women did experience a complication of pregnancy, specifically growth delay in one fetus and preeclampsia in another. While the sample size was small, it was ethnically diverse including 3 Caucasian women, 3 African-American women, 2 Hispanic women, and 1 Asian-American woman. Future studies will include examining the efficacy within specific ethnic and racial populations.

Second, researchers were not blinded to the purpose of the study, introducing the possibility of bias when assessing our primary outcomes. Finally, the lack of a comparison group limits the ability to draw conclusions about improved outcomes compared to usual prenatal care. However, this is a pilot study to determine the feasibility of a novel system, with plans for more rigorous studies in the future addressing these and other limitations.

Conclusions

In the future, prenatal care is likely to incorporate more personalized care that integrates mobile technology, individualized risk stratification, and remote monitoring. As such, this study is the first to demonstrate the feasibility of using a digital health platform to remotely collect data in near real-time and to stratify for high-risk outcomes using an effective alert system. Future studies will compare prenatal care assisted by mobile health technology compared to routine care evaluating comparative-effectiveness and patient-centered outcomes.

Acknowledgments

Thank you to Dr Haywood L Brown, president of the American Congress of Obstetricians and Gynecologists, for feedback regarding study and application.

Conflicts of Interest

Andrew Meltzer and Julia Oh have stock options in the health technology company that created Babyscripts.

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Corrigenda and Addenda

Correction of: Supporting Goal-Oriented Primary Health Care for Seniors with Complex Care Needs Using Mobile Technology: Evaluation and Implementation of the Health System Performance Research Network, Bridgepoint Electronic Patient Reported Outcome Tool

Carolyn Steele Gray[1,2], MA, PhD; Walter P Wodchis[2,3,4], MAE, MA, PhD; Ross Upshur[1,5], MA, MSc, MD, CCFP, FRCPC; Cheryl Cott[6], DipPT, BPT, MSc, PhD; Brian McKinstry[7], MD, FRCPE, FRCGP; Stewart Mercer[8], MBChB, BSc, MSc, PhD, MRCGP, FRCGP; Ted E Palen[9], PhD, MD; Tim Ramsay[10,11], PhD; Kednapa Thavorn[4,10,11], PhD; Project Collaborators And Technology Partner, QoC Health Inc[1]

[1]Bridgepoint Collaboratory, Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, ON, Canada

[2]Institute of Health Policy, Management and Evaluation,, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

[3]Toronto Rehabilitation Institute, Toronto, ON, Canada

[4]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada

[5]Department of Family and Community Medicine, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

[6]Department of Physical Therapy, University of Toronto, Toronto, ON, Canada

[7]The Usher Institute of Population Health Sciences and Informatics, Centre for Population Health Sciences, University of Edinburgh, Edinburgh, United Kingdom

[8]School of Medicine, University of Glasgow, Glasgow, United Kingdom

[9]Institute for Health Research, Colorado Permanente Medical Group and Kaiser Permanente Institute for Health, Denver, CO, United States

[10]Ottawa Methods Centre, Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, ON, Canada

[11]School of Epidemiology, Public Health and Preventative Medicine, University of Ottawa, Ottawa, ON, Canada

Corresponding Author:
Carolyn Steele Gray, MA, PhD
Bridgepoint Collaboratory
Lunenfeld-Tanenbaum Research Institute
Sinai Health System
1 Bridgepoint Drive
AM.37
Toronto, ON M4M 2B5
Canada
Phone: 1 416 461 8252 ext 2908
Fax: 1 416 461 0656
Email: carolyn.steelegray@sinaihealthsystem.ca

Related Article:

Correction of: https://www.researchprotocols.org/2016/2/e126/

(JMIR Res Protoc 2016;5(4):e194) doi:10.2196/resprot.6719

The authors of "Supporting Goal-Oriented Primary Health Care for Seniors with Complex Care Needs Using Mobile Technology: Evaluation and Implementation of the Health System Performance Research Network, Bridgepoint Electronic Patient Reported Outcome Tool" (JMIR Res Protoc 2016;5(2):e126) would like to make changes in the results section of the abstract as well as in the results section of the body of the article. In both instances the CIHR funding number should read: (CIHR-143559) instead of (CIHR-348362).

The authors would also like to change the funding number in the acknowledgements section with regard to the CIHR Planning and Dissemination Grant. The bracket should read (CIHR-137200) instead of (CIHR-328229).

The authors would also like to change the order of affiliations 1 and 2 so that “Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada” becomes affiliation 2 and “Bridgepoint Collaboratory, Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, ON, Canada” becomes affiliation 1. This changes the order of affilition for author Walter Wodchis from 1,3,4 to 2,3,4. The affiliation of author Ross Upshur is now rearranged from 2,5 to 1,5 and the affiliation of Project Collaborators And Technology Partner, QoC Health Inc is now 1 which was previously 2.

The last and final correction is that the authors would like to change their email address from csteele@bridgepointhealth.ca to carolyn.steelegray@sinaihealthsystem.ca.

These changes have been corrected in the online version of the paper on the JMIR website on October 13, 2016 together with publishing this correction notice. 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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Original Paper

Adjuvant Endocrine Therapy in Breast Cancer: A Novel e-Health Approach in Optimizing Treatment for Seniors (OPTIMUM): A Two-Group Controlled Comparison Pilot Study

Ari Meguerditchian[1,2,3,4], MSc, MD; Robyn Tamblyn[1,5,6], PhD; Sarkis Meterissian[2,3,4], MSc, MD; Susan Law[7,8], PhD; Jaroslav Prchal[3,9], MD; Nancy Winslade[6], MHPE, PharmD; Donna Stern[9], MD

[1]Clinical and Health Informatics Research Group, McGill University, Montreal, QC, Canada
[2]Department of Surgery, McGill University, Montreal, QC, Canada
[3]Department of Oncology, McGill University, Montreal, QC, Canada
[4]Breast Clinic, McGill University Health Centre, Montreal, QC, Canada
[5]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada
[6]Department of Medicine, McGill University, Montreal, QC, Canada
[7]Department of Family Medicine, McGill University, Montreal, QC, Canada
[8]Research Centre, St. Mary's Hospital, Montreal, QC, Canada
[9]Department of Oncology, St. Mary's Hospital Center, Montreal, QC, Canada

Corresponding Author:
Ari Meguerditchian, MSc, MD
Clinical and Health Informatics Research Group
McGill University
1140 Pine Avenue West
Montreal, QC
Canada
Phone: 1 514 934 1934 ext 32999
Fax: 1 514 843 1633
Email: ari.meguerditchian@mcgill.ca

Abstract

Background: In women with hormone receptor positive breast cancer, adjuvant endocrine therapy (AET) is associated with a significant survival advantage. Nonadherence is a particular challenge in older women, even though they stand to benefit the most from AET. Therefore, a novel eHealth tool (OPTIMUM) that integrates real-time analysis of health administrative claims data was developed to provide point-of-care decision support for clinicians.

Objectives: The objectives of the study are to determine the effectiveness of a patient-specific, real-time eHealth alert delivered at point-of-care in reducing rates of AET discontinuation and to understand patient-level factors related to AET discontinuation as well as to assess integration of eHealth alerts regarding deviations from best practices in administration of AET by cancer care teams.

Methods: A prospective, 2-group controlled comparison pilot study will be conducted at 2 urban, McGill University–affiliated hospitals, the Royal Victoria Hospital and St. Mary's Hospital. A minimum of 43 patients per study arm will be enrolled through site-level allocation. Follow-up is 1.5 years. Health care professionals at the intervention site will have access to the eHealth tool, which will report to them in real-time medical events with known associations to AET discontinuation, an AET adherence monitor, and a discontinuation alert. Cox proportional hazard ratios with 95% confidence intervals will estimate risks of AET discontinuation. Tests for significance will be 2-sided with a significance level of $P<.05$.

Results: This protocol has been approved and funded by the Canadian Institutes of Health Research. The study will evaluate site-level differences between AET discontinuation and AET adherence and assess care team actions at the intervention site. Participant enrollment into this project is expected to start September 2016 with primary data ready to present by June 2018.

Conclusion: This study will offer an opportunity to verify the feasibility of integrating an eHealth tool that aims to improve the long-term management of breast cancer in a high-risk population by allowing more timely intervention to prevent or rapidly address AET discontinuation.

(JMIR Res Protoc 2016;5(4):e199) doi:10.2196/resprot.6519

KEYWORDS

administrative claims; health care; breast neoplasms; medical informatics applications; aromatase inhibitors; telemedicine; health services for the aged; medication adherence

Introduction

Antiestrogen Therapy in Seniors With Breast Cancer: An Effective Anticancer Strategy

Adjuvant endocrine therapy (AET) inhibits the estrogenic stimulation that drives breast cancer growth [1-4]. In women with hormone receptor positive breast cancer, AET is associated with a significant survival advantage [2,5-8]. For instance, tamoxifen reduces the relative risk of recurrence and death from breast cancer by 46% and 26%, respectively [6], with maximal benefits attained from at least 5 years of therapy [9-13]. Similar outcomes are reported with aromatase inhibitors [10,14-17]. Therefore, when taken for at least 5 years, AET is a low-risk, easily administered treatment that constitutes an ideal strategy in reducing the impact of disease in women with hormone receptor positive breast cancer.

Defined as the extent to which patients take a medication as prescribed [18-22], adherence is the most important modifiable factor that can potentially compromise treatment outcome [23,24]. Adherence problems lead to worsening of disease, increased hospitalizations and health care costs, and death [25-31]. Suboptimal adherence can be due to factors related to patient, provider, and health care system characteristics [18,21]. Despite the magnitude of breast cancer as a health problem and the impressive survival benefits of AET, nonadherence rates of more than 20% have been noted in tightly controlled clinical trials [32-34]. However this does not accurately reflect the reality of vulnerable patients such as older women, who tend to be underrepresented in research studies [35-38].

Limited studies show that adherence to AET is a particular challenge in older women [39]. Paradoxically, these women stand to benefit the most from AET, because breast cancer is hormone receptor positive in more than 80% of women 65 years and older [40-46], older patients are often precluded from other more toxic forms of systemic treatment such as chemotherapy [47], and the use of AET simplifies managing breast cancer in seniors by eliminating the need for other forms of treatment. For example, radiotherapy can be omitted in patients 70 years and older after breast conserving surgery for stage I disease, providing they receive AET [48,49]. Specifically, in patients older than 65 years old, AET has been shown to improve 15-year survival by at least 21% [50]. Consequently, the International Society of Geriatric Oncology recommends that seniors with hormone receptor positive breast tumors benefit from AET, because there is no evidence of age-related differences in the efficacy of tamoxifen and aromatase inhibitors [50,51].

Because close to 40% of breast cancers in Canada are diagnosed in women 65 years and older and 61% of deaths from this disease occur in women 70 years and older [52], it is crucial that we gain a better understanding of problems associated with AET adherence in this population.

Adherence to Adjuvant Endocrine Therapy: Tackling Challenges in Older Women

Conventional strategies in documenting adherence to AET (eg, chart review, patient self-report, metabolite measurement, pill counts) are limited by their reliability and applicability [53-57]. They do not correspond well to the reality of taking AET, a self-administered daily treatment that requires minimal interaction with the care team, for seniors who often have other comorbidities (and thus additional prescriptions). As a result, opportunities to identify problems throughout the course of treatment and intervene are limited [58,59].

Generated for the purpose of directing payment, administrative claims constitute a source of potentially complete health care information covering all services provided to a patient, including outpatient drugs [60]. We have previously demonstrated that pharmacy claims were superior to a national cancer registry in reporting delivery of outpatient self-administered treatments. Initiation of AET was documented in an additional 55% of patients in comparison to registry data from the National Cancer Data Base [61].

Online adjudication processes of drug insurance programs and electronic storage of claims data ensure both timeliness and longitudinal compilation of information on drug utilization. This can be used to assess adherence to AET by seniors by calculating the medication possession ratio (MPR) based on refill rates, which reflect the availability of medication supply [62]. Defined as the ratio of total days covered by medication divided by the number of days needing the medication [21,63], the MPR estimates the proportion of days on which medication is taken and appears to be a better predictor of therapeutic outcomes compared to self-report or pill count [64-66].

Using pharmacy claims from all Quebec breast cancer patients (1998-2007), we have shown that adherence to AET among older women is suboptimal across each of the 5 years of treatment, falling below 75% at the fifth year [67,68]. We have shown that 37% of patients experience discontinuation of some duration within the first year [67]. Using health service claims, we have further demonstrated that hospitalizations, addition of new drugs during therapy, switch in AET type (tamoxifen versus aromatase inhibitor), and depression are associated with higher rates of nonpersistence.

To date, very few studies have used pharmacy claims to characterize AET adherence in seniors with breast cancer. Using the cohort of Quebec women aged 70 years and older (1998-2005), our group has demonstrated that 32% of older patients discontinued AET at some point during therapy and 20% of these women permanently abandoned therapy, thus losing the significant age-specific survival advantage provided by this treatment [50,69,70]. We have also shown that treatment discontinuation was more frequent in seniors who had

encountered irregularities and gaps in quality in other aspects of breast cancer care.

Medical Office of the XXIst Century: A Novel eHealth Tool to Optimize Breast Cancer Care Delivery in Seniors

Medical Office of the XXIst Century (MOXXI) is a novel clinical informatics system that provides patient-specific, point-of-care documentation and decision support through real-time processing of health services claims [71-73]. This platform also allows analysis of treatment plan variations. The disease-specific, real-time, point-of-care informatics support provided by MOXXI has been associated with better, safer care. For example, in the case of cardiovascular medications, physicians who received automated alerts from MOXXI regarding low treatment adherence (based on a real-time feed from the provincial pharmacy claims database) were significantly more likely to review the patient's drug profile and take appropriate action [73]. Another MOXXI application directed at older adults provides real-time alerts to physicians regarding the risk of fall-related injury in relation to the patient's psychoactive medications. This eHealth tool has been shown to result in treatment plan modifications in 24.6% of patients and a reduction of injury risk by 1.7 injuries per 1000 patients [74,75].

The integration of eHealth tools such as MOXXI represents a unique opportunity to address challenges in the delivery of care for older women diagnosed with breast cancer [76]. With multiple medical comorbidities, extensive health service use, and frequent deviations from best practices for cancer treatment, this group stands to benefit the most from the development of a comprehensive cancer care quality strategy addressing all components of treatment, continuously integrating all aspects of their health, and supporting treatment decisions specific to their needs [77,78].

Purpose and Objectives

The aim of this study is to verify if a patient-specific eHealth tool (OPTIMUM) that integrates real-time analysis of administrative claims data and provides point-of-care risk assessment to care teams will optimize breast cancer treatment by increasing adherence and persistence to antiestrogen therapy in patients aged 65 years and older.

The first objective is to determine the effectiveness of OPTIMUM's patient-specific, real-time eHealth alerts in reducing rates of AET discontinuation in older women with breast cancer and understand patient-level factors related to AET discontinuation.

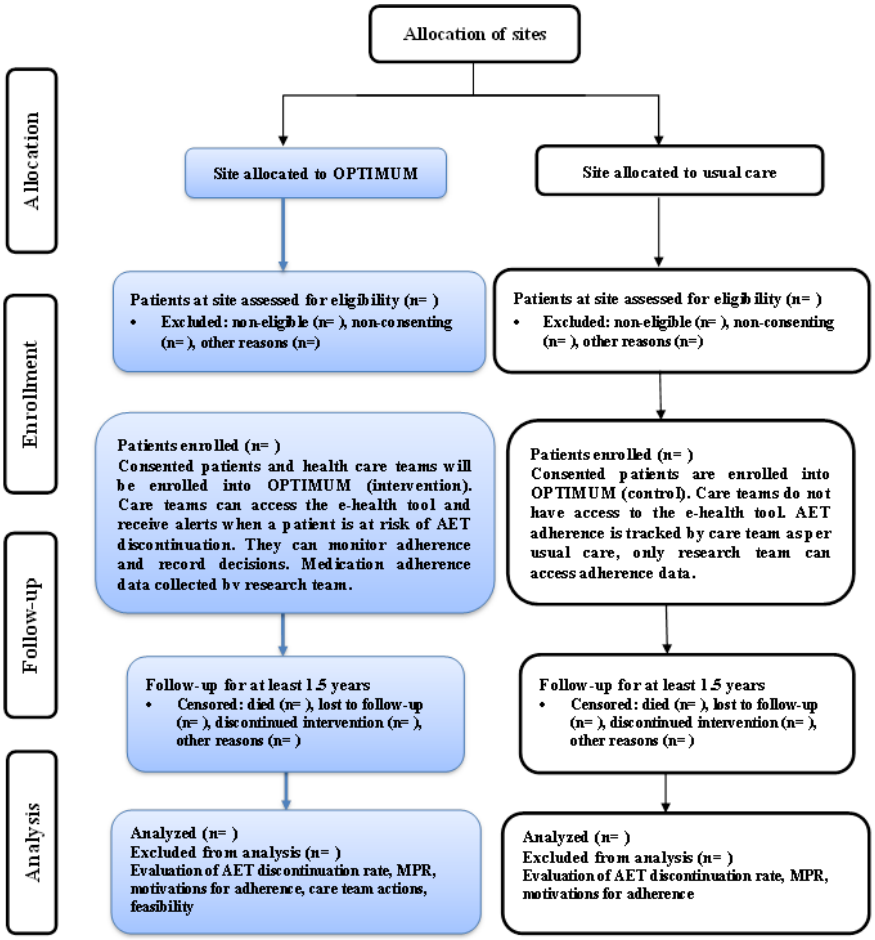
The second objective is to assess integration of the eHealth alerts reporting deviations from best practices in administration of AET by evaluating cancer care team responses.

Methods

Overview

A prospective, 2-group controlled comparison pilot study will be conducted to test the hypothesized benefits of the OPTIMUM eHealth tool with integrated alerts in managing AET in seniors with breast cancer (see Figure 1 for study flow). The benefits of the intervention will be assessed by comparing patients of care teams using the OPTIMUM eHealth tool with patients of care teams contemporaneously provided usual care. The follow-up will last 1.5 years based on previous findings by our group that the median time to first AET discontinuation in 3180 Quebec women (aged 70 years and older) with early stage breast cancer was 1.5 (range 0.5-3.4) years [69]. Ethics approval will be obtained before initiating the study.

Figure 1. Flowchart of study design: a prospective intervention study with a contemporaneous control group.



Study Population and Setting

The study will take place at 2 urban hospitals in Montreal, Canada: the Royal Victoria Hospital (RVH) and St. Mary's Hospital (SMH). These hospitals were selected for comparable resources and treatment standards. Both hospitals are affiliated with McGill University and benefit from its clinical trials infrastructure. In addition, both sites have similar multidisciplinary care teams consisting of surgical, medical, and radiation oncologists and an oncology nurse specialist. Staff and support resources are allocated at the institution level, where patient management is standardized. A total of 1168 new breast cancer patients were treated at both sites in 2012 with about 40% of the women being over the age of 65 years [79].

Eligibility Criteria

Eligible patients from the 2 study sites will be identified by the oncology nurse specialist. To be eligible to participate in this study, patients must be 65 years or older, able to give consent, and diagnosed with incident (nonmetastatic) breast cancer after having undergone breast surgery for stages I-III disease. Patients must have had medical insurance with the Régie de l'Assurance Maladie du Québec (RAMQ) for at least 1 year prior to surgery and have histologically confirmed breast adenocarcinoma with hormone receptor positive disease. Patients must have no history of AET use prior to the diagnosis of breast cancer, expect to initiate AET or have only recently initiated AET (less than 6 months), and be free of previous discontinuation events.

Recruitment

Patients will be recruited exclusively from the breast centers participating in the study (RVH and SMH). Advertisements will be placed in the registration areas, waiting rooms, and clinical care areas. Care teams (physicians, oncology nurses, and rehabilitation specialists) will facilitate identification of eligible patients and secure their permission to be approached by a study coordinator who will inform patients about the study and provide a detailing pamphlet. Only patients and health care professionals who have provided a standardized consent form with their signatures will be enrolled in the study. Both patients and care teams will be aware that the intervention site will receive the eHealth tool to test the study hypothesis. However, only the health care professionals will know if their site has the intervention based on their site's receipt of the eHealth tool. This intervention is not expected to impact the care of patients at the control site because AET adherence optimization is part of best practices. For additional validation, adherence of participants at the control site can be compared to historical population-based adherence data [67,68].

Intervention Allocation

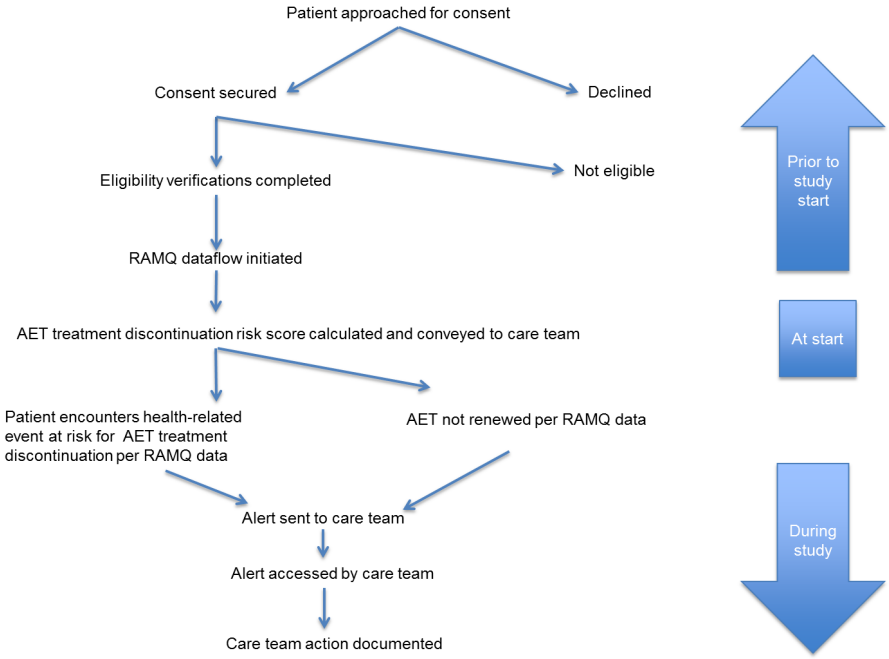
All eligible patients who provide consent will be enrolled into OPTIMUM. The intervention allocation will occur at the site level. The care team at RVH will have access to the OPTIMUM eHealth tool (intervention). At SMH, the care team will continue to deliver care according to standard processes (control group).

The control and intervention sites were selected for their similarities in source population, breast cancer volume, practice profiles, and academic affiliation. In addition, both institutions recently underwent administrative and physical reorganizations of the same magnitude. RVH completed their transition several months earlier than SMH, which enabled the process of logistical implementations related to the intervention and ethics approval for this pilot to start earlier there.

Intervention: An eHealth Tool

The intervention site care team will receive the following 3 OPTIMUM eHealth alerts (for care team process flow, see Figure 2).

Figure 2. Process flow for care teams.



Electronic Alert of Increased Adjuvant Endocrine Therapy Discontinuation Risk

Through real-time analysis of health service claims, OPTIMUM will generate this alert when a hospitalization, emergency room visit, addition of new medications, or change in AET drug occurs (see Multimedia Appendix 1-2 for examples of alerts from another eHealth tool trial). We have previously demonstrated that the occurrence of these during AET negatively impacts treatment adherence. The care team will be prompted by the eHealth tool to log its actions upon receipt of these alerts. The choice of actions is at the discretion of the care team and may include performing telephone follow-up with patient, performing telephone follow-up with community pharmacist, arranging for return to clinic with doctor, arranging for return to clinic with nurse, or ignoring the alert (see Multimedia Appendix 1-3 for examples of another eHealth tool and Multimedia Appendix 4 for the types of actions the care teams can select when faced with an alert).

Adherence Monitor

As the treatment progresses, OPTIMUM will provide a graphic representation of adherence to AET over time for each patient (see Multimedia Appendix 3 for example).

Electronic Discontinuation Occurrence Alert

Through real-time analysis of pharmacy claims including information on renewal date and number of pills dispensed, OPTIMUM will generate an electronic alert when there is a gap in AET prescription renewal within 10 days of the expected date. This threshold was determined from secondary analysis of our previous publications [67,68], which found that most patients who did not discontinue permanently renewed AET within 10 days. Again, the care team will be prompted by the eHealth tool to log its actions upon receipt of these alerts. The choice of actions are at the discretion of the care team and may include performing telephone follow-up with patient, performing telephone follow-up with community pharmacist, arranging for return to clinic with doctor, arranging for return to clinic with nurse, or ignoring the alert (see Multimedia Appendix 1-3 for examples of another eHealth tool and Multimedia Appendix 4 for the types of actions the care teams can select when faced with an alert).

Control Site

Care teams at the hospital assigned as control site will follow up with patients according to standard processes of care and will not have access to the eHealth tool.

Sample Size

A minimum of 120 patients will be approached to obtain a pilot sample size of 43 patients per arm [80,81]. This assumes comparable care standards between arms and among clinicians, an enrollment rate of 75%, a 5% loss to follow-up for infrequent cases of patient migration or opting out of the government drug plan [68], with a proportion of 20% permanently discontinuing at the control site [67,68] and 14% in the intervention group (minimally clinical important risk difference of 6%, a relative effect of 30%).

Data Sources

The following data sources will be linked to obtain important patient, disease, and clinical information and verify study outcomes (see Textbox 1).

Registrant database of insured persons documents year of birth, gender, 3-digit postal code, and date of death for all Quebec residents eligible for provincial health insurance coverage (approximately 99% of the population of Quebec), as well as dates for any noninsured periods [82,83].

RAMQ medical service claims database (RAMQ-MD) contains records for all services provided within Quebec's public health insurance plan by physicians remunerated under the fee-for-service system (approximately 96% of physicians in Quebec). This database includes encrypted physician license number, physician speciality, service date, code for the service provided, location of service delivery (eg, community health services center, hospital) and primary diagnosis codes (*International Classification of Diseases, Ninth Revision* [ICD-9]). Previous studies have demonstrated that diagnostic codes in medical service claims have high specificity, high positive predictive value, and high negative predictive value, estimated at above 90% for all 3 indicators [84].

RAMQ drug insurance eligibility database contains start and end dates of patient eligibility for public drug insurance as well as the type of drug plan.

RAMQ prescription claims database (RAMQ-Rx) contains claims for prescription drugs dispensed to all Quebec residents insured under the public drug plan. It includes encrypted physician license number, Drug Identification Number of drug dispensed, date the medication was dispensed, quantity dispensed, and duration of the prescription. Our group has shown that the accuracy of this database in identifying the correct drug dispensed is over 99% [85].

MedEcho is the hospital's discharge database, which includes admission date, principal and secondary diagnoses, and services performed for all discharges from acute care hospitals in the province. The first hospital-based service for breast cancer is considered the patient's index date.

Hospital chart includes all clinical notes of treatment decisions and clinical course.

The RAMQ links the above data sources using the *numéro d'assurance-maladie*, a unique identifier attributed to each Quebec resident and common to these databases. Appropriate clearance has been obtained from the *Commission d'accès à l'information du Québec* for the use of these population databases.

Textbox 1. Data sources and look-back periods with type of information extracted.

Registrant database of insured persons—12 month prior to index date

- Date of Birth
- Health insurance eligibility status

RAMQ medical service claims database (RAMQ-MD)—24 months prior to index date

- Validation of index date
- Medical services received

Drug insurance eligibility database—12 months prior to index date

- Verification of coverage eligibility

RAMQ prescription claims database (RAMQ-Rx)—12 months prior to index date

- Drugs received
- Polypharmacy

MedEcho—12 months prior to index date

- Index date ascertainment
- Admissions
- Discharges
- Emergency department visits

Confounding Variables

Patient Demographics (Fixed Covariates)

Age at diagnosis will be obtained from the registrant database. Socioeconomic status information will be obtained using the RAMQ-Rx database. A variable will be created grouping patients according to income supplementation received by the government. Patients will either "not qualify for a supplement," "qualify for some supplement," or "qualify for maximum supplement."

Disease Characteristics (Fixed Covariate)

We will identify the patient's breast cancer stage using topography and morphology (ICD-9) codes recorded in the hospital's discharge database (MedEcho).

Treatment Characteristics (Fixed Covariates)

We will characterize delivery and date for each component of breast cancer care (itemized below) using medical services billing codes in the RAMQ-MD and prescription drug claims in the RAMQ-Rx databases. As previously discussed, claims offer the opportunity to accurately monitor breast cancer patient progress through the cancer care continuum because they cover all services provided regardless of practitioner or site.

- Breast surgery: mastectomy, lumpectomy, no surgery
- Axillary surgery: sentinel lymph node biopsy, axillary lymph node dissection, no lymph node surgery
- Radiation therapy: consultation with radiation oncology, delivery of external beam radiation therapy, no radiation therapy

Systemic therapy: consultation with medical oncology, delivery of systemic chemotherapy, no chemotherapy

AET initiation: 3 variables will be created—choice of drug (tamoxifen, anastrosole, letrosole or exemestane), timeliness of treatment initation (1 year or less), and whether the patient switched type of AET during follow-up

Other Medical Conditions (Fixed Covariates)

Romano's adaptation of the Charlson comorbidity index will be used to measure each patient's baseline risk of discontinuing in relationship to their health status using ICD-9 codes listed in claims in the 12 months prior to the diagnosis of breast cancer. In addition, the MedEcho database will be used to document the number of emergency department visits and inpatient admissions for each 12-month period following AET start.

Polypharmacy (Fixed Covariates)

Drug claims for the 12 months preceding AET start, supplied by the RAMQ-Rx, will be classified according to the American Hospital Formulary Classification to determine the baseline number of different categories of non-AET drugs prescribed at the start of the AET treatment.

Physician Characteristics (Fixed Covariates)

Prescribing physician specialty, supplied by the RAMQ-Rx, may influence a patient's adherence to treatment. Therefore, the specialty of the first physician to prescribe AET to the patient will be identified. We will calculate the number of women with a breast cancer diagnosis that this first prescribing physician billed a medical service claim for in the year prior to initiating the patient's treatment. In addition, the physician's experience in treating breast cancer patients will be obtained. Finally, the number of different physicians who prescribed the patient's AET will be recorded. No information that can potentially identify physicians will be collected.

Definitions of Outcomes

The primary outcome is an AET discontinuation event defined as failure to refill an AET prescription within 10 days after the due refill date. The first due refill day preceding a gap of 10 days would be considered the date of discontinuation event. Permanent AET discontinuation will be defined as failure to refill an AET prescription before the end of the first year of treatment. First-year adherence will be measured by the MPR, defined as the proportion of days covered by medication supply in the treatment period. Actions taken by care teams upon receipt of an alert from the OPTIMUM eHealth tool will be observed and logged with the purpose of developing future AET adherence intervention strategies. These actions could be part of a drop-down menu and may include: perform telephone follow-up with patient, perform telephone follow-up with community pharmacist, arrange for return to clinic with doctor, arrange for return to clinic with nurse, or ignore the alert.

Operationalization of Outcomes

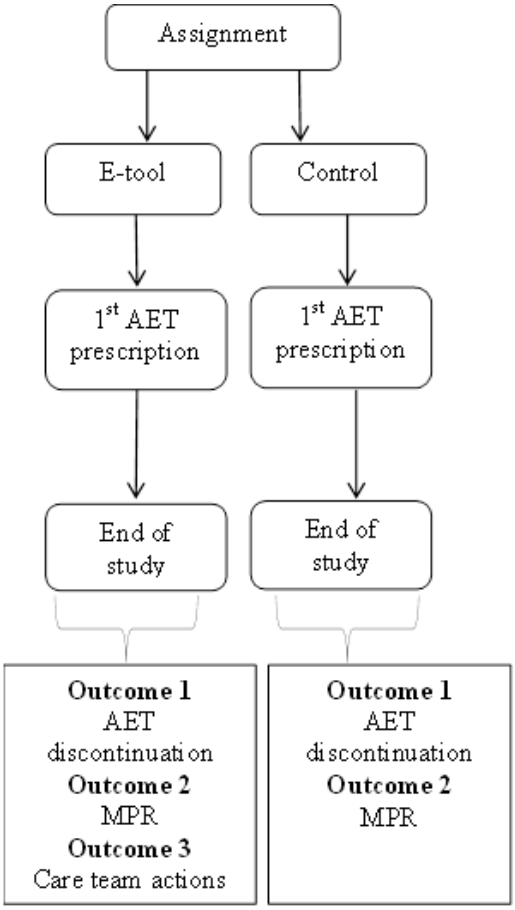
Visual representation of outcomes to be quantified during the course of the study and according to the study arm is shown in Figure 3.

AET discontinuation will be assessed by determining the proportion of patients permanently discontinuing AET treatment, proportion of patients reinitiating after a discontinuation of AET treatment, and the mean time to AET treatment reinitiation. This will be calculated in both the intervention and control arms. These outcomes will then be compared between both arms at the end of the study by the research team.

The MPR will be assessed as the mean MPR, and the proportion of patients that maintain an MPR of 80% or more. This will calculated in both intervention and control arms. Outcomes will be compared between both arms at the end of the study by the research team.

Types of actions taken by health care teams upon alert receipt will be assessed qualitatively and quantitatively in the intervention arm. As detailed above, the eHealth tool users will be prompted to document actions in response to an alert through a drop-down function in OPTIMUM. These actions will be logged in real-time when a notification is accessed and recorded. The outcome will be tabulated at the end of the study by the research team.

Figure 3. Outcomes by study arm.



Statistical Analysis

Assessing Effectiveness of the OPTIMUM eHealth Tool at Reducing Adjuvant Endocrine Therapy Rates of Discontinuation

In order to assess if the OPTIMUM eHealth tool has an impact on adherence, rates of AET discontinuation and MPR will be evaluated and compared between the intervention and control groups at the end of the follow-up period. Univariate and multivariate Cox proportional hazards regression models will be used to analyze the association between rates of AET discontinuation in patients managed with the OPTIMUM eHealth tool versus those in usual care, while adjusting for known patient clinical and demographic factors. These factors include age, hospitalizations, type of AET, depression, Charlson Comorbidity Index, and polypharmacy at baseline [69].

Time to treatment discontinuation will be measured using Kaplan-Meier analysis. The MPR will be calculated at the end of the study period. Patients will be classified as adherent if they maintain an MPR of 80% or more. Univariate and multivariate logistic regression analysis will be used to assess the association between the OPTIMUM eHealth tool and maintaining an MPR of 80% of more while adjusting for known risk factors. The proportion of patients discontinuing in each group (intervention vs usual care) and restarting medication will be compared using a chi-square test. The mean time to restart will be compared using a *t* test in those who restart after a treatment discontinuation event.

Assessing Integration of eHealth Alerts Concerning Deviations From Best Practices

Actions taken by health care teams in response to alerts (intervention arm) will be documented and assessed both qualitatively and via descriptive statistics. Descriptive statistics will be used to evaluate the most common action performed upon receiving an alert, frequency of log-ins to visit the patient's profile, frequency of viewing the adherence monitor, frequency and types of actions selected from the drop-down menu, or other actions such as change in treatment plan.

Confidentiality

Identity Protection

In order to protect confidentiality for study participants, all identifying information will be removed from the files prior to analysis. Therefore, research data transactions will be performed on deidentified data only using a unique study number assigned to each subject (includes patients and physicians). Only this number will be used on research documents that relate to the subject. Team members will be required to sign a confidentiality agreement with the principal investigator prior to accessing the information. The linkage table of subject names and corresponding study numbers will be kept in a secure locked location accessible only to the principal investigator (or his delegate). No names will be released and only grouped data will be presented in oral or written scientific communications. Identifying information will be destroyed 5 years after publication of findings.

Data Storage

Collected research data will be saved on research servers independent from and outside of the 2 clinical care sites. These servers are located at McGill University's data center, and access to them is protected by alarm system and 24-hour guard surveillance. In addition, informatics data transactions through these servers occur in the context of a private network and require username and password. Transactions are recorded and trackable by our in-house information technology networks specialist. Access to the server is restricted; it has the latest and most sophisticated protection against unauthorized intrusions and potential damage. This type of design offers a high level of data security in the event that a computer is lost or stolen.

Ethical Considerations

The OPTIMUM study will be conducted according to ethical principles stated in the Declaration of Helsinki (2013). This study received ethics approval from McGill University Health Centre Research Ethics Board on August 16, 2016. Consent forms will take into consideration the well-being, free-will, and respect of the participants (including respect of their privacy).

Results

Participant enrollment into this project is expected to start in September 2016 with primary data ready to present by June 2018.

Discussion

Over 40% of breast cancers in Canada occur in women 65 years and older. AET is an effective approach in reducing recurrence and cancer death in these women. Unfortunately, adherence to AET in this population is suboptimal.

This study aims to use a 2-group controlled comparison pilot study to verify the feasibility of integrating eHealth tools that aim to improve the management of the breast cancer in this high-risk population by allowing more timely intervention to prevent or rapidly address treatment discontinuation. Our group has already developed a successful model of using information technology to provide real-time decision support and feedback to care teams on patient-specific risk profiles. With the knowledge generated from this research, we plan to develop an informatics tool that would provide health professionals with a new generation of decision-support tools specific to the older cancer patients' needs. As this study is a pilot, feedback from care teams on ease of integrating the eHealth tool into existing workflows will support and guide the launch of a larger scale longitudinal study.

Our multidisciplinary team of scientists brings together research expertise from medicine, surgery, nursing, pharmacy, psychology, and evaluative sciences in developing the next generation of informatics-enabled tools in optimizing breast cancer care. Research will take place at the Clinical and Health Informatics Research Group. The Group is experienced in handling electronic clinical data systems such as hospital clinical data warehouses, RAMQ administrative databases, and clinical competency data through the Medical Council of Canada/College of Physicians of Quebec. Over the past decade, it has developed extensive know-how in developing value-added health informatics tools to improve health outcomes.

Acknowledgments

This protocol has been approved and funded by the Canadian Institutes of Health Research.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Visual depiction of the type of patient-specific alerts that can be provided to the health care professional borrowed from another trial on the effectiveness of MOXXI in improving care quality. This is an example of a patient-specific, real-time MOXXI alert provided to the care team regarding a prescription duplication and specific drug-related risk.

[PNG File, 194KB - resprot_v5i4e199_app1.png]

Multimedia Appendix 2

Visual depiction of the type of patient-specific alerts that can be provided to the health care professional borrowed from another trial on the effectiveness of MOXXI in improving care quality. This is a notification of events associated with an increased risk of drug-related issue (ie, emergency department visits).

[PNG File, 522KB - resprot_v5i4e199_app2.png]

Multimedia Appendix 3

Visual depiction of the type of patient-specific alerts that can be provided to the health care professional borrowed from another trial on the effectiveness of MOXXI in improving care quality. This is a graphical representation of drug adherence over time.

[PNG File, 64KB - resprot_v5i4e199_app3.png]

Multimedia Appendix 4

Example of how MOXXI, an eHealth tool, can be used to document an action and its rationale upon receipt of a patient-specific alert. In this example, the action is to stop a drug, and the drop-down list follows with reasons for changing the prescription.

[PNG File, 120KB - resprot_v5i4e199_app4.png]

Multimedia Appendix 6

Protocol approval and review by the Canadian Institutes of Health Research.

[PDF File (Adobe PDF File), 293KB - resprot_v5i4e199_app6.pdf]

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Abbreviations

AET: adjuvant endocrine therapy
ICD-9: International Classification of Diseases, Ninth Revision
MPR: medication possession ratio
MOXXI: Medical Office of the XXIst Century

RAMQ: Régie de l'Assurance Maladie du Québec
RAMQ-MD: RAMQ medical service claims database
RAMQ-Rx: RAMQ prescription claims database
RVH: Royal Victoria Hospital
SMH: St. Mary's Hospital

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Protocol

Assessing the Impact and Cost of Short-Term Health Workforce in Remote Indigenous Communities in Australia: A Mixed Methods Study Protocol

John Wakerman[1], MBBS, MTH, FACRRM, FAFPHM; John Humphreys[2], PhD; Lisa Bourke[3], PhD; Terry Dunbar[4]; Michael Jones[5], PhD; Timothy A Carey[6], PhD; Steven Guthridge[7], MBBS, MTH, FAFPHM; Deborah Russell[2], MBBS, PhD; David Lyle[8], MBBS, PhD, FAFPHM; Yuejen Zhao[7], MBBS, PhD; Lorna Murakami-Gold[6], EBTCH, MEd, RN

[1]Flinders NT, School of Medicine, Flinders University, Darwin, Australia

[2]Monash University School of Rural Health, Monash University, Bendigo, Australia

[3]University Department of Rural Health, The University of Melbourne, Shepparton, Australia

[4]Yaitya Purruna Indigenous Health Unit, University of Adelaide, Adelaide, Australia

[5]Psychology Department, Macquarie University, Sydney, Australia

[6]Centre for Remote Health, Flinders University and Charles Darwin University, Alice Springs, Australia

[7]Northern Territory Department of Health, Darwin, Australia

[8]Broken Hill University Department of Rural Health, The University of Sydney, Broken Hill, Australia

Corresponding Author:
John Wakerman, MBBS, MTH, FACRRM, FAFPHM
Flinders NT
School of Medicine
Flinders University
Building 4, Cnr University Drive North and University Drive West, Charles Darwin University, Casuarina
Darwin, 0815
Australia
Phone: 61 8 89467556
Fax: 61 8 89467599
Email: john.wakerman@flinders.edu.au

Abstract

Background: Remote Australia is a complex environment characterized by workforce shortages, isolated practice, a large resident Indigenous population, high levels of health need, and limited access to services. In recent years, there has been an increasing trend of utilizing a short-term visiting (fly-in/fly-out) health workforce in many remote areas. However, there is a dearth of evidence relating to the impact of this transitory workforce on the existing resident workforce, consumer satisfaction, and the effectiveness of current services.

Objective: This study aims to provide rigorous empirical data by addressing the following objectives: (1) to identify the impact of short-term health staff on the workload, professional satisfaction, and retention of resident health teams in remote areas; (2) to identify the impact of short-term health staff on the quality, safety, and continuity of patient care; and (3) to identify the impact of short-term health staff on service cost and effectiveness.

Methods: Mixed methods will be used. Administrative data will be extracted that relates to all 54 remote clinics managed by the Northern Territory Department of Health, covering a population of 35,800. The study period will be 2010 to 2014. All 18 Aboriginal Community-Controlled Health Services in the Northern Territory will also be invited to participate. We will use these quantitative data to describe staffing stability and turnover in these communities, and then utilize multiple regression analyses to determine associations between the key independent variables of interest (resident staff turnover, stability or median survival, and socioeconomic status, community size, and per capita funding) and dependent variables related to patient care, service cost, quality, and effectiveness. The qualitative component of the study will involve in-depth interviews and focus groups with staff and patients, respectively, in six remote communities. Three communities will be high staff turnover communities and three characterized by low turnover. This will provide information on service quality, impact on resident and visiting staff, and patient

satisfaction with the services. The research team will work with staff, patients, and a key stakeholder group of senior policymakers to develop workforce strategies to maintain or attain remote health workforce stability.

Results: The study commenced in 2015. As of October 2016, fieldwork has been almost completed and quantitative analysis has commenced. Results are expected to be published in 2017.

Conclusions: The study has commenced, but it is too early to provide results or conclusions.

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KEYWORDS

remote health; rural workforce; fly-in/fly-out; rural health services; health services, Indigenous

Introduction

In Australia, mortality rates increase with increasing distance from major cities [1]. Access to health services declines with increasing remoteness; consequently, rates of preventable admissions to hospital increase markedly with increasing remoteness [2]. Therefore, nowhere is it more urgent to ensure the strongest possible primary health care system than in remote areas, including in Indigenous communities, in order to prevent illness, serious complications, and the avoidable expense of hospitalization.

There has always been a need for some visiting services to small, remote settlements where population size does not support a full range of resident primary and specialist services [3]. More recently, there has been an increasing reliance on short-term or "fly-in/fly-out" (FIFO) or "drive-in/drive-out" (DIDO) services to overcome the health workforce recruitment and distribution problems in remote Australia, and a concomitant proliferation of private staffing agencies contributing to this workforce trend [4]. Increasing use of short-term or agency staff, who move from place to place or are one-off visitors, has raised significant concerns about the impact on patients and resident health service staff [5].

The provision of primary health care by nonresident staff in remote areas of Australia is characterized by different forms of visiting services [3]:

1. Specialist medical outreach services;

2. Hub and spoke or outreach arrangements for various allied health and specialized programs, such as women's health educators or mobile dental services;

3. "Orbiting staff" who spend significant periods of time (12 months or more) in one or two specific communities, self-regulate stress levels, and work elsewhere for periods then return to the same communities where orientation is not required;

4. Long-term shared positions, such as month-on/month-off, where the same practitioners service the same communities;

5. Experienced locum relief for resident staff; and

6. FIFO/DIDO or short-term or agency staff who move from place to place.

Although the need for short-term relieving or locum staff is legitimate, expedient, and should be met, there are associated risks that may increase in situations where the resident team is partially or largely replaced by short-term staff. The limited available evidence suggests that these risks include increased stress on resident staff, increased costs, decreased effectiveness of services resulting in increased hospital admissions, and suboptimal coordination of services. The House of Representatives Standing Committee on Regional Australia has expressed concern "that a FIFO heath workforce will undermine a residential health workforce and lead to the closure of existing facilities" (p 151 [5]).

The high turnover associated with short-term staff results in existing staff members repeatedly orienting new staff [6], which in turn results in additional pressure on long-term staff who become more stressed [7]. The "emerging lack of parity in their employment terms and conditions granted to the FIFO and DIDO workforce" also makes retaining existing long-term staff more difficult (p 17 [8]).

Over time, resident remote area staff develop a detailed knowledge of their communities and those communities' health needs. A resident registered nurse or midwife is more engaged with the local community and better placed to function effectively in a remote setting than visiting teams [9]. The effectiveness of primary health care services is predicated on strong relationships, good communication, and trust, especially in Aboriginal communities [10].

Short-term staff may not have the knowledge and experience necessary for clinical work in remote Australia [4,6,11]. Cultural competence is important when providing health services to Aboriginal communities [10], and there are concerns about a lack of preparation for remote practice of short-term staff [8].

Effective health care in remote settings requires the coordinated implementation of health care plans involving different health professionals. However, it is difficult to both coordinate multiple visiting services and effectively implement these plans with a preponderance of short-term staff [6]. This can result in the constant "bombardment" of communities, which have neither accommodation nor resident staff capacity to support visiting professionals or to allow for necessary skills development [10]. An absence of stable and strong resident remote primary health care teams risks the "hollowing out" of these communities [5].

International evidence in relation to outreach (visiting) services is scant [12]. In Australia, there is "a dearth of empirical evidence" relating to the increasing trend of a short-term, visiting health workforce in remote areas, and its impact on the existing workforce and the effectiveness of current services [5]. The recent parliamentary enquiry recommended further research

into the economic impact and the service impact of short-term FIFO staff in order to inform an appropriate health policy response. This is a pressing national health workforce issue that, to date, has not been informed by comprehensive, rigorous, and reliable research evidence.

Given these concerns about the potential adverse effects of FIFO/DIDO remote health staffing, the aim of the study described in this paper is to gather rigorous evidence of the extent to which a high level of short-term staffing in remote communities influences service acceptability to patients and the impact on permanent resident primary health care staff, service effectiveness, and cost. The specific objectives of the study are:

1. To identify the impact of short-term health staff on the workload, professional satisfaction, and retention of resident health teams in remote areas;

2. To identify the impact of short-term health staff on the quality, safety, and continuity of patient care; and

3. To identify the impact of short-term health staff on service cost and effectiveness.

Methods

The study is underpinned by a logic model that links health service inputs (workforce), outputs, and outcomes. A mixed methods approach will capture the best-available quantitative data and in-depth primary data collected from stakeholder interviews and focus groups. A mixed methods approach is necessary because (1) this is a complex health system issue that includes service delivery in an equally complex, remote, cross-cultural context; (2) some measures are quantitative by nature (eg, staff turnover rate) and others are qualitative (eg, patient experience); and (3) some quantitative measures are likely to require explanatory qualitative data to be thoroughly understood. The quantitative and qualitative components of the study are described separately subsequently, followed by how they are integrated to address each study objective. The study has been approved by the Central Australian Human Research Ethics Committee (HREC-15-296) and the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (2015-2363).

Setting and Participants:

The study sites include all 54 remote clinics managed by the Northern Territory (NT) Department of Health, covering a population of 35,800. The study period will be 2010 to 2014. This period will generate data related to approximately 480 full-time equivalent staff, 1,621,000 primary health care visits, and 271,000 hospital admissions. In addition, we have support for the project from the peak body for Aboriginal Community-Controlled Health Services, the Aboriginal Medical Services Alliance of the Northern Territory (AMSANT), and we will individually invite 18 remote community-controlled health services to also participate.

Measures

Measures of Staff Stability

The extent of utilization of short-term primary health care workers will be determined by calculating:

1. Annual resident primary health care workforce turnover (this includes resident doctors, nurses, and Aboriginal Health Practitioners) as measured by (number of leavers per year × 100)/average number employed per year;

2. Workforce stability as measured by (number of original entrants surviving at the end of each year × 100)/number of original entrants; and

3. Median survival of staff members.

These will be the major measures of inputs as per the underpinning logic model.

Quality and Cost-Effectiveness Outcomes

These measures will be used to evaluate quality of health care provision (objective 2) and cost-effectiveness (objective 3). The outputs are (1) expenditure by clinic and per capita (relates to objective 3) and (2) utilization as measured by attendances per clinic (relates to objective 2).

Quality indicators include (1) the proportion of diabetics with a chronic disease management plan, (2) proportion of eligible adults with an annual Adult Health Check, (3) proportion of diabetics with proteinuria on appropriate renal protective medication, (4) proportion of patients with cardiac disease on acetylsalicylic acid, (5) timely antenatal care, (6) Pap smear coverage, (7) immunization coverage, and (8) proportion of children screened for anemia (objective 2).

Intermediate outcomes include (1) numbers of medical retrievals by clinic (objective 2) and (2) preventable admissions to hospital by clinic (objective 2). Clinical outcomes include (1) proportion of known diabetics with blood sugar controlled (HbA_{1c}<7%) (objective 3), (2) proportion of known hypertensives with controlled blood pressure (objective 3), and (3) mortality estimates by location (objective 3).

A number of potential confounding variables that may contribute to dependent variables of interest will be considered in the regression model. They include (1) measures of socioeconomic status, (2) variability of funding and staffing between clinics, and (3) size of communities (related to economies of scale).

Several additional factors may potentially limit the analysis. These include:

1. Patient migration. With declining health, there is a small movement of people to larger centers [13]. We know that there is approximately 90% accuracy in identifying place of residence [14].

2. The relationship of primary health care utilization and hospital admission is not linear [15].

3. Specialist and allied health outreach visits. The effectiveness of these services is affected in a similar fashion by high staff turnover.

4. Quality of governance.

5. Intergenerational changes in attitude toward employment.

Data Sources and Feasibility

This study uses NT Government administrative datasets, including hospital admissions, primary health care visits, patient travel, government payroll, and accounting system. A remote health administrative roster and outreach diaries are also available for analysis. The NT Aboriginal Health Key Performance Indicators, including all quality measures, are routinely collected by both government and nongovernment health services. Data are comprehensive and reliable. Given appropriate ethics and data custodian approvals, data are available and accessible at a deidentified individual level, such as diagnosis codes for patients, position classifications for health staff, employee start and end dates, and personnel and operational expenses. All these data have been investigated previously by members of the research team in other studies. Quality, completeness, and accuracy of the data are acceptable for this project. All these data have been collected consistently throughout the study period.

Statistical Analysis

The quantitative component of the study has three elements that will be addressed as follows.

Description of Longevity of Clinic Staffing

The statistical approach to the first element will be addressed using descriptive statistics for quantitative measures of staff turnover and stability for the period from 2010 to 2014 (see Measures of Staff Stability). Because staff commencement and departure dates are recorded, survival methods will also be used to describe staff loss as a function of time, which allows for the possibility of right-censoring for staff who have not left at the time of study end.

Association Between Staff Stability and Outcomes

The second element of study design will utilize multiple regression analyses to determine associations between the key independent variables of interest (resident staff turnover, stability or median survival and socioeconomic status, community size, and per capita funding) and the dependent variables related to patient care, service cost, quality, and effectiveness.

Moderation of the Association Between Staff Stability and Outcomes

The third element will test whether socioeconomic status, community size, and per capita funding have an effect on the relationship between staff turnover on the dependent variables of interest via generalized linear models. That is, is the effect of staff turnover dependent or independent of socioeconomic status, community size, and per capita funding?

For both the second and third elements, formal statistical inference (hypothesis testing) will employ the nonparametric bootstrap method due to the expected nonnormal distribution of the quantitative dependent variables.

Analyses will be stratified to compare between government and nongovernment services, as well as by age groups (to examine intergenerational differences) and gender.

Sample Size

Based on a minimum practically important effect size of a partial r^2 of 5% when controlling for potentially confounding variables that explain 10% of the variance, an effective sample size of 260 patient records is required to achieve statistical power of .9 at the .01 (two-tailed) level of statistical significance. Because patients will be effectively cluster sampled from the participating clinics and substantial within-clinic correlation is expected, we assume a Kish design effect of 2.0, leading to a recruitment aim of 520 patients that can be easily achieved.

Qualitative Methods

Study Sites and Participants

To assess patients' and remote health professionals' experiences of FIFO health care, to provide contextual information to the previously described statistical analyses, and to confirm the contribution of FIFO/DIDO to workforce turnover rates, six study sites will be examined using qualitative methods. Initial quantitative assessment of resident workforce turnover, stability, and median length of stay will differentiate between high and low staff turnover communities (stage 1). In stage 2, clinics from the upper and lower quartiles of turnover in NT will be invited to participate until three sites at either end of the turnover range (high and low) agree to participate.

In each of the six consenting study sites, two local community-based coresearchers (hereafter referred to as "coresearchers"), one male and one female, will be employed to work as part of the research team. The process of recruitment of female and male coresearchers at each study site will depend on the recommendations from community Elders, leaders, and key organizations to ensure the male and female coresearchers will be able to work together and work with multiple families in the community. Selection of suitable coresearchers is a critical and important process because this complex and multifaceted role will provide a cultural and linguistic interface with community members in each consenting study site. The coresearchers will assist with participant recruitment, organization, group facilitation, ensuring the research protocol is adapted to local cultural protocols and practicalities, interpreting, and back-translation for those participants for whom English is not their first language. The role is not restricted to these activities, but is adapted to ensure the research is culturally appropriate and the information gained is genuine. Individualized training (including a full explanation of the project, ethical processes to recruit participants, and the conduct of focus groups with Aboriginal community members) will be delivered for the coresearchers and tailored to their existing experience, skills identified, needs, and aspirations. The aim is to collect qualitative data from health professionals as well as patients.

First, after written consent is provided, researchers will conduct semistructured, face-to-face individual interviews with resident health professionals [16]. Individual interviews allow for confidentiality when perspectives may be diverse. For cultural

safety reasons related to power differentials, the coresearchers may not wish to undertake individual interviews with resident health professionals. These interviews will explore resident staff experiences of short-term periodic staff, specifically issues of effectiveness of service delivery, motivation to work and remain in remote areas, job satisfaction, workload and stress, community engagement, and possible strategies to stabilize the workforce. Short-term staff will also be interviewed about their work, integration into the team, relationships with the community, and their perspective of effective service delivery. All interviewees will have the opportunity to raise issues about health care that they believe are important.

Second, coresearchers will recruit patients to participate in either semistructured, face-to-face individual interviews or focus groups, as appropriate. The coresearchers will cofacilitate the focus groups and either interview or identify the appropriate interviewer from the team [17]. Coresearchers with team members will discuss and come to agreement with community participants which method is culturally safe and preferred, considering issues of cultural safety, confidentiality, use of services, and preference of individuals. Focus groups tend to be more culturally appropriate and allow for a community rather than an individual narrative. At the same time, there may be community or individual issues best not discussed in an open forum. We estimate four interviews with patients as well as four focus groups (led by coresearchers and supported by another team member) will be conducted in each community, with approximately 10 participants in each group. Focus groups will be gender specific and respect age differences and clan differences. These group discussions will explore health service issues, including acceptability, experiences with staff and services, relationships with health service staff, and managing health issues that require sensitivity in relation to cultural issues. Although there will be guiding discussion points for the focus groups and the semistructured interviews, participants will have the opportunity to "tell their story" and express related information around the personal, family, and community impacts of short-term and high turnover of staff in the clinics. The focus will be on accurately recording these "stories" by taking notes, taping, and back-translating. All interviews and focus groups either will be audio recorded or have notes taken depending on participants' consent. Coresearchers will also be encouraged to reflect on their experiences as researchers, through written or oral recordings, to contribute to understanding the research process, the context of the research, findings, and their summary of the findings.

Third, regional center-based specialist and retrieval staff will also be interviewed to assess quality of remote area services and specific issues such as medical evacuations from remote communities.

Analysis

Interview and focus group recordings will be transcribed and analyzed with the assistance of NVivo. The patient focus group, patient interview, and health professional interview data will be analyzed separately because the transcripts are derived from different methods with different types of respondents (ie, they are different datasets). To begin, three researchers will read all transcripts to identify relevant issues. Community-based coresearchers will be asked to read transcripts or listen to audio recordings from their own community. Three researchers and the coresearchers will together identify codes and the three researchers will independently code each dataset. The three researchers and coresearchers will then agree on major themes for each dataset that blend codes and include local knowledge. These themes aim to describe the issues, underpinnings, and contexts that explain health care in these study sites [18]. Following, narrative analysis will be conducted to capture the stories of how the FIFO workforce has or has not shaped health and health care in these communities focusing on the patient stories [19]. Sampling high and low turnover clinics will allow comparison of service and contextual issues that accelerate or impede turnover of staff. There will also be comparison of findings from government and Aboriginal Community-Controlled Health Services.

Integration of Quantitative and Qualitative Information

Quantitative and qualitative data will be triangulated to address the three study objectives as follows:

1. The impact of visiting short-term health staff on resident health teams in remote areas will be measured by (stage 1) analysis of remote staff turnover, stability, and median survival to determine high and low turnover communities [20] and (stage 2) in-depth interviews with long-term staff, including Aboriginal Health Practitioners, remote area nurses, and medical officers to determine impact on staff work life (eg, morale, workload, stress, and intention to stay). Interviews with short-term staff will document similar issues as well as preparation for remote areas, work satisfaction, and level of community engagement.

2. Impact on the quality, safety, and continuity of patient care will be assessed through quantitative analysis of service quality data (as specified subsequently), in-depth interviews and focus groups with patients about their experience of the impact of short-term staff and their satisfaction with and acceptability of services, and interviews with specialist and retrieval staff about the quality of remote consultations and perceived need for medical evacuations.

3. Impact on service cost and effectiveness will be assessed by an analysis of expenditure, utilization, medical retrieval, and clinical outcome data in remote clinics for each community.

Triangulation of quantitative and qualitative data will assess whether the influence of high short-term staff utilization on objective markers of quality, cost, and effectiveness of health care services is paralleled in staff satisfaction, patient satisfaction, and service acceptability.

Knowledge Exchange

Knowledge exchange is an integrated feature of the project. The research team has had extensive experience in research translation and has published on the measurement of research impact [21]. The knowledge exchange strategy will be multifaceted and include in-depth interviews with staff and patients to determine current and potential strategies to maintain or achieve remote health workforce stability; feedback to the study sites through the researchers; establishment of a key

stakeholder group; presentations to national conferences; presentations to smaller forums, such as invited seminars to Commonwealth Department of Health staff; meetings with senior policymakers at Federal and State levels; and peer-reviewed publications. The key stakeholder group will comprise senior policy makers from NT Department of Health, Top End and Central Australian Health Services, NT Primary Health Network, AMSANT, the National Rural Health Alliance, and the Commonwealth Department of Health. Working with the key stakeholder group, workforce strategies will be developed based on research findings through "collaborative problem solving between researchers and decision makers that happens through...interaction between decision makers and researchers and results in mutual learning through the process of planning, producing, disseminating, and applying existing or new research in decision making" (p 15 [22]).

Discussion

This study aims to build the currently deficient evidence base relating to a complex, real-world health systems issue: the impact of short-term staffing on the quality and costs of remote primary health care services. The study involves working in an equally complex remote, cross-cultural setting, involving multiple primary health care providers. It is a challenging real-world problem that requires a comprehensive, mixed methods approach to understand both the "what" and "why." The direct involvement of health services, local researchers, a high-level key stakeholder group, and a comprehensive knowledge exchange strategy will help generate solutions and maximize the impact of the results on policy and practice.

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Authors' Contributions

JW conceived the study, contributed to design, and drafted the paper. JSH contributed to the conceptualization and design of the study, and assisted with drafting the manuscript. LB and TD contributed to the design of the study, particularly the qualitative component, and provided comments on the manuscript. MJ, SG, DL, YZ, and DR contributed to the design of the study, particularly the quantitative component, and provided comments on the manuscript. TC contributed to the design of the study and provided comments on the manuscript. LMG contributed to the drafting of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AMSANT: Aboriginal Medical Services Alliance of the Northern Territory
DIDO: drive-in/drive-out
FIFO: fly-in/fly-out
NT: Northern Territory

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Protocol

Existing Models of Maternal Death Surveillance Systems: Protocol for a Scoping Review

Saloua Abouchadi[1,2,3], MD, MPH; ASM Shahabuddin[2], MPH, AMPHM; Wei Hong Zhang[3], MD, MPH, PhD; Tabassum Firoz[4], MD, MSc, FRCPC; Yvon Englert[5], PhD, MD; Chakib Nejjari[1], PhD, MD; Vincent De Brouwere[2], MD, MPH, PhD

[1]Ecole Nationale de Santé Publique, Rabat, Morocco

[2]Institute of Tropical Medicine, Maternal and Reproductive Health Unit, Antwerp, Belgium

[3]School of Public Health, Université Libre de Bruxelles, Brussels, Belgium

[4]The Warren Alpert Medical School, Department of Medicine, Brown University, Providence, RI, United States

[5]Hôpital Erasme, Laboratoire de Recherche en Reproduction Humaine, Université Libre de Bruxelles, Brussels, Belgium

Corresponding Author:
Saloua Abouchadi, MD, MPH
Ecole Nationale de Santé Publique
Madinat Al Irfane
Rue Lamfadel Cherkaoui
Rabat,
Morocco
Phone: 212 537683162
Fax: 212 537683161
Email: s.abouchadi@yahoo.fr

Abstract

Background: Maternal mortality measurement remains a critical challenge, particularly in low and middle income countries (LMICs) where little or no data are available and maternal mortality and morbidity are often the highest in the world. Despite the progress made in data collection, underreporting and translating the results into action are two major challenges that maternal death surveillance systems (MDSSs) face in LMICs.

Objective: This paper presents a protocol for a scoping review aimed at synthesizing the existing models of MDSSs and factors that influence their completeness and usefulness.

Methods: The methodology for scoping reviews from the Joanna Briggs Institute was used as a guide for developing this protocol. A comprehensive literature search will be conducted across relevant electronic databases. We will include all articles that describe MDSSs or assess their completeness or usefulness. At least two reviewers will independently screen all articles, and discrepancies will be resolved through discussion. The same process will be used to extract data from studies fulfilling the eligibility criteria. Data analysis will involve quantitative and qualitative methods.

Results: Currently, the abstracts screening is under way and the first results are expected to be publicly available by mid-2017. The synthesis of the reviewed materials will be presented in tabular form completed by a narrative description. The results will be classified in main conceptual categories that will be obtained during the results extraction.

Conclusions: We anticipate that the results will provide a broad overview of MDSSs and describe factors related to their completeness and usefulness. The results will allow us to identify research gaps concerning the barriers and facilitating factors facing MDSSs. Results will be disseminated through publication in a peer-reviewed journal and conferences as well as domestic and international agencies in charge of implementing MDSS.

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KEYWORDS

maternal mortality; surveillance systems; completeness; usefulness; scoping review; protocol

Introduction

In September 2011, the World Health Organization Commission on Information and Accountability for Women's and Children's Health announced 10 recommendations which focused on strengthening country and global accountability [1]. To achieve better results countries need to improve their health information systems, develop civil registration and vital statistics systems, implement innovative approaches to count and review maternal deaths, and monitor progress [2].

Maternal mortality measurement remains a challenge especially in low and middle income countries (LMICs) [2]. Only five among those 139 countries have functional civil registration and vital statistics systems, which are the preferred source of data for counting deaths and defining their causes [3]. In the absence of such systems, censuses, household surveys, and special studies are currently used to collect retrospective data on maternal mortality. Consequently, the maternal mortality ratio is not often accurate. In addition, the uncertainty of statistics derived using these methods tends to be very large, and data are not generally available at the subnational level. Such limits make data inappropriate for proactive response, planning, or resource allocation [4].

On the path of ending preventable maternal mortality, the Maternal Death Surveillance and Response approach was launched in 2012 by the World Health Organization and partners after the failure of many LMICs to implement the approach Beyond the Numbers, which had been launched in 2004 [5].

Despite the progress made in collecting data, many questions remain unanswered such as how to better implement the various maternal death surveillance systems (MDSSs). The underreporting and poor use of results of MDSSs for action are two major additional challenges in LMICs. At present, there are no systematic or scoping reviews published that address the question about MDSS performance and the use of their results for decision making.

Considering the importance of the issue, we propose a protocol for a scoping review covering the existing models of MDSSs with the objective of better understanding the factors that influence the completeness and usefulness of MDSSs.

We propose to map and synthesize the available literature to identify and describe current models of MDSSs and explore factors affecting their completeness and usefulness.

Methods

Protocol Design

We plan to undertake a scoping review, an approach which has been growing in popularity for the last few years as a useful tool that can provide a broad overview of a topic [6]. The scoping review methodology was chosen for this particular study because there is little literature in this field. In addition, a scoping review will facilitate the identification of knowledge gaps and opportunities that exist pertaining to an emerging subject of interest [6].

Our protocol was developed by using the York methodological framework proposed by Arksey and O'Malley [7], detailed by Levac et al [8], and further refined by the Joanna Briggs Institute (JBI) [9,10]. This methodology outlines a 5-stage approach: (1) identify the research question; (2) identify relevant studies; (3) select studies; (4) chart the data; and (5) collate, summarize, and report the results, with an optional consultation exercise. The first author of this paper developed the draft protocol which was revised upon receiving feedback from all coauthors. Consideration will be given to revising the methodology as needed throughout the review process.

Inclusion Criteria

The inclusion criteria consist of three parts as identified by the JBI: participants, concept, and context [9].

Participants

This scoping review will include women of reproductive age deceased during pregnancy, childbirth, or puerperium until one year after termination of pregnancy. *Women of reproductive age* refers in general to all women aged 15 to 49 years [11]. According to the International Classification of Diseases, Tenth Revision, a maternal death is a death of a woman while pregnant or within 42 days of termination of pregnancy [12]. These deaths are subdivided into two groups: (1) maternal death due to direct cause, indirect cause, or unknown/unspecified cause and (2) other deaths during pregnancy, childbirth, and puerperium due to coincidental causes [12]. A late maternal death is the death of a woman from direct or indirect causes more than 42 days but less than one year after termination of pregnancy [12].

Concept: Intervention and Outcomes

We will include all the reporting systems related to the maternal mortality surveillance that detect and/or monitor maternal deaths, help understand the underlying factors contributing to the deaths, and stimulate and guide actions to prevent future deaths. MDSSs include review systems such as audits, maternal death reviews, and confidential enquiries. For describing the MDSS implementation process and challenges, we will consider studies performed both at national and subnational level.

We will focus on two specific attributes of a surveillance system: external completeness and usefulness [13]. External completeness applies to the reporting process and relates to whether the data available to the surveillance system reflect the true number of cases affected by a given condition. The numbers of maternal deaths reported will be compared to the estimated number when the information is available. Usefulness implies that surveillance results are used for public health action [14,15]. This attribute will be considered according to the objectives of the MDSS. We will describe the MDSS effect on decision making at national and subnational level and identify actions that have been taken as a result of MDSS outputs.

Context

We will not limit the context of our scoping review to a particular setting or country.

Types of Studies

For the purpose of our scoping review, we will include both quantitative and qualitative research studies. Other publications such as opinion papers, reports, and government guidance will be also taken into consideration.

Information Sources and Search Strategy

The search strategy will include published and gray literature. As recommended by the JBI, a three-step search strategy will be utilized [9]. The first step is an initial limited search of two online databases which are relevant to our topic: PubMed and Web of Science. Medical subject headings terms from PubMed have been used at the start to determine the words used to search in PubMed. The search strategy can be found in Multimedia Appendix 1. We have combined search terms focused on maternal mortality, surveillance systems, and attributes of surveillance systems (completeness and/or usefulness).

This initial search will be then followed by an analysis of the text words contained in the title and abstract of retrieved papers and of the index terms used to describe the articles. A second search using all the identified keywords and the index terms specific to each database will be undertaken across all accessible databases and websites. The search will then be performed using the following additional electronic databases: POPLINE, Cochrane Effective Practice and Organisation of Care Group, and Public Health Interventions Cost Effectiveness Database. We will conduct further searches in the following sources of gray literature: WHO Library, *Banque de données en santé publique*, African Journals OnLine, Maternal Death Surveillance and Response Action Network, INDEPTH Network, and Google Scholar.

The search strategy will be modified as necessary to accommodate database differences. Additional keywords, sources, and potentially useful search terms may be discovered and incorporated into the search strategy. Finally, the reference lists of all identified reports and articles will be searched for additional studies. Search results will be imported into reference management software (Reference Manager, Thomson Reuters Corp), and duplicate citations will be removed. No restrictions of language or date limit will be applied for our search strategy.

Study Selection Process

Two reviewers (SA and ASh) will independently screen titles and abstracts to check for relevance to the review. The reviewers will exchange at the middle and the end of screening process to discuss their selection of articles and to refine the search strategy, if needed. Additional keywords, sources, and potentially useful search terms may be discovered and incorporated into the search strategy.

Using the same process, the reviewers will subsequently screen the full text and apply the inclusion criteria for potentially relevant articles that were not excluded by looking at the title or the abstract. All discrepancies between reviewers will be resolved by a single arbitrator (VDB).

Extraction of the Results

A draft tool has been developed according to the JBI results extraction instrument to record the information from the articles [9]. The extracted data will include study characteristics (eg, study population, setting, study time period, data sources, study size, study design). For describing the MDSS, extracted data will be based on key elements for the description of a surveillance system [13,14,16] which include national legislation, main stakeholders, surveillance objectives, type of surveillance, geographic coverage, time of data collection, data sources/data providers, reporting process/data flow, case definition, type of data collected, data management, resources needed, data analysis and dissemination of results, participant privacy/ data confidentiality/system security, and eventually healthcare system constraints. To evaluate the MDSS, two attributes will be considered: completeness and usefulness (described in Multimedia Appendix 2). The two reviewers will independently extract data from three articles to ensure interreader reproducibility. The form will be then sent to all team members for final comments and suggestions before implementing it for screening articles. Data extraction will be an iterative process; the charting table may be updated if other additional unforeseen data are identified.

Results

Currently, the abstracts screening is under way and the first results are expected to be submitted for publication by mid-2017. The review decision process and its results will be detailed using the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 1) [17]. Data analysis will involve quantitative analysis (eg, frequency analysis) of existing models of MDSSs.

The synthesis will also include qualitative analysis using a thematic analysis [18] of the factors that influence completeness and usefulness. Categories will be generated using the main themes and text will be coded manually according to each category. Broad categories of themes can be grouped as follows [13]:

1. Factors related to the health care system (eg, lack of personnel)

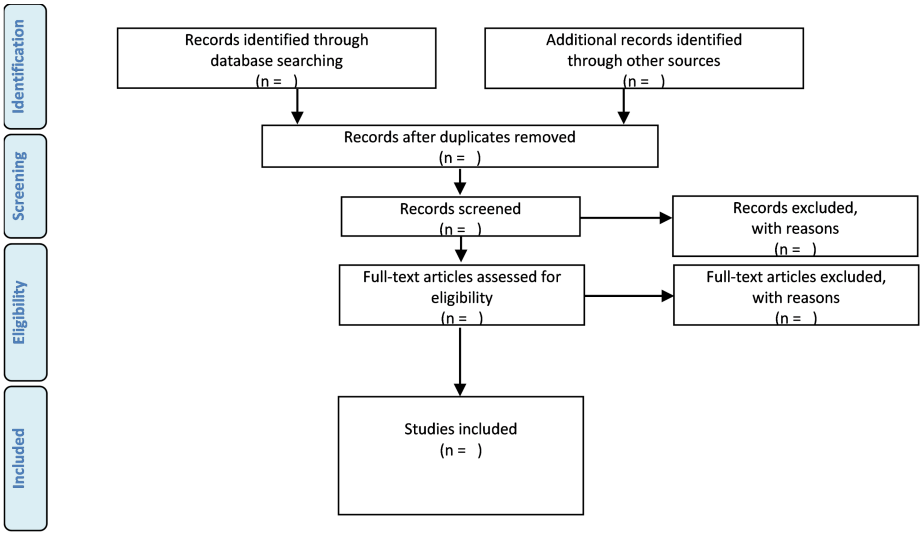
2. Factors related to the data providers (eg, lack of interest, training, adherence, confidentiality issues/concerns of the data providers, proper supervision, knowledge on the objectives, usefulness of the surveillance system)

3. Factors related to the structure and functionality of the system (eg, notification process, reporting form, electronic data entry system, surveillance protocol, resources, visibility of the surveillance system and its data)

4. Factors related to external circumstances or constraints (eg, government ownership and commitment, liability and punitive measures).

Additional steps include annotating emerging themes and patterns and readjusting the categories and relationships between them, testing emergent propositions through systematic searches of coded text, and searching for alternative explanations through systematic searches of uncoded text.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the scoping review process [17].



The synthesis of the reviewed materials will be presented in a tabular form complemented by a narrative format. The tables will show the results as in the chart for results extraction in Multimedia Appendix 2. The narrative summary, made by categories, will describe how the results relate to the review objectives. The results will be classified in main conceptual categories that will be obtained during the results extraction.

Specific factors that influence completeness and usefulness will be grouped by domain, and the final list of factors will be determined and agreed on by all the authors.

Discussion

This scoping review will provide a broad overview and comparison of different MDSSs. We will describe factors related to their completeness and usefulness. Currently, 103 LMICs are in the process of implementing MDSSs among which 46% apparently are functioning [5]. However, informal discussions with several people in charge of implementing MDSSs show that the systems are not functioning well, and no paper showing any type of empirical result has been published so far. Furthermore, the barriers to completeness and translating the recommendations generated by MDSSs into action have yet to be examined in depth.

By including all MDSSs, we will capture findings from those well-resourced settings. The lessons learned from successful experiences such as the implementation of Confidential Enquiry into Maternal Deaths (United Kingdom) and in the surveillance of morbidity and near miss case reviews may contribute to further improving and enhancing MDSSs in LMICs.

Potential gaps in the field will be identified and the results will inform future research directions on barriers and facilitating factors of MDSSs; hence, we expect our findings will be useful for the country teams and United Nations agencies in charge of implementing of MDSSs and interesting to networks and researchers who are working on this topic. The results will also be published in a peer-reviewed journal.

We will use rigorous and transparent methodology by following the JBI guidelines for scoping reviews. To ensure a broad literature search, the search strategy includes five electronic bibliographic databases, reference lists of items, and the most important sources of gray literature. However, there is a possibility of missing potentially relevant articles due to noninclusion of other sources.

The data-charting form will be pretested by the reviewers and revised as necessary before implementation. Each citation and article will be reviewed by two independent reviewers. Our use of a bibliographic manager will ensure that all citations and articles will be properly accounted for in the process.

Finally, it may not be possible to develop recommendations for practice from the results of this scoping review as no assessment of methodological quality or rating of level of evidence will be carried out.

Acknowledgments

We thank Mr Mohamed El Halfaoui for his careful editing.

Authors' Contributions

SA developed the initial protocol and search strategy followed by appraisal from VDB and inputs from all other authors. SA and ASh will conduct the screening and apply the inclusion/exclusion criteria with third-party arbitration by VDB when necessary. Included articles will be subjected to data extraction and synthesis by SA and ASh with verification by VDB. All authors have approved the final version of this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Search term strategy in PubMed (July 2016).

[PDF File (Adobe PDF File), 35KB - resprot_v5i4e197_app1.pdf]

Multimedia Appendix 2

Draft of the data-charting form.

[PDF File (Adobe PDF File), 25KB - resprot_v5i4e197_app2.pdf]

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Abbreviations

JBI: Joanna Briggs Institute
LMICs: Low and middle income countries
MDSS: Maternal Death Surveillance System
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Enhancing Self-Efficacy for Help-Seeking Among Transition-Aged Youth in Postsecondary Settings With Mental Health and/or Substance Use Concerns, Using Crowd-Sourced Online and Mobile Technologies: The Thought Spot Protocol

David Wiljer[1,2,3], PhD; Alexxa Abi-Jaoude[2], MPH; Andrew Johnson[2], BA; Genevieve Ferguson[2], MEd; Marcos Sanches[2,3], MSc; Andrea Levinson[2,3], MD, MSc; Janine Robb[3], RN, MSc; Olivia Heffernan[2], BA; Tyson Herzog[2], BA; Gloria Chaim[2,3], MSW; Kristin Cleverley[2,3], RN, PhD; Gunther Eysenbach[3,4], MD, MPH; Joanna Henderson[2,3], PhD; Jeffrey S Hoch[3,5,6], MA, PhD; Elisa Hollenberg[2], MSW; Huan Jiang[3,7], PhD; Wanrudee Isaranuwatchai[3,5], PhD; Marcus Law[3,8], MD, MBA, MEd; Sarah Sharpe[9], MSc; Tim Tripp[2], MLIS; Aristotle Voineskos[2,3], MD, PhD

[1]University Health Network, Toronto, ON, Canada

[2]Centre for Mental Health and Addiction, Toronto, ON, Canada

[3]University of Toronto, Toronto, ON, Canada

[4]Centre for Global eHealth Innovation, Toronto, ON, Canada

[5]Centre for Excellence in Economic Analysis Research (CLEAR), St. Michael's Hospital, Toronto, ON, Canada

[6]Department of Public Health Sciences, University of California, Davis, CA, United States

[7]Cancer Care Ontario, Toronto, ON, Canada

[8]Michael Garron Hospital, Toronto, ON, Canada

[9]QoC Health, Toronto, ON, Canada

Corresponding Author:
David Wiljer, PhD
University Health Network
190 Elizabeth Street
R. Fraser Elliott Building RFE 3S-411
Toronto, ON M5G 2C4
Canada
Phone: 416-340-6322
Email: david.wiljer@uhn.ca

Abstract

Background: Seventy percent of lifetime cases of mental illness emerge prior to age 24. While early detection and intervention can address approximately 70% of child and youth cases of mental health concerns, the majority of youth with mental health concerns do not receive the services they need.

Objective: The objective of this paper is to describe the protocol for optimizing and evaluating Thought Spot, a Web- and mobile-based platform cocreated with end users that is designed to improve the ability of students to access mental health and substance use services.

Methods: This project will be conducted in 2 distinct phases, which will aim to (1) optimize the existing Thought Spot electronic health/mobile health intervention through youth engagement, and (2) evaluate the impact of Thought Spot on self-efficacy for mental health help-seeking and health literacy among university and college students. Phase 1 will utilize participatory action research and participatory design research to cocreate and coproduce solutions with members of our target audience. Phase 2 will consist of a randomized controlled trial to test the hypothesis that the Thought Spot intervention will show improvements in intentions for, and self-efficacy in, help-seeking for mental health concerns.

Results: We anticipate that enhancements will include (1) user analytics and feedback mechanisms, (2) peer mentorship and/or coaching functionality, (3) crowd-sourcing and data hygiene, and (4) integration of evidence-based consumer health and research information.

Conclusions: This protocol outlines the important next steps in understanding the impact of the Thought Spot platform on the behavior of postsecondary, transition-aged youth students when they seek information and services related to mental health and substance use.

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KEYWORDS

mental health; substance use; help-seeking; participatory action research; eHealth; mobile applications; crowd-sourcing; transition-aged youth

Introduction

The onset of mental illness across the lifespan is highest among children and youth, with 70% of cases emerging before age 24 [1]. Despite the known benefits of early identification and treatment, evidence shows that at-risk members of this age group have great difficulty accessing and receiving the kinds of mental health services they need [2-6]. Untreated mental health concerns in emerging adulthood increase the risk of enduring mental illness, and are also associated with greater risk of dropping out of school, unemployment, youth justice involvement, bullying, traumatic release from care, and self-medication with alcohol and other drugs [7,8]. Most alarmingly, suicide is the second leading cause of death among Canadian youth, and is attributed to 20% of all deaths among young adults aged 15 to 24 [7]. Studies have reported that 10% of students have considered suicide at least once during their time at university or college [9-11].

The current social and medical system makes the act of help-seeking a relatively unlikely choice for many transition-aged youth (for the purposes of this study we define transition-aged youth as those aged 16-29 years) [3,4,12,13]. Youth in Ontario experience barriers in accessing appropriate services, information, and advice because the system is "fragmented, spread across several ministries, and offered in a variety of care settings" [14]. The barriers associated with help-seeking in young adults vary, and are highest when there is lower access to health services, less support from family and friends, and a lower sense of self-worth [15]. The stigma attached to mental illness, as well as embarrassment and fear of confidentiality breaches, are other major barriers associated with help-seeking among young adults [6,11,16-20].

Mental health literacy, or "knowledge and beliefs about mental disorders which aid their recognition, management, or prevention" [21], is generally poor among transition-aged youth, with many unable to identify the signs of a mental health problem or determine when professional help is needed [11,22,23]. When youth do seek mental health information, they do so through a *needs-driven approach*, typically searching for information only when there is a specific purpose [24]. Research shows that youth prefer informal avenues of information and support such as friends, family, or significant adults, rather than more formal sources such as psychologists, psychiatrists, or family doctors [6,17,20,25]. This informal help-seeking behavior can, however, result in risks; these sources are not always equipped with sufficient knowledge or skills to provide mental health support or information.

Enabling youth to seek and access mental health services is vital to the sustainability of a health care system [25]. With more than 90% of youth using the Internet [26-28], Web-based electronic health (eHealth) and mobile-based health (mHealth) interventions have been identified as promising tools for reaching this age group [11,27,29-32], potentially bridging the gap for hard-to-reach populations such as young males who have been reluctant to seek services [22,33,34]. The online environment provides transition-aged youth with the "opportunity to interact with, share, view, and access information through a number of convenient formats" [35,36]. Websites that are easy to navigate and visually engaging are preferred by many young people [24], while interactive elements, such as coaching and crowd-sourcing, are effective and well-received [25]. These less-formal or less-specialized online or mobile mental health interventions and resources have been shown to be effective avenues to engage transition-aged youth [25,30,31,37-41] and enhance "their capacity to correctly recognize, identify, and receive help for psychological disorders in a manner that is both accessible and nonthreatening" [15]. Such interventions can cross geographic barriers, reduce wait times, provide anonymity, and actively engage youth in facilitating mental well-being [13,41-43].

Youth-driven projects have been shown to increase participation in mental health care, better address youth concerns, and produce more relevant outcomes [44-47]. However, there are currently few solutions (cocreated with youth and health professionals that address existing needs and gaps) that are able to integrate evidence and experience. This project, driven and cocreated by transition-aged youth in postsecondary settings, will enhance and test an open-source eHealth and mHealth intervention (Thought Spot) that aims to involve their peers and enable them to identify and overcome barriers to obtaining help for mental health-related issues. Thought Spot is designed to improve attitudes and enhance self-efficacy for help-seeking for mental health support and services, and thereby increase the utilization of appropriate mental health and wellness services.

The objective of this paper is to describe the protocol for optimizing and assessing Thought Spot, a Web- and mobile-based platform cocreated with end users, that is designed to improve the ability of transition-aged youth in postsecondary settings to access mental health services.

Methods

Theoretical Basis and Protocol Implementation

Drawing on social-cognitive theory as a guiding conceptual construct, this study will investigate the impact of

crowd-sourced, socially constructed, and evidence-informed online and mobile technologies on *self-efficacy* to access and utilize mental health and wellness services. Social-cognitive theory recognizes individuals as being self-organizing, proactive and self-reflective [48-50] and conceptualizes self-development, adaptation, and change as being embedded within a broad network of socio-structural influences and psychological factors [28,51-53]. This study will draw from a theory of help-seeking that proposes a 4-stage process: awareness, expression, availability and willingness [22]. The process begins with an awareness of symptoms and the appraisal of having a problem that may require intervention. This awareness must then be articulated or expressed by the help-seeker in plain language that can be understood by others, and sources of help must be available and accessible [22]. Finally, the help-seeker must be willing and able to access support and disclose their concerns [22].

Thought Spot Developmental Process: Cocreation

The Thought Spot platform was originally developed through the Mental Health Innovation Fund, a program established by the Ontario Ministry of Training, Colleges and Universities. While the original collaboration included the University of Toronto's Faculty of Medicine (the lead organization), the Centre for Addiction and Mental Health (CAMH), Ryerson University, Ontario College of Art and Design (OCAD) University, and ConnexOntario, the project was always envisioned as a student-led innovation project focused on improving postsecondary students' access to, and navigation within, mental health and addiction services. To achieve this goal, the idea of a digital map of *all* addiction and mental health services, starting with the Greater Toronto Area (GTA; Ontario, Canada), was proposed. This map would be developed in partnership with students, educators, and health service providers. It was envisioned that the map would respond effectively to the challenges presented by an often-fragmented system of mental health services available to students (eg, on-campus services and community-based services are funded separately, making navigation between services challenging). Creating an online mapping platform was seen as a way to increase access and ease of navigation, and to address other barriers such as stigma and a lack of mental health literacy. It was proposed that the scope of the map would be informed by a *social determinants of health* perspective, and its dissemination would be through Internet and mobile devices. The aim of the strategy was to support direct help-seeking intentions, attitudes, and behaviors by increasing knowledge of appropriate services for postsecondary students, and minimizing the need for intermediaries (ie, friends, family, family physician).

Project leaders at CAMH identified an open-source software (Ushahidi) that could both display mapped information and allow for crowd-sourcing, a strategy aimed at supporting the sustainability of the Thought Spot platform and allowing for the participation of youth in its development. Second, the project team initially *seeded* the map with data supplied by collaborating organization Kids Help Phone and project partner ConnexOntario. From that starting point, the team used a participatory model of engagement to work with 65 university and college students to develop the platform. The students were recruited from institutions across the GTA to work on all aspects of the project. Students were organized into 2 teams, focusing respectively on production and development, to lead the development of the digital intervention, as well as several working groups that focused on specific aspects of the project, including design, promotion, and knowledge translation. The participatory approach defined specific roles for student leadership and student decision-making. A project steering committee balanced student and organizational input, enabling students to make a wide variety of key decisions on issues such as the name of the project, the logo, project management, and product design. This work included the organization of the original *seeded* mental health resource data with a taxonomy, which became the basis for categories through which users would enter the map and/or filter the data. The categories include health and wellness, sex and relationships, legal and financial, work and school, spirituality and well-being, and friends and family. Through this work the students developed Thought Spot as a platform that aimed to:

1. Mobilize other students to share their knowledge about services.

2. Discover wellness options in their area.

3. Build peer networks.

4. Read reviews and comments from peers about services.

5. Add their own *thought spots* or services.

In order to create a mobile version of Thought Spot, the project hosted Hackathought, an open digital hackathon event in Toronto in November 2014. This work led to the development of a native mobile app (iOS and Android), as well as a *responsive* design of the Thought Spot website, which allows for optimal viewing across a range of devices (eg, desktop computer monitors, tablets, and mobile devices). These platforms were all completed in March 2015.

Thought Spot Functionalities

User-generated information has been entered in the Thought Spot platform for over 1000 mental health and wellness *spots* (eg, campus health centers, mental health and substance use services, peer support, crisis information, public parks, libraries, yoga studios). The platform has been further developed through a series of workshops in which teams of students verified the *spots* and customized them for peers seeking services, adding commentary and information that students would want to know in language that speaks directly to them.

The main functionality of the Thought Spot platform allows users to geo-locate themselves and search for *spots* through an interactive map (Figure 1). *Spots* can be searched according to cost, hours, catchment, and other parameters such as the availability of specific lesbian, gay, bisexual, transgender, transsexual, two-spirit, intersex, questioning, queer, and Aboriginal services (Figure 2). Once an appropriate spot has been located, users can access more specific information about the service (such as accessibility, languages offered, and wait list information), allowing them to decide whether the service is right for them (Figure 3).

Additional functionality includes crowd-sourcing, an increasingly important data-gathering technique that allows users of a content-rich resource to submit revised and/or new information that, after vetting, is fed back into the resource [54]. Thus, Thought Spot users can add additional *spots*, allowing them to grow the platform and shape it according to their needs and interests (Figure 4). This built-in crowd-sourcing functionality also includes the ability for users to give a simple *thumbs up* or *thumbs down* rating to individual services, and to make comments about particular services (Figure 5). Finally, building on an idea that came from the winning entry from the *Hackathought* event, users can find *wellness walks* built into the map (Figure 6). These routes are intended to reinforce the overall wellness focus of Thought Spot by encouraging students to take healthy breaks from their studies and other activities, and to explore the city in which they are studying, and become more connected with its communities. A functional Web version of Thought Spot [55] and a mobile app (for iOS and Android) are readily available online via free download. These platforms have gone through a series of usability testing sessions with student participants, using the state-of-the-art facilities and expertise at the University Health Network (UHN) Centre for Global eHealth Innovation. The current state of the platform has been assessed at Technology Readiness Level 6 [56].

Figure 1. Users can use the Category section to locate specific types of spots in their surroundings.

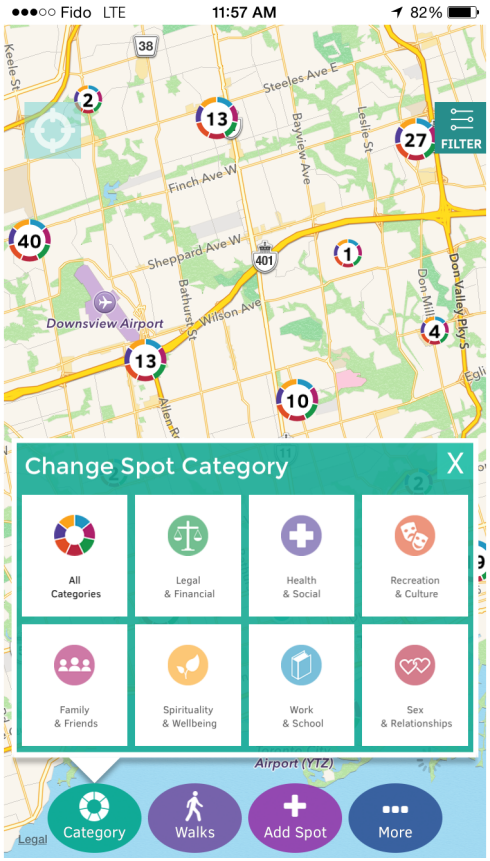


Figure 2. To further narrow down search results, users can apply filters to their searches. Only locations that fit within the filters will be displayed on the map.

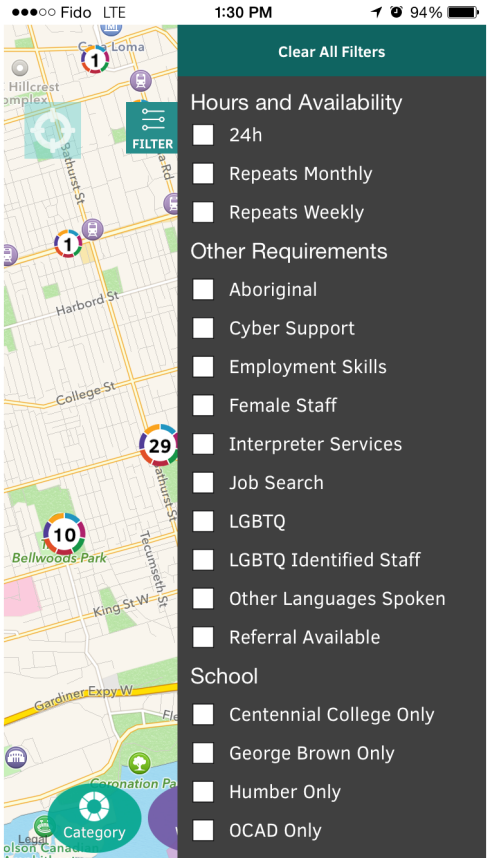


Figure 3. When users select a certain spot on the map, they will be provided with the spot's details. Users can either get general information about the location, or see reviews left by other users.

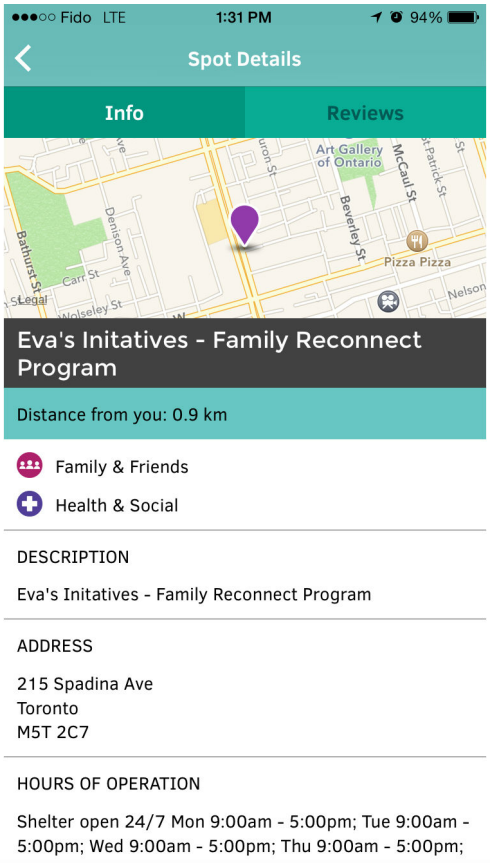


Figure 4. Users can contribute to the Thought Spot community by adding their own mental health and/or well-being spots. These spots are reviewed and assessed by members of the Thought Spot team before becoming available to the public.

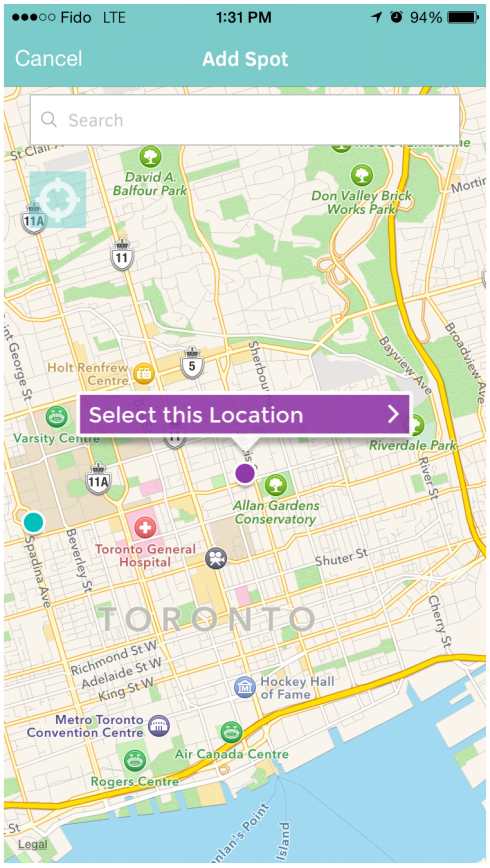


Figure 5. Users can post reviews about spots. These reviews will be available to others who may be interested in accessing that resource.

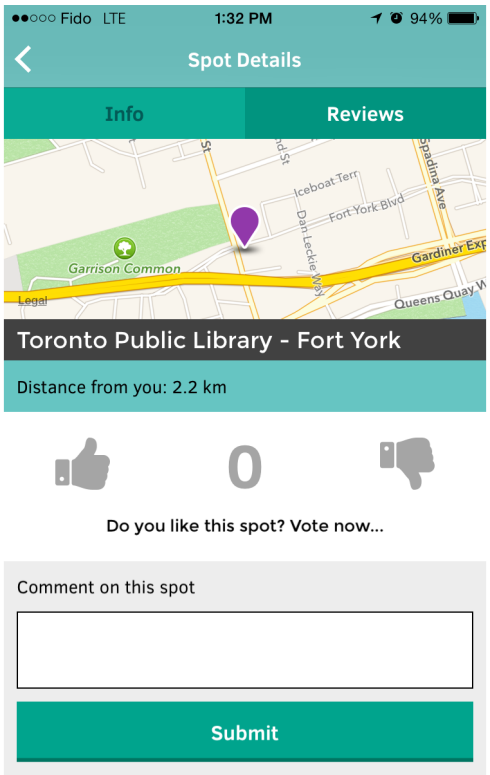
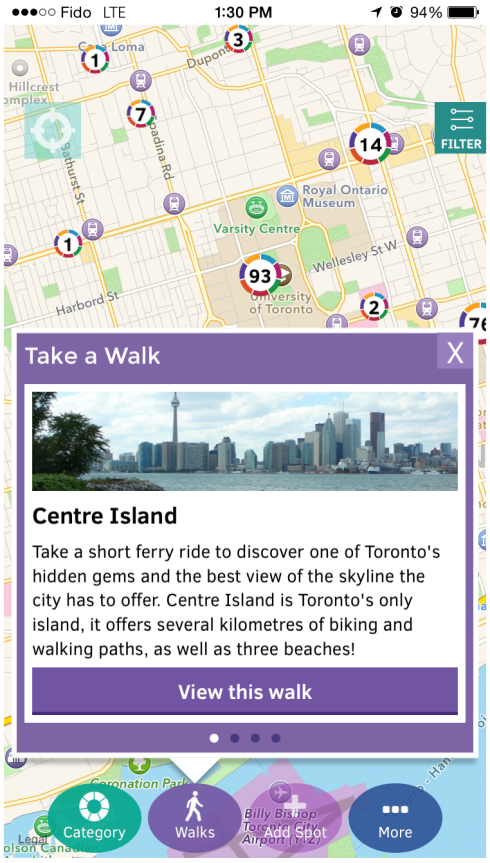


Figure 6. There are predesigned routes designed for users to take walks around their neighbourhood to increase their awareness of the resources available.



Optimization Process and Research Methodology

The current study to optimize the Thought Spot platform will be conducted in two distinct phases, which will aim to (1) optimize the Thought Spot Web and mHealth platform through youth engagement, and (2) evaluate the impact of Thought Spot on self-efficacy for mental health help-seeking and health literacy among university and college students through a randomized controlled trial (RCT).

Participants will be recruited across 3 participating postsecondary institutions in the GTA: University of Toronto, Ryerson University, and George Brown College, which have respective enrolments of 84,556, 38,000, and 31,187 students [57-59]. Recruitment strategies will include invitation letters on public university bulletin boards, health and technology academic department listservs, student groups, Residence Life staff, and social media (Twitter, Facebook, and Instagram). All participants will be required to sign a consent form prior to being recruited into either phase of the study. Once participants have provided informed consent, they will fill out a nonidentifiable demographics form. This demographic information will be used for comparison purposes, reporting findings, and preparing formal evaluation reports.

To take part in Phase 1 of the project, participants must be transition-aged youth (16-29 years) [60] of any gender who are currently enrolled in part-time or full-time studies at any Canadian postsecondary institution. To take part in Phase 2, participants must be transition-aged youth (16-29 years) [60] of any gender who are currently enrolled in part-time or full-time studies of one of the 3 participating postsecondary institutions. All participants must have functional competency in English. Phase 2 participants must also currently be seeking mental health support or have a self-identified need for mental health support, and must have access to digital devices compatible with the Thought Spot digital platform. Participants who self-identify as having been hospitalized within the last 3 months for a mental health or addictions concern will be excluded from both phases of the study.

Phase 1: Optimization of mHealth Intervention

The Thought Spot platform and its implementation will be optimized using a model of engagement in which transition-aged youth attending colleges and universities colead all aspects of the project [60]. Students will have ownership of process, product, and deliverables. The engagement goal is to create a context in which students draw on their strengths and lived experiences, and in the process increase their health literacy, reduce mental health stigma, and become advocates for good mental health. The research question for Phase 1 is: *How can the Thought Spot intervention be optimized to enhance its current functionality, and increase the potential for its sustainability and adoption among postsecondary students, through youth engagement?*

The goals of Phase 1 are to (1) optimize the Thought Spot platform to more effectively meet the needs of end-users; (2) explore students' motivations and identify personal, behavioral, and environmental influences that will affect their uptake of the

Thought Spot platform; and (3) assess Thought Spot's feasibility, usability, and acceptance by the target population.

Participatory Action Research and Participatory Design Research

Through the use of participatory action research (PAR) principles, students across the GTA will be recruited and engaged to drive the optimization of the Thought Spot platform. PAR focuses on improving health and reducing health inequities by involving the target population via an iterative cycle of reflection, data collection, and action [61,62]. The research is initiated and shaped with people affected by a specific issue, in partnership with academic researchers [61-65]. This PAR strategy will encompass different levels of involvement, from passive participation to self-mobilization. Participation incentives will vary depending upon the individual's role and involvement.

Participatory design research (PDR) will also be employed. PDR is typically conducted by technology companies to allow for the direct involvement of the target audience in codesigning the technologies that they use. This design model is critical to gaining credibility among transition-aged youth [66]. This study will utilize various strategies, identified in the framework for *Participatory Design of Evidence-based Online Youth Mental Health Promotion, Prevention, Early Intervention, and Treatment* [67], to engage with students to codesign and inform various aspects of the project. These strategies will include codesign workshops (prototyping), usability testing, and focus groups, as described in the framework [67].

Research Process

Using PAR and PDR techniques, students will cocreate relevant engagement activities with the research team to obtain information from the target audiences, in order to optimize the Thought Spot platform and inform the second phase of this project. Students will be provided with relevant training on research methodology so that they can fully participate throughout the research process. Nonstudent facilitators and researchers will also be involved in this youth engagement process, and will be present during the engagement activities.

Students will be involved in the following activities in Phase 1 of the project:

1. Project oversight and input as a member of the Thought Spot Student Group (TSSG) and/or various subworking groups.

2. Engagement activities to assess the feasibility, usability, and acceptability of the intervention, and to inform the optimization of Thought Spot and potential outcomes.

3. Crowd-sourcing workshops (online and in person) to update and verify the resources on the Thought Spot map.

Students will also cocreate and provide feedback on various aspects of Phase 2 of the project, including outcome measures, recruitment and engagement strategies, study administration, and knowledge translation and dissemination strategies.

Engagement activities will be developed and facilitated with consenting members of the TSSG to explore our research questions and gain input from additional students. These engagement activities may include focus groups, interviews, and design workshops. A sample question guide has been developed by the research team for the engagement activities, but it will be modified (with the students) for each engagement activity prior to implementation (Table 1). We will also assess Thought Spot's feasibility, usability, and acceptance by the target population, using the USE (usefulness, satisfaction, and ease-of-use) Questionnaire [68].

We may also use the various scales (eg, help-seeking scale, mental health self-efficacy scale) intended to be implemented in the RCT phase to inform questions asked during engagement activities, and to gather reflections from students about outcomes.

Table 1. Sample question guide developed by the research team for engagement activities.

Parameter	Question
Help-Seeking	How is accessing mental health services, or asking for mental health or substance use support, perceived by your friends?
	Have you ever searched for mental health, substance use, or wellness services for yourself or for someone else? What was your experience looking for this information?
Motivation/Uptake	What impact do you think Thought Spot could have on how students look for help?
	What are some barriers or challenges that might prevent you from using Thought Spot?
Optimization and Usability	What would you add or change to the app to make it more likely for you, or other students, to use Thought Spot?
	What changes, or enhancements, do you think will impact how students look for help?
Recruitment	We are planning to host a series of codesign workshops to help us improve Thought Spot. Codesign workshops allow students to work with researchers as partners in the development and refinement of products. What are the best methods to advertise to, or recruit, students for the codesign workshops? Why?

Note-takers will be present during all activities to document the discussions and outcomes. Flip charts and any other documentation will be collected and collated. Audio recorders will be used to record small group discussions. All audio recordings will be transcribed and analyzed.

During Phase 1 of the study, we anticipate that several enhancements will be identified to increase Thought Spot's functionality, interactivity, and crowd-sourcing ability, in preparation for the implementation phase (Phase 2). We will explore the acceptability and feasibility of incorporating coaching or peer mentorship within the platform. The prototype

will also be integrated with evidence-based consumer health literature sourced from Portico, CAMH's online portal, and elsewhere. Working with the *Journal of Medical Internet Research* (JMIR), we will also explore the potential of linking Thought Spot with other evaluated online mental health interventions and mobile apps. Our technology partner, Quality of Care (QoC) Health, will develop the newly optimized version of Thought Spot and provide support for quality assurance and secure infrastructure. The prototype will be enhanced to include more robust user analytics and feedback mechanisms. Several enhancements will be made using QoC Health's technology Engagement Platform (Technology Readiness Level 9) [56].

Ethical Considerations

Student participants will be given training and support through the project to ensure adequate research skills, mental health and addictions knowledge, and support regarding self-care, coping and stigma [69]. We will actively encourage students with lived experiences of mental health concerns and/or substance use to participate through our recruitment efforts. However, participants will not be asked to publicly disclose or discuss their mental health status at any point throughout the engagement activities. We will be engaging vulnerable individuals in this process, and protocols will be put in place to monitor and respond to participants' needs at various stages in the study. Access to appropriate mental health crisis support will be identified for each university or college recruitment site, and information regarding services will be provided to all participants. Key members of the research team will be able to provide emergent clinical input or direction, should the need arise. These members of the research team will also provide direction and training to ensure appropriate, meaningful, and effective engagement with youth, especially vulnerable youth.

Analysis Plan

Data gathered during the various engagement activities will be thematically analyzed by qualified members of the research team and interested students. These data sets will be used to answer the research questions and inform Phase 2 of the project (ie, the RCT). We will use a thematic analysis process [70] to review the collected data, generate codes, develop themes, and present the findings in a final report. Collated notes and transcripts will be provided to students, to verify their accuracy and elicit feedback on the analysis.

A descriptive statistical analysis will be conducted on all sociodemographic responses. Acceptance and feasibility will be analyzed using the USE Questionnaire [68] . Means and standard deviations for each category of the questionnaire will be analyzed. The extent of participants reporting high, medium, or low levels of satisfaction on the USE Questionnaire will also be calculated.

Using the study results, we will identify specific enhancements to the Thought Spot platform. We anticipate enhancements will include (1) user analytics and feedback mechanisms, (2) peer mentorship and/or coaching functionality, (3) crowd-sourcing and data hygiene, and (4) integration of evidence-based consumer health and research information. Modifications will be made to the platform by QoC Health, with oversight provided by the TSSG and the research team. The modified platform will undergo usability testing at the UHN Centre for Global eHealth Innovation.

We will also use gender-based analyses of the data in both phases. Mental illness and substance use disorders develop and present in different ways, and at different rates, for young females and young males. For example, young females aged 15-24 years have higher rates of depression than their male counterparts (9% vs 5.3%); however, young males are more likely to suffer from substance use disorders than young females (4.7% vs 1.7%) [71]. Data regarding participants' gender identities and orientations will be voluntarily and confidentially collected at intake. Results will be analyzed to assess similarities and differences between and among gender groups. This comparison will help us to identify unique help-seeking needs and patterns to better tailor the intervention, and ensure it is inclusive of all gender identities and sexual orientations.

Phase 2: Randomized Controlled Trial

An RCT, with 2 arms, will be conducted in Phase 2 to assess the impact of Thought Spot on self-efficacy for mental health help-seeking and health literacy among our target population. Students in the intervention arm will have access to the Thought Spot platform (online and mobile versions), while the control arm will receive usual care (access to campus health services, Web- and print-based information materials). The study will last 6 months. Participants in the intervention arm will receive an in-person tutorial on how to use Thought Spot, as well as access to an online *tour the app* video. Data will be collected from participants through online questionnaires at baseline, 3 months, and 6 months. The full procedure regarding the design of the RCT and administration of the intervention will be codeveloped with students in Phase 1.

The main outcome measure will be changes in help-seeking intentions, measured by the General Help-Seeking Questionnaire (GHSQ), which will be administered at baseline, 3, and 6 months. This scale is composed of 10 items measured in a 7-point Likert scale that ranges from *Extremely Unlikely* to *Extremely Likely*. The items are sources of help (eg, parent, friend, family doctor) and the participants are asked their likelihood of seeking help from each source. The 10 items are usually split into *informal help sources*, *formal help sources*, and *I would not seek help from anyone*.

We will also use the Actual Help-Seeking Questionnaire (AHSQ) and Attitudes Toward Seeking Professional Psychological Help Scale-Short Form (ATSPPH-SF) to measure secondary outcomes: help-seeking behaviors and help-seeking attitudes. These scales are most often used in help-seeking studies [72], and have been used in similar studies and with similar populations, often together [13,22,73,74].

Adequate internal consistency has been reported for the GHSQ in studies of high school students aged 12-19 years (Cronbach alpha range of .70–.90) [75,76] and university students (Cronbach alpha=.67) [77], as well as adequate validity and very good test-retest reliability (r=.86) [75]. The correlation between intentions to seek mental health care for personal-emotional problems and actually seeking care has been

found to be positive and significant for the GHSQ (r s[218])=.17, P<.05). The ATSPPH-SF has demonstrated good internal consistency (Cronbach alpha range of 0.82–0.84), 1-month test-retest reliability of 0.80, and a correlation of 0.87 with the longer ATSPPH scale, among samples of college students [78-80].

In addition to these scales, we also plan to explore self-reported changes in self-stigma using the Self-Stigma of Seeking Help Scale [81] and self-efficacy using the Youth Efficacy/Empowerment Scale - Mental Health [82]. We will also gather data on demographics and general mental health status (Global Appraisal of Individual Needs - Short Screener, Canadian/CAMH version) [83] to examine trends, comparisons, and correlations between the study groups.

Power Analysis

The outcome considered for our power calculation is the average of the GHSQ scale for the formal sources, although similar effect and sample sizes are expected for the informal sources.

To determine the sample size required to test the primary hypothesis that the Thought Spot intervention will cause a greater change in help-seeking intentions than usual care, a series of Monte Carlo simulations were carried out (with 10,000 replications under each test scenario) using SAS System 9.4 for Windows [84]. These simulations assume that the primary hypothesis will be tested using mixed-effect models to account for the longitudinal design, and linear contrasts between time and arm to compare the changes from baseline in both arms. We assume that the test will be 2 tailed and with a critical Cronbach alpha level of 0.05. In order to simulate the data, the means, standard deviations, and within-subject associations are assumed to follow published data that have used similar study designs [73,74]. Based on previous research using the GHSQ [47], a small effect size, equivalent to a Cohen's d of 0.25, was considered (ie, an average change in the GHSQ of 0.41, which is equivalent to a change of 15%), within-subject correlation of 0.6, attrition rate of 40%, and power of 80%. Based on these simulations and specifications, a sample of 236 subjects per arm at baseline is required, which amounts to 472 subjects in total. If 40% attrition is applied to this initial sample, we will be left with 142 subjects per arm (283 in total) after 9 months, at the conclusion of the study.

Statistical Analyses

All analyses will be carried out using SAS System 9.4 for Windows. Statistical tests will be 2 sided, with confidence levels of 0.05. Prior to testing, a series of univariate analyses will be carried out to ensure that model assumptions are met. To address the primary study hypothesis, a mixed-effect model will be used to account for the longitudinal nature of the data, and for attrition. Missing values will be treated with maximum likelihood estimation in SAS PROC MIXED, which uses all available information in the data. Intention-to-treat analysis will be used; all patients will be analyzed as they were originally allocated after randomization. As a sensitivity analysis, the final model will be fitted only with subjects for whom there is complete data. Formal help-seeking score will be the dependent variable, with study groups (intervention and control) and time points as predictors, and relevant sociodemographics collected at baseline as covariates to control for possible confounding. The interaction between study group and time will be included in the model, and linear contrasts will be used to compare the groups, specifically regarding the change from baseline to the final time point. Similar models will be used to address the exploratory hypotheses, which examine different scales and trends, on the effect of the intervention over time. Bonferroni adjustment will be used to control the Type I error rate if multiple comparisons are desired. Generalized estimating equations will be used for the AHSQ, since this scale is binary.

Other Analyses

A sex- and gender-based analysis will be completed when analyzing data for Phases 1 and 2. An economic evaluation of the Thought Spot intervention compared to usual care will also be explored to determine the potential cost-effectiveness and financial implications of sustainable and widespread use of Thought Spot throughout Canadian postsecondary campuses. The evaluation will be conducted from the perspective of future potential Thought Spot funders (eg, other Canadian postsecondary institutions). The primary outcome to be assessed will be the change in helping-seeking intentions among the target population.

Approach to Bias Control

We are using computer-generated random allocation of subjects to the intervention and control arms, by means of the Research Randomizer website [85]. This will be a partially blind study, in that the process of inviting students and collecting data will not be done by the researchers. Missing values will be minimized by sending reminders to participants at least 3 times, and the offer of an honorarium at the end of the fourth data collection point. It is possible that students in the control group may use Thought Spot, so we will ask control subjects at the end of the final survey whether they accessed Though Spot during the study. This approach will allow us to carry out a sensitivity analysis to exclude control subjects who accessed Thought Spot. To mitigate this possibility, we will investigate password protecting the platform or tracking email addresses through a sign-in process during the trial period. We cannot guarantee that control subjects will not interact with intervention subjects, causing some contamination, but given the personal nature of mental health conditions, we believe this risk will not be highly prevalent.

Certain members of the research team were involved in the development of the original Thought Spot platform. To avoid bias or perception of bias, the scientific lead for the project, who was not involved in the development of the original Thought Spot platform, will oversee the RCT.

Hypotheses: Phase 2

We hypothesize that transition-aged youth who receive the intervention will show a greater improvement in intentions for, and self-efficacy in, help-seeking for mental health concerns, compared to those who are allocated to the control group (usual care; resource pamphlet). We also hypothesize that participants in the intervention arm will show greater improvements in health literacy, increased self-efficacy in managing their mental health

concerns, and a reduction in mental health stigma, compared with the control arm.

Results

Phase 1 of this study is currently underway and will continue until August 2017. It is anticipated that this phase of the study will result in the optimization of Thought Spot and provide important information for refining Phase 2 of the study. The results of Phase 1 will be based on principles of cocreation and coproduction, and will be guided by PAR and PDR.

Phase 2 will be carried out between September 2017 and September 2019. Phase 2 will allow us to test our primary hypothesis that transition-aged youth who receive the intervention will show a greater improvement in intentions for, and self-efficacy in, help-seeking for mental health concerns. Results will be available following the conclusion of each phase.

Discussion

Research indicates that eHealth and mHealth interventions for youth mental health should provide information in 3 primary areas: positive mental health or mental wellness; mental illness (eg, myths, symptoms); and help-seeking strategies and methods for accessing mental health services [24]. Transition-aged youth have reported that they want help in a number of areas: determining if there is a mental health problem, and finding support or help; being empowered by the provision of health information, without an intermediary [35]; and the ability to connect with peers [24].

Transition-aged youth generally trust online sources for health advice [86], and university students are likely to first seek help online [28]. At the time of one study, almost one-third (31%) of teenagers (ages 12-17) and 72% of young adults (ages 18-29) were found to seek health information online, including mental health information on issues such as drug use and depression [87]. The ongoing development of our Thought Spot platform, in a way that is cocreated and crowd-sourced, will inform and contextualize the design and methods for the target population, and may influence the efficacy of the intervention.

Transition-aged youth living with a mental illness are more likely than those not living with a mental illness to report engaging in various social networking activities that promote connectivity, anonymity, and making online friends, and activities that enable independent living skills and overcoming social isolation [87,88]. A recent scoping review of youth mental mHealth interventions found that the “flexibility, interactivity, and spontaneous nature” of mHealth interventions encouraged “persistent and continual access to care outside of clinical settings” for transition-aged youth [89]. Emerging evidence suggests that a *coach* (peer or professional) can improve outcomes using computer-based and mHealth interventions without the need for an intermediary such as parents, a physician, or other service providers [35]. To this end, we expect Thought Spot to be a powerful tool to bridge the health literacy gap, and facilitate appropriate help-seeking for this population.

The open-source crowd-sourcing software used in this project allows the Thought Spot map to be scalable to any jurisdiction, and adapted as needed. While the intervention will initially be implemented and evaluated within the GTA, the reach of Thought Spot can be expanded to other interested jurisdictions. Using an open-source crowd-sourced approach allows significant potential to scale this project to a national and international level. Integrating the existing Thought Spot technology into QoC Health will allow for a rapid scale-up with its robust team, user-centered approach to design, and strategic partnerships. The ability to crowd-source within Thought Spot will be open to students and to any service provider that has been mapped (or wants to be mapped), and is key to the currency and sustainability of the resource. Crowd-sourced data within Thought Spot will be monitored continuously through the platform, and will be verified and self-corrected by end-users themselves.

Thought Spot has the potential to be implemented or scaled in provincial, national, and international contexts. This platform provides a significant opportunity to address the information- and help-seeking needs of transition-aged youth by integrating access to consumer health information, pulling from both CAMH’s existing portfolio of public information (including a significant stock of information already developed for youth populations) and an array of other, high-quality, publicly accessible information.

Conclusions

This protocol outlines the important next steps in understanding the role of the Thought Spot platform on the behavior of postsecondary, transition-aged students when seeking information and services related to mental health and addiction issues. Phase 1 of the study will allow for the continuation of cocreating and coproducing a solution that will be further optimized to meet the needs of its target population. The first phase will have the added benefits of potentially raising awareness of mental health issues, and providing an opportunity for students to become involved in ensuring that their peers have timely access to appropriate services. Phase 2 of the study will explore the efficacy of the crowd-sourced platform in improving students’ sense of self-efficacy and their ability to seek appropriate information and services in a timely manner. The results of the RCT study will further contribute to our understanding of how best to support postsecondary, transition-aged students who are seeking information and support related to mental health and addiction concerns.

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Conflicts of Interest

Sarah Sharpe is a cofounder and shareholder in QoC Health.
Gunther Eysenbach is the editor-in-chief and publisher of JMIR.

Multimedia Appendix 1

CIHR reviewers comments, which have been taken into account within the protocol.

[PDF File (Adobe PDF File), 309KB - resprot_v5i4e201_app1.pdf]

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Abbreviations

AHSQ: Actual Help-Seeking Questionnaire
ATSPPH-SF: Attitudes Toward Seeking Professional Psychological Help Scale - Short Form
CAMH: Centre for Addiction and Mental Health
eHealth: electronic health
GHSQ: General Help-Seeking Questionnaire
GTA: Greater Toronto Area
JMIR: Journal of Medical Internet Research
mHealth: mobile health
OCAD: Ontario College of Art and Design
PAR: participatory action research
PDR: participatory design research
QoC: Quality of Care
RCT: randomized controlled trial
TSSG: Thought Spot Student Group
UHN: University Health Network
USE: usefulness, satisfaction, and ease-of-use

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Protocol

Cognitive Behavior Therapy for Anxious and Depressed Youth: Improving Homework Adherence Through Mobile Technology

Pamela Wilansky[1], PhD, CPsych; J Mikael Eklund[2], PhD; Tracy Milner[3], MCISc(OT); David Kreindler[4,5], MD; Amy Cheung[4], MD; Tim Kovacs[6], PhD; Shahin Shooshtari[7], PhD; Arlene Astell[8,9], PhD; Arto Ohinmaa[10], PhD; Joanna Henderson[1], PhD, C.Psych; John Strauss[11], MS, MD, FRCP(C); Rosemary SL Mills[7], PhD

[1]Child, Youth and Family Services, Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada

[2]Department of Electrical, Computer and Software Engineering, University of Ontario Institute of Technology, Oshawa, ON, Canada

[3]BrainFx, Inc., Pickering, ON, Canada

[4]Division of Youth Psychiatry, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

[5]Centre for Mobile Computing in Mental Health, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

[6]Department of Computer Science, Faculty of Engineering, University of Bristol, Bristol, United Kingdom

[7]Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

[8]Ontario Shores Centre for Mental Health Sciences, Whitby, ON, Canada

[9]School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom

[10]School of Public Health, University of Alberta, Edmonton, AB, Canada

[11]Shannon Centennial Informatics Lab, Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada

Corresponding Author:
Pamela Wilansky, PhD, CPsych
Child, Youth and Family Services
Centre for Addiction and Mental Health
University of Toronto
Intergenerational Wellness Building, 6th floor rm 6232
80 Workman Way
Toronto, ON, M6J 1H4
Canada
Phone: 1 416 322 5176
Fax: 1 416 583 1235
Email: pwilansky@frameworkcentre.com

Abstract

Background: Anxiety and mood disorders are the most common mental illnesses, peaking during adolescence and affecting approximately 25% of Canadians aged 14-17 years. If not successfully treated at this age, they often persist into adulthood, exerting a great social and economic toll. Given the long-term impact, finding ways to increase the success and cost-effectiveness of mental health care is a pressing need. Cognitive behavior therapy (CBT) is an evidence-based treatment for mood and anxiety disorders throughout the lifespan. Mental health technologies can be used to make such treatments more successful by delivering them in a format that increases utilization. Young people embrace technologies, and many want to actively manage their mental health. Mobile software apps have the potential to improve youth adherence to CBT and, in turn, improve outcomes of treatment.

Objective: The purpose of this project is to improve homework adherence in CBT for youth anxiety and/or depression. The objectives are to (1) design and optimize the usability of a mobile app for delivering the homework component of CBT for youth with anxiety and/or depression, (2) assess the app's impact on homework completion, and (3) implement the app in CBT programs. We hypothesize that homework adherence will be greater in the app group than in the no-app group.

Methods: Phase 1: exploratory interviews will be conducted with adolescents and therapists familiar with CBT to obtain views and perspectives on the requirements and features of a usable app and the challenges involved in implementation. The information obtained will guide the design of a prototype. The prototype will be optimized via think-aloud procedures involving an iterative process of evaluation, modification, and re-evaluation, culminating in a fully functional version of the prototype that is ready for optimization in a clinical context. Phase 2: a usability study will be conducted to optimize the prototype in the context of treatment

at clinics that provide CBT treatment for youth with anxiety and/or depression. This phase will result in a usable app that is ready to be tested for its effectiveness in increasing homework adherence. Phase 3: a pragmatic clinical trial will be conducted at several clinics to evaluate the impact of the app on homework adherence. Participants in the app group are expected to show greater homework completion than those in the no-app group.

Results: Phase 3 will be completed by September 2019.

Conclusions: The app will be a unique adjunct to treatment for adolescents in CBT, focusing on both anxiety and depression, developed in partnership with end users at every stage from design to implementation, customizable for different cognitive profiles, and designed with depression symptom tracking measures for youth made interoperable with electronic medical records.

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KEYWORDS

mHealth; mobile app; youth; anxiety; depression; cognitive behavior therapy; homework

Introduction

Background

Mobile technology has the potential to make mental health treatments more effective and efficient in alleviating mental health problems [1-4]. In particular, youth anxiety and depressive disorders may benefit from the use of mobile technology to improve treatment. The incidence of these disorders peaks during adolescence [5-7], putting them among the top 5 causes of illness and disability in the world [8]. Their persistence into adulthood often takes a great toll on daily functioning in social, work, and family contexts, reducing health-related quality of life [9,10], and placing a heavy financial burden on society and health care services [11,12]. Given the long-term impact of these disorders on individuals, families, and society and their high economic burden, increasing the effectiveness of early treatment could have a significant impact. Cognitive behavior therapy (CBT) is the established efficacious treatment for anxiety and depressive disorders. It has been shown to be an effective treatment for anxiety and depression in children and youth across a wide range of ages [13-19] and using various modes of delivery (eg, individual and group) [20,21]. Notwithstanding CBT's effectiveness, many individuals are not successfully treated and continue to have significant symptoms [22-24]. For example, in a systematic review of CBT for anxiety in young people, anxiety diagnoses were still present at the end of treatment in more than one-third of participants [23]. Increasing the success of CBT in treating adolescents would result in a lower rate of relapse. A promising target for increasing the success of CBT is the homework component.

The Role of Homework in Cognitive Behavioral Therapy Success

The theory underlying CBT combines cognitive and behavior theories to suggest that negative thinking patterns and learned responses underlie emotional responses and behaviors [25,26]. Treatment aims at helping adolescents recognize the links between maladaptive thoughts, negative emotions, and maladaptive behaviors in order to replace them with more positive thinking and adaptive behaviors. The acquisition of new ways of thinking and new behaviors occurs through learning processes: cognitive learning, classical and operant conditioning, shaping, maintenance, and generalization. As in all learning, practice is essential. New concepts and skills introduced in the treatment session are practiced in problematic situations outside the session to promote experiential learning and generalization to new situations in daily life. For example, graduated exposure to feared situations is used to lessen anxiety. Behavioral activation (eg, engaging in pleasurable or mastery activities) is used to reduce depressed mood. Activities such as these comprise the homework assignments to be carried out between sessions, selected together with the therapist, in order to aid progress toward therapy goals [27]. Thus, given the centrality of experiential learning in CBT, homework is an essential component of treatment.

Typical therapy sessions last an hour a week and in large measure are devoted to planning and processing the efforts made outside the session [28]. At the end of the session, a homework assignment is introduced and explained, usually consisting of a practice exercise based on what was learned in the session, outlined on a worksheet with space to complete the task. For example, an adolescent might be asked to complete a thought record about an upcoming anxiety-provoking situation, such as a math test at school. The worksheet is to be completed and returned at the next session. The session begins with a review of the homework to reflect on the task as well as the difficulties that may have been encountered and what has been learned [29]. Treatment guidelines for administering homework are designed to support the conduct of homework: assignments should be meaningful, relevant to the central goals of therapy, relevant to the focus of the therapy session, agreeable to patient and therapist, appropriate to the patient's sociocultural context, doable (concrete, specific, and appropriate to current skill level and level of functioning), have a clear rationale, include a backup plan that anticipates potential obstacles and how to handle them, be initially practiced in the session, and include written instructions [30]. These guidelines are designed to ensure that patients are prepared to continue practicing during the week in between therapy sessions.

Support for Practice and Learning

Reflecting homework's critical importance for the success of treatment, there is a direct association between homework completion and outcomes of CBT for anxiety or depression across a wide age range [28,31-34]. However, rates of homework completion are uniformly low across the age spectrum. Studies of adolescents in CBT for depression show that completion rates hover at approximately 50%, are highly

variable, and tend to decline across sessions [28,35,36]. These findings may be partly attributable to insufficient support for practice and learning during the interval in between therapy sessions. Although the guidelines for administering homework are intended to ensure that practice occurs, much depends on the patient's ability to continue practicing without the support that was provided during the treatment session. Whereas in-session learning occurs with the help of a therapist who provides encouragement, feedback, and problem-solving support, learning outside the session is a self-directed effort. The absence of the therapist's support during the intervals between sessions may jeopardize the conduct of homework assignments.

Consistent with this interpretation, adolescents' reflections on CBT homework suggest that they experience insufficient support for doing homework. In a CBT program for depression [37], adolescents regarded homework as important, but reported not always completing the assigned exercises because they did not feel motivated or found it too time-consuming. In another CBT program for depression, which consisted of a computerized program designed as a self-help computer game [38], adolescents gave various reasons for not completing homework, including lack of interest and not having a helpful resource. These findings suggest that homework as traditionally administered provides insufficient support for learning. Rates of homework completion may improve if greater support were provided. Adolescents especially are likely to benefit from enhanced support. Adolescence is a period of ongoing cognitive development involving growing understanding of abstract concepts relevant to CBT, and thus a time when support for learning is likely to be particularly important [39].

The Role of Mobile Tools

Mobile tools have the potential to facilitate many of the treatment processes involved in CBT [2,40]. In particular, given the essential role of homework in CBT, they have been conceptualized as a means by which the therapy setting can reach beyond the clinic to the patient's everyday environment [41]. A mobile homework app may support learning between sessions in numerous ways, including making homework materials accessible and easy to keep track of; aiding memory and understanding of the lesson learned during the treatment session; providing coaching and suggestions (eg, through a help function); promoting intrinsic motivation (eg, through goals and challenges, rewards, feedback on progress [42,43]); facilitating self-monitoring of symptoms and changes (eg, through visual displays); and enhancing homework review and troubleshooting (eg, by summarizing results for discussion). In summary, mobile delivery of homework may provide a means of supporting the continuation of learning during the intervals in between treatment sessions.

The purpose of the proposed research is to design and evaluate a mobile CBT homework app that provides a support system for young people in therapist-led treatment for anxiety and/or depression. We expect that the app will improve homework completion by supporting learning; that is, by facilitating access to assignments, memory and understanding of lessons, motivation to practice, self-monitoring, and review of homework results. Given the impact of cognitive skills on learning, an app is most likely to support learning if it is delivered in a manner consistent with the patient's cognitive skills (eg, abstract reasoning, and executive functioning skills such as planning, implementing, and reflecting) and presented in a way that is meaningful. To this end, the proposed app will be designed to enable analytics for ongoing improvement and customization for different patterns of cognitive strengths and challenges compared with others (cognitive profiles) [44,45].

Current Empirical Support for Cognitive Behavioral Therapy Homework Tools

There are very few existing evidence-based mobile mental health apps [46-48]. Only a handful of apps are relevant to CBT homework and all of these are in the early stages of development. Of those designed for adolescents, several focus specifically on self-monitoring: *Mobile Mood Diary* [49,50], *mobiletype* [51-55], and a daily pain diary [56,57]. Research on these tools suggests that they are useful and acceptable to adolescents. Adolescents complied with daily diaries and momentary sampling and seemed to prefer mobile versus paper methods for self-monitoring. Mood graphs appeared to facilitate discussion in the therapy session. An intervention to facilitate self-monitoring as well as skills practice for pain management was evaluated as usable and acceptable by adolescents and their parents, and preliminary evidence indicated that it had a beneficial effect on coping skills [57].

One mobile app provides full homework support for youth in CBT: Smartphone-enhanced Child Anxiety Treatment (SmartCAT [58]), a comprehensive system to support clinician-directed CBT treatment for anxiety. SmartCAT is designed to enhance the practice of CBT skills outside the clinic by reminding children to practice, motivating practice through rewards, enabling personalized support by the therapist, and facilitating patient-therapist interaction. The central feature of the app is a skills coach, which delivers ecological momentary interventions by cueing children to answer a series of questions about recent events and guiding them through a series of steps. A feasibility study conducted with 9 anxious youth between 9 and 14 years of age indicated good compliance with the skills coach (82.8% response to cueing). Participants rated the app as highly usable.

Several apps relevant to CBT homework have been developed for adults, all providing full homework support: *PE Coach* [59,60], *PsychAssist* [61], and a general therapy support system [62]. All 3 systems contain psychoeducation and homework assignments for each component of treatment. They also include forms for completing activities and a system for scheduling activities and sending reminders. With the exception of *PE Coach*, they are equipped with separate interfaces for patient and therapist and include features to facilitate the review and troubleshooting of homework. All have been positively evaluated as easy to use and helpful. While their clinical effectiveness has yet to be examined, there is preliminary evidence that the general support system [62] increases homework completion and reduces symptoms. How suitable the systems are or how easily they could be adapted for youth is unknown.

In summary, a small handful of CBT homework apps exist ranging in scope from specific to comprehensive and varying in their stage of development. User evaluations indicate that the apps are perceived as useful and acceptable. The findings provide tentative support for several features: ready access to each assignment along with material to aid memory and understanding of lessons and the purpose of the assignment; reminders to complete homework; a skills coach; a means of obtaining personalized support; and graphics depicting trends over time to facilitate homework review and reflection on progress. However, it remains unclear how usable and acceptable these designs are. With the exception of *Mobile Mood Diary*, user evaluations were conducted following the design stage, which risks constraining the evaluation and requiring significant redesign later on. A guiding principle of user-centered design is that end users be involved from the outset of the design stage in order to ensure good usability [63,64]. As well, with the exception of *PsychAssist*, user evaluations were conducted in a single round instead of iterative rounds involving modification of the design followed by evaluation of the new design. An iterative process of evaluation will ensure good usability by progressively eliminating usability problems until no further significant problems are identified.

We will address these methodological issues by including end users from the outset and conducting usability evaluations iteratively. We will also adhere to a design approach recommended for sensitive areas like mental health [65,66], in which design begins in a nonclinical context to ensure a safe design before evaluating usability in the context of treatment (see below). In addition, the design will include a data collection system that enables analytics for ongoing improvement and customization of the app for different cognitive profiles. As well, we will use new technology described below to support our app's client self reports use with electronic medical records (EMRs). The expansion of EMR use in clinical care has underscored the dated method most clinicians use to collect patient self reports (ie, paper). Finally, we will move the app from research into practice through a collaborative process guided by integrated knowledge translation and implementation frameworks [67-69]. This involves collaboration among those who develop, deliver, and support the innovation guided by a plan that is monitored and evaluated at each step [68-70].

Objectives

The purpose of the proposed research is to design and evaluate a mobile CBT homework app for adolescents to use as an adjunct to therapist-led treatment for anxiety and/or depression. The objectives are to (1) design and optimize the usability of a mobile app for delivering the homework component of CBT for youth with anxiety and/or depression, (2) assess the app's impact on homework completion, and (3) implement the app in CBT programs.

Methods

Feasibility and Requirements Analysis

The growth of wireless communications supports the feasibility of using mobile technology in CBT. In 2014, wireless networks reached 99% of Canadians [71]. Smartphones are a common part of everyday life for growing numbers of Canadian adolescents. Rates of cellphone usage have been increasing across a wide range of groups. Cellphone users between the ages of 14 and 17 have led the way in recent years, as shown by a 75% increase in usage rates among youth between 2011 and 2012, and usage among adults is catching up [72,73]. US data indicate that youth, minorities, and those with low levels of income and education have higher-than-average rates of cellphone usage, suggesting that high usage is not confined to privileged groups, although access to service may be more tenuous among those with lower incomes [74,75]. Cellphone use among anxious and/or depressed adolescents may be even higher than that of other adolescents, given research showing that greater use of text messaging and talking via the Internet was associated with higher social anxiety [76].

The objective is to develop an app that can be used as an adjunct to therapist-directed treatment to support homework completion. The software app will be built for multiple operating system platforms that permit the transmission of data to and from a robust, secure, and reliable database server and a fairly small local app. This enables the design of a tool with rich graphics and interactive features without requiring a large memory capacity and data storage on the user's device (smartphone, tablet, or computer). Data will be stored on the server instead of the device itself, allowing for the proposed analytics. There will be a small local app so that, when WiFi is not accessible, data can be stored on the app and uploaded later. Having a fairly small local app will make it easier to install the app, and provisions will be made to allow for a basic data plan to be sufficient for the end user. With a password-protected account, users will be recognized by the server and, upon logging in, the app will connect to the CBT data on the server. Each time users log in, they will be able to pick up where they left off. A separate portal for therapists will be included to facilitate the review of homework by providing access to homework results if adolescents give consent; other functions may be added, contingent on design input from end users. We will use an HTML5-based framework providing an interactive experience on the majority of mobile devices and platforms including iOS and Android.

The server will consist of a database and the necessary server software to enable secure connectivity by the mobile apps and users. The database will store the assignment and the patients' responses/entries along with timestamp information for analytical use for both optimization of the system and assessment of the app's effectiveness.

Interoperability With Electronic Medical Records

We will build public domain depression symptom tracking measures for patients' treatment response that will be made interoperable with EMRs via an HL7-based health information technology (IT) platform [77], which uses open standards for health data, authorization, and user interface integration for full HL7 interoperability with a variety of EMRs from different vendors. Harvard University and Boston Children's Substitutable Medical Applications and Reusable Technology (SMART) apps [78] is a health IT platform for creation of third party apps using open source application programming interface (API) with

well-defined data models that predictably presents specific patient-level data. Multiple apps have been created using SMART, and recently the new HL7 Fast Healthcare Interoperability Resources (FHIR) specification has been added to SMART. FHIR uses a RESTful API for queries, in addition to standard data models and Web formats such as JSON and XML. FHIR can be used as a standalone interoperability standard, or together with existing widely used standards, such as HL7 v2 and v3.

How will SMART on FHIR mitigate interoperability gaps? Historically it has been difficult to get information from patients into EMRs. Various media were used (eg, external hard disk drives and USB drives). Without a usable interface, human delivery (aka, the sneakernet) was a main way to enable patient data to be entered or imported into an EMR. SMART on FHIR solves the sneakernet problem by using (1) an international health information standard, HL7, which has been embraced by all major EMR vendors, and (2) flexible, modular Web-based APIs (apps) that support external reading from or writing to the EMR. For these reasons, the recent arrival and early success of SMART on FHIR technology has been met with great enthusiasm by the medical informatics community and large EMR vendors.

Overview of Approach

The essential content of the app will consist of practice exercises drawn from the manual of an empirically supported 12-week CBT program for younger adolescents [79-80]. The user interface and other features of the app will be designed and evaluated in 3 phases following a user-centered design approach. An easy-to-use software interface is essential to the effectiveness of a tool and it should be as good as it can be before the tool is tested for its effectiveness in improving treatment processes and treatment outcomes. Therefore, we will optimize usability before evaluating clinical effectiveness. The process is user-centered from the outset involving end users (youth, therapists) participating in multiple iterative rounds of design, testing, redesign, and retesting until the interface is deemed easy to use, acceptable, and ready for implementation [64]. In the area of mental health, ethical guidelines emphasizing the protection of patients against harm [65,66] suggest that, to ensure a safe design, the process should begin outside the context of treatment with end users who are similar to the target patient end users but are free of diagnosed mental health problems. Once the design is deemed safe, further rounds of testing and refinement are conducted with target end users who are diagnosed and in treatment. Finally, clinical testing is done to evaluate the impact of the tool on treatment processes and outcomes.

Following these guidelines, the development of the app will involve 3 phases: an initial stage of prototype design and usability evaluation conducted outside the context of treatment to ensure a safe design (Phase 1) followed by usability optimization conducted with patients in treatment (Phase 2), and finally, an effectiveness study to assess the effects of the app on homework completion and explore its impact on treatment outcomes and treatment cost-effectiveness in a pragmatic clinical trial (Phase 3).

Implementation Plan

To ensure successful implementation of the app across Canada, the project team includes an experienced health technology partner and multiple stakeholder representatives (end users, researchers, treatment providers, health system decision-makers) who will work collaboratively to review results and make design decisions at every step, assist in driving implementation during and post project, and evaluate the quality of the implementation process. Our technology partner, BrainFx, Inc., will lead the app's commercialization including ongoing collaboration with the implementation team for maintenance, updates, and enhancements that will continue to keep the app relevant and responsive beyond the project. In addition to their experience in developing and commercializing a digital clinical assessment tool (BrainFx 360), they provide expertise in neurofunctional assessment and in advanced analytics to support ongoing improvement and customization of the app for different cognitive profiles. Treatment providers represent 5 test sites that were chosen based upon their varied geographic location (eg, rural vs urban), type of setting (eg, community vs psychiatric hospital vs general hospital with psychiatric division), specialization (eg, generalist clinics vs mood and anxiety specialization; psychiatric hospital vs youth-focused hospital), and interprofessional staffing (eg, psychiatrist, psychologists, nurses, social workers). These variations will facilitate the identification of implementation barriers and generalization of the results from the present study to other locations. The test sites have also been chosen for their commitment and ability to embed and sustain the app in their current practice based on having clinicians who practice CBT with youth who are anxious and/or depressed. They include the Centre for Addiction and Mental Health (Toronto, ON), Canadian Mental Health Association (York Region & South Simcoe, ON), SickKids (Toronto, ON), Markham Stouffville Hospital (Markham, ON), and Sunnybrook Health Sciences Centre (Toronto, ON).

Phase 1: Prototype Design and Usability Optimization in a Nontreatment Context

The purpose of Phase 1 is to design and develop a fully functional (programmed) prototype with input from adolescents and therapists who are familiar with CBT, and thus able to contribute to the design of a CBT homework app.

Exploratory Interviews

First, exploratory interviews will be conducted individually or in small focus groups of adolescents and of therapists to obtain participants' views and perspectives on the requirements and features of a usable design and on issues pertaining to implementation. Participants will receive a CAD$30 gift card as an honorarium.

Sample

We will recruit (1) up to 10 adolescents between 12 and 18 years of age who can read and speak English, do not have a profound learning disability that could interfere with engagement in CBT, and have had some experience of CBT for anxiety and/or depressive disorders (have previously been or currently are in CBT), and (2) up to 10 CBT therapist (eg, psychologist,

social worker, nurse, or occupational therapist) who have led at least 2 CBT groups for anxious and/or depressed adolescents and/or provided individual CBT to at least 5 anxious and/or depressed adolescents.

Procedure

Interviews with adolescents and therapists will be video and audiotaped. Following a warm-up discussion about their use of mobile apps in general (what apps are appealing, how they choose apps), adolescents and therapists will be asked about their experience with CBT homework, using a list of homework activities as a reference: what challenges were involved in doing/administering homework, what they liked and what they disliked about it, any suggestions for improving it, and whether a mobile app would be a helpful tool. To guide design decisions, they will also be asked to provide input on potential design features, such as reminders to do homework (what form, how frequent), rewards for doing exercises (what kind), tips to get unstuck, a way to get feedback and help (what kind, from app or therapist), a way to display homework at the next session, and whether therapists would like to have a separate portal (serving what functions). Similarly, they will be asked for design advice to make the app appealing to use for youth and therapists (eg, colors, navigation tools). Finally, they will be asked about the contexts in which a CBT homework app would likely be used (where, when, and how), and any concerns regarding implementation (eg, access to WiFi, privacy and security, availability of support, negative effects).

Data Analysis

The video and audiotapes will be transcribed and analyzed using conventional content analysis [81] to group statements into themes, issues, and suggestions in order to reveal insights, ideas, or concerns. We will review the results to settle on the design of an initial prototype. This design will then be programmed and made compatible with major operating systems (eg, Apple iOS, Android, Windows Phone) and accessible from smartphones.

Think Aloud Study

Next, a think aloud study will be conducted to evaluate and optimize the usability of the initial prototype through an iterative process of evaluation, modification, and re-evaluation.

Sample

Optimization will be conducted with a sample of up to 10 youth between 12 and 18 years of age who can read and speak English, do not have a profound learning disability, and have had some experience of CBT for anxiety and/or depressive disorders, and up to 10 CBT therapists. Participants in the exploratory interviews may be included in the think aloud sample. The sample size is based on evidence regarding the number of evaluators typically required to reach saturation (ie, to detect most usability problems, ~5) [82,83] and allows for more evaluation cycles than may be required. The sample will be distributed across iterative cycles of evaluation and improvement, each involving up to 5 evaluators whose feedback is used to modify and reprogram the prototype for the next cycle. Cycles continue as long as new problems are identified. Two cycles are often sufficient [84,85].

Procedure

The think aloud method [65] involves verbalizing thoughts while performing a task. It is effective for usability testing because it helps identify which interface features users find intuitive and easy to use and which require improvement and further evaluation [65]. Participants will be scheduled for individual video and audiotaped sessions with an interviewer in a quiet setting that facilitates thinking aloud. Adolescents and therapists will both be given tasks to complete with the user interface for patients (eg, finding specific pieces of information, navigating to a specific part of the app, doing an exercise). They will be instructed to verbalize their thoughts continuously as they work through the tasks, while the interviewer makes field notes of problems observed. If the prototype design includes a separate therapist interface, therapists will complete several additional tasks using that interface.

A heuristic evaluation by usability specialists will also be conducted. Up to 5 mobile app developers will be asked to inspect the user interface and independently rate the extent to which it meets established usability principles for software systems [86] (eg, error prevention, recognition and recovery from errors, aesthetic and minimalist design, help and documentation).

Data Analysis

Think aloud transcripts and interviewer field notes will be analyzed by performing a content analysis [87] to reveal issues with usability, such as unclear instructions, unintuitive icons, and difficult navigation sequences. Following each iterative cycle, we will review the results and modify the prototype for the next cycle. The process will culminate in a usable design that is ready for further evaluation and optimization in a clinical context.

Phase 2: Usability Optimization in the Context of Clinical Treatment

The purpose of Phase 2 is to evaluate and improve the usability of the prototype in the context of a 12-week course of CBT treatment. Associations between cognitive profiles and user experience will be explored to better understand how to customize the app for different cognitive profiles. This phase will result in a usable app that is ready to be tested for its effectiveness.

Sample

An independent sample will be recruited consisting of 20 youth in CBT and their therapist **s**, distributed approximately equally across 5 clinics that provide CBT treatment for youth with anxiety and/or depression. Participants will receive a CAD$30 gift card as an honorarium. Youth will be recruited from among 12- to 18-year olds with a primary diagnosis of anxiety (general anxiety disorder, separation anxiety, social anxiety, panic disorder) and/or depression (major depressive disorder, dysthymic disorder). Informed consent will be obtained from youth, their primary caregiver, and their therapist. Youth receiving medication will be included if they were on a stable dose for approximately 6 weeks prior to and throughout participation. Those with a primary diagnosis of obsessive-compulsive disorder or post-traumatic stress disorder,

and those with comorbid psychosis or substance dependence will be excluded because they require different CBT strategies from those that are the focus of this research. Those who are behind by 2 or more school grades or have a profound learning disability will be excluded, given the cognitive and verbal nature of CBT. Substance use and mild learning difficulties will not be exclusion criteria. Based on intake rates of approximately 1 per week at each clinic, we expect to recruit 5 youth per week. Interest in trying the app is expected to be high. Two evaluation cycles, each with up to 10 youth and their therapists, should be sufficient to reach saturation [82], but the sample size allows for an additional cycle if needed. Youth will be given the choice of receiving a smartphone to use or using their own. They will be compensated for the cost of a basic service plan (voice, text, Internet) for 12 weeks to use the app.

Sample Characteristics

To describe the sample, confirm diagnoses, and explore how individual attributes may affect the user experience, youth will be assessed using the following measures administered to them and their primary caregiver/guardian by a clinical psychology graduate student research assistant (RA) trained in the administration of the measures: the Achenbach Scales [88] to assess general symptomatology, completed by youth and caregiver; the Multidimensional Anxiety Scale for Children 2nd ed. (MASC-2 [89]) completed by youth and caregiver; the Child Depression Inventory 2nd ed. (CDI-2 [90]) completed by the youth; the Anxiety Disorders Interview Schedule (ADIS [91]) conducted with youth and caregiver; and selected tests from the BrainFx 360 digital clinical assessment of neurofunction [92] (performance assessment by a trained administrator focusing on complex cognitive skills: divided attention, delayed memory for auditory and visual input, mental flexibility, abstract reasoning, executive functioning skills in the areas of planning, organizing, implementing, and reviewing/reflecting). The Achenbach Scales, MASC-2, and CDI-2 will be administered in a secure Web-based format. The ADIS is a semistructured interview that will be administered either over the phone or in person according to preference. Both methods have been shown to be reliable [93]. The ADIS is the optimal research interview to assess anxiety disorders, but also includes all Diagnostic and Statistical Manual of Mental Disorders criteria for depression. In addition, information will be obtained about demographic characteristics (youth age, gender, and grade; parental education, occupation, and family income) and comfort with technology (experience with computers, smartphones, tablets, and the Internet–where used, frequency of use, comfort level).

Procedure

Prior to beginning CBT treatment, the RA will meet individually with youth to explain the purpose of the evaluation, describe the procedure for obtaining their feedback on the usability of the app, and administer the pretreatment assessment. Before the first therapy session, the site coordinator will meet with each youth to demonstrate how to use the app and provide contact information in the event of technical problems, and with therapists to train them on the app and how to use it to introduce and review homework. Therapists will meet with the coordinator periodically to discuss experiences and any technical issues.

The usability evaluation by youth will be done via a short weekly interview conducted upon arrival at the therapy session. The interview will focus on the app's usability for the assignment given at the end of the previous session. We will assess the efficiency of the app, via ratings of the app's learnability (how easy to figure out and remember what to do), ease of use (the time and number of steps it takes to operate, need for technical support), and error tolerance (how free of error messages, app's ability to prevent/recover from use errors). We will also assess satisfaction with the app, via subjective ratings of its learnability (access to the assignment, memory and understanding of the lesson, motivation to practice, coaching and suggestions, self-monitoring of symptoms and changes), usability (how easy it was to use), and likeability (of specific design features). In addition, open-ended questions will be asked about: (1) where, when, and how the app was used (to understand context of use), (2) problems using the app (to identify usability problems), and (3) how the app supported homework completion (to understand the usefulness of the app). The final evaluation interview will include additional items focusing on overall experiences and impressions of the app, ratings of the app's overall efficiency (learnability, ease of use, error tolerance), and overall satisfaction with the app (usefulness, usability, likeability). Open-ended questions will be asked about features most and least liked, facilitators and barriers to use, any negative experiences associated with the app (eg, intrusion on privacy or fear of such an intrusion), how much the app supported learning (ratings of support for access to assignments, memory and understanding of lessons, motivation, coaching and suggestions, self-monitoring, review of homework), and any suggestions for improvement.

The usability evaluation by therapists will be done via an interview following the final session, through open-ended questions about the usefulness of the app for reviewing and troubleshooting homework, whether there were any negative effects of using the app, and any suggestions for improvement.

A heuristic evaluation by usability specialists will also be conducted, as in Phase 1. Up to 5 mobile app developers will be asked to inspect the user interface and independently rate the extent to which it meets established usability principles for software systems [86] (eg, error prevention, recognition and recovery from errors, aesthetic and minimalist design, help and documentation).

Data Analysis

Content analysis will be performed on responses to open-ended questions to reveal contexts of use, usability issues, features most and least liked, facilitators and barriers, any anticipated negative effects, usefulness of the app for homework completion, and suggestions for improvement. Responses will be summarized in narrative form and frequencies of each category will be calculated. Descriptive statistics will be performed on the Likert-type ratings to measure central tendency (mode) and variability (frequencies). The cognitive skills assessment will yield clustering profiles outlining areas of strength and challenge as compared with others, permitting an exploratory qualitative analysis of associations between cognitive profiles and the usability evaluation data. The results

of the study will be used to determine whether the app is usable and safe to use in the context of treatment, and thus is ready for a clinical trial of its effectiveness and acceptability in a treatment context, and to further improve the app before proceeding.

Phase 3: Evaluation of Effectiveness

The purpose of Phase 3 is to evaluate the impact of the app on homework completion. We hypothesize that participants in the app group will show greater homework adherence than those in the no-app group. To test the hypothesis, a pragmatic clinical trial will be conducted at the same 5 clinic sites as in Phase 2. CBT is well supported by randomized controlled trials of its efficacy when delivered in different ways, including computerized formats as described above. Therefore, the purpose of this phase is not to determine CBT efficacy, but rather to provide evidence that homework (ie, the practice of CBT skills and strategies) can be effectively delivered in a mobile format [94]. Thus, the main objective is to assess the impact of the app on homework completion compared with CBT treatment-as-usual (ie, paper-based homework delivery). We will also obtain end user evaluations of the app's usability in the context of treatment. Finally, we will also conduct exploratory analyses to assess the impact of the app on symptom improvement and cost-effectiveness, and to examine associations between cognitive profiles and homework completion as well as user experience.

Study Design

We will conduct a multisite, randomized controlled pragmatic clinical trial in routine clinical settings to test the app's effectiveness under real-world conditions in order to enhance external validity and ensure successful implementation without sacrificing scientific rigor. A pragmatic clinical trial also suits the nature of mHealth technologies, which require ongoing improvement and are subject to rapid technological change [95-97]. After pretreatment assessment, participants will be randomly assigned to receive a manualized CBT treatment either with app support (app group) or without it (no-app group). Youth assigned to CBT with the app will receive CBT treatment for 12 weeks with the app included (app group). They and their therapists will be shown how to use the app. Youth assigned to receive CBT treatment for 12 weeks with paper-based homework will be in an active control condition (no-app group). Both groups will be in treatment for 12 weeks, the typical duration of CBT. However, therapists in both the app and no-app groups will be able to provide additional sessions should they deem it clinically relevant. Duration of CBT will be recorded and group differences will be analyzed. Following the pretreatment assessment and exclusions, participants providing informed consent will be randomly assigned to treatment group. Random assignment will be done at each test site separately by the site coordinator. At each site, half the participants will be assigned to each group in order to control for site-specific variables (eg, type of CBT delivered, professional background of therapist). To assess the app's effectiveness both immediately and over time, assessments will be done at the end of the 12-week treatment (posttreatment) and again after 6 months (follow-up 1) and 12 months (follow-up 2). At each time-point, participants will receive a CAD$30 gift card as an honorarium.

Sample Size and Power

Given the low rates of homework completion in research to date, we expect that the app will have at least a moderate effect on homework completion compared with the no-app group [28,35,36]. A power calculation, based on a comparison between 2 groups (app vs no-app) across 4 occasions (pre, post, follow-up 1, follow-up 2) for a single measure, indicates that a sample size of 35 for each group would provide power of 0.84 to detect a moderate effect size for homework completion at $\alpha = .05$. To allow for dropouts [98], we will recruit 100 youth between 12 and 18 years of age (10 per group at each site). As noted earlier, treatment dropout rates can be substantial and adherence to homework is often quite low. This has been taken into account in calculating the sample size. The expectation is that compliance will be greater for the app than the no-app group. Based on previous research with youth [98], we expect a 10% rate of attrition at each of the 2 follow-ups.

Recruitment

Recruitment will be the same as in Phase 2. In previous work in our clinics, consent rates have been 80% or higher. Interest in using the app is expected to be high. Typically, intake at the test sites is approximately 1 per week and the wait-list period is at least 12 weeks for noncrisis patients. Therefore, based on intake and consent rates and assuming sequential recruitment, we will recruit at a rate of 5 youth per week across the 5 sites, reaching an overall sample of 100 within 6 months. Posttreatment assessments would be completed at the end of treatment (ie, 3 months later), and the follow-ups 6 and 12 months thereafter. The same inclusion and exclusion criteria apply as in Phase 2.

Measures

At pretreatment, as in Phase 2, we will assess (1) demographic characteristics and comfort with technology to characterize the sample, and (2) cognitive skills to examine associations between cognitive profiles and homework completion as well as user experience.

During treatment, homework completion will be assessed weekly. The quantity (amount) as well as the quality (appropriateness) of homework will be assessed, based on evidence that they both relate to treatment outcome [99]. Multiple sources of homework information (adolescent, therapist, data logged by the app) will be obtained to address potential differences between sources [99,100]. Adolescents will assess the quantity and quality of their homework upon arriving at the session, by rating on a 5-point scale how much of it was completed and how well it was done, using 2 items from the Homework Rating Scale II [101], an internally consistent measure of homework quantity and quality developed for use with adults [102]. The 2 items have not previously been tested with adolescents and will be pilot-tested in this study. Two additional measures of homework quantity will be obtained by asking adolescents to estimate the number of days and the number of hours they spent doing homework [103]. Therapists will assess homework completion following the session. They will assess homework quantity by rating the proportion of assigned homework that was completed (from 0% to 100%), a

method used in previous research [36,103]. They will rate the quality of the work on a 6-point scale [104], using criteria specified for each assignment; this measure has been found to predict treatment outcome [103]. A third source of information about homework quantity will be obtained in the app group from data logged by the app: the proportion of the task completed, the time spent on the task, and the number of visits to the assignment page.

At pre, post, and each follow-up, treatment outcomes will be assessed. Anxiety and depression will be assessed using the same instruments as in Phase 2: the Achenbach Scales, which assess general symptomatology as reflected in internalizing problems, and externalizing problems, which often co-occur with anxiety and depression [105], the MASC-2, the CDI-2, and the ADIS. Other outcomes also will be assessed. Maladaptive cognitions will be assessed using the Children's Automatic Thoughts Scale [106], in which youth rate the frequency over the past week of a set of 40 self-statements describing negative thoughts about physical threats, social threats, personal failure, and hostile intent. Quality of life will be assessed by the Pediatric Quality of Life Inventory [107,108], in which youth rate 23 self-statements assessing physical, emotional, social, and school functioning.

At posttreatment, a usability evaluation will be conducted with the app group (youth and therapists) following completion of the posttreatment assessment, using the same protocol as in Phase 2. To examine differences in client satisfaction between the app and no-app groups, will be assessed posttreatment (following the usability evaluation in the app group) via the Client Satisfaction Questionnaire (CSQ [109,110]), an 8-item global measure of satisfaction with service comprised of statements phrased as questions to be answered on a 4-point scale ranging from 1 (poor) to 4 (excellent). The CSQ is a well-established measure with good psychometric properties [110] that has been used in numerous studies with diverse patient samples, including children and adolescents in CBT [111,112]. Treatment fidelity will be assessed by an integrity-to-protocol checklist [113], which therapists will complete after each session. The checklist yields a proportion score reflecting the rate of adherence to the CBT treatment manual. Finally, health economic cost data will be obtained to assess cost-effectiveness of the app. Cost data will consist of technology costs, including detailed micro costing of the app program (eg, program costs, smartphone-related costs, server costs, maintenance), and the cost of time and other resources needed to integrate the app into routine clinical practice by therapists and clinics.

Data Analysis

To assess the app's effectiveness, differences between the app and no-app groups will be examined with respect to homework completion. We will also explore group differences in treatment outcomes. Although randomization will be used to mitigate group differences, potential differences between groups will be examined. If differences are found on variables that may be related to homework completion or treatment outcome (symptom severity/diagnosis, age, sex distribution, history of psychotherapy and pharmacological interventions, comorbid mental health problems, therapist), these variables will be included as covariates in the analyses. Descriptive analyses will be performed on demographic characteristics, comfort with computers, and retention rates (participants assessed at posttreatment and follow-ups). To avoid bias in parameter estimates, missing data will be handled by performing intent-to-treat analyses, in which missing values are replaced using the last observation carried forward, a method appropriate for randomized designs [114].

Homework Completion

Effects of the app on homework completion will be analyzed separately for homework quantity and quality. Psychometric properties of the measures will be examined and correlations will be computed to examine congruence between adolescent and therapist sources of information. If warranted, aggregate scores will be computed; otherwise, separate analyses will be done using different measures. To test the hypothesis that the quantity and quality of homework will be greater in the app compared with the no-app group, we will test group differences in quantity and quality scores. We will also explore timing effects, given evidence suggesting that homework completion varies over time and may decrease over the course of treatment [36]. Scores for the first 4, middle 4, and final 3 weeks of homework will be averaged, creating 3 assessment points, and a mixed-model repeated measures multivariate analysis of the variance will be performed with the between factor of group (app vs no-app), the within factor of time (early, middle, late), and the 2-way interaction of group × time.

Exploratory analyses will also be performed. Subgroup analyses will explore differences in the app's impact on homework completion as a function of test site and gender. Correlations will explore relations between cognitive profiles and homework completion. For the app group, psychiatric and cognitive assessment data will be aggregated and advanced analytics will be performed to examine predictive relations between patient attributes (anxiety, depression, cognitive profile) and the quantity and quality of homework completion. These analyses will include homework completion data logged by the app (proportion of the task completed, the time spent on the task, and the number of visits to the assignment page).

Treatment Outcomes

For exploratory purposes, we will examine group differences in treatment outcomes. Group differences in anxiety and depression will be analyzed for both dichotomous (diagnosis) and continuous (symptom severity) measures. For each diagnosis (presence vs absence), chi-square tests will be performed comparing the number of youth meeting criteria for diagnosis at pre versus post, pre versus follow-up 1, and pre versus follow-up 2. For each of the continuous measures of symptom severity, following the recommended approach for trials with pre, post, and follow-up measures [115], a repeated measures multivariate analysis of the covariant will be performed in which the between factor is group (app vs no-app) and the within factor is time (pre, post, follow-up 1, follow-up 2), to compare group and time effects and interactions between group and time, using the pretreatment value as a covariate. Where significant effects are found, simple contrasts will be conducted to ascertain where the significant differences lie. Group differences in maladaptive

cognitions (overall score) and quality of life (overall score), will be analyzed in the same way. Effect sizes will be calculated comparing the effects of app vs no-app on each of the outcomes. Analyses will also be performed to establish clinical significance and the reliable change index [116]. Subgroup analyses will explore differences in the app's impact on treatment outcomes as a function of test site and gender.

If the analyses reveal significant group differences in treatment outcomes, additional exploratory analyses will be performed to aid interpretation of the data. To explore whether better homework completion (greater quantity and/or quality) or something unique about the mobile technology is most likely responsible for group differences in treatment outcomes, we will examine associations between homework completion and treatment outcomes separately for the 2 groups. Mobile devices may increase patient engagement and empowerment [1,117] and reduce concern about the perceived stigma associated with receiving treatment [118], resulting in beneficial effects on treatment that are independent of homework completion. Accordingly, regression analyses (ordinary least squares, logistic) would be performed to predict each of the dichotomous (diagnosis) and continuous (symptom severity) outcomes at posttreatment, follow-up 1, and follow-up 2 from measures of homework completion, controlling for the pretreatment value of the outcomes. A finding of group differences in the strength of associations between homework completion and treatment outcomes would suggest that an improvement in homework completion is not the only mediator of app effects on treatment outcome.

Finally, if treatment outcomes are better for the app compared with the no-app group, exploratory mediation analyses will be performed for the app group to assess whether homework completion (quantity, quality) affects treatment outcomes indirectly through support for learning (ratings of how much the app supports access to assignments, memory and understanding of lessons, motivation to practice, coaching and suggestions, self-monitoring of symptoms and changes, review of homework). To test for mediation, we will perform tests of indirect effects using a regression-based path-analytic approach [119,120].

Usability Evaluation

To identify usability issues, content analysis will be performed on the usability evaluation data, as in previous phases. An exploratory qualitative analysis will be performed to examine associations between cognitive profiles and the usability evaluation data in order to further improve the user experience and customize it for different cognitive profiles.

Client Satisfaction With Service

To examine differences between the app versus no-app groups in client satisfaction, a *t*-test will be performed on total CSQ scores. Levels of satisfaction will be compared with norms established in other studies of youth in CBT treatment [111,121].

Treatment Fidelity

Proportion scores computed from the integrity-to-protocol checklist will be analyzed to compare the app and no-app groups with respect to therapists' adherence to the CBT treatment manual.

Cost-Effectiveness of CBT with App Support

Cost-effectiveness will be computed for several treatment outcomes (anxiety, depression, quality of life) using the cost data described above (dollar values). An incremental cost-effectiveness ratio will be calculated for the measures at posttreatment and follow-ups 1 and 2. The analysis will use a health care sector perspective. Costs that are equal in both treatment alternatives will be excluded, because they would not impact the results. The study will use Ontario provincial list costs for health care services and market values for other resources when available. All costs will be shown in current values using the Canadian Consumer Price Index. Costs over 1 year will be discounted at a 5% discount rate and a sensitivity analysis will use 0% and 3% discount rates. We will follow Canadian Agency for Drugs and Technologies (2006) guidelines [122], the Institute of Health Economics economic evaluation report [123], and methods for costing the alternatives and performing the cost-effectiveness analysis (CEA) [124]. The cost and effectiveness outcomes will be further analyzed using economic decision modeling techniques. The modeling will include consideration of the uncertainty in both effectiveness measures and different cost variables using probabilistic sensitivity analysis techniques that allow simulation of the expected outcomes using a cost-effectiveness plane that shows the estimated incremental cost and effectiveness estimates and their mean value. Further, the results will be shown using the Cost Effectiveness Acceptability Curves, the most widely used tool to show the probability that the new technology will be accepted with different societal willingness to pay for it. The modeling part of the CEA will use state of the art modeling practices and International Society for Pharmacoeconomics and Outcomes Research good modeling guidelines [123,125,126].

Results

Phase 3 will be completed by September 2019. Ethics approval has been received for Phase 1 of the study from the Research Ethics Board at the Centre for Addiction and Mental Health.

Discussion

The app will be a unique adjunct to treatment for adolescents in CBT, focusing on both anxiety and depression, developed in partnership with end users at every stage from design to implementation, customized for different cognitive profiles, incorporating data analytics to support ongoing analysis and improvement, and designed with public domain depression symptom tracking measures for youth made interoperable with EMRs.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer Review Comments from CIHR.

[PDF File (Adobe PDF File), 70KB - resprot_v5i4e209_app1.pdf]

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Abbreviations

ADIS: anxiety disorders interview schedule
API: application programming interface
CBT: cognitive behavior therapy
CDI-2: Child Depression Inventory 2nd ed
CEA: cost-effectiveness analysis
CSQ: client satisfaction questionnaire
EMR: electronic medical record
FHIR: fast healthcare interoperability resources
IT: information technology
MASC-2: Multidimensional Anxiety Scale for Children 2nd ed
RA: research assistant
SMART: substitutable medical applications and reusable technology
SmartCAT: smartphone-enhanced child anxiety treatment

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Protocol

Supporting Heart Failure Patient Transitions From Acute to Community Care With Home Telemonitoring Technology: A Protocol for a Provincial Randomized Controlled Trial (TEC4Home)

TEC4Home Healthcare Innovation Community[1‡]

Digital Emergency Medicine, Department of Emergency Medicine, University of British Columbia, Vancouver, BC, Canada

‡See acknowledgements section for the list of collaborators

Corresponding Author:
C/o Kendall Ho, MD, FRCPC
Digital Emergency Medicine
Department of Emergency Medicine
University of British Columbia
105-2194 Health Sciences Mall
Vancouver, BC
Canada
Phone: 1 604 822 8389
Fax: 1 604 822 8389
Email: kendall.ho@ubc.ca

Abstract

Background: Seniors with chronic diseases such as heart failure have complex care needs. They are vulnerable to their condition deteriorating and, without timely intervention, may require multiple emergency department visits and/or repeated hospitalizations. Upon discharge, the transition from the emergency department to home can be a vulnerable time for recovering patients with disruptions in the continuity of care. Remote monitoring of heart failure patients using home telemonitoring, coupled with clear communication protocols between health care professionals, can be effective in increasing the safety and quality of care for seniors with heart failure discharged from the emergency department.

Objective: The aim of the Telehealth for Emergency-Community Continuity of Care Connectivity via Home Telemonitoring (TEC4Home) study is to generate evidence through a programmatic evaluation and a clinical trial to determine how home telemonitoring may improve care and increase patient safety during the transition of care and determine how it is best implemented to support patients with heart failure within this context.

Methods: This 4-year project consists of 3 studies to comprehensively evaluate the outcomes and effectiveness of TEC4Home. Study 1 is a feasibility study with 90 patients recruited from 2 emergency department sites to test implementation and evaluation procedures. Findings from the feasibility study will be used to refine protocols for the larger trial. Study 2 is a cluster randomized controlled trial that will include 30 emergency department sites and 900 patients across British Columbia. The primary outcome of the randomized controlled trial will be emergency department revisits and hospital readmission rates. Secondary outcomes include health care resource utilization/costs, communication between members of the care team, and patient quality of life. Study 3 will run concurrently to study 2 and test the effectiveness of predictive analytic software to detect patient deterioration sooner.

Results: It is hypothesized that TEC4Home will be a cost-effective strategy to decrease 90-day emergency department revisits and hospital admission rates and improve comfort and quality of life for seniors with heart failure. The results from this project will also help establish an innovation pathway for rapid and rigorous introduction of innovation into the health system.

Conclusions: While there is some evidence about the effectiveness of home telemonitoring for some patients and conditions, the TEC4Home project will be one of the first protocols that implements and evaluates the technology for patients with heart failure as they transition from the emergency department to home care. The results from this research are expected to inform the full scale and spread of the home monitoring approach throughout British Columbia and Canada and to other chronic diseases.

ClinicalTrial: ClinicalTrials.gov NCT02821065; https://clinicaltrials.gov/ct2/show/NCT02821065 (Archived by WebCite at http://www.webcitation.org/6ml2iwKax)

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KEYWORDS

heart failure; telemedicine; remote sensing technology; emergency service, hospital; hospitalization; quality of life

Introduction

Telehealth for Emergency-Community Continuity of Care

Chronic diseases, of which heart failure is a prototypical example, increase significantly with age, resulting in poorer quality of life and increased health care costs for seniors. Although electronic home monitoring using sensors that can send data to clinicians is identified in the literature as a useful way to support seniors at home, a key limitation is the absence of evidence on supporting the transition from acute care (hospital) to community (home) settings. These individuals are particularly at risk of becoming ill again shortly after a hospital discharge and can benefit greatly from home telemonitoring to best manage symptoms and avoid deterioration. To address this need, the proposed project Telehealth for Emergency-Community Continuity of Care Connectivity via Home Telemonitoring (TEC4Home) will investigate the effectiveness of innovative home telemonitoring technology to support seniors transitioning from hospital to home and to improve communication between acute and community care clinicians. This eHealth-enabled innovation initiative will result in evidence-informed improvements in cost effectiveness, health outcomes, and end-user experiences; timely health system knowledge translation and adoption; and judicious commercialization of emerging eHealth innovations into practice.

Heart Failure: Population and Challenges

In the Western world, approximately 1% to 2% of the adult population has heart failure; however, in seniors, the prevalence rises to more than 10% [1]. In the United States alone, heart failure accounts for 2.4 million hospitalizations and 300,000 deaths annually [2]. Patients aged over 65 years with heart failure account for more than 80% of deaths and prevalent cases in the United States and Europe [3,4]. Canadian statistics from 2013-2014 indicate that heart failure ranked fourth nationally as the cause for hospitalization, accounting for 59,428 patients (2.0% of all hospitalizations) with a high average length of stay (9.2 days) [5]. In British Columbia, heart failure accounted for 7,562 admissions (1.9% of all hospitalizations) with an average length of stay of 8.8 days. In Canada, the proportion of seniors is expected to increase from 15% in 2013 to between 23% and 28% in 2061, with the most significant increase during the period between 2013 and 2030 [6]. This increase, accompanied by a corresponding rise in raw numbers of patients with heart failure in this population, will place a significant financial burden on the health system.

The British Columbia Ministry of Health has identified home telemonitoring as a priority to assist patients with heart failure to safely receive care at home and limit hospitalization. In 2013, the Ministry partnered with TELUS Health to carry out a limited pilot study in two British Columbia regions on home telemonitoring of seniors with heart failure, with remote innovations that track their blood pressure, heart rate, oxygen saturation, weight, and heart failure symptoms. The findings from this pilot established a strong case for expanding this program provincially, paying special attention to patients transitioning from hospitals to homes. Our proposed TEC4Home study contributes directly to this provincial priority by conducting a province-wide randomized controlled trial (RCT) to evaluate the efficacy of this innovative home telemonitoring tool, scale up the telemonitoring program in British Columbia, and establish a pathway to judiciously introduce new home telemonitoring technologies over time.

Readiness of the Proposed Technology

Telemonitoring has been researched in a wide variety of contexts for the management of chronic diseases [7]. This approach is increasingly being trialed in Canada for chronic disease management but is not yet part of standard of care [8]. Telemonitoring of heart rate, blood pressure, oxygen saturation, and daily body weight using biometric sensors are ready for incorporation into clinical utilization. We will work with TELUS Health, a medium enterprise in health care and one of our technology partners, to scale up and extend the home telemonitoring platform for heart failure in British Columbia.

We will also work with Sentrian, a small enterprise based in Aliso Viejo, California, Unites States, to introduce a predictive analytics platform into TEC4Home to evaluate its readiness in home telemonitoring for commercialization in British Columbia. Predictive analytics is defined as “the practice of extracting information from existing data sets in order to determine patterns and predict future outcomes and trends” [9]. Currently, telemonitoring relies on clinicians to detect data abnormalities from each sensor and interpret the combination of these signals to determine the state of wellness of the patients. Predictive analytics uses computer software to carry out data mining to intelligently screen for abnormal signals, in isolation or in combination, and present these episodes to the clinicians for further interpretation and action. This improves detection and reduces the frequency of false alarms. The Sentrian platform uses machine learning and feedback to animate predictive analysis and improve its accuracy over time [9]; its Remote Patient Intelligence approach can increase the sensitivity of detection of true abnormal events and reduce the incidence of false positive signals, thereby allowing clinicians to appropriately focus their attention on significant events and reduce distractions from false alarms. In May 2015, this technology commenced its journey through a US trial on patients with chronic obstructive pulmonary diseases. In TEC4Home, we will apply Sentrian’s Remote Patient Intelligence platform to test its effectiveness as a software aid to clinicians monitoring patients with heart failure.

Description of the Gaps and Inefficiencies To Be Addressed

Literature Gap

Clinical studies demonstrate that heart failure patients with optimal self-management and health professional support

experience fewer emergency department and hospital admissions and an improved quality of life. Such self-management has also been demonstrated to minimize health care costs. Home telemonitoring has been advocated as a solution to support patients in the community to avoid unnecessary acute care interventions [7]. Clinical studies to date have demonstrated promising but inconsistent evidence for home telemonitoring of heart failure patients: some suggest good efficacy while others suggest no overall benefits [10-13]. A recent meta-analysis suggested that a subpopulation of heart failure patients who had been discharged from the hospital within 28 days benefited preferentially from home telemonitoring in reducing mortality and all-cause hospitalizations [14]. In addition, automated device-based telemonitoring and mobile telemonitoring appeared to be more effective compared to other forms of home telemonitoring such as video-consultations, interactive voice response, and Web-based telemonitoring [14]. Clinical trials targeting this specific population are needed to validate the meta-analysis findings. Involving both acute care and community care health professionals for optimal communication and joint development of criteria for monitoring, which is not well examined in current published studies, will be necessary to properly evaluate this population of heart failure patients who are being discharged from the emergency department for convalescence at home. A rigorous economic evaluation of implementation of home telemonitoring for heart failure patients from a variety of hospitals on a provincial scale—a complex health system intervention—remains lacking in the literature. TEC4Home will fill this literature gap.

Patient Engagement Gap

Home telemonitoring has been shown to promote patient activation in effective self-care, resulting in improved quality of life [15]. Evidence demonstrates that electronic technologies showing patients their own physiologic parameters promote changes in patient behavior by increasing self-efficacy and knowledge to ultimately impact health outcomes for many conditions and across different user groups [16]. This approach can support patient-centered care by providing improved access, safety, and quality of care while also enhancing communication between patients, health professionals and care teams [17]. There is a gap in the literature regarding the motivational aspect of telemonitoring for seniors transitioning from hospitals to home—a population that has the potential to be more engaged to either prevent rehospitalization or cope with recovery after a visit to the emergency department. By providing telemonitoring technology, the present project fills the knowledge gap on patient motivation and home telemonitoring.

Pilot Project Findings

The British Columbia Ministry of Health and TELUS Health piloted a home health monitoring system in an initiative beginning in 2013. A pilot evaluation in 2013-2014 with 192 patients found that the level of self-care activation increased by 34%, patient management of symptoms improved from 20% on enrollment to 60% on discharge from the 3-month program, and cost of utilization of acute care and physician services decreased by 71% at one site (n=61) and 77% at a second site (n=131) when compared to the immediate 3-month period prior. Most patients (98%) were satisfied with the service, and 100% stated they would recommend the service. Issues identified in this pilot study included the need for a better feedback loop of the data back to the patients themselves, problems with usability of the screen interfaces for clinicians in accessing patient data, and the need to improve documentation to better align data with the provincial health information systems for administrative purposes. Also, this pilot did not examine how this system could support patient recovery among those who were hospitalized. The present project will address issues with the pilot data by improving the effectiveness of home telemonitoring technology on hospitalized patients during their transition from hospital to home, developing secure screen interfaces to communicate patient conditions to patients and clinicians, and implementing home telemonitoring policies to align data integration.

Technology Innovation Gap

Home telemonitoring technologies and predictive analytics are rapidly changing. Many inventions by small and medium enterprises (SMEs) are developed in isolation from health systems, thereby failing to fully address the health care gaps to systemically improve service delivery. In order to ensure timely and judicious incorporation of these innovations, a robust mechanism is needed to assist companies to understand the needs of patients and the health care system, align their novel developments to address real-world problems, and evaluate their effectiveness through well-designed clinical studies.

The TEC4Home health-care innovation community plans to use this 4-year project to address these four important gaps in home telemonitoring for seniors with heart failure by:

- Introducing the use of sensors and data analysis software to optimize home telemonitoring of seniors with heart failure post–emergency department discharge
- Establishing communication pathways between acute care and community care health professionals in order to effectively supervise the patient's transition of care to the home
- Scaling up of the management of heart failure patients in different care contexts across British Columbia while conducting an RCT and evaluation based on the Triple Aim framework. The Triple Aim framework provides an approach to evaluating health systems using three dimensions (user experience of care, health of populations, and cost effectiveness) [18]
- Supporting the partnership between the SMEs to introduce and commercialize telemonitoring technologies to the mainstream health care service delivery

TEC4Home: A Description of the eHealth-Enabled Care Delivery Program

The TEC4Home program consists of two aspects: the technology supplied by TELUS Health and Sentrian and a clinical arm to promote communication between acute and community health professionals and between patients and clinicians.

The Technology

The TELUS Health Remote Patient Monitoring (RPM) solution has three components: sensors, patient station, and clinician

station. The sensors (blood pressure cuff, pulse oximeter, and weight scale), measure patients' blood pressure, pulse rate, oxygen saturation, and weight and can be self-applied by the patients without help. These sensors collect the patient's biometric measurements and send the readings to the patient station. The patient station consists of a software application on a mobile tablet that collects sensor data and presents a series of questions to assess presence of any symptoms such as dizziness, shortness of breath, coughing, or swelling. All of the data entered are transmitted to a data hub where the patient's data is analyzed, collated, and displayed. The clinician station consists of a software application on a mobile tablet or a personal computer that is used by clinicians to view patient data. Alerts are flagged if one or more sensors show biometric data falling outside of the normal range set for the patient or if the patient reports serious problems such as syncope. The monitoring clinicians then decide on and initiate actions accordingly. TELUS Health RPM can be connected by either cellular wireless or broadband Internet, and dial-up Internet access is available if required.

The Sentrian Remote Patient Intelligence platform is incorporated to augment the clinician station software, simultaneously receiving and analyzing sensor signals. Abnormalities detected are flagged by the clinicians, who can then decide upon appropriate actions. These actions are subsequently entered into the software so that over time, machine learning algorithms will be customized to the patient's own physiologic behaviors, thus resulting in more accurate identification of true abnormalities and a reduction of false alarms.

A clinical monitoring, evidence-based protocol developed with the cardiologists from Cardiac Care BC and standardized for heart failure patients guides the monitoring clinicians as to what to flag as "normal" or "needing of acute critical care." Patients are asked to submit their biometric measurements once a day after discharge from the emergency department. The monitoring clinician can then review and manage a large number of patients by sorting them according to number of alerts and priority level within 12 hours of data submission. Standardizing the protocol has several advantages: regular application of evidence-based interventions to decrease variance; consistent practice among monitoring clinicians from a range of disciplines, early identification of abnormal signs and symptoms to start home-based interventions, and promotion of consistent patient self-management. A series of additional questions can be added by the monitoring clinicians to refine and customize the client monitoring plan based on clinical assessment of the individual's needs.

Health Professional Communication Pathway

Upon discharge of a heart failure patient from the emergency department, emergency physicians will generate an electronic treatment plan that provides updates for the patient and monitoring clinicians. This plan will contain appropriate limits of monitoring criteria (eg, the range of acceptable blood pressure and heart rate, oxygen saturation lower limits, or weight gain or loss per day), and anticipated therapeutic interventions if abnormal results occur.

Patients are requested to submit their data daily between 6:00 AM and midnight. The monitoring clinicians can track a cluster of patients remotely, and if abnormal measurements such as a precipitously low blood pressure occur, an alert will be triggered. The health professionals can then choose one of five actions: take note and continue to monitor the next set of data to determine if the abnormality persists, call the patients to assess directly, send an alert to the patient's family physician, contact the on-call cardiologist for consultation, or contact an on-call emergency physician to seek advice on management of admission to the emergency department.

It is important to note that in case of health emergencies or very abnormal biometric measurements, patients are instructed to call for help immediately by contacting ambulance services to go to the emergency department and not wait for the monitoring clinician to contact them.

Improving Outcomes and Cost Effectiveness of Seniors With Heart Failure

The TEC4Home evaluation will involve measuring outcomes in each of the Triple Aim arms.

Health outcomes: TEC4Home is expected to decrease 90-day readmission rates and improve clinical outcomes by increasing the safety and quality of care for seniors with heart failure at home after discharge from the emergency department.

Patient experience: A reduction in the readmission rates translates to improved quality of life for heart failure patients. Conceivably, home telemonitoring also provides peace of mind and security to patients, reducing anxiety about if or when to return to the emergency department. Participating in the collection of biometric measurements daily should also help increase patient engagement and understanding of their condition, in turn optimizing self-management. The additional data sharing between health care professionals (emergency and family physicians) is expected to result in improved communication and continuity of care during the transition from emergency department to home, directly benefiting patients.

Cost-effectiveness: An anticipated reduction of resource utilization (eg, emergency department visits and readmissions) will result in a cost savings to the health care system.

Fostering a Patient-Oriented Approach

Three patient and caregiver representatives with self and family experiences in heart failure management are members of the TEC4Home health-care innovation community. Their testimonies reflect their perspectives in heart failure management and their vision of how home telemonitoring will help optimize heart failure management. Their insights are fully incorporated into the protocol. The patient and family voice will continue to be integrated in TEC4Home throughout the project.

Potential for Scalability of TEC4Home

Our project is scalable by design from its inception because it is supported by the Ministry of Health with TELUS Health as the technology partner and includes clinical organizations across the province. This innovation community allows us to quickly disseminate our findings to other health authorities/communities

throughout the province and easily organize large-scale implementation and evaluation of this technology. In addition to the progressive expansion of our scaling up of testing and our cluster randomization trial, the Ministry of Health considers implementation of home telemonitoring as a key provincial strategy.

Ethical, Social, and Legal Issues

TELUS Health RPM passed two iterations of Privacy Impact Assessments plus privacy addendums prepared by the two participating health authorities during its pilot phase. This work involves ongoing engagement with the privacy leads of the health authorities and the Ministry though the Home Health Monitoring and Enabling Service's Privacy and Security Working Group.

Our steering committee members, including our patient representatives, will be intimately involved throughout this process. We will also request continual feedback from our patient advisory committee on these issues. In subsequent years, as we scale up this project to the remaining health authorities, we will continually engage with the leadership in each authority while incorporating best practices developed through implementation in Phase I.

Integration of eHealth Innovation Solutions Into Care Delivery Programs

Both the TELUS Health monitoring platform and Sentrian's predictive analysis for Remote Patient Intelligence will be integrated into TEC4Home clinical studies, and data gathered during this period will inform clinical decisions. Clinicians will be asked for feedback on the TEC4Home platform in terms of its utility in the screening and analysis of the patient's sensor data and the resultant recommendation of action plan. As a result, this SME combination of Sentrian and TELUS Health will enable integration of our eHealth innovation solution into the health care delivery system through a unique, scalable, and generalizable model of

- Having a rigorous experimental approach involving a community of scientific researchers and experienced clinicians to trial innovative technologies
- Being able to rapidly compare new technologies against the traditional gold standard, and once improvement is proven, having the evidence and means to rapidly introduce the innovation into the marketplace
- Using a provincial route to rapidly integrate innovation into health care and support the evolution of the Home Health Monitoring and Enabling Service through a 4-year cycle

Methods

Approach

Our project hypothesis is that TEC4Home will be a cost-effective strategy to decrease 90-day emergency department revisits and hospital admission rates and improve comfort and quality of life for seniors with heart failure.

Our evaluation includes three studies: (1) a feasibility study to introduce TEC4Home to health professionals and patients and to refine implementation and evaluation procedures, (2) a cluster RCT across British Columbia to evaluate the impact of TEC4Home with heart failure patients discharged from the emergency department and in particular the effect of this technology on rates of emergency department revisits and hospital admissions, and (3) an innovation study to run concurrently with the cluster RCT at an additional emergency department site to establish a pathway for rapid and rigorous introduction of innovation into the health system.

A cluster approach will be used to engage and allocate emergency department sites, replicating the introduction and integration of this intervention as a program and facilitating scalability to other locations. In this way, health professionals may participate in collective quality improvement, thereby ensuring that findings can be understood in context.

Study 1: Feasibility Study (Months 7-12)

Purpose

The purpose of this initial feasibility study will be to assess implementation and research procedures, identify areas of quality improvement, and inform any refinement of the RCT design. The 6-month study will implement and evaluate the clinical care path for heart failure patients being discharged from the emergency department or hospital at Vancouver General Hospital (VGH) and St. Paul's Hospital (SPH), two urban hospitals in the Vancouver region. Drawing upon the Institute for Healthcare Improvement's quality improvement model [19], this phase will allow us to gather patient and health professional feedback about the process in terms of patient journey and clinical workflow.

Participants and Recruitment

We will recruit patients over a 6-month period from VGH and SPH emergency departments. All patients presenting with heart failure to emergency departments will be approached and screened for study inclusion. To be eligible for participation, patients must be aged 65 years or older with a firm diagnosis of heart failure (ie, one of the following: clinical diagnosis, chest x-ray shows interstitial or pulmonary edema, echocardiogram shows reduced ejection fraction or diastolic dysfunction). Patients need to be deemed stable for discharge from the emergency department by treating emergency physicians and will be required to sign informed consent and be willing to actively participate, have the physical and cognitive ability to perform vital sign measurements as scheduled, have the ability and agreement to engage in self-management, and have no English language or technology barriers. They must also have a family physician that consents to participating. Patients who require hospital admission for long-term observation or do not have a family physician will be excluded. Note that these criteria will be the same across all three studies. Given the numbers of heart failure patients presenting in the emergency department in this setting and the eligibility criteria, we expect approximately 150 patients would be eligible to enroll. A minimum 60% consent rate yielding a sample size of 90 patients across both hospitals is estimated with a maximum attrition rate of 15%. Study 1 is designed as a feasibility study to test and improve procedures, with a purposive sample gleaned from the feasibility study sites; thus a power calculation has not

been included. Information gathered during this phase (ie, consent and attrition rates) will inform and refine the design of the cluster RCT.

Patients' own family physicians will be invited to participate and feedback will be collected from all involved (patients and health care professionals) to improve the approach. Emergency department personnel (physicians and nurses) will be engaged to participate in implementing TEC4Home as part of regular practice and will be invited to participate in the research as a quality improvement effort.

Process and Outcome Measurement

Our primary and secondary outcomes are aligned with the Triple Aim framework (ie, experience of care, population health, and cost/utilization). The primary outcome will be whether or not a patient returns to an emergency department, is hospitalized, or dies within 90 days following discharge. Secondary outcomes are reduction in cost as compared to usual care, improvement of communication during transition of care, quality of life (QoL), patient experience of care, and reductions in mortality and morbidity. Working with the Patient-Centered Performance Measurement and Improvement team in British Columbia, QoL and Patient-Reported Experience Measures (PREM) will be refined during Study 1.

Additionally, patient and health professional experience and satisfaction will be collected via interviews to gather quality improvement information. For health professionals, this will include gathering perspectives on the perceived impact of the home telemonitoring.

Procedures and Data Collection

Eligible patients will be invited to consent once stabilized in the emergency department. Measures and tools will be administered in order for patients to assess the research process and to inform Study 2. A prestudy survey will be administered to patients that includes social demographics, health related QoL as measured by a Patient-Reported Outcome Measure (PROM) (ie, Short Form Health Survey, SF-8) [20], patient activation (ie, Patient Activation Measure, PAM-13) [21], self-care and management (ie, European Heart Failure Self-Care Behavior Scale, EHFScBS-9) [22], health care utilization, and patient attitudes towards technology. Health care utilization and patient attitudes towards technology will be assessed by instruments developed and/or adapted by the study team. Patients will receive training and be equipped with the TEC4Home system prior to discharge from the emergency department. Patients will be monitored at home for 60 days with technical support and data will be collected from biosensors and patient self-reported health status twice daily. Thirty days after the 60-day monitoring period (ie, 90 days later), each patient will be administered a poststudy survey including the QoL, patient activation, self-care and management, health care utilization, and attitudes towards technology components of the prestudy survey in addition to items related to end-user experience including satisfaction with the TEC4Home experience and usability, perceived value, willingness to pay for this type of service/equipment based on an estimated cost provided to them in the survey, and relative value of components of the service. End-user experiences will be assessed using the System Usability Scale [23], while patient satisfaction and experiences will be assessed using survey tools developed by the research team. Patients across both sites will be invited to take part in individual interviews to help investigators firmly understand their experiences using TEC4Home and to provide in-depth information to illustrate, explain, and account for outcomes.

Emergency department personnel will receive training prior to TEC4Home roll out (ie, monitoring protocol and communication strategy). At the end of the 6-month study period, all participating health professionals will be asked to take part in an end-of-study survey and interview to provide feedback on satisfaction, usability, experiences with the monitoring protocol and communication strategy, and TEC4Home's impact on transitions for patients. Participating patients' family physicians will be contacted and invited to participate and will be asked to provide information on how the TEC4Home feasibility study and communication strategy worked from their perspective. They will complete the same poststudy survey as emergency department personnel and will indicate their permission to be contacted for a follow-up interview similar in focus to that conducted with emergency department personnel. Monitoring clinicians will provide feedback via structured telephone interviews on usability, the monitoring protocol, and communication strategy with a focus on quality improvement to refine and inform the design of the trial to follow (Study 2). After preliminary review of the interview data for key themes relating to quality improvement of the model, focus groups will be conducted at each hospital site, with a mix of emergency department personnel, family physicians, and patients, specific to the communication strategy and issues of transition with the goal of gathering information to direct adjustments/quality improvements for the trial phase.

Analysis

Hospital data captured and analyzed to assess outcomes will include patient revisits and admission rates within the 90 days postdischarge from the emergency department (60 days of monitoring and 30 days of additional follow-up) and days saved. Regression analysis will be used to analyze the impacts of age, gender, ethnicity, living circumstances, and attitudes towards technology on the outcomes. Individual level administrative data for heart failure patient revisits to emergency department and admission will be reviewed. Costs per patient for equipment, set-up, connectivity, and monitoring will be calculated and included in the analysis.

Content analysis of patient and health professional interviews will be used to identify themes and resulting recommendations for quality improvement of both implementation and evaluation processes to inform Study 2.

Study 2: Cluster Randomized Controlled Trial (Months 20-44)

Study Hospitals and Patients

All hospitals with an emergency department in British Columbia will be invited to participate. A total of 30 hospitals will be selected for inclusion in the study based on their similarity to

other hospitals in key characteristics (see Intervention and Control Population section). All patients presenting with heart failure to emergency departments will be approached and screened for study inclusion. As noted earlier, patient inclusion/exclusion criteria are identical to those stated in Study 1.

Intervention and Control Population

Study hospitals will be selected and matched with control hospitals in pairs based on the 90-day emergency department revisit or hospital admission rate prior to randomization, emergency department staffing (ie, ratio of certified emergency physicians to family physicians in emergency department workforce, number of individual physicians), service area population, and annual number of emergency department visits. One hospital in each pair will be randomly assigned to receive the TEC4Home intervention and the other will remain with usual care. Hospitals will be matched and randomized within each Health Authority in British Columbia, as each Authority will commence the trial at different times according to the size of the population it serves. Sites in Health Authority groupings will enroll in the 18-month study period (in descending order according to size of population served) at the beginning of each subsequent month. At the end of each Authority's 18-month trial period, emergency departments will participate in an additional total 90 days of monitoring (60 days) and follow-up (30 days) to ensure complete data is gathered for any patients enrolled within the last month of the study period. The intent of this approach is to maximize geographic balance for both equitable opportunity and generalizability purposes. Hospitals for which no appropriate match can be identified will be excluded.

Power and Sample Size

Based on prestudy data, the expected proportion of patients experiencing the primary outcome in the control hospitals is 12% with a standard deviation across hospitals of approximately 2.4%. This SD yields an intraclass correlation coefficient of .005. Based on Ministry of Health/TELUS data from their home monitoring pilot, we expect that the intervention will reduce the proportion of patients with the primary outcome to 6%. If 30 hospitals are included in the study with an average recruitment of 30 patients per hospital (900 patients in total), the study will have a power of 84%, assuming a 2-sided alpha level of .05. We will pair-match hospitals on selected baseline variables and adjust for baseline outcome rates in the analysis to increase the power and to compensate for an intraclass correlation that may be higher than the value used in the calculation. Based on recent Vancouver Coastal Health Authority discharge data, approximately 33 heart failure patients are discharged from the emergency department per 100,000 people per year. Assuming 60% of these patients will be eligible and consent to enroll in the study, 20 patients will be enrolled per 100,000 population per year. We expect that 3 million people will be serviced by the study sites. Over an enrollment period of 18 months, we are confident that we will be able to recruit our planned sample size of 900 patients.

Process and Outcome Measurement

For both the feasibility study (Study 1) and cluster RCT (Study 2), the primary outcome goal is to reduce emergency department revisits/admissions measured by the proportion of patients who have an emergency department visit or admission within 90 days following discharge. This will be measured via hospital data and patient self-report postintervention. This aligns with the Triple Aim goal of improving population health [24]. Secondary outcomes related to the Triple Aim goal of cost effectiveness are reduction in cost as compared to usual care measured by utilization relative to patient outcomes and experience measured via hospital data as well as patient self-report. Reduction in cost metrics to ascertain cost utility (ie, number of emergency department visits saved; quality-adjusted life years) will be assessed via PROM including QoL measure. Outcomes related to the Triple Aim goal of improved patient experience of care are improved QoL for heart failure patients and improved experience of care (eg, continuity of care, comfort) as measured by the PREM tool. Other population health-related outcomes include reduction in mortality as measured by hospital data and reduction in morbidity as tracked through patient sensor data and self-report.

Primary and secondary outcomes will be identical to the feasibility study. The primary outcome will be whether or not a patient returns to an emergency department, is hospitalized, or dies within 90 days following discharge (60 days of which the patient will be monitored). Utilization data (eg, emergency department visits and admissions) will be assessed by accessing hospital and provincial database records as well as through patient self-reporting of utilization after the study period; the former is the primary method, and the latter will be considered in sensitivity analysis.

Data Collection Procedures

Both control and intervention patients will complete pre- and poststudy period surveys as described in Study 1. The ultimate primary and secondary outcomes will be subject to further development and refinement as necessary by the project team as informed by the feasibility study. Patient screening and training to use the TEC4Home system will occur as in the feasibility study. Patients will be monitored at home for one month during which data will be collected daily from the patient station biosensors (eg, blood pressure) and self-reported health indicators (eg, dizziness). Pre- and postintervention surveys will be administered to patients, recording social demographics and QoL as measured by the PROM and PREM tools. Postsurveys will include self-report items related to health system utilization including family physician visits, emergency department visits, and lab work.

Analysis

We will use descriptive analysis to compare baseline characteristics of emergency departments and individuals. For the primary analysis, an intent-to-treat hierarchical (mixed-effects) logistic regression model will be fit to compare the proportions of patients who experienced the primary outcome in the intervention and control arms. This model will adjust for baseline characteristics at both the emergency

department (eg, prestudy emergency department revisit/hospitalization rate, service area population) and patient (eg, age, gender) level. As hospital records will supply emergency department revisit/hospital admission data, missed outcome events will be rare. Monitoring data will be analyzed using statistical process control charting techniques to allow a more comprehensive understanding of patient's health condition over time.

Sex and Gender Analysis

No sex and/or gender specific analysis will be conducted. While there may be some sex differences in the incidence and prevalence of heart failure, our intervention is intended to establish a mechanism for the prevention and management of symptoms common to both groups. However, if sex and/or gender themes were to arise out of the qualitative data collected regarding patient experience, they would be explored.

Cost-Effectiveness Evaluation

Cost-effectiveness analysis and cost-utility analysis will be conducted. We will assess the incremental costs of the home monitoring platform relative to usual care and further track costs related to all utilization during the 90-day postdischarge period. Utilization will include hospital admissions, emergency department visits, community family physician and other health provider visits, drugs, and laboratory and other tests obtained outside the hospital. Utilization will be captured through hospital administrative databases and a simple resource utilization questionnaire administered to patients at the time of patient outcome data collection. The questionnaire will be developed during the study. In order to evaluate cost effectiveness, administrative data regarding health services utilization (in particular, emergency department revisits/hospitalizations) for cases and controls will be compared. Differences in utilization rates will then be used to determine differences in cost for both patient groups based on average costs for heart failure patients. Incremental costs will be compared to incremental benefits (ie, primary and secondary outcomes) in order to determine the cost per life year gained and cost per quality adjusted life year gained. A societal perspective will be taken in the analysis as both government and patient out-of-pocket costs will be captured. Probabilistic sensitivity analysis will be conducted in order to assess the robustness of the results through variation of key parameters.

Study 3: Innovation Testing (Months 20-38)

During the trial period, a concurrent but separate test study will be conducted. This will entail the recruitment and engagement of an additional emergency department site during an 18-month period. The purposively selected site will be an emergency department in the Metro Vancouver area that is not involved in the cluster RCT (ie, Study 2). The innovation study will compare usual monitoring protocol to the same protocol with the addition of Sentrian intelligent monitoring software.

The goal of this study is to determine the value of the Sentrian innovation and demonstrate the value of this system to health professionals. Given the numbers of heart failure patients presenting in the emergency department in this setting over 18 months and the eligibility criteria, we expect approximately 135 patients would be eligible to enroll. Note that inclusion/exclusion criteria are the same as in the previous two studies. A minimum 60% consent rate yielding a sample size of approximately 80 patients is estimated with a maximum attrition rate of 15%. Patients will be randomized into one of two groups as they present to the emergency department: (1) regular monitoring or (2) monitoring plus Sentrian intelligent monitoring software. This innovation study is not about the outcome of revisits or admissions; rather the purpose is to determine how best to measure utilization and health professional experience in terms of decision support (that is, how the information provided by the Sentrian technology alters the physicians' decision processes). Therefore the purpose is not to develop a model for clinical suggestions but rather to test the impact of Sentrian predictive model on physicians' clinical decisions for this patient population. Because this study is not designed for a definitive comparison, no power calculation has been included. The primary outcome for this study will be health care utilization and will be measured by patient self-reporting as well as administrative data during the full 90-day follow-up (60 days monitoring, 30 days additional tracking). We will also collect health professionals' perspectives around how this innovation impacted decision support.

Surveys and interviews with health professionals will elicit their experiences regarding the value of the Sentrian innovation for decision support. Areas of inquiry will include the amount of time and degree of concern about patients versus assurance for clinical decision support (ie, does it reduce the amount of personnel power for monitoring and increase human capacity by augmenting intelligence of monitoring?). Study 3 will produce evidence for the introduction of this particular innovation into a full trial, as well as define the pathway for introduction of other innovations developed by SMEs. This additional exploration will provide a flexible innovation framework and a pathway for SMEs to continuously test new innovation and integrate new technology into standard care practice.

Implementation and Evaluation Timeline

Phase 1 (Months 0-15)

Planning and Preparation (months 0-6): Activities include forming a Steering Committee and working group committees and finalizing protocols for testing and data collection materials. Emergency departments from the Vancouver area will be selected and trained.

Study 1: Feasibility Study (months 7-12): Patients will be enrolled and data will be collected over a 6-month study period.

Postfeasibility Study Quality Improvement (months 13-15): Final data collection will be completed with patients and health care providers. Integrative analysis of quantitative and qualitative data will be conducted.

Phase 2 (Months 15-44)

Trial Preparation (months 15-17): Results from the feasibility study will be used to refine procedures and protocols. Recruitment and data collection materials will be created.

Emergency departments from across the province will be engaged for potential inclusion in the trial.

Enrollment and Training (months 18-23): Emergency department sites will be enrolled and randomized. Site champions/leads will be identified. Protocols for patient recruitment and data collection will be established at each site and personnel will be trained.

Study 2: Cluster RCT (months 20-44): The cluster RCT will be conducted separately within each Health Authority, with initiation into the study occurring on a monthly basis from months 20-24. Regular meetings with each site will be set up to sustain engagement, flag potential problems, and address any challenges.

Study 3: Innovation Study (months 24-44): This innovation test will compare usual monitoring protocol to the same protocol with the addition of Sentrian intelligent monitoring software. This additional exploration will provide a flexible innovation framework and a pipeline for SMEs to continuously test new innovation and integrate new technology into standard care practice.

Phase 3 (Months 40-48)

Knowledge Translation and Sustainability Planning (months 40-48): An integrated analysis of all data collected will be conducted. Results will be shared with the project team and participating sites. Findings and recommendations will be drafted and disseminated. Meetings, publications, presentations and other venues will be used to engage all stakeholders and to collectively set prioritization for next steps as we plan to spread and scale up TEC4Home.

Results

This project was awarded funding in October 2015 from the Canadian Institutes of Health Research via the eHealth Innovations Partnership Program. Matching funds were provided by the Michael Smith Foundation of Health Research and TELUS Health.

Patient enrollment into the feasibility study commenced in October 2016. Results from the feasibility study are expected by summer 2017. The provincial RCT is expected to roll out January 2018.

Discussion

TEC4Home focuses on the application of eHealth to help seniors stay safely at home for longer. Specifically, the project will evaluate the use of home telemonitoring technology to support patients during the transition of care between acute and community settings. While there is some evidence for home telemonitoring being effective, it is often limited to one system (acute or community) and has conflicting results. TEC4Home will extend existing research by studying the use of this technology across the two health care settings and also look at the communication between health professionals and patients. It will also create an infrastructure to not only test existing technology but incorporate emerging sensors into practice in a judicious manner.

As our population continues to age and as technology continues to become more ubiquitous, TEC4Home offers a channel to respond to both. This protocol will generate evidence through a programmatic evaluation and a clinical trial to determine how home telemonitoring may improve care and increase patient safety during the transition of care and how it is best implemented to support patients within this context.

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Conflicts of Interest

None declared.

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Abbreviations

EHFScBS-9: European Heart Failure Self-Care Behavior Scale
PAM-13: Patient Activation Measure
PREM: Patient-Reported Experience Measure
PROM: Patient-Reported Outcome Measure
QoL: quality of life
SF-8: Short Form Health Survey

SME: small or medium enterprise
SPH: St. Paul's Hospital
VGH: Vancouver General Hospital

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Toronto, ON, M5A 3Y5
Phone: (+1) 416-583-2040
Email: support@jmir.org