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Protocol

Use of a Therapeutic, Socially Assistive Pet Robot (PARO) in Improving Mood and Stimulating Social Interaction and Communication for People With Dementia: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Socially assistive robotics is a growing area for geriatric research.

Objective: This single-blind, randomized controlled trial (RCT) aims to investigate the use of PARO, a therapeutic, socially assistive pet robot, in improving mood, and stimulating social interaction and communication for people with dementia in the community.

Methods: For the study, 40 community-dwelling older Chinese adults (≥60 years) with mild to moderate dementia will be recruited and randomly assigned to the PARO therapy group or the psychosocial activities control group. Both treatments consist of six, 30-minute weekly sessions, which will be conducted in a geriatric day hospital. Subjects in both groups will be assessed by a trained research assistant at baseline (pre-), during, and post-treatment. Mood (assessed with a simplified face scale), social interaction, and communication (ie, facial expressions and reactions towards each treatment, assessed with an observation table) will be the primary outcome measures. Secondary outcome measures will include assessments on cognitive function (Mini-Mental State Examination) and depressive symptoms (Cornell Scale for Depression in Dementia), as well as caregiver burden (Zarit Burden Inventory). Subjective impression towards each treatment and qualitative comments from the caregivers, facilitator, and therapists will also be obtained.

Results: Recruitment to the pilot study began in 2014 and the last subject is expected to complete their post-treatment assessment in 2015.

Conclusions: This will be the first RCT using PARO to improve mood, and stimulate social interaction and communication in the care of older people with dementia, as well as provide an evidence basis for the use of PARO in dementia care in Hong Kong.

Trial Registration: The Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12614000037606; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12614000037606 (Archived by WebCite at http://www.webcitation.org/6Xi7uXdu9).

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KEYWORDS

dementia; elderly; PARO; randomized controlled trial; robot-assisted therapy; socially assistive robots

Introduction

With a rapidly ageing population, dementia has become an important public health issue worldwide [1]. In Hong Kong, there are over one million people aged 60 and above who had dementia in 2009, and by the year 2039, this is projected to increase to over three million [2]. Non-pharmacological interventions are recommended as the preferred first-line treatment for people with dementia [3,4], with cognitive stimulation therapy being the most studied [5]. The finding from a recent systematic review of cognitive stimulation therapy on optimizing cognitive function of older adults with mild to moderate dementia was comparatively robust and promising. However, the majority of studies have focused on cognitive abilities (eg, memory performance, problem solving, and communication techniques), and the effects on psychological and social aspects remain inconclusive [6,7].

Activities, especially in group settings such as social support groups, may be of psychological and social benefits to people with dementia by reducing depression and improving quality of life [8]. Yet, a great challenge remains with respect to how to stimulate these older people to respond and participate in such activities. Furthermore, owing to a lack of manpower for many day care centres in Hong Kong [9], few provide stimulating social activities for those with dementia. As a result, older adults with dementia spend most of the time sitting around in an environment that is not home, only effectively providing respite care for their family caregivers. Inadequate social engagement can be detrimental, as it magnifies the feelings of loneliness that often accompany the progression of dementia [10]. Other studies have also associated low social engagement with cognitive decline [11] and increased mortality [12].

In recent years, socially assistive robots have been developed for elderly care, particularly companion robots [13,14]. Anecdotal reports, as well as two systematic reviews to date, suggest that robot-assisted therapy is a potentially cost-effective treatment for dementia as it has the potential to improve mood, encourage social interaction and communication, and therefore enhance the well-being of the elderly, and decrease the workload of their caregivers [15,16]. Furthermore, the reported psychosocial effects have been more striking than the results achieved by conventional therapies [17].

Amongst the recent literature on the use of socially assistive robots in elderly care, the most widely studied is PARO (Figure 1). PARO is a therapeutic, socially assistive pet-type robot with an appearance of a baby harp seal, and is equipped with different kinds of sensors, including tactile, light, audition, temperature, and posture. Thus, it can respond to different stimulations (eg, striking and holding) given by the users, or recognize the direction of voice from them. It was designed by Shibata et al [18], and has been used with positive and promising results since 2003 in many countries including Japan, Denmark, Canada, Italy, and the United States [19-22]. In 2009, PARO was certified as a type of neurological therapeutic device by the Food and Drug Administration (FDA) in the United States (Registration number: 3009118691) [23]. In 2010, a caregiver's manual for robot therapy was published to achieve effective therapy [24,25].

Several intervention trials demonstrated promising effects of participating in PARO therapy in increasing motivation, improving mood, reducing stress, and increasing social communication in elderly people [22,26-28]. Positive effects of PARO therapy on mood, social interaction and communication, as well as cortical neuron activity have also been reported in people with dementia [21,29,30]. A recent pilot randomized controlled trial (RCT) reported that for older people with dementia, PARO therapy had a moderate to large positive influence on their quality of life [31]. More recently, the potential therapeutic benefits of PARO for the treatment of neurological diseases have also been published [32]. Although positive effects of PARO therapy in people with dementia or other brain disorders have been reported in various populations, many were observational studies or involved small numbers of subjects. Other interventions, such as animal-assisted therapy, appeared to have beneficial effects on mood, and increased social interaction and communication in people with dementia [33-35]. However, there are many concerns with animal-assisted therapy such as allergies, cleanliness, and the unpredictable nature of live animals.

To date, the potential benefits of PARO therapy in Hong Kong Chinese have not been systematically examined. Given the successful application of PARO therapy, and the encouraging findings of its positive effects on mood and social interaction and communication, it is suggested that PARO therapy is both feasible and acceptable to elderly people with dementia. Therefore, in this study protocol, we describe the design of a RCT aiming to confirm the findings of our pilot data (see Piloting in the Method section), by providing an evaluation of the effectiveness and benefits of the use of PARO in dementia care in Hong Kong.

The primary objective of the present study is to examine whether robot-assisted intervention using PARO in older Chinese adults with mild to moderate dementia improves mood, and stimulates social interaction and communication compared to psychosocial activities by conducting a methodologically rigorous RCT. Secondary objectives are to examine the effects of PARO therapy on cognitive function, depressive symptoms, and caregiver burden compared to those of psychosocial activities.

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Figure 1. PARO, a social robotic seal.

Methods

Study Design

This is a single-blind RCT comparing PARO therapy and psychosocial activities in the elderly with dementia. Treatment outcomes will be assessed at baseline (pre-), during, and post-treatment. The study will be carried out in Shatin Hospital, a geriatric day hospital located in Shatin, New Territories, Hong Kong. The protocol for this study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12614000037606) and has been approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. The study design is detailed in Figure 2.

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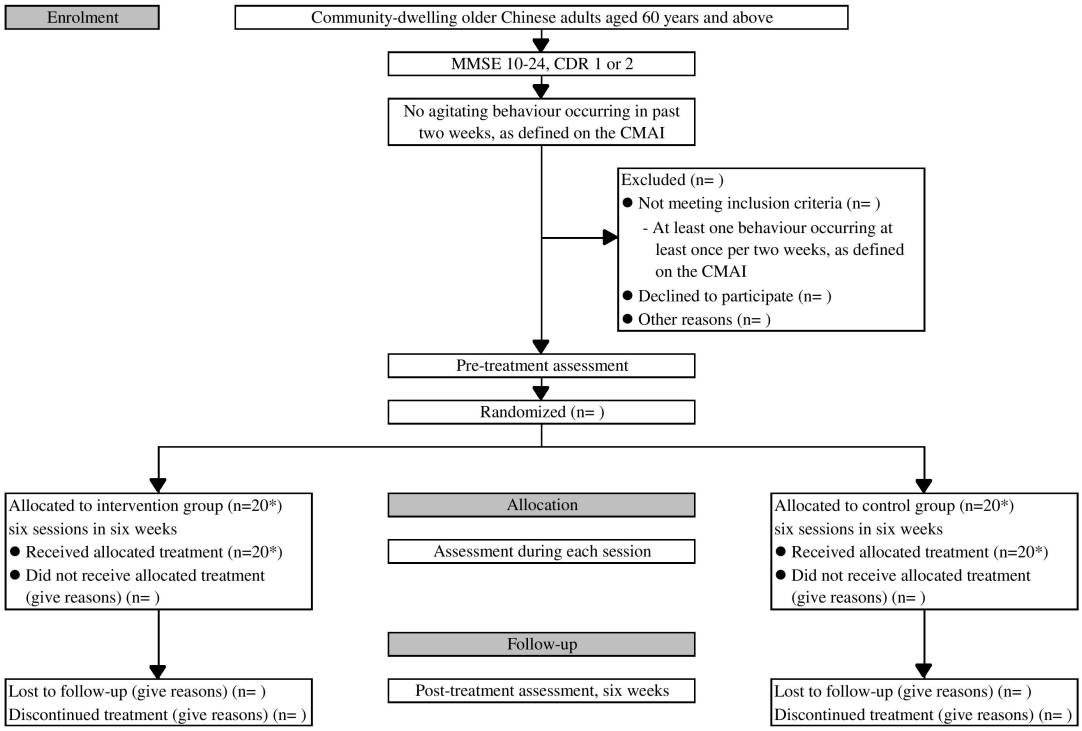
Figure 2. Flow chart of the study design. *Indicates the target number of subjects. CDR: Clinical Dementia Rating, CMAI: Cohen-Mansfield Agitation Inventory, and MMSE: Mini-Mental State Examination.



Subjects

Overview

The study population will include 40 community-dwelling older Chinese adults with mild to moderate dementia. Recruitment will occur through clinical referrals from community dementia day care centres, geriatric outpatient clinics, nurse-led memory clinics, and day hospitals. Those who are potentially eligible will be invited to a face-to-face screening assessment including an elicitation of a medical history, medications, and hospitalization for eligibility confirmation. To be eligible for the study, subjects must meet the inclusion and exclusion criteria described in the following sections.

Inclusion Criteria

Community-dwelling older Chinese adults aged ≥60 years will be screened using the Mini-Mental State Examination (MMSE) [36,37]. Those who score between 10-24 with a diagnosis of dementia will be screened for eligibility to the study. Diagnosis of dementia will be based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Severity of dementia will be determined using Clinical Dementia Rating (CDR), a widely used clinical staging instrument for dementia [38,39]. Subjects with mild to moderate dementia (CDR 1 or 2) will be further assessed for the presence of agitated behaviour using Cohen-Mansfield Agitation Inventory (CMAI) [40].

Exclusion Criteria

Individuals who exhibit any behavioural and psychological symptoms of dementia (at least one item of CMAI scoring ≥2) will be excluded from the study. Subjects will also be excluded if they have severe medical conditions which limit their abilities to complete the course of treatment. Concurrent psychotropic medication will be allowed without restriction, but any change in psychotropic prescriptions over the course of the treatment period will be monitored. In addition, those who are currently participating in other studies, experimental therapies, or blinded treatments will be excluded.

Informed Consent

For eligible individuals, the study will be introduced to the subjects and their caregivers. Written informed consent will be obtained from every eligible subject agreeing to participate, as well as their caregivers prior to the study. If a subject is unable to give written informed consent, proxy consent will be obtained.

Baseline Assessment and Randomization

After obtaining written informed consent, a baseline (pre-treatment) assessment will be performed. Subjects will be randomized into either the intervention or the control group. A

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study coordinator will randomize subjects by means of a computer-generated list of random numbers in blocks of six, stratified by gender. Treatment assignments will be concealed in consecutively-numbered sealed envelopes, which will be opened sequentially upon subject enrollment. As it is a single-blind study, the subjects and the study coordinator will not be blinded to the treatment assignment. However, the study coordinator will not take outcome measurements. All investigators and outcome assessors will be blinded to the treatment assignment.

Intervention Group

The PARO therapy will take place for 30 minutes once a week over a six week period, and will be delivered in a quiet room that is isolated from the common unit (ward) in the Occupational Therapy Department of Shatin Hospital, with minimal environmental distractions. The number of sessions, the length of each session, and the time frame of this study were decided based on the results of our pilot study (see Piloting of this section) and other PARO intervention studies which reported small or significant changes in mood, social interaction, and communication [15]. Given this, one 30-minute session per week for six consecutive weeks would allow sufficient time for identifying significant changes, and would also reduce the burden of commitment for subjects.

The PARO therapy will be delivered in a structured, small-group approach, in which a group of three to four subjects will be arranged to sit around a table with PARO in the centre. The subjects in each group can be substituted by subjects from other groups to optimize the chance of conducting each session. A facilitator who is familiar with the PARO caregiver's manual will deliver the PARO therapy. Research team therapists will train the facilitator and monitor the sessions.

The PARO therapy is based upon a standardised framework, and involves activities around the concepts of engaging, social interaction, and communication. There are six stages/themes, including (1) introducing PARO, (2) baby-sitting PARO, (3) grooming PARO, (4) feeding PARO, (5) making over PARO, and (6) wardrobe PARO. During each session, the facilitator will show PARO to each subject and demonstrate how PARO responds. Subjects will be encouraged to touch and hold PARO, describe the features and appearance of PARO, and help take care of PARO. The session will proceed for at least 30 minutes. With one session per week, there will be at least a total of 180 minutes of the treatment in the six week period.

Control Group

Subjects assigned to the control group will be invited to practise a variety of psychosocial activities including a range of table games (eg, Chinese checkers, Jenga, board games etc). The activities will be held on exactly the same schedule as the intervention group (one 30-minute session per week for six weeks). All activities will be carried out in groups of three to four subjects, and will be facilitated by the same facilitator of the intervention group. The sessions will proceed for at least 30 minutes. With one session per week, there will be at least a total of 180 minutes of the treatment in the six week period.

Outcome Measures

Measurement of outcomes will take place at pre-, during, and post-treatment. Mood, social interaction, and communication (ie, facial expressions and reactions towards each treatment) will be the primary outcome measures. Secondary outcome measures will include cognitive function and depressive symptoms, as well as caregiver burden. Pre-treatment and post-treatment assessments will be administered by a trained research assistant who will remain blinded to group allocation. Outcome measures administered at each time point are described in Table 1. Attendance at each session will be recorded for all subjects in the study.

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Table 1. Schedule of assessments.

Assessments	Screening	Pre-treatment	Treatment session number						Post-treatment
			1	2	3	4	5	6	
MMSE[a]	√ [g]								√
CDR[b]	√								
CMAI[c]	√								
Demographics, lifestyle, and social characteristics		√							
Simplified face scale			√	√	√	√	√	√	
Observation table[d]			√	√	√	√	√	√	
CSDD[e]		√							√
ZBI[f]		√							√
Subjective impression questionnaire			√	√	√	√	√	√	
Qualitative comments from caregivers, facilitator, and therapists									√

[a]Mini-Mental State Examination (MMSE)

[b]Clinical Dementia Rating (CDR)

[c]Cohen-Mansfield Agitation Inventory (CMAI)

[d]Facial expressions and reactions towards each treatment

[e]Cornell Scale for Depression in Dementia (CSDD)

[f]Zarit burden interview (ZBI)

[g]The √ indicates at which point of the study the respective assessments will take place.

Demographics, Lifestyle, and Social Characteristics

Demographic information such as age, gender, marital status, educational background, living status, lifestyle factors (eg, smoking and alcohol intake), social supporting network (eg, measures of participation in day care centre, cognitive/memory training, community activities, and supporting groups), attributes of the owners of pet (ie, animal preference, ever kept pets, and plan to keep pets) [41], and child care experiences will be extracted from pre-treatment questionnaires.

Primary Outcomes

Simplified Face Scale

A simplified face scale will be used to assess mood state before and after each session. This very brief, pictorial scale of mood uses a sequence of 7 faces and does not require reading literacy [27]. The original face scale contains 20 drawings of a single face arranged in serial order by rows, with each face depicting a slightly different mood state [42]. However, sometimes the subjects were confused by the original face scale because it contained too many similar images. Thus, the scale was simplified by using only 7 images from the original set. The 7 faces range from very happy at the left to very sad at the right.

Observation Table

In order to objectively examine changes in subjects' social interaction and communication (ie, facial expressions, and reactions towards PARO or the psychosocial activities), treatment sessions will be videotaped and charted on an every-minute basis with an observation table by reviewing the videotaped clips after each treatment session. The observation table is a modified version of the one originally developed by Wada et al [24]. Responses will be classified into several categories, including expression, gaze, and interactions with PARO or the psychosocial activities, other subjects, facilitator, and therapists. The frequency of each response will be added, and depending on the duration of each session, the highest possible item-score is 30. The amount of time spent on verbal encouragement (prompting) offered will also be recorded.

To assess the inter-rater and intra-rater reliabilities of the modified observation table, a convenience sample of 11 community-dwelling older Chinese adults with mild cognitive impairment or mild to moderate dementia with a mean age of 80.5 (range 73-88 years, SD 4.9), of which 82% (9/11) were female, and with a mean MMSE score of 16.5 (range 9-24, SD 5.9) were recruited to receive a single 30-minute PARO therapy. The therapy sessions were videotaped and observed by two raters (one occupational therapist and one medical researcher) who independently marked the subjects' facial expressions and reactions towards PARO on the modified observation table on an every-minute basis (with standardized rating criteria), on two different occasions with an interval of two to four weeks. Intraclass correlation coefficient (ICC) was used to measure the reliability of the ratings. The ICC of the inter-rater reliability was.95-1.00 and the ICC of the intra-rater reliability was.87-1.00 [43].

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Secondary Outcomes

Mini-Mental State Examination (MMSE)

The Mini-Mental State Examination (MMSE) is a validated scale to assess cognitive performance in both research and clinical settings [36]. It contains 20 items and scores range from 0-30, with a higher score denoting better cognitive function. The Chinese version of the MMSE has good psychometric properties, with satisfactory internal consistency (Cronbach's alpha=.86) and test-retest reliability (alpha=.78), and good inter-rater reliability (ICC=.99) [37].

Cornell Scale for Depression in Dementia (CSDD)

The Cornell Scale for Depression in Dementia (CSDD) is a validated scale used to assess the signs and symptoms of major depression in patients with dementia [44]. The information is elicited through two semi-structured interviews, one with the patient and one with the caregiver. The scale is divided into the following five sub-scales (1) mood-related signs, (2) behavioural disturbance, (3) physical signs, (4) cyclic functions, and (5) ideational disturbance. There are 19 items, of which each can be given a score ranging from 0 (absent) to 2 (severe). The total score ranges from 0-38; a higher score denotes greater levels of depression. The Chinese version of the CSDD demonstrated satisfactory internal consistency (Cronbach's alpha=.84) and inter-rater reliability (kappa=.43-.89) [45,46].

Zarit Burden Inventory (ZBI)

The Zarit Burden Inventory (ZBI) is a validated scale to assess caregiver burden [47]. It contains 22 items, each of which can be given a score ranging from 0 (never) to 4 (nearly always). The total score ranges from 0-88; a higher score denotes greater perceived caregiver burden. The Chinese version of the ZBI showed a good internal consistency reliability (ICC=.99, split half correlation coefficient=.81) [48].

Other Assessments

Subjective Impression Questionnaire

Subjective impression of PARO will be assessed at the end of each session of the PARO therapy by adopting four items from studies conducted by Shibata et al [29,49], with two of them reflecting subjects' preference towards PARO and the other two for understanding their own feelings when interacting with PARO and their readiness to receive the PARO therapy. The four questions are (1) Is PARO cute/ugly?, (2) Do you like/dislike PARO?, (3) Is playing with PARO fun or boring?, and (4) Do you want to play with PARO again? For the group assigned to the psychosocial activities, four similar questions will be used (1) Is the activity interesting/not interesting?, (2) Do you like/dislike the activity, (3) Is the activity fun or boring?, and (4) Do you want to join the activity again?

Qualitative Comments

Qualitative comments from the caregivers, the facilitator, and the therapists will also be obtained from semi-structured qualitative interviews. Interviews will be conducted within one month of completing the treatment program. For the caregivers, the interviews will explore their perceptions of the impact of dementia on the subjects' daily lives, experiences of the interventions that were designed to improve mood and encourage social interaction and communication since diagnosis, and feedbacks after the treatments. For the facilitator and the therapists, the interviews will elicit information about the subjects' reactions towards each treatment. Furthermore, the challenges of subject recruitment, treatment implementation, as well as the factors associated with interest in engagement and adherence of the treatments will also be obtained.

Piloting

Prior to the study, a pilot study was performed to explore the feasibility and potential benefits of PARO therapy in older adults with dementia. Using a pre-post single group design, community-dwelling older Chinese adults with mild cognitive impairment or mild to moderate dementia were recruited to receive six sessions of the PARO therapy (one 30-minute session per week for six consecutive weeks) in Shatin Hospital. The PARO therapy was delivered in a structured, small-group approach, in which a group of 3-4 subjects were arranged to sit around a table with PARO in the centre. An occupational therapist familiar with the PARO caregiver's manual delivered the PARO therapy (Figure 3). The mean age of the 7 subjects that completed the PARO therapy was 78.6 (range 72-87, SD 5.3), of which 43% (3/7) were female, and with a mean MMSE score of 19.3 (range 16-22, SD 2.8). Using the Wilcoxon signed ranks test, there was a significant improvement in mood, as evaluated by the simplified face scale, following the PARO therapy (P=.02). Social interaction and communication was evaluated by video analysis of facial expressions and reactions towards PARO using a time sampling method where the 30 minutes of video were divided into 30 units, and each one minute unit was checked for the occurrence of each facial expression and reactions towards PARO. The analysis showed that the frequency of neutral expressions during the six 30-minute sessions was high (mean observed frequency of the six sessions was 27 minutes out of 30 minutes), followed by smile (13 minutes out of 30 minutes), and laugh (9 minutes out of 30 minutes). Furthermore, all subjects gently stroked or held PARO during the interaction, and talked directly with PARO in a dyadic relation as if it was a real living pet. In addition, there was a positive trend in depressive symptoms, as evaluated by CSDD (P=.03) and a falling trend in caregiver burden, as evaluated by ZBI (P=.02) immediately following the PARO therapy. All subjects completed the six-session PARO therapy, with the attendance rate of 100%. Thus, our findings provide important preliminary support for the use of social robot in engaging older patients with dementia in a day care setting. The questionnaires and assessment protocols have been pilot-tested.

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Figure 3. PARO therapy.

Sample Size Calculation

Sample size calculations were based on the effects on mood in the pilot study: a sample size of 15 subjects per group will allow us to detect differences among the mean values of face scale scores (0.63, SD 0.74) between pre- and post-interventions using one sample *t* test (alpha=.05 and power=.9). Given that the attrition rate of 20% was observed in a previous PARO study of people with dementia [30], we will estimate a more conservative attrition rate of 25%, and thus we will recruit a total of 40 subjects.

Statistical Analysis

Double data entry, consistency check, and data cleaning will be performed prior to data analysis. An intention-to-treat (ITT) analysis will be carried out, in that all available data will be included, without considering the subjects' compliance to the allocated treatment. Mean and standard deviation will be used for continuous variables while frequency and percentage will be used to describe the distribution of ordinal and categorical variables. Unpaired tests will be used for the primary analysis. Differences between the intervention and control groups in relation to outcome measures will be compared using an analysis of variance (ANOVA) or independent *t* tests. In order to increase precision in estimating the effect of interest, the analysis of covariance (ANCOVA) will be used to take into account the possible confounding effects of the covariates, such as age, education, etc. A mixed-model, repeated-measures ANCOVA will be used to compare the reactions towards each treatment captured by the observation table in both groups. The effect size will be computed to show the magnitude and direction of the effect of the intervention group relative to the control condition for each outcome variable. Data analyses will be conducted by SPSS Statistics software. A $P<.05$ will be taken as the level of statistical significance. The 95% confidence interval around the differences will be calculated.

Results

Recruitment to the pilot study began in 2014 and the last subject is expected to complete the post-treatment assessment in 2015.

Discussion

Significance of the Study

The proposed study is, to our knowledge, the first RCT of the use of PARO in improving mood, and stimulating social interaction and communication compared to psychosocial activities in older Chinese adults with mild to moderate dementia in a day care setting in Hong Kong. The results could have particular importance given the rise in the prevalence of dementia in our society.

Study Strengths and Limitations

The proposed study has several notable methodological strengths. The use of videotaped observations will allow us to capture subjects' facial expressions and reactions towards each treatment during the treatment sessions, of which standard questionnaires or proxy interviews may miss. The modified observation table assesses the degree to which people with dementia will respond with the treatment by videotaped observation, which has the advantage in that ratings were specifically developed in the context of social interaction and communication between elderly patients with dementia and PARO or the psychosocial activities and other subjects, the facilitator, and therapists. Inter-rater and intra-rater reliabilities of the table have been developed. Another strength of the proposal is the measurement of various variables including caregiver burden, and qualitative components from the

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caregivers, facilitator, and therapists, which could reflect mood and social behaviours in another perspective.

There are several limitations in the protocol. Although behavioural and psychological symptoms of dementia occur frequently in people with dementia, we will confine our study population to mild to moderate dementia, and will exclude those with behavioural and psychological symptoms of dementia, limiting the generalizability of the results to a wider population. It has been suggested that interventions for those with behavioural and psychological symptoms of dementia should tailor the person's specific needs and capabilities [50]. As such, an individual-based setting may be more appropriate to those with behavioural and psychological symptoms of dementia, while a group-based setting is preferred to examine the use of PARO in stimulating social interaction and communication. Moreover, subjects will be recruited through clinical referrals from community day care centres, clinics, and day hospitals; they may not represent all older adults with dementia in the community. In addition, the simplified face scale, CSDD, ZBI, and the subject impression questionnaire are self-reported. Misreporting and non-reporting may occur.

Conclusions

This proposed study will provide an evaluation of the effectiveness and benefits of the use of PARO in older Chinese adults with mild to moderate dementia in a day care setting. Results of this study would showcase a novel activity to improve mood, and stimulate social interaction and communication in community care of older people with dementia, as well as provide an evidence base for the use of such social robots. Further research is warranted to examine the use of PARO in managing behavioural and psychological symptoms of dementia using individualized approaches.

Conflicts of Interest

Takanori Shibata is the developer of PARO.

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Abbreviations

ANCOVA: analysis of covariance
ANOVA: analysis of variance
CDR: clinical dementia rating
CMAI: Cohen-Mansfield Agitation Inventory
CSDD: Cornell Scale for Depression in Dementia
DSM-IV: diagnostic and statistical manual of mental disorders
ICC: Intraclass correlation coefficient
ITT: intention-to-treat
MMSE: Mini-Mental State Examination
RCT: randomized controlled trial
ZBI: Zarit Burden Inventory

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Protocol

A Neurofeedback-Based Intervention to Reduce Post-Operative Pain in Lung Cancer Patients: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Thoracic surgery appears to be the treatment of choice for many lung cancers. Nevertheless, depending on the type of surgery, the chest area may be painful for several weeks to months after surgery. This painful state has multiple physical and psychological implications, including respiratory failure, inability to clear secretions by coughing, and even anxiety and depression that have negative effects on recovery.

Objective: The aim of this study is to evaluate the effect of a neurofeedback-based intervention on controlling acute post-surgery pain and improving long-term recovery in patients who undergo thoracotomy for lung resection for non-small cell lung cancer (NSCLC) at an academic oncologic hospital.

Methods: This study will be based on a 2-parallel group randomized controlled trial design, intervention versus usual care, with multiple in-hospital assessments and 2 clinical, radiological, and quality of life follow-ups. Participants will be randomized to either the intervention group receiving a neurofeedback-based relaxation training and usual care, or to a control group receiving only usual care. Pain intensity is the primary outcome and will be assessed using the Numeric Pain Rating Scale (NRS) in the days following the operation. Secondary outcomes will include the effect of the intervention on hospital utilization for pain crisis, daily opioid consumption, anxiety, patient engagement, blood test and chest x-ray results, and long-term clinical, radiological, and quality of life evaluations. Outcome measures will be repeatedly taken during hospitalization, while follow-up assessments will coincide with the follow-up visits. Pain intensity will be assessed by mixed model repeated analysis. Effect sizes will be calculated as mean group differences with standard deviations.

Results: We expect to have results for this study before the end of 2016.

Conclusions: The proposed innovative, neurofeedback- and relaxation-based approach to support post-surgery pain management could lead to significant improvements in patient short and long-term outcomes.

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KEYWORDS

acute post-surgical pain; lung cancer; neurofeedback; relaxation; video games; virtual environments

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Introduction

Background

Lung cancer has been the most common cancer worldwide since 1985, both in terms of incidence and mortality [1-3], and it is among the top five most frequently diagnosed cancers in Italy [4]. Thoracic surgery appears to be the treatment of choice for many lung cancers. Nevertheless, depending on the type of surgery, the chest area may be painful for several weeks to months after surgery. Indeed, after a thoracotomy, patients often suffer from a persistent pain [5-7] due to the skin incision or deeper tissue injuries, costovertebral joint disruption, resection or fracture of ribs or sternum, and further irritation of the pleura by thoracostomy tubes [8,9]. This painful state has multiple implications, including respiratory failure due to limiting inspiration (because deep breathing requires stretching the incision), or an inability to clear secretions by coughing [10]. Acute pain after surgery can become chronic and persist for more than a year in 21%-67% of patients [11,12]. Moreover, a lot of clinical and demographic factors can contribute to the development of chronic postsurgical pain including psychological conditions (anxiety or depression states), previous surgery, other simultaneous pain, injuries of the chest wall, youth, female gender, and increased levels of pain and analgesic use in the perioperative period [13].

Cooley et al [14] have shown that a high level of post-operative pain in lung cancer patients may exacerbate the fear that movement or physical activity will worsen their condition. This belief can lead to catastrophic appraisals of pain sensations that promote a self-perpetuating cycle of behavioral avoidance, hypervigilance, or distress symptoms [15-18], as well as reduced social activity and global perceptions of decreased health [13]. Researchers investigating psychological aspects of persistent pain have shown that the tendency to focus on pain and to negatively evaluate one's ability to deal with pain, pain-related anxiety, fear, and helplessness are associated with increased pain, psychological distress, and physical disability [19]. Post-thoracotomy pain syndrome and its social consequences have been also investigated by a nationwide study in Denmark [20] that highlighted how partial nerve injury and general pain hyperresponsiveness influence daily activities, even 12-36 months after surgery.

These data highlight the importance of finding effective, early interventions in the presence of painful medical procedures [17,19]. Several studies have demonstrated the effectiveness of non-pharmacological techniques (eg, relaxation) that, in addition to traditional treatments, are able to significantly reduce the acute pain and distress associated with invasive medical procedures [21,22]. Patients who undergo relaxation techniques in different health care settings suffering from acute or chronic pain have been shown to experience less pain compared to those who only undergo traditional treatments [23-27]. In particular, Syrjala et al [28] conducted a study to evaluate the effectiveness of cognitive-behavioral techniques and relaxation in reducing cancer-related pain and found that patients who received these type of treatments, in addition to medical care, reported less pain than the control groups. Although further analyses are required [29], relaxation is a non-pharmacological intervention that may control pain in cancer patients [30].

Many non-pharmacological interventions and interactive new technologies, such as video games and virtual reality environments, can greatly impact pain reduction. By playing a game or being immersed in a virtual environment, users experience an attentional competition between a highly salient sensation (pain) and a consciously directed focus on some other information processing activity [31]. The consequence is a reduced pain perception [32-35], as well as observed changes at a neuroanatomical level. Hoffman et al [36,37] conducted an fMRI study to monitor the brain activity in healthy subjects receiving thermal brain stimulation and showed that virtual reality alone significantly reduced the worst pain and pain unpleasantness, as well as pain-related brain activity in the insula and thalamus. Moreover, combined opioid plus virtual reality exposure reduced pain reports more effectively than did opioid alone on all subjective pain measures [38]. These studies demonstrate that, by distracting subjects from a highly salient sensation of pain, virtual reality may change not only the psychological perception of pain, but also the neuroanatomical networks involved in its modulation [39].

Serious games and virtual realities have been used in different contexts to modulate pain perception. In a recent review, Keefe et al [40] affirmed that virtual reality-based behavioral programs can be used to reduce acute or chronic pain among patients undergoing different medical interventions and rehabilitation programs, such as burn wound care, needle-related procedures, intravenous placement, dental treatments, or postoperative pain. In addition, actively participating in distracting tasks have effects not only on concurrent pain experiences, but long term as well, such as the vividness of memories associated with a traumatic event [33], functional performance, energy level, and time of recovery [34].

Since relaxation, distraction, and new technologies have beneficial effects on pain reduction, we propose to implement a research protocol that, by merging these factors, could help post-operative lung cancer patients to cope with acute pain generated by surgery. The technology that best suits our aim is based on the brain-computer interface (BCI) method, which enables a quick measure of brain activity while providing a neurofeedback (based on simple visual or auditory stimuli, or complex virtual environments) to help the user modulate her/his brain activity to accomplish her/his intents [41]. One of the most user-friendly, simple-to-use and low-cost BCI devices on the market is produced by NeuroSky, who sell a non-invasive, dry biosensor that can read electrical activity in the brain to determine attention and relaxation states. The device, called MindWave, is a portable electro encephalogram (EEG) developed to capture neural activity using three dry electrodes (located beneath the ears and the forehead), and decode them by applying specific algorithms. The MindWave device provides information on a user’s delta, theta, alpha, beta, and gamma brainwave band power levels [42]. The power levels can be interpreted by comparing them to themselves, and with each other, to determine relative quantity and temporal fluctuations [43]. Despite that the MindWave device cannot be used to deeply and precisely monitor the EEG brain activity, it is

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effective in recording the level of attention and relaxation of the user through the analysis of brain wave synchronization and desynchronization [44]. Moreover, the MindWave device works with engaging applications that help users to improve their abilities to reach attentive or relaxed states by giving them specific visual and auditory feedbacks in response to their brain activity.

We believe that the MindWave and its associated applications can benefit patients in the following ways (1) train them in relaxation techniques, (2) engage them in active tasks, and (3) by receiving motivation neurofeedback, push them to continuously improve their performance. Moreover, due to its ease of use, MindWave can be used by patients the precise moments they are experiencing acute pain.

Our goal is to help patients with lung cancer post-operative acute pain gain better control of their symptoms using this innovative, neurofeedback-based pain-control strategy. We hypothesize that patients randomized to receive the intervention will have better pain outcomes, measured by pain intensity, and better medical and psychological outcomes compared with patients receiving usual care.

Primary Aim

Our primary aim is to evaluate the effect of neurofeedback on pain control in patients with lung cancer who have been recently operated on.

Secondary Aims

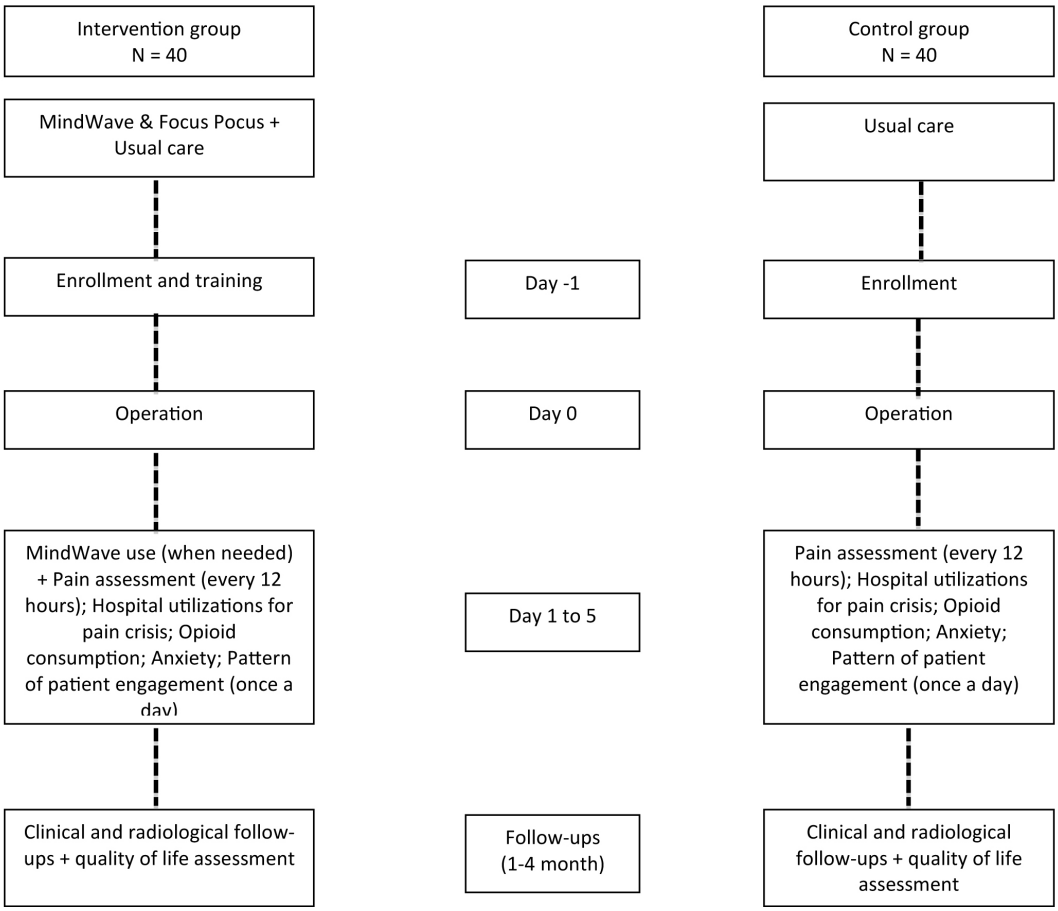
Secondary outcomes include evaluating the effects of neurofeedback on (1) hospital utilization for pain crises, (2) daily opioid consumption, (3) level of anxiety, (4) participants' pattern of engagement with the MindWave tool, and (5) blood test and chest x-ray results. Long-term outcomes also include clinical, radiological, and quality of life evaluations at the 1 and 4 month follow-ups.

Methods

Trial Design

This study is based on a 2-parallel group randomized controlled trial design (intervention vs usual care), with multiple in-hospital assessments and 2 follow-ups (at 1 and 4 months) based on clinical, radiological, and quality of life assessments. Follow-ups will coincide with the follow-up visits. The research design is shown in Figure 1.

Figure 1. Schematic representation of the trial design.



Participants

Participants included in this study will be recruited from the thoracic surgery unit of the European Institute of Oncology (IEO), Milan, Italy. To be considered eligible to participate, patients must fulfill all of the following inclusion criteria (1) they must be aged ≥18 years, (2) able to consent for self, (3) have a primary diagnosis of non- small cell lung cancer

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(NSCLC), and (4) they must have undergone a thoracotomy for lung resection <12 hours prior to the first pain assessment. Ineligible patients will be defined as those who (1) have any significant medical or psychiatric comorbidities (other than depression or anxiety), (2) cognitive impediments that would prevent them from being able to utilize the MindWave device, (3) have a known history of substance abuse, and (4) are simultaneously participating in any other research protocols that may have an impact on pain intensity.

Recruitment Procedure

All patients who are planned to undergo a thoracotomy for lung resection at the European Institute of Oncology, thoracic surgery unit, are considered potential candidates for the present study. Once admitted in the hospital, they will be screened by a trained research assistant to verify their eligibility. Eligible patients will be asked to sign the informed consent, and then randomly assigned to the intervention or control groups. All participants will be instructed to continue to receive medical care from physicians as usual. Subjects included in the intervention arm will be trained on the use of the technology and relaxation technique prior to the operation by a research assistant. They will also receive a MindSet device and tablet with the app Focus Pocus installed on it, for the entire duration of hospitalization (5 days).

Intervention

Framework for Intervention

This neurofeedback-based pain-management program is based on the hypothesis that a relaxation training that provides users an immediate feedback on their performance, as well as a playful environment that moves the patient's focus from the painful sensation to a specific task can be effective in reducing acute pain perception. In fact, the use of engaging and fun mini-games encourages patients to exercise important psychological processes that underlie their ability to control their own brain responses and, consequently, their behavior.

Hardware and Software Equipment

Powered by NeuroSky's Brainwave Technology, the Mindwave headset is a slim, plastic device which fits comfortably, if not unobtrusively, over the user's left ear (see Figure 2). The Mindwave mobile device uses a single sensor positioned on the forehead to allow users to view their brainwaves in real-time. The Mindwave headset picks up the brain's electrical activity and divides the signal by frequency into various types of waves, allowing it to infer how relaxed (as measured by alpha and theta waves) or concentrated (as measured by beta and gamma waves) users are. In order to allow the headset to filter out non-brain related electrical activity, a 'reference' contact, in the form of a clip that attaches to the earlobe, is included. The MindWave mobile device can connect, via bluetooth, to different devices, and works with most modern operating systems (Windows X or newer, Mac OS X 10.6.5 or newer) and mobile devices running Android or iOS. Its battery life is rated at 8-10 hours with a single AAA battery. Although it will take a minute or two to adjust the headset the first time the user puts it on, setup is relatively simple.

The MindWave mobile costs approximately 100 euros (€) and comes bundled with many free and paid applications, but we limited our choice to those available for the iPad tablet specifically as it is one of the most confortable devices (in terms of portability, weight, and usability) that can be used by bedridden patients. After having tested all the existing iOS-based apps, we opted for the one called "Focus Pocus-BrainControl". Focus Pocus is a mix of mini-games that uses live brain electrical activity (ie, EEG) from the NeuroSky MindWave device to alter the circumstances of the player. What happens in the game depends on how relaxed the player is. Focus Pocus attracted our attention for the following reasons (1) ease of use, and has a very high-quality interface, yet is low in cost, (2) the games are engaging and fun with a unifying theme, (3) provides cognitive exercises designed by qualified experts, (4) can be used anywhere and anytime without specific supervision, (5) has been already used for scientific purposes [45,46], (6) designed to provide an environment to practice the relaxation skill (other than attention, impulse-control, and memory), (7) can register the user's training performance in terms of time of use and achievements, and (8) rewards the users' progress by providing them behavior ratings at the end of each trial. With respect to relaxation, for example, in the Focus Pocus BrainControl games, the outcome of any relaxing experience is the result of the content presented, the environment in which it is presented, and the person's readiness to learn. This readiness depends on relaxation (a "state" factor) as well as being able to control impulses and ignore internal (into the game) and external (pain sensation) distractions. In order to guarantee improvement in performance, the difficulty levels of the games are adaptive, and can be adjusted on a per game basis to the performance of the users.

A screenshot of one of the of the Focus Pocus games is shown in Figure 3. A single electrode on the Neurosky headset (placed on the forehead) is able to pick up a few simple and characteristic brainwaves (created by activity in populations of neurons), some that have been shown to be enriched when the subject is awake and attentive (eg, beta waves), and some when the subject is relaxed (eg, alpha waves). Neurosky has developed algorithms to funnel these and other brain waves into measures of "focus" and "meditation." In particular, in this game, the player needs to attain a certain level of meditation to win a duel with an evil necromancer. The idea is that through these different activities, the players would be exercising mental capacities that would generalize outside the game (when they experience acute pain, for example).

For the present protocol, 2 provided tablets and MindWave mobile devices will be used at the same time on 2 different patients. They will be given to the patients the day before the operation and left at subjects' bedside for the duration of their hospital stay. The nurses and the patients will be asked to take care of the devices. The MindSet device and its sensor contact points will be cleaned regularly with an alcohol-based cleaner and a soft cloth included in the MindSet casing to prevent cross-infection and to guarantee good signal quality.

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Figure 2. The MindWave mobile device.

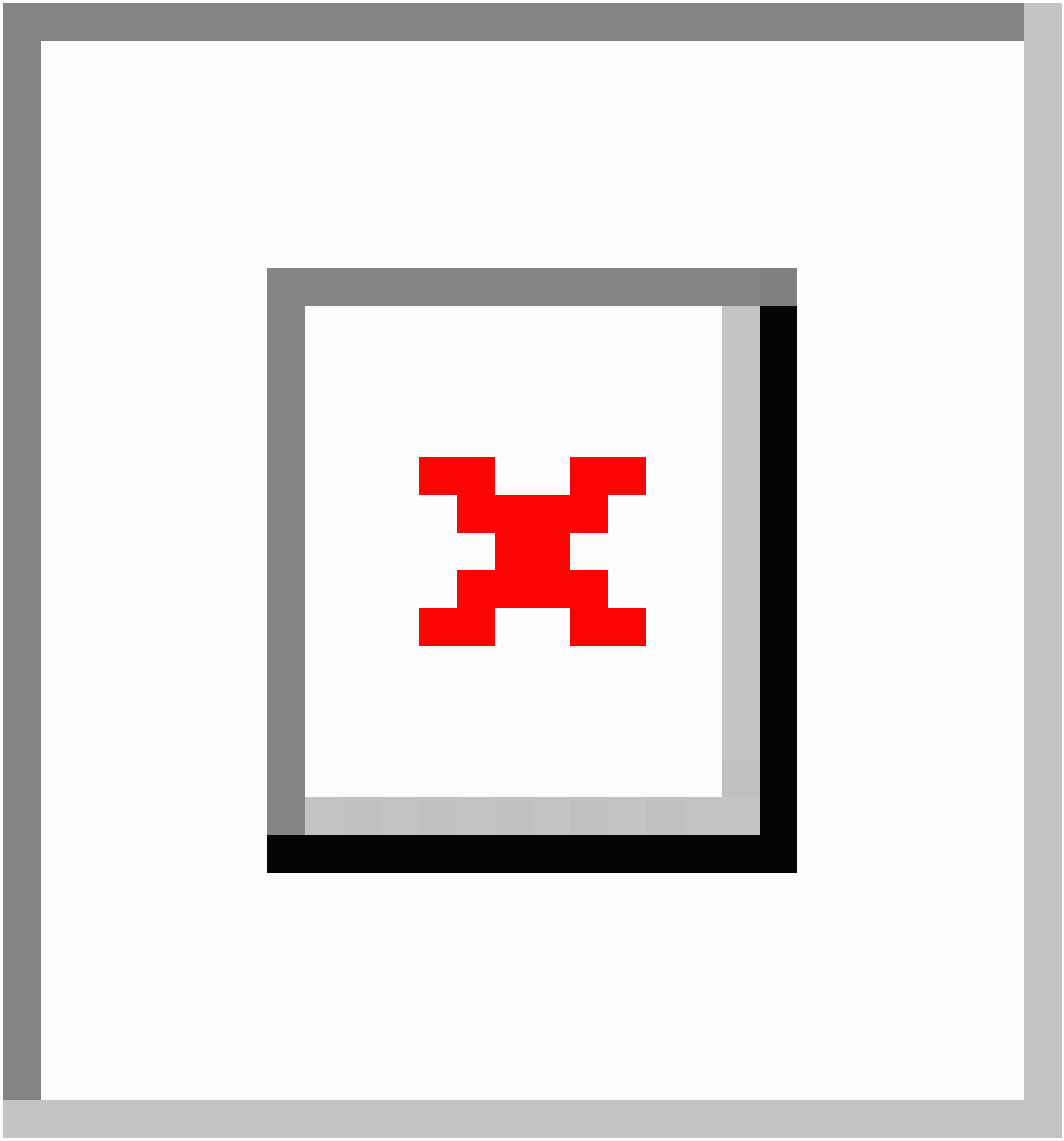

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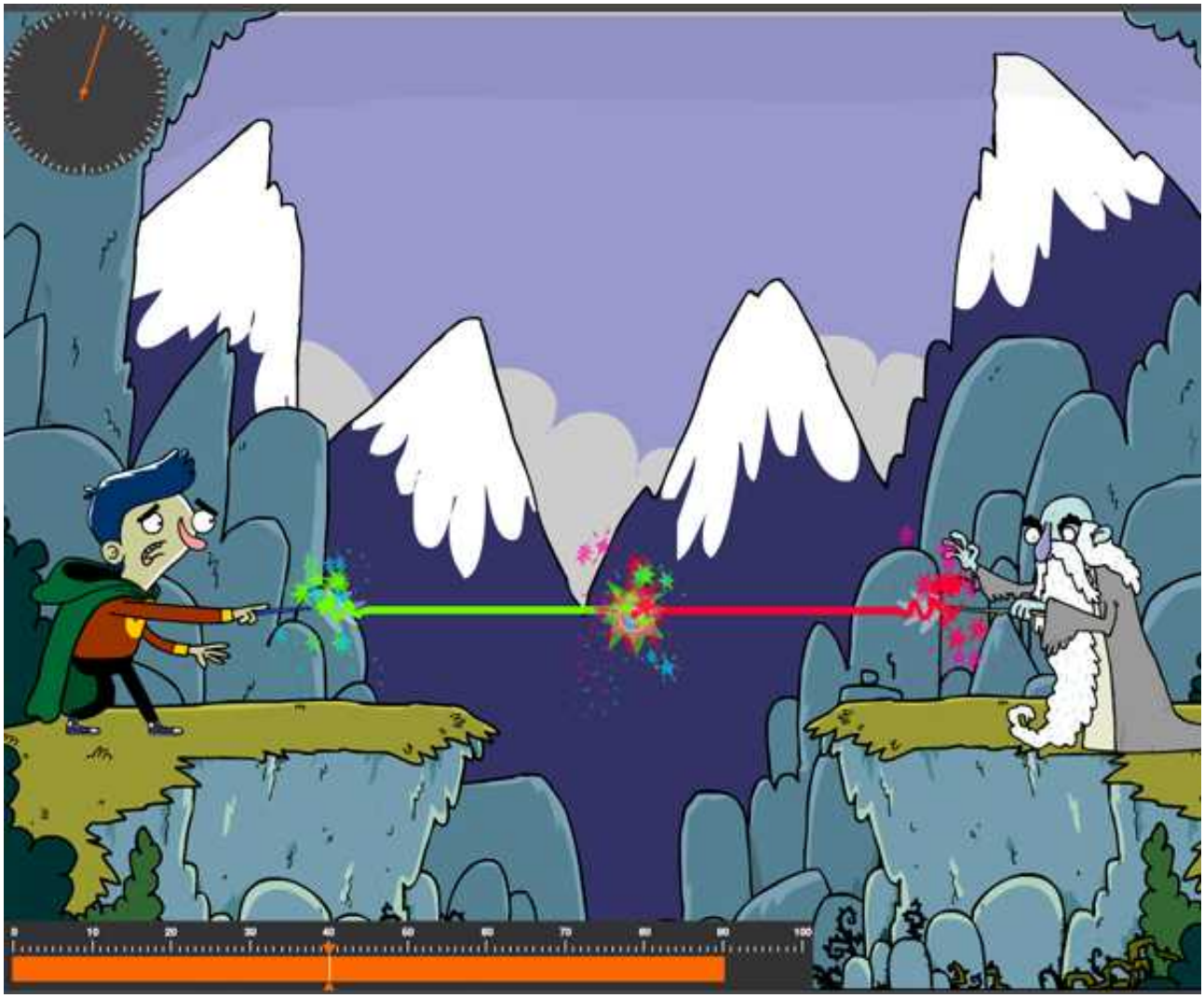
Figure 3. A screenshot of one of the Focus Pocus mini-games.



Procedure

Training

Prior to the surgery (usually the day before), participants will participate in an in-hospital intensive education (45-60 minutes) training session when they are not yet experiencing post-operative pain. During the training, an expert research assistant will explain to each patient how, when, and for how long the MindWave and the Focus Pocus app should be used. After that, the patient will be encouraged to practice the use of the tool by him/herself under the supervision of the research assistant. Once the patients become autonomous with the device, the training session will end, and the MindWave and tablet to be used until their discharge from the hospital will be provided.

Intervention Group (Neurofeedback and Usual Care)

Patients included in the intervention arm will continue to receive the standard care consisting of intercostal analgesia and intravenous pain killers. In addition to it, they will be encouraged to use the MindWave device to manage their pain on-demand and every time they think they need it. During the hospitalization period, patients assigned to the intervention group will also be asked to evaluate their pain over the past 12 hours on a daily basis until their discharge from hospital.

Control Group

Subjects assigned to the control arm will receive only the standard care. In adjunct, they will also be asked to evaluate their pain over the past 12 hours, every day starting from the operation until their discharge from hospital.

Randomization and Blinding

An independent researcher with no direct contact with the participants will use a computer-generated randomization with a 1:1 ratio and permutated blocks to optimize balance in each treatment arm. Due to the nature of the study, participants, care providers, and researchers cannot be blinded for the allocated treatment. However, the data analysis will be blind, as all of the patients receive a unique study code, under which their data is stored in the database.

Outcome Evaluation

Data Collection Materials

We will assess one primary outcome and several secondary outcomes. A number of validated instruments will be used to assess the outcomes at multiple time points during the hospitalization and follow-ups. The patients, both in the treatment and in the control arms, will be asked to complete

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them at specific time-points without the supervision of the research assistants. Hospital nurses will be asked if they completed all the outcome measures, as requested by the protocol, at the end of each day. Demographic and clinical information of each participant will be also collected.

Primary Outcome

The primary outcome measurement is pain intensity, measured as a continuous outcome. It will be assessed quantitatively with the Numeric Pain Rating Scale (NRS) [47]. The paper version of the questionnaire will be self-administered. Participants will be asked to complete it starting from 12 hours after the operation, and every 12 hours during the entire hospitalization period.

Secondary Outcomes

Several secondary outcomes will be measured at various time points during the hospitalization (Textbox 1). Clinical, radiological, and quality of life will be also assessed at the 2 follow-ups (at 1 and 4 months). The clinical and radiological assessment is part of the post-operative routine. However, it will be included in the outcome measures of the present protocol because we expect that a reduction of pain immediately after the operation can result in a better clinical and radiological long-term outcome. Quality of life will be also assessed using the EORTC QLQ-C30 (version 3.0).

Textbox 1. Secondary outcomes measured.

- The number of events in which the patient reports severe, uncontrolled, and causing distress pain that requires urgent and unplanned care visits
- Opioid consumption, measured quantitatively as oral morphine equivalent daily dose
- Anxiety, measured by the State-Trait Anxiety Inventory (STAI) scale
- The pattern of patient engagement with the MindWave tool, assessed quantitatively by the number and length of time each subject uses it (as recorded by the software). Usability and satisfaction with the tool will be also investigated.
- A blood test and chest x-ray will be also performed at the end of the hospitalization period in order to determine if the intervention group shows a better x-ray outcome and fewer infections, due to more physiotherapy because of reduced pain

Statistical Analysis

Sample Size Estimation

A sample size of 80 subjects, 40 per arm, is sufficient to detect a difference of 1.5 between the two groups (control vs intervention) in pain intensity scores, assuming equal standard deviation of 2.5, using a two-tailed *t* test of difference between means, with 80% power, and a 2-sided alpha of .05. Patients in the experimental group who decide to never use the device during hospitalization will be excluded from the study.

Statistical Analysis

Statistical analysis will be conducted with the SPSS Software, version 22, with an alpha of .05 set a priori for all analyses. Descriptive statistics will be used to summarize baseline demographic characteristics by study arm. Continuous variables will be compared between the two groups using a *t* test and categorical variables will be compared using a chi-square test. Pain intensity, our primary outcome, measured longitudinally, will be assessed by mixed model analysis of variance with treatment assignment as the between-group factor and time as the within-subject factor. Effect sizes will be calculated as mean group differences with standard deviations. A similar approach will be used to analyze continuous secondary outcomes while categorical outcomes will be analyzed by chi-square tests.

Ethics and Informed Consent

The hospital internal ethical committee reviewed and approved the study protocol. Upon meeting eligibility criteria, participants will be informed about the study and asked to sign two copies of the informed consent, one for them and the other for the study team. During the enrollment visit and the entire duration of the study, trained research assistants will be available to answer the patients' questions and to give them additional information.

Results

We expect to have results for this study before the end of 2016.

Discussion

Principal Findings

The idea to implement this protocol originated from the need to find an on-demand, pain control strategy that helps lung cancer patients to better tolerate acute pain that often arises in the days immediately after surgery. A prompt reduction of pain is fundamental to reduce the risk of respiratory failure and/or the inability to clear secretions by coughing, as well as the probability to develop long-term negative physical and psychological conditions that can significantly interfere with a full recovery.

Biofeedback-based training usually guarantees a persistent learning, even when the machine-guided training ends up [48]. In other words, once users have learned to control their emotions through the machine-guided relaxation training, they usually become able to practice the relaxation techniques without any external help. We argue that this can be applicable to the neurofeedback method, such that, once learned to control pain through relaxation with the help of the MindWave device, patients can continue to use the techniques at home, without the need for any external devices. Therefore, not only effective immediately after the operation, the hospital training can become a great resource to self-manage pain at home. Moreover, giving patients the concrete opportunity to control their pain on-demand is fundamental considering that the most acute pain tends to

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appear during the night, when the effect of pharmacological treatment decreases and the medical support is at a minimum.

Our main endpoint will serve to evaluate the immediate effect of neurofeedback on pain control. If our results are positive, this technique could be used in combination with traditional pharmacological treatments to improve the patients' post-operative experience, reduce the use of analgesic, and improve long-term physical and psychological outputs.

A challenge of this research protocol is the use of neurofeedback to reduce pain perception. While relaxation, virtual reality, and gaming have been demonstrated to be effective in reducing pain, there is no data on the efficacy of neurofeedback and related applications. Nevertheless, we believe that neurofeedback has great potential to reduce pain through relaxation for the following three reasons. First, receiving feedback determined by a specific mental activation can facilitate behavioral modifications and learning of relaxation techniques. Second, compared to traditional visual feedback, a more complex feedback coming from a virtual game can encourage a greater involvement of the patient, and consequently, distraction from the painful sensation. Finally the MindWave system is a cheap, user friendly device that can be easily used by patients without the supervision of the research assistant.

Limitations

The main limitation of the present study is the number of channels and poor precision of the MindWave device in recording the user's brainwaves. However, since brainwave analyses are not the focus of this study, we do not consider it a critical limitation. Future studies could make use of more sophisticated devices that are currently being advertised but are not yet available on the market.

Another limitation stems from our use of the Focus Pocus app on adult cancer patients, as it was originally developed to train children with specific attentive disorders. Even if the proposed mini-games are suitable for adults, it would be useful, in the future, to develop ad hoc apps tailored to adults' preferences and abilities.

Conclusions

To our knowledge, this is the first clinical trial evaluating the impact of a neurofeedback-based intervention on pain management. We hope that our results will lead to larger trials to demonstrate more robust evidence. If our hypotheses are confirmed, the proposed method can be applied to post-operative patients and, in general, to patients suffering from acute pain to reduce care costs and improve overall patient outcomes.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

BCI: Brain-computer interface
NSCLC: Non-small cell lung cancer

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Protocol

A Mobile Phone and Web-Based Intervention for Improving Mental Well-Being in Young People With Type 1 Diabetes: Design of a Randomized Controlled Trial

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Abstract

Background: Young people with type 1 diabetes experience elevated levels of emotional distress that impact negatively on their diabetes self-care, quality of life, and disease-related morbidity and mortality. While the need is great and clinically significant, a range of structural (eg, service availability), psychological (eg, perceived stigma), and practical (eg, time and lifestyle) barriers mean that a majority of young people do not access the support they need to manage the emotional and behavioral challenges of type 1 diabetes.

Objective: The aim of this study is to examine the effectiveness of a fully-automated cognitive behavior therapy-based mobile phone and Web-based psychotherapeutic intervention (*myCompass*) for reducing mental health symptoms and diabetes-related distress, and improving positive well-being in this vulnerable patient group.

Methods: A two-arm randomized controlled trial will be conducted. Young people with type 1 diabetes and at least mild psychological distress will be recruited via outpatient diabetes centers at three tertiary hospitals in Sydney, Australia, and referred for screening to a study-specific website. Data will be collected entirely online. Participants randomized to the intervention group will use the *myCompass* intervention for 7 weeks, while at the same time a control group will use an active placebo program matched to the intervention on duration, mode of delivery, and interactivity.

Results: The primary outcome will be mental well-being (ie, depression, anxiety, diabetes-related distress, and positive well-being), for which data will be collected at baseline, post-intervention, and after 3 months follow-up. Secondary outcomes will be functional (work and social functioning and diabetes self-care), biochemical measures (HbA1c), and mental health self-efficacy. We aim to recruit 280 people into the study that will be conducted entirely online. Group differences will be analyzed on an intention-to-treat basis using mixed models repeated measures.

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Conclusions: We hypothesize that scores on the outcome measures will improve significantly for young people who use the mobile phone and Web-based intervention compared to the control group. *myCompass* is a public health intervention that is broadly available and free to use. If effective, the program has the capacity to provide convenient and accessible evidenced-based care to the large group of young people with type 1 diabetes who do not currently access the psychosocial support they need.

Trial registration: Australian New Zealand Clinical Trials Registry: ACTRN12614000974606; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=366607 (Archived by WebCite at http://www.webcitation.org/6YGdeT0Dk).

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KEYWORDS

type 1 diabetes; depression; diabetes-related distress; Internet intervention; randomized controlled trial

Introduction

Background

Type 1 diabetes is one of the most common chronic diseases of childhood [1]. It is a leading cause of global disease burden [2], and prevalence rates are increasing [3,4]. Insulin deficiency, the hallmark feature of type 1 diabetes, requires life-long management of a complex and demanding self-care regimen that aims to optimize glycemic control and prevent the onset of potentially fatal short- (eg, hypoglycemia and diabetic ketoacidosis) and long-term (eg, micro-vascular and macro-vascular disorders, peripheral nerve disease, and blood vessel disease) health complications [1]. How well young people cope with the challenges of type 1 diabetes, while simultaneously negotiating the normal developmental tasks of childhood, adolescence, and the transition to adulthood, has important implications for their overall physical health, psychological well-being, quality of life, and life expectancy [5].

People with type 1 diabetes feel challenged emotionally by the daily hassles, frustrations, and worries that stem from having a serious and chronic medical condition [6], and are at greater risk of common mental health problems, especially depression, than their peers without diabetes [7,8]. This is clinically important because of the links between psychological morbidity and such adverse health outcomes as greater diabetes symptom burden and functional impairment, decreased diabetes self-care, poorer glycemic control, higher rates of diabetes complications, and failure to transition from pediatric to adult diabetes services [9-11]. Even mild (subclinical) emotional distress has been demonstrated in longitudinal studies to predict "worse-than-expected" clinical and psychological outcomes in adulthood for young people with diabetes, including recurrent hospital admissions for diabetic ketoacidosis [12].

A meta-analysis of interventions for clinical and subclinical depression clearly demonstrated the benefits for mental health and diabetes outcomes [13], yet most young people with type 1 diabetes do not receive the psychological support they need to manage the emotional and behavioral challenges of their diabetes [14,15]. Barriers to obtaining psychological support include insufficient providers of mental health services, poor mental health literacy (ie, lack of knowledge of signs and symptoms), the prioritization of physical symptoms in traditional models of diabetes care, and a range of practical constraints (eg, time, lifestyle, and financial) [6]. Furthermore, there is evidence that many young people with type 1 diabetes find it difficult to discuss mental health issues with their health care providers [15], thus delaying and/or avoiding seeking psychosocial support. There is, therefore, considerable opportunity to improve mental and physical health outcomes for young people with type 1 diabetes by increasing access to psychosocial support that reduces geographic, temporal, and financial barriers to access, and offers advantages of user confidentiality and anonymity.

As an important part of the everyday lives of young people [16,17], the Internet has demonstrated its potential to overcome many of the barriers to accessing mental health services [18], evolving as a popular, efficient, and clinically effective means of delivering empirically supported psychological interventions to the public, including people with diabetes [19-22]. Young people report feeling empowered and comfortable exploring sensitive and stigmatized issues online [23], and online resources, including websites, forums, and social networking sites, are increasing in popularity as sources of mental health support [16,17,24]. Surprisingly, however, there is little research examining the efficacy of Internet delivered psychotherapeutic interventions for reducing distress and improving psychological well-being in young people with type 1 diabetes.

Therefore, the current study seeks to evaluate the feasibility, acceptability, and clinical effectiveness for improving mental well-being in young people with type 1 diabetes of a fully-automated mobile phone and Web-based intervention, *myCompass*. Grounded in cognitive behavior therapy (CBT), the *myCompass* program has been demonstrated in a randomized controlled trial (RCT) to reduce symptoms and functional impairment in members of the community with mild to moderate levels of depression, anxiety, and stress [25]. Additional pilot data from an uncontrolled study suggest that not only general distress but also diabetes-specific emotional problems are improved (unpublished data by Clarke, Proudfoot, and Ma, 2014).

Study Aims and Hypotheses

Our primary hypothesis is that young people with type 1 diabetes who use the *myCompass* program for 7 weeks will report fewer mental health symptoms (depression, anxiety, and diabetes-related distress), and improved positive well-being compared to an active placebo control group. Our secondary hypothesis is that use of *myCompass* will lead to greater

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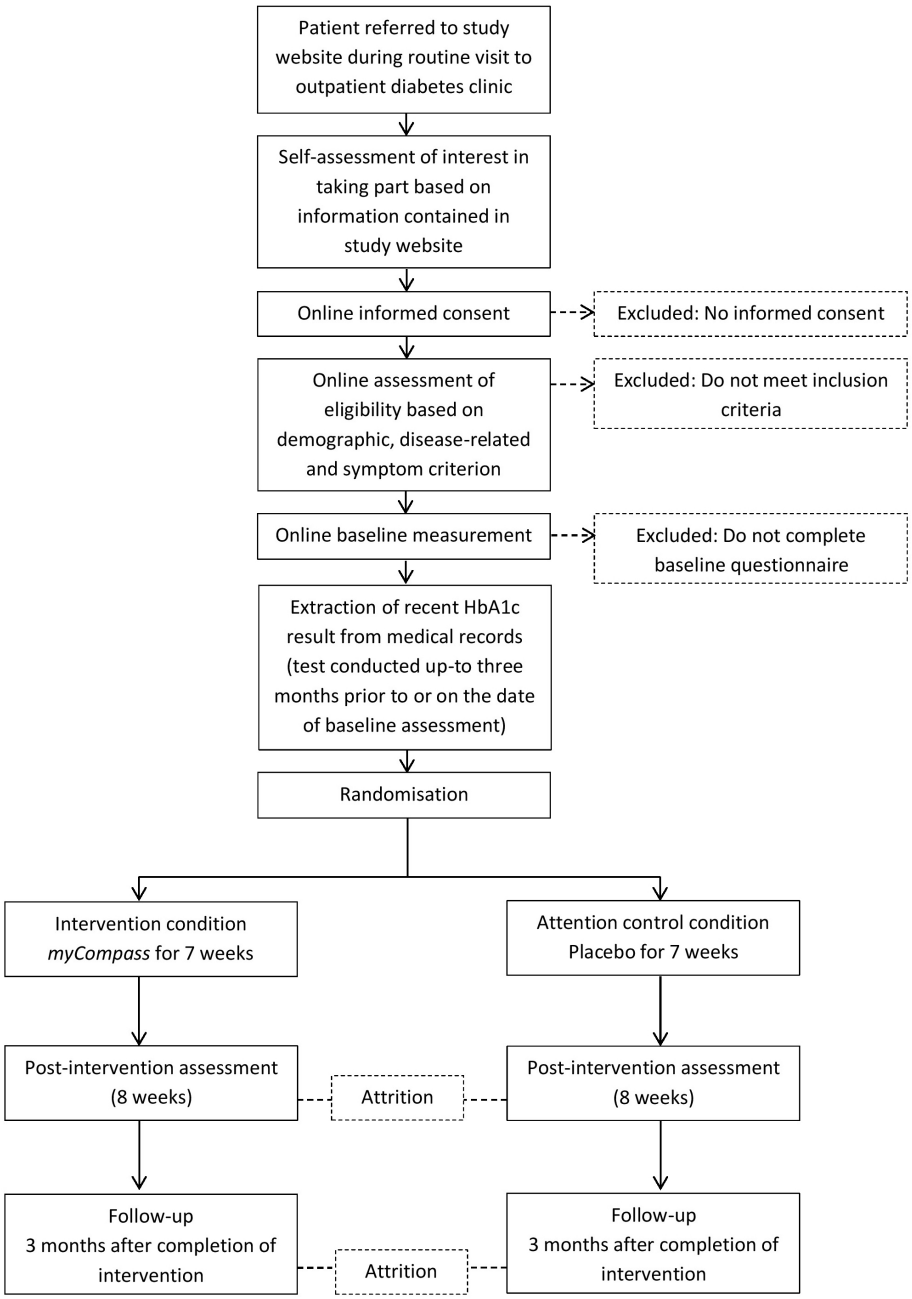
functional gains (diabetes self-care, and work and social functioning), and improvements in glycemic control than the comparison intervention.

Methods

Study Design

A 2 (conditions) x 3 (time) RCT design is planned. Participants will be randomized to either the *myCompass* intervention or an active placebo intervention, and each group will have full program access for 7 weeks. Outcomes will be assessed at baseline, post-intervention (8 weeks), and three months follow-up (Figure 1).

Figure 1. Study flow chart.



Participants

Recruitment

Participants will be young people with type 1 diabetes recruited via diabetes services at three hospitals in Sydney, Australia: The Sydney Children's Hospital, Westmead Hospital, and St Vincent's Hospital. Clinical staff at each service will provide potential participants with written information about the study and an invitation to take part during a routine visit. Information will describe the study and instruct interested individuals to

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access a study-specific website to complete an online consent form and screening survey.

Eligibility

Young people will be eligible for the trial if they are an Australian resident aged between 16-25 years (inclusive), have an email address and Internet access (via mobile phone, and computer or tablet), were diagnosed with type 1 diabetes by a specialist clinician, and have at least mild symptoms of psychological distress. In light of research suggesting that mental health problems (especially those in the subclinical range) in people with diabetes may, in part, reflect disease-specific distress [26], and given calls for routine screening of both general and diabetes-specific distress in diabetes patients [27], a young person will meet our inclusion criteria if they have a mean score of ≥2 on the Diabetes Distress Scale (DDS) [28], and/or a total score of ≥5 on the on the Patient Health Questionnaire (PHQ) [29]. Exclusion criteria include the inability to read English easily, previous use of the *myCompass* intervention, and current psychotic symptoms (total score of ≥2 on the Psychosis Screening Questionnaire (PSQ) [30] (Textbox 1). Screening will be automatically stopped and appropriate feedback provided if any responses indicate ineligibility.

Textbox 1. Inclusion and exclusion criteria.

Criteria

- Inclusion
  - Consent to participate
  - Age 16-25 years
  - Type 1 diabetes, diagnosed by an endocrinologist
  - Access to an Internet-enabled mobile phone and computer/tablet
  - Patient Health Questionnaire (PHQ-9) score of ≥5 and/or Diabetes Distress Scale score of ≥2
- Exclusion
  - Inability to read English with ease
  - Previous experience with the *myCompass* program
  - Psychotic symptoms
  - Non-residence in Australia

Ethical Concerns and Consent

The study protocol has been approved by the Ethics Committee at St Vincent's Hospital, which is certified by the National Health and Medical Research Council in Australia (HREC/14/SVH/31), and research governance bodies at each of the participating hospitals. The protocol is registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12614000974606).

Intervention and Control

myCompass

The *myCompass* program [31] is a fully-automated public health intervention with no therapist input that can be accessed via any Internet-enabled mobile phone, tablet, or computer (Figure 2). Developed by mental health researchers at the Black Dog Institute, the program assesses users' self-reported mental health symptoms on registration, and delivers a personalized intervention that provides round-the-clock self-monitoring of moods and behaviors (via mobile phone, tablet, or computer), and access to twelve interactive evidence-based learning modules (via tablet and computer). The modules provide skills training drawn from cognitive behavioral, interpersonal, problem solving, and positive psychology therapies, and cover such topics as solving problems, managing fear and anxiety, tackling unhelpful thinking, dealing with stress and overload, and increasing pleasurable activities. Each module comprises three 10-minute sessions and has practice activities and home-tasks assigned. Users are encouraged to complete at least two modules, either of their own choosing or from recommendations provided on registration.

In addition, users can schedule short message service (SMS) or email reminders to facilitate self-monitoring. Reminders can be used to receive and print graphical feedback about self-monitoring (including contextual information) on mobile phones or computers to monitor change and assist identification of triggers. It is also possible to receive helpful facts, mental health-care tips, or motivational statements by SMS or email. Registering to use the program is free, and users are not billed for the SMSs they receive. A detailed description of the *myCompass* intervention is provided in Proudfoot et al [25].

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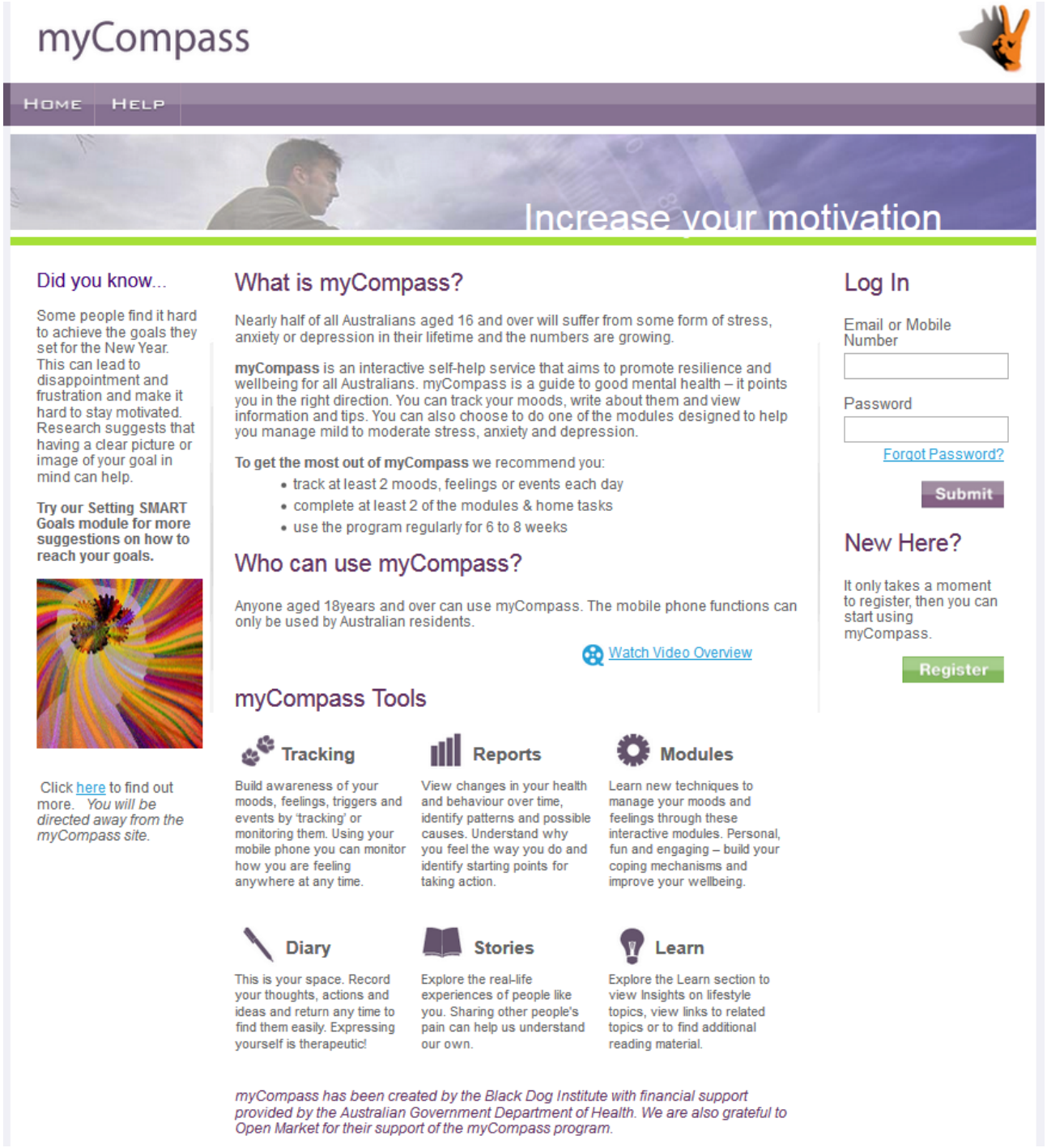
Figure 2. Screenshot of myCompass.



Active Placebo

The comparator intervention will be an Internet-delivered program called *LiveWell* which delivers health information about a range of topics including skin care, mobile phone use, home environment, casual work, healthy food, and relationships. Developed by the research team to match *myCompass* on duration and mode of delivery, the program also contains practice activities, home tasks, and factual SMS messages (sent to participants once-weekly), and a symptom check at 4 weeks, to replicate the interactivity of *myCompass*, but has no therapeutic content.

Procedure

Participants will have access to the full intervention on their mobile phones and computer devices for 7 weeks. Although participants will be encouraged to use the programs ad libitum during the intervention period, it will be recommended that they complete at least two program modules in their own time. Assessment will be conducted completely online. At each assessment time-point, participants will receive an email asking them to log into the study website to complete the outcome measures. The email sent at 3-months follow-up will also prompt participants to visit their diabetes specialist for assessment of glycosylated haemoglobin (HbA1c).

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Randomization

Randomization to either *myCompass* or the active placebo intervention will be carried out after baseline measurement, according to a sequence generated by a computerized random-number generator [32] using permutated blocks of 2, 4, and 8. The randomization process will be facilitated by a researcher not involved with the study. Participants will receive login details for their respective interventions by email.

Measures

The assessments that will be completed at baseline, post-treatment, and 3-months follow-up are summarized in Table 1. Demographic data will include gender, age, marital status, highest education level, and whether the young person is currently working and/or studying. Disease-related information will include age at diagnosis, treatment modality, and diabetes complications status. Participants will also nominate their general practitioner (GP) and diabetes specialist in order to facilitate risk management and the collection of HbA1c results by research personnel.

Table 1. Measures used at screening, baseline, post intervention, and 3- month follow-up.

Measure	Screening	Baseline	Post-test	3 months
Demographic and disease-related variables		X[a]		
Psychosis Screening Questionnaire (PSQ)	X			
Patient Health Questionnaire-9 (PHQ-9)	X		X	X
Generalized Anxiety Disorder-7 (GAD-7)		X	X	X
Diabetes Distress Scale (DDS)	X		X	X
Warwick-Edinburgh Mental Well-being Scale (WEMWBS)		X	X	X
Work and Social Adjustment Scale (WSAS)		X	X	X
Summary of Diabetes Self-Care Activities (SDSCAS)		X	X	X
Hyperglycemia/Hypoglycemia scale		X	X	X
Glycosylated haemoglobin (HbA1c)		X	X	X
Mental Health Self-Efficacy Scale (MHSES)		X	X	X

[a]The X indicates the time-points at which the specific measure will be administered.

Primary Outcome Measures

Depression Symptoms

The Patient Health Questionnaire-9 (PHQ-9) [29] contains 9 items assessing the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for major depressive disorder (MDD). The scale has excellent psychometric properties [33], and identifies similar rates of MDD when compared to semi-structured clinical interviews of DSM criteria in both adults [34] and adolescents [35]. It is used widely as a screening tool for depression, and is frequently included as outcome measures in studies of online interventions (eg, [36,37]). Scores of 5, 10, 15, and 20 are used as cut-off points for mild, moderate, moderately severe, and severe depressive symptoms, respectively.

Anxiety Symptoms

The Generalized Anxiety Disorder-7 Questionnaire (GAD-7) [38] contains 7 items assessing DSM-IV criteria for generalized anxiety disorder (GAD). The scale is well-validated as a screener for GAD [33], used frequently in an online format (eg, [36,37]), and shows good sensitivity and specificity for anxiety disorders generally [39]. Scores of 5, 10, and 15 represent cut-off points for mild, moderate, and severe anxiety symptoms, respectively.

Diabetes-Related Distress

The Diabetes Distress Scale (DDS) [28] is a 17-item scale that assesses the following four areas of diabetes-related emotional distress (1) emotional burden, (2) physician-related distress, (3) regimen-related distress, and (4) diabetes-related interpersonal distress. Scores on the DDS are calculated as the mean of all items and range from 1-6, with scores of >2 indicating "*little or no distress*", and ≥3 indicating "*high distress*". Data support the psychometric adequacy of the DDS when used in adult and adolescent samples [28,40].

Well-being

The Warwick-Edinburgh Mental Well-being Scale (WEMWBS) [41] is a 14-item scale that measures mental well-being through the concepts of positive affect, psychological functioning, and interpersonal relationships, and is validated for measuring mental well-being in young people aged ≥16 years [42]. Scores range from 14-70, with higher scores indicating more positive mental well-being.

Secondary Outcome Measures

Work and Social Adjustment

The 5-item Work and Social Adjustment Scale (WSAS) [43] is a measure of the impact of mental health problems on daily functioning in the following five domains (1) work, (2) social leisure activities, (3) private leisure activities, (4) home

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management, and (5) personal relationships. Scores range from 0-40, with higher scores indicating poorer adjustment. Meyer et al [44] provide data supporting the psychometric adequacy of the WSAS when used in an online format.

Diabetes Self-Care

The 11-item Summary of Diabetes Self-Care Activities Scale (SDSCAS) [45] will be used to measure diabetes self-management. Participants rate how many days out of the past seven they have engaged in such activities as healthy eating, exercise, testing blood sugar, and foot care. Mean scores are calculated for each area and range between 0-7, with higher scores representing better self-care. Reviews support the reliability and validity of the SDSCAS as a self-report measure of diabetes self-management [45].

Glycemic Control

The 7-item Hyperglycemia Scale and 7-item Hypoglycemia Scale [46] will be used to assess participants' self-reports of symptoms associated with high and low blood glucose, respectively. Additionally, as an objective indictor of glycemic control, participants' HbA1c results will be retrieved from medical records (see Figure 1). The measurement of HbA1c provides an index of glycemic control over the preceding 2-3 months, and is useful for evaluating whether a person has achieved and maintained their treatment targets, as well as estimating their risk of chronic diabetes complications [47].

Process Measures

Mental Health Self-Efficacy

The Mental Health Self-Efficacy Scale (MHSES) assesses people's confidence in managing issues relating to their mental health using six, 10-point Likert scale items. Item scores are summed to obtain an overall measure (ranging from 6-60), with higher scores indicating greater mental health self-efficacy. The MHSES yields reliable and valid data, and is sensitive to change [48].

Program Usage

Usage will be examined for the *myCompass* group with respect to three indices, namely, frequency of logins, frequency of self-monitoring, and number of modules attempted.

Risk Management Protocol

If any participant indicates a significant worsening of their psychological distress (defined as a score of >19 on the PHQ-9 either midway through the intervention period, at post-intervention, or follow-up) they will be sent an email from the research team advising them to contact their GP to arrange face-to-face support. A second email, sent 3 days later, will seek confirmation that contact with the GP has been made. If no contact has been made, or if no reply email is received, participants will be informed by email that the principal investigator of the study will contact their nominated GP to recommend they receive appropriate face-to-face support.

Results

Sample Size

The RCT of *myCompass* yielded an average between-group effect size on symptom outcomes of d=0.5 [25]. Van Bastellar et al [22] also reported controlled effect sizes of an online intervention for people with diabetes in the vicinity of d=0.5 for diabetes-related distress and depressive symptoms. Assuming an attrition rate of 50% [49,50], a total sample of 240 participants at follow-up (120 per arm) is the minimum required to detect between-group differences on self-report outcomes of .5 standard deviations with 80% power.

Nevertheless, we will aim for a final sample size 280 participants (140 per arm), as we have pilot data showing that this will enable us to detect a clinically meaningful decrease in HbA1c of 0.5% with power at 80%. This is based on analysis of clinic patients at Sydney Children's Hospital, revealing a standard deviation of 1.04 for the change in HbA1c over 3 months. Recruitment is currently underway for this study.

Statistical Analysis

Analyses will be completed with SPSS 22 software. Chi-squares (categorical variables) and *t* tests (continuous variables) will be used to compare demographic and disease-related variables and baseline scores on the outcome measures for the intervention and attention control groups. Similar analyses will be performed comparing participants who do (non-dropouts) and do not (dropouts) return completed questionnaires at each of the post-intervention and follow-up assessments to explore possible biases in study attrition.

Outcomes at each time point will be analyzed on an intention-to-treat basis using linear mixed modeling (LMM) [51], with time points as a within-group factor and intervention as a between-group factor. In LMM, incomplete cases are included in the analysis, and all available data is used to obtain parameter estimates. The interaction of time and study condition will be of primary interest in each analysis, with a significant interaction indicating a group difference in the pattern of change over time in the outcome of interest. Significant interactions will be explored using sets of Bonferroni adjusted comparisons of the two groups at post-intervention and 3-month follow-up. All effects will be tested at $P<.05$, with adjustment according to the number of contrasts in each set. Within- and between-group effect sizes will be calculated using Cohen's d (based on the pooled standard deviation).

Discussion

Principal Findings

Reviews have highlighted the need for flexibility and innovation in reducing the substantial unmet need for psychosocial care in young people with type 1 diabetes [6,15]. To our knowledge, this study will be the first to examine the effectiveness of a fully-automated, self-help intervention that is generic in its content and delivered via the Internet to computers, tablets, and mobile phones for reducing mental health symptoms and improving mental well-being in this vulnerable patient group.

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myCompass is a public health intervention of demonstrated efficacy [25]. We hypothesize that general and diabetes-specific distress and psychological well-being will improve significantly in young people randomized to *myCompass* for 7 weeks compared to those randomized to an active placebo intervention.

Intervening to reduce psychological distress in young people with type 1 diabetes is important as emotional difficulties are associated with poorer self-care and high disease-related morbidity and mortality [9-11]. Furthermore, in the absence of treatment, psychological distress during the transition from childhood to adulthood may persist throughout life, thereby substantially increasing the longer-term personal and societal burden of the disease [12]. The preferred communication media of young people [52], delivering mental health care via the Internet and mobile phones may be particularly attractive to many young patients who are reluctant to access traditional face-to-face supports. Moreover, if found to be effective, *myCompass* is broadly available free of charge and could potentially reach large numbers of young people with type 1 diabetes for whom service availability and cost are major barriers to access.

Previous studies of psychological interventions for people with diabetes have tended to focus on depressive symptoms and diabetes-specific outcomes (eg, diabetes-related distress and diabetes self-care). By taking a broader approach and examining general and disease-specific distress (depression, anxiety, and diabetes-related distress), functional outcomes (work and social adjustment, and diabetes self-care), and positive mental health, this study provides a comprehensive evaluation of the effects of the web and mobile phone program on variables known to correlate with quality of life and health outcomes in people with diabetes [53,54]. An additional strength of this study is the examination of potential moderators (eg, demographic and disease-related variables, and mental health self-efficacy) of the effect of the intervention on outcome measures. These analyses may assist in identifying the young people with type 1 diabetes who are most likely to benefit from psychosocial support delivered via the Internet.

Limitations

Recruitment of participants through tertiary hospital diabetes outpatient clinics is an obvious limitation of this study, and means that our findings may not generalize to young people with type 1 diabetes managed outside the hospital system. Nevertheless, because it can be difficult to recruit young people into RCTs [55], and given our target sample size of 280, we feel that the proposed recruitment strategy will ensure timely and cost-effective data collection. In addition, recruitment via hospitals will enable us to examine the potential advantages and disadvantages of including the *myCompass* intervention as part of routine specialist care for young people with type 1 diabetes.

Another possible limitation relates to the brevity of the study and the time intervals for measurement. Whereas the proposed assessments (immediately post-intervention and at 3-months follow-up) are sufficient to demonstrate change in the primary and secondary outcome measures, a longer-term follow-up is necessary to determine the consistency of the study findings and the pattern of the effects of the intervention over time. For this reason, consent will be sought from participants at 10 months for a supplementary 12 months follow-up assessment. Separate ethics approvals will be obtained for this part of the study and the data will be analyzed and reported independently of this project.

Conclusions

The increasing prevalence of type 1 diabetes, the heightened risk of emotional difficulties in young people with the disease, and the substantial unmet need for psychosocial support, make a compelling case for trials of novel mental health interventions in this patient group. Using popular everyday tools such as mobile phones, tablets, and the Internet, this project will be the first to examine the effectiveness of a fully-automated, self-help intervention without diabetes-specific content for reducing distress and improving well-being for young people with type 1 diabetes. The *myCompass* intervention is widely accessible, with over 14,000 registrants since 2012. The program has the capacity to provide convenient, accessible (24 hours a day, 7 days a week), and clinically effective psychosocial care at no cost to young people who might otherwise have limited access to (or choose not to access) alternative sources of psychosocial support.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

CONSORT-EHEALTH checklist V1.6.2 [56].

[PDF File (Adobe PDF File), 82KB - resprot_v4i2e50_app1.pdf]

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Abbreviations

CBT: Cognitive behavior therapy
DDS: Diabetes Distress Scale
DSM: Diagnostic and Statistical Manual of Mental Disorders
GAD: Generalized anxiety disorder
GP: General practitioner
HbA1c: Glycosylated haemoglobin
MDD: Major depressive disorder
MHSES: Mental Health Self-Efficacy Scale
PHQ: Patient Health Questionnaire
RCT: Randomized controlled trial
SDSCAS: Summary of Diabetes Self-Care Activities
SMS: Short message service
WEMWBS: Warwick-Edinburgh Mental Well-being Scale
WSAS: Work and Social Adjustment Scale

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Protocol

Effectiveness, Mediators, and Effect Predictors of Internet Interventions for Chronic Cancer-Related Fatigue: The Design and an Analysis Plan of a 3-Armed Randomized Controlled Trial

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Abstract

Background: Internet interventions offer advantages that especially cancer survivors who suffer from fatigue could benefit from. Given the growing number of such patients, Internet interventions could supplement and strengthen currently available health care.

Objective: This paper describes the design and analysis plan that will be used to study 2 Internet interventions aimed at reducing severe fatigue in cancer survivors: a mobile ambulant activity feedback therapy supported through a weekly email by a physiotherapist and a weekly Web- and mindfulness-based cognitive therapy supported online by a psychologist. The data resulting from this trial will be used to (1) investigate the effectiveness, (2) investigate potential mediators of these interventions, and (3) explore participant characteristics that can predict the effect of these interventions.

Methods: A 3-armed randomized controlled trial is proposed that compares both Internet interventions with an active control condition that solely consists of receiving psycho-educational emails. The intervention period is 9 weeks for all 3 conditions. Six months after baseline, participants in the control condition can choose to follow 1 of the 2 experimental Internet interventions. Outcomes are measured in terms of fatigue severity, mental health, and self-perceived work ability. All are Web-assessed at baseline, 2 weeks after the intervention period, and at 6 and 12 months after baseline. Fatigue severity, mindfulness, physical activity, expectations and credibility of the intervention, therapeutic working alliance, sleep quality, and sense of control over fatigue are assessed 3 times during the intervention period for identifying mediators of the interventions. Recruitment is performed nationally throughout the Netherlands through patient organizations and their websites, newspapers, and by informing various types of health professionals. All participants register at an open-access website. We aim at including 330 cancer survivors who have finished curative-intent cancer treatment at least 3 months previously, and have been suffering from severe fatigue ever since. All cancer types are included. A detailed analysis plan is described to address the research questions, which allows for individual variation, and fully exploits the longitudinal design.

Results: Recruitment started in April 2013 and will proceed until April 2015.

Conclusions: This paper describes a systematic trial design for studying 2 different interventions for chronic cancer-related fatigue in order to gain insight into the effectiveness and mediators of the interventions. This design will also be used to identify

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predictors for the interventions' effect on fatigue. By publishing our hypotheses and analysis plan before completion of data collection, this paper is a first step in reporting on this trial comprehensively.

Trial Registration: The Netherlands National Trial Register (NTR3483). (Archived by WebCite at http://www.webcitation.org/6NWZqon3o).

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KEYWORDS

fatigue; cancer survivors; chronic disease; Internet interventions; mindfulness-based cognitive therapy; motor activity; behavior therapy; accelerometry; effect predictors; mediation; Bayesian statistics; latent growth analysis

Introduction

Background

Behavioral interventions have shown to effectively relieve psychological and physical complaints in cancer survivors. However, the effect on the individual is less explicit, because patients differ greatly in the ways they experience and respond to such interventions. Therefore, when studying such an intervention, individual differences and temporal aspects need to be appreciated. This paper presents a detailed analysis plan for studying behavioral interventions that satisfies such needs.

The protocol of a 3-armed randomized controlled trial is described to study the effectiveness, mediators, and effect predictors of 2 different Internet interventions that share the same aim: reducing fatigue for cancer survivors. Due to its longitudinal design and multiple assessments during the intervention, the temporal development of relevant factors rather than pre-post differences can be studied. Latent growth analysis can be performed and mixture models can be run, which allow for individual variance in growth trajectories. Furthermore, full longitudinal mediation analyses can be performed on the most important potential mediators of both interventions, and differentiating effect predictors can be identified in order to allocate individuals to the most suitable intervention.

The goal of this paper is to present our trial design, hypotheses, and analysis plan. This paper will therefore be the basis for a number of papers that will present the results of the trial. We will first provide brief background information on the research population, the relevance of Internet interventions for this population, and introduce the 2 Internet interventions that are the subject of this trial. Next, the importance of identifying mediating and predicting factors for the intervention effect is discussed. In the remaining sections, we give a detailed description of the trial's design, our hypotheses, and the analysis plan for handling the data that the trial will collect. The analysis plan is written in general terms, in order to facilitate the use of this strategy in other contexts, and to keep this paper focused. Consequently, the extended background of—and reasoning for—the specific hypotheses will be presented in future papers that will focus on the results of the proposed analyses.

Chronic Fatigue and Cancer

Cancer-related fatigue is defined as "a persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity, and interferes with usual functioning" [1]. It is 1 of the most prevalent and distressing long-term consequences of cancer [2], interferes with the activities of daily living, work ability [3], and maintenance of social relations, and consequently impacts patients' well-being [4]. As the number of cancer survivors in the Netherlands is expected to increase rapidly, with a growth of over 50% in the 10-year prevalence between 2009 and 2020 [5], there is a strong need for effective and accessible treatments.

The etiology of cancer-related fatigue probably involves the deregulation of several interrelated physiological, biochemical, and psychological systems [6]. There is no definite somatic explanation for the persistence of fatigue after cancer [7-9], and estimates of the proportion of cancer survivors who suffer from persistent fatigue vary widely [8,10]. However, research has shown that if fatigue continues 3 months after treatment, it is unlikely to decrease of its own accord [8]. The term chronic cancer-related fatigue (CCRF) is used in this paper for severe fatigue that continues for 3 months or longer after cancer treatment completion.

Management of Chronic Cancer-Related Fatigue

Currently, both pharmacological treatments and nonpharmacological treatments are applied to the effective management of CCRF; see the overview articles published by Ahlberg et al [9] and Koornstra et al [11]. Guidelines state that if no primary association can be found for the persistence of fatigue with a somatic condition, behavioral interventions should also be considered [1]. The previously reported effects of nonpharmacological interventions on fatigue vary widely, as can be seen in the overview of recent meta-analyses in Table 1. Effect sizes tend to be higher when the intervention targets fatigue, and when increased fatigue was an inclusion criterion for the study. Not all studies that were included in the meta-analyses primarily targeted fatigue, therefore effect sizes might not be representative for nonpharmacological interventions that target fatigue.

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Table 1. Ten recent meta-analyses considering nonpharmacological interventions for cancer patients that included off-treatment fatigue.

Meta-analyses (off treatment)	Intervention type	ES[a] (95% CI)	Fatigue reduced (*P*-value)
Jacobsen 2007 (k[b]=4%)	Psychological	d[c] = 0.10 (0.02-0.18)	Yes (<.05) [12]
Jacobsen 2007 (k=29%)	Activity-based	d=0.05 (-0.08-0.19)	ns [12]
Kangas 2008 (100%)	Psychological	WMES[d](r[e]) = 0.51 (0.10-0.92)	Yes (.015) [13]
Kangas 2008 (100%)	Exercise	WMES(r) = 0.13 (-0.77-1.02)	ns (.784) [13]
Speck 2010 (100%)	Exercise	WMES(r) = 0.54 (0.19-0.90)	Yes (.003) [14]
Brown 2011 (k=54%)	Exercise	WMES(r) = 0.31 (0.22-0.40)	Yes [15]
Duijts 2011 (n=31%)	Behavioral techniques	SMD[f](f[g]) = 0.16 (0.08-0.23)	Yes (<.001) [16]
Duijts 2011 (n[h]=42%)	Exercise	SMD(r) = 0.315 (0.10-0.53)	Yes (.004) [16]
Cramp 2012 (100%)	Exercise	SMD = 0.37 (0.18-0.55)	Yes [17]
Tomlinson 2014 (100%)	Exercise	SMD(r) = 0.61 (0.33-0.88)	Yes [18]

[a]ES = Effect size; values are positive when the intervention was able to reduce fatigue more compared to the control condition.

[b]k=percentage of studies

[c]d=Cohen's d

[d]WMES = weighted means effect size

[e]r=random effects

[f]SMD = standardized mean difference

[g]f=fixed effects

[h]n=percentage of participants

Behavioral interventions are often based on energy balance models and/or stress coping models [12,19]. In energy balance models, CCRF is seen as a consequence of deconditioning and prolonged inactivity during cancer and its treatment. Secondary fatigue arises as a result of detraining and can lead to a downward spiral. In stress coping models, CCRF is conceptualized as a result of ineffective coping strategies and prolonged stress response [20]. Cognitive behavioral treatments that are based on these theories include physical activity interventions, exercise interventions [14,17,21,15,22], and mindfulness-based cognitive interventions [23-26] and have been shown to help reduce CCRF in previous studies [12,13]. However, all these interventions require the patient to travel to a health care facility, which can be a burden to the patient. Therefore, introducing effective interventions in a home-based setting could improve the health care options for this group.

Potential Benefits of Internet Interventions

Internet interventions offer advantages that cancer survivors who suffer from fatigue could especially benefit from. They have been found to be as effective as face-to-face therapies for a wide range of disorders, such as posttraumatic stress disorder, burnout or chronic stress, and depression [27-32]. Internet interventions have the ability to reach a wider range of patients compared to face-to-face interventions, especially severely fatigued patients, those with limited mobility, or patients in rural or even remote areas. Also, patients may benefit from the home-based setting of Internet interventions as these patients can practice more often, are less bound to the availability of care professionals, and can incorporate the intended behavioral change directly into their daily routine. Moreover, visiting a health care facility may no longer be desirable for some cancer survivors due to negative associations with the disease process or because they no longer want to be identified as a cancer patient and prefer the anonymity of their own environment.

Internet Interventions for Fatigue

Overview

In the Netherlands, to our best knowledge there are currently 3 Internet interventions that aim to reduce chronic fatigue: (1) an experimental mobile intervention aimed at changing physical activity behavior for participants with chronic fatigue syndrome [33]; (2) the Web-based mindfulness-based cognitive therapy "Minder Moe Bij Kanker" [34]; and (3) a Web-based cognitive behavior therapy for severely fatigued breast cancer survivors, which is the subject of the current CHANGE study (trial registration NTR4309) [35].

This paper describes the design and analysis plan that studies the first 2 of these Internet interventions in a randomized controlled trial. Each of these 2 interventions is described below.

Mobile Activity Management Intervention: Ambulant Activity Feedback Therapy

The ambulant activity feedback therapy (AAF) is a mobile intervention that utilizes an ambulant activity coaching system, supported weekly by a physiotherapist through email [33]. The activity coaching system was developed by Roessingh Research and Development (Enschede, The Netherlands) and consists of a mobile phone and an accelerometer (Multimedia Appendix 1) that communicate through Bluetooth [33].

In this intervention, the patient works to meet personal activity goals and subgoals that will be defined together with the therapist. The coaching system supports this process by showing

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real-time feedback about the accumulated activity of the patient relative to a personalized line of reference and tailored hourly feedback messages. Both the line of reference and the set of feedback messages of the activity coaching system can be adjusted by the therapist through a Web portal (see Figure 1 and Multimedia Appendix 2). Patients also have access to a Web portal where they can monitor their past personal activity records. Consequently, patients are expected to gain insight in their activity pattern and on how to increase or balance their daily activity in a way that improves their energy levels. More information about AAF is given in Wolvers and Vollenbroek-Hutten (in press) [36].

Figure 1. Screenshot of the Web portal for the ambulant activity feedback therapy (Dutch).

Web-Based Mindfulness-Based Cognitive Therapy

Mindfulness-based cognitive therapy (MBCT) [37] adds elements of cognitive therapy to the mindfulness-based stress reduction program that was originally developed by John Kabat-Zinn [38]. The Helen Dowling Institute (Bilthoven, the Netherlands) developed a 9-week Web-based, therapist-guided, individual MBCT (eMBCT) specifically designed to reduce cancer-related fatigue [23]. On a personal Web page (see Figure 2 and Multimedia Appendix 3), each patient can download audio files of mindfulness exercises and read information about a specific mindfulness theme each week. Patients write down their experiences of following the mindfulness exercises in a log. On an agreed-upon day of the week, the therapist replies to this log, thereby guiding the patient through the program. It is hypothesized that by learning to raise awareness of their present experience nonjudgmentally and openly, the patient can become aware of potentially ineffective coping strategies that prolong stress and fatigue [39,40]. Patients learn to use a detached perspective as a skill to prevent the escalation of automatic negative thinking patterns. MBCT also teaches patients how to accept fatigue, physical limitations, or pain. The protocol of the eMBCT is discussed more extensively in the article by Bruggeman-Everts et al [34].

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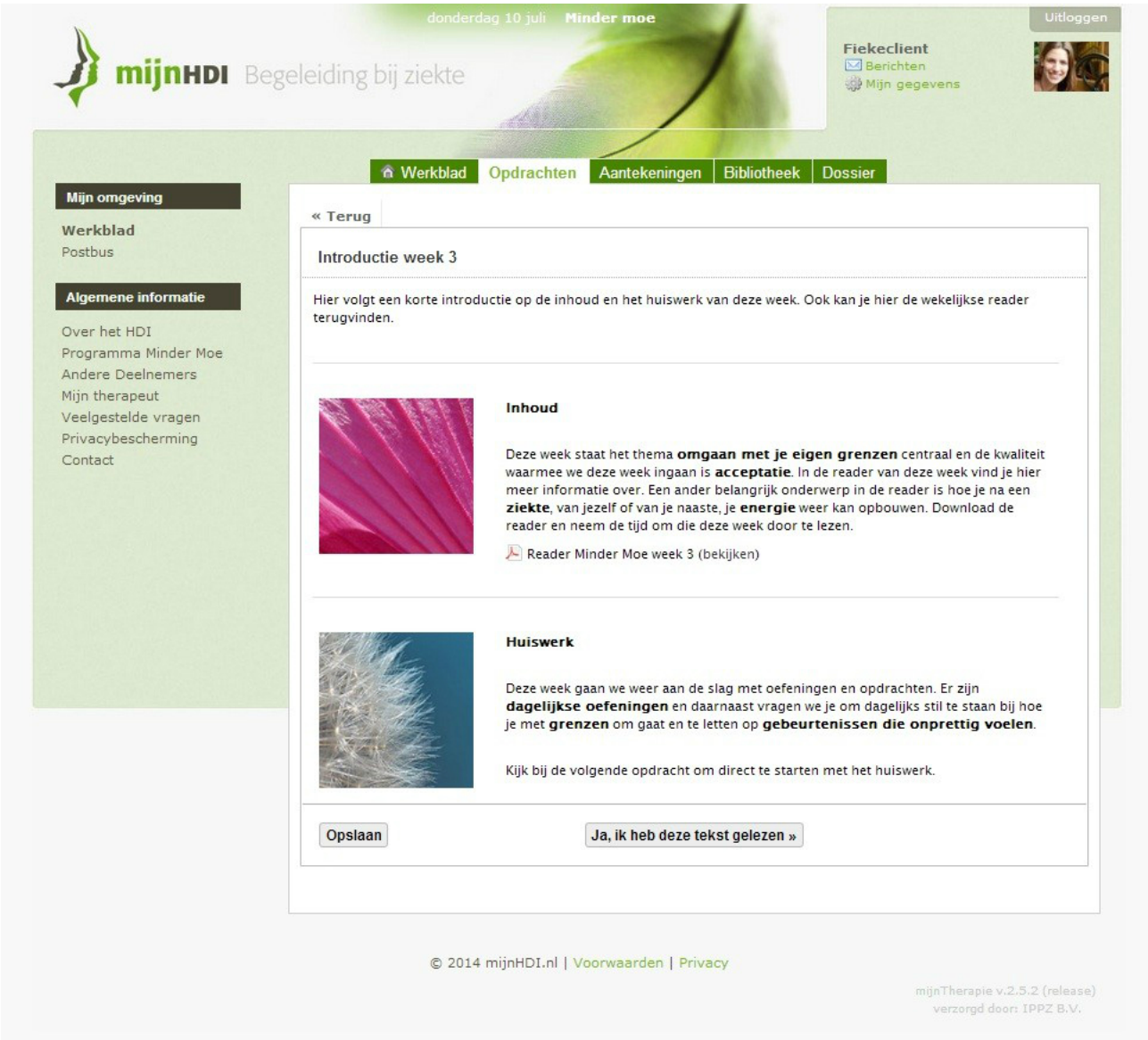
Figure 2. Screenshot of the Web portal for eMBCT (Dutch).



Effectiveness

Overview

Our primary question is whether both interventions are effective in reducing fatigue. Therefore, the interventions will be compared to an active control group in a randomized controlled trial. The advantage of this design, as compared to a waiting-list control group, is that we can control for nonspecific influences of the trial, such as receiving attention. Also, we expect that in an active control group, fewer participants will drop out than in a waiting-list control group.

Usually, results of interventions are presented in terms of an average improvement of the relevant outcome measure. However, practice shows that individuals benefit differently from interventions [41]. Therefore, the proposed trial will aim to identify individual fatigue trajectories, since that seems to be more informative and helpful in improving health care provisions for CCRF-patients than just presenting averages.

Mediators

To optimize interventions in terms of efficiency and effectiveness, treatment-specific and nonspecific working mechanisms should be identified that account for each intervention's effect on fatigue. Knowledge about these mechanisms is an important prerequisite for improving the efficiency of interventions by shifting focus or shortening the intervention. Also, effectiveness can be increased by improving and tailoring the relevant items, subjects, or exercises, as well as improving the way these are embedded in the intervention. Therefore, the second objective of this study will be to identify the working mechanisms underpinning the interventions.

By using a 3-armed randomized design, it is possible to study both treatment-specific (differentiating) and nonspecific working mechanisms. Also, by assessing important factors multiple times during the intervention, important time-specific information can be acquired.

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Effect Predictors

Although we expect that, in general, both interventions are effective, personal factors, medical factors, and demographics may determine the effect that each intervention has on fatigue [41]. We do not expect all individuals to benefit similarly from the interventions. Therefore, studying potential predictors of each intervention's effect will give us important input to inform both patients and caregivers and allow them to set reasonable expectations.

CCRF has a multifactorial character (eg, physical, cognitive, motivation); therefore, studying the effect predictors of 2 theoretically differing interventions simultaneously might also reveal differentiating predictors for both therapies. By applying such knowledge carefully, the overall effectiveness of interventions that aim to reduce CCRF can be increased.

Methods

Design

A randomized controlled trial is performed including 3 parallel conditions: 2 experimental conditions (AAF and eMBCT) and a minimal intervention control condition. The intervention period is 9 weeks for all 3 conditions. Both experimental conditions are made as similar as possible in terms of time-investment and contact intensity with the therapist. Outcomes are self-reported and are Web-assessed at baseline (T0), 2 weeks post-intervention (T1), and at 6 months (T2) and 12 months (T3) after baseline. Figure 3 shows a schematic summary of the trial design.

The baseline assessment consists of 3 time-points: (1) T0a, the assessment to check eligibility; (2) T0b, the main baseline assessment taken after the eligibility check and informed consent, but naive of condition; and (3) T0c, directly after randomization for assessing the participant's credibility and expectancy about the condition. All participants are invited to fill out short questionnaires in weeks 1, 2, 3, 4, 6, and 9 (Mi) of the intervention period in order to study mediation of the interventions.

After T2, patients in the control condition are offered 1 of the 2 experimental interventions, again in a research setting. Please note that the first 4 participants of this trial were randomized to 1 of the experimental conditions for the second semester, but to minimize dropout, all other patients will be allocated based on their own preference. During this second intervention period, these participants will again be assessed in weeks 1, 2, 3, 4, 6, and 9 (Mi'), the second week after the intervention (T1'), and 6 months after the second allocation (T2'). Participants in the control condition that are preferentially allocated to eMBCT after T2 do not wear the accelerometer during the second semester.

The protocol allows delay within the intervention period of a maximum of 2 weeks in case of, for example, illness or holiday. For all participants, the duration of their participation is approximately 12 months. Additional qualitative feedback will be obtained through explorative interviews with a subset of participants in the experimental condition shortly after T1 or T1'.

This trial was approved by the Twente Medical Ethical Committee (Enschede, the Netherlands) under number P12-26 and has been registered at The Netherlands National Trial Register under number NTR3483 [42].

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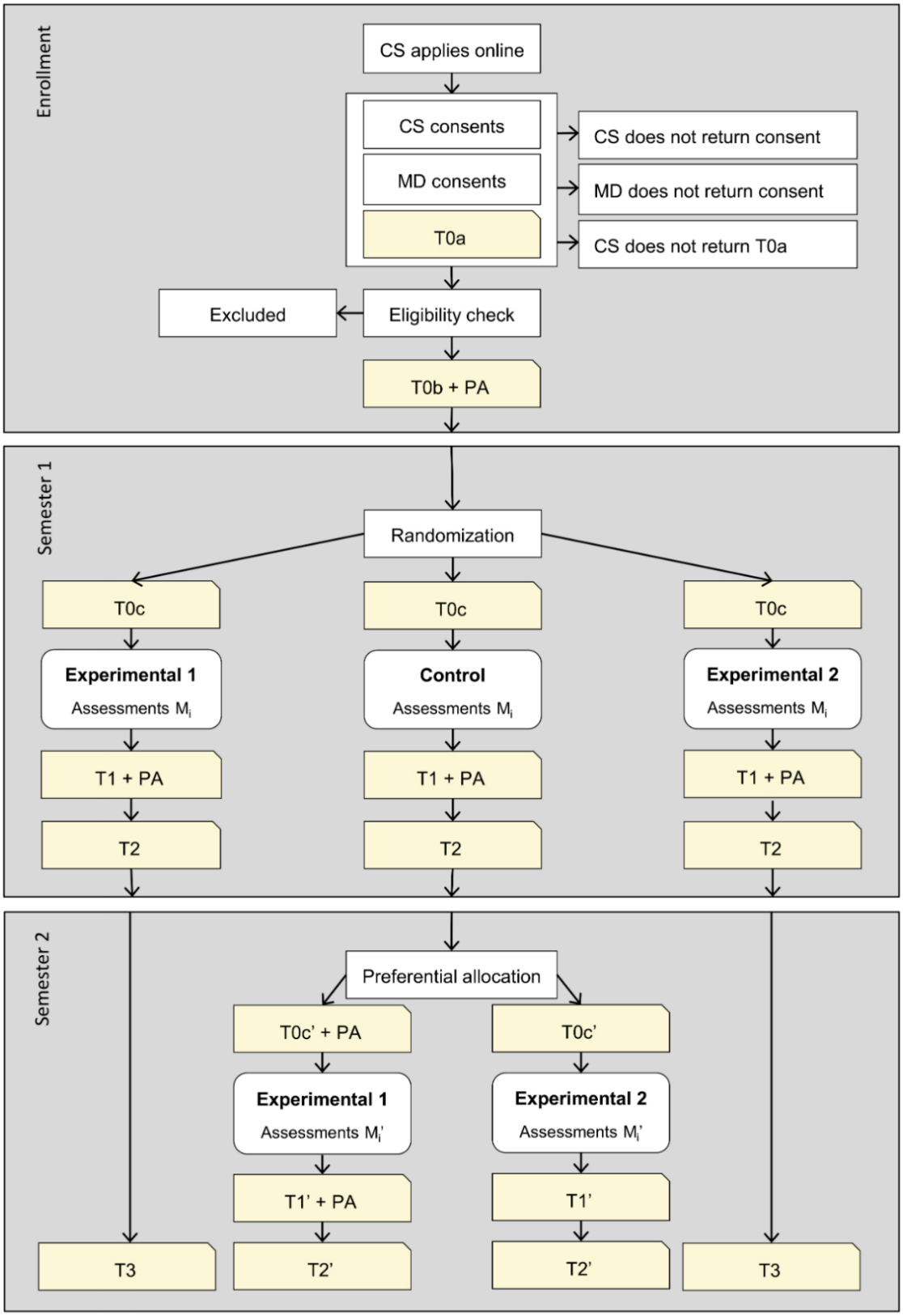
Figure 3. Flow chart of trial design. CS = cancer survivor; MD = medical doctor; PA = physical activity; T0(a-c)-T3 are the main assessments; Mi and Mi' represent assessments in week (i =) 1, 2, 3, 4, 6, and 9 of the intervention. For addressing the primary research questions of effectiveness, only data from the first semester will be used.



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Study Sample

Recruitment

Participants are recruited in the Netherlands by advertisements in the newsletters of patient associations (both digital and print), on relevant websites, in regional newspapers, and through social media. Furthermore, participants also are recruited through oral presentations given to cancer patients and in other cancer-related seminars and symposia for patients, caregivers, or both.

Social media and online advertising can be strong tools for reaching a large group of people [43] or even specific patients [44,45]. However, the sample might be younger, more highly educated, and might comprise more females compared to the Dutch CCRF population [46]. However, it will lead to a sample that represents the targeted population for such Internet interventions, and we are likely to include participants who would not have opted for therapy that includes traveling to a health care facility.

Eligibility

The following criteria are used to check eligibility for participation in the trial:

- Completion of a curative-intent treatment for cancer at least 3 months ago (checked by participant's medical doctor). For this study, surgery, chemotherapy, radiotherapy, immunotherapy, and/or stem cell transplantation are considered treatment. However, hormonal therapy, the use of anti-inflammatories, and monitoring visits are not considered treatment for this study.
- Patient has been suffering from severe fatigue for at least 3 months.
- Patient scores 35 or higher on the fatigue severity subscale of the Checklist for Individual Strength (CIS).
- Aged 19 years old or older.
- At least 18 years old at disease onset.
- Capable of reading and writing in the Dutch language and of using the Internet (implicit eligibility criterion accounted for during registration, but not checked explicitly).

If patients meet 1 or more of the following criteria, they are excluded from participation:

- Indication of current disease or tumor activity (checked by the participant's medical doctor).
- Current or former severe psychiatric morbidity, for example, major depression, psychosis, or schizophrenia (checked by the participant's medical doctor).
- Being dependent on a wheelchair for daily activity (self-report).
- Recurrence of cancer during the course of the study (self-report).
- Current substance abuse, except for smoking.
- Previously attended the eMBCT of the Helen Dowling Institute.

In addition to the mentioned exclusion criteria, please note that:

- Mild depression is not an exclusion criterion. A score of 20 points or higher on the Hospital Anxiety and Depression Scale (HADS) during baseline is considered indicative of depression [47]. Therefore, if the patient scores 20 points or higher, he or she will be contacted by a psychologist from the Helen Dowling Institute to determine whether the participant has suicidal ideation or suffers from other severe psychiatric morbidity. A participant will only be excluded if, according to the involved psychologist, that is the case.
- Comorbid somatic diseases—such as cardiovascular diseases, cerebrovascular diseases, diabetes, hypertension, and arthritis that are not treatable but are a possible cause of fatigue—are not exclusion criteria but will be registered during the study. Although this choice will probably lead to an underestimated effect size compared to studies that do exclude patients with comorbidities, we expect that such a sample will lead to a better representation of the CCRF population.
- Participants are requested not to take part in any other therapy directed at overcoming fatigue during the study.
- Data of participants who report pregnancy or recurrence of cancer during the course of the study will be excluded from analysis since the fatigue they experience cannot be considered to be of a chronic character according to our definitions. However, if requested, these patients will be allowed to finish the intervention.

Procedures

Participants apply for inclusion in the study at the project website [48,49].

Informed Consent

After online registration, participants receive the patient information and informed consent form by direct mail. They are requested to sign and return the informed consent in a prepaid envelope. Also, they receive a registration confirmation by email with login details for the participant's Web portal on the project website. Participants are requested to complete assessment T0a as a check on eligibility. Also, the participant's medical doctor is consulted to check 3 of the eligibility criteria: finished curative-intent treatment for cancer more than 3 months ago, no current signs of cancer activity, absence of current or former major psychiatric disease.

Randomization

If the eligibility-criteria are met, the researcher confirms the participant's enrollment. Subsequently, the activity sensor is given to the participant and its setup is explained in a face-to-face meeting in the participant's home or another mutually convenient location. The second baseline assessment starts (T0b), followed by randomization of the participant to 1 of the 3 conditions by a script embedded in the researchers' Web portal and uses the random function of php (rand(1,3)) [50]. The researchers can neither influence nor predict the outcome of the randomization process. Subsequently, the researcher emails the participant about the outcome of randomization, requests the participant to complete the third baseline assessment (T0c), and assigns the participant to a therapist in case the participant has been randomized to an experimental condition. Participants who do not fill out T0c are considered as not being included. The allocation of a therapist

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is based on current availability of the therapists who are involved in the trial.

Research Conditions

Both experimental conditions are described in the Introduction and will be described more extensively in an article on eMBCT by Bruggeman-Everts et al [34], and a paper on the development of the AAF intervention by Wolvers and Vollenbroek-Hutten (in press) [36].

Active Control Condition

Patients who are assigned to the control condition receive weekly emails containing standard psycho-educational texts about CCRF in order to minimize the dropout rate, following the design of Postel et al [51]. An example of the information that is offered in this minimal intervention control condition is given in Multimedia Appendix 4 and overlaps completely with the information that is given during both experimental interventions. This condition controls for receiving information on CCRF and for being involved in eHealth research.

Nonadherence and Withdrawal

Participants who do not adhere to, or withdraw from, the study or the intervention are contacted by phone and asked for the reason for nonadherence or withdrawal. Participants who want to stop with the intervention are asked to complete a post-intervention assessment at T1 and follow-up assessments at T2 and T3. Participants who withdraw from the study are asked to answer the questions of the fatigue severity subscale of the CIS online or during a telephone conversation.

Assessments

All self-reported questionnaires are Web-assessed via a Web portal on the project website [48,49], developed by Roessingh Research and Development. Participants receive an email when an assessment becomes available and can log in to the Web portal to complete the questionnaires. During the intervention period, each assessment is available for 1 week, but can stay open longer if therapy is postponed due to, for example, illness or holiday. If a participant has not completed it within 6 days, he or she is reminded by email at least once to complete the questionnaire. Within each assessment, the questionnaires are grouped on the basis of importance and subject. Item sequences of the questionnaires for the mediating factors and outcome measures differ between the assessments. Personal data is stored separately from the research data. An overview of all the assessments is shown in Tables 2 and 3.

Physical activity data is collected using the same device as that used for the ambulant activity feedback therapy: a 3D-accelerometer (ProMove 3D) combined with a mobile phone that collects the accelerometer data and sends it to a secured Web server at Roessingh Research and Development [52]. However, the mobile phone does not give feedback on activity, but does state whether the system is working properly and sends an error message if the connection to the sensor fails. Participants are reminded by email to wear the accelerometer on the day before the start of the week in which they will be using it.

Outcome Measures

Fatigue

Fatigue severity will be assessed with the CIS, which consists of 20 items that score on a 7-point Likert scale [53,54]. The CIS has 4 subscales (fatigue severity, motivation, concentration, and physical fatigue) of which the fatigue severity subscale will be used as the primary outcome (8 items, range: 8-56 points). The CIS has shown good discriminative validity in a working population [55], is sensitive to changes in the chronic fatigue syndrome population [56], and has previously been used with cancer survivors [7,57]. The CIS strongly resembles the Multidimensional Fatigue Inventory, which is often used in international studies [54]. Fatigue severity will be assessed at T0a, T0b, M3, M6, M9, T1, T2, and T3. However, the other 3 subscales will only be assessed at T0b, T1, T2, and T3.

Mental Health

Mental health will be assessed from the results of 2 questionnaires: the Positive and Negative Affect Scale (PANAS [52]) and the HADS [58], both of which are included in an item bank for cancer survivors [59]. The PANAS consists of 20 items that score on a 5-point Likert scale and has 2 subscales: positive and negative affect. The HADS consists of 14 items on a 4-point scale, has been validated for a Dutch-speaking population [60], and has previously been used to assess psychological distress in cancer patients [61]. Mental health will be assessed at T0a, T1, T2, and T3.

Perceived Ability to Work

The work ability score, which is assessed with the first question of the work ability index [62,63], will also be used as an outcome parameter. It asks: “Imagine that your working ability in the best period of your life is rated 10 points. How would you rate your working ability at the present moment?” It is assessed at T0b, T1, T2, and T3.

Working hours and the level of absenteeism are assessed with questions from the Trimbos and iMTA questionnaire on costs associated with psychiatric illness (TiC-P) [64]). These will be assessed at T0b, T2, and T3.

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Table 2. Assessments of outcome measures and potentially mediating factors.

Outcome Measures and Potentially Mediating Factors		Parameters	T0[a]	Mi/Mi'[b]	T1/T1'	T2/T2'	T3
Primary outcome	Fatigue severity	CIS fatigue severity subscale: 8 items on a 7-point Likert scale.	a, b	3,6,9	x	x	x
Secondary outcomes	Other dimensions of fatigue	CIS physical and cognitive fatigue and motivation subscales: 4 items for each subscale, all on a 7-point Likert scale.	b		x	x	x
	Affect	PANAS: 20 items on a 5-point Likert scale.	a		x	x	x
	Psychological distress	HADS: 14 items on a 4-point scale.	a		x	x	x
	Self-perceived ability to work	Work ability score: 1 item on a 0-10 numeric rating scale (NRS).	b		x	x	x
	Return to work and working hours	Adapted questions of the TiC-P.	b			x	x
Primary mediating factors	Mindfulness	Freiburg Mindfulness Inventory short form [65,66]: 14 items on a 4-point Likert scale.	b	3,6,9	x	x	x
	Physical activity (PA)	Accelerometer: ProMove 3D [52]. Both summative PA and daily PA decline will be considered.	b	3,6,9[c]	x		
	Sleep quality	Subjective Sleep Quality Scale [67]:15 items (yes/no), and 1 self-conceptualized item (yes/no) that translates into: "Did you use sleep medication?"	b	3,6,9	x	x	x
	Sense of control over fatigue	Self-Efficacy Scale [56]: 7 items on a 4-point Likert scale.	b	3,6,9	x	x	x
	Credibility and expectancy	Credibility and Expectancy Questionnaire [68]: 6 items of which 4 are on a 9-point Likert scale, and 2 items on a 0-100 NRS.	c, c'	1,2,4			
	Working alliance	Working Alliance Inventory short form [69,70]: 12 items on 5-point scale; subscales: goal, task, bond.		1,2,4			
Secondary mediating factors	Perceived physical activity	Four self-conceptualized questions on perceived activity volume, comparative volume, and satisfaction with volume.	b		x	x	x
	Self-efficacy on activities	Selected items from the self-efficacy scales of Bandura [71] and Rodgers [72,73]: 13 items on a 0-100 NRS; subscales: planning and coping.	b		x		
	Catastrophizing	Fatigue Catastrophizing Scale [74,75] 9 selected items on a 5-point Likert scale.	b		x		
	Fear of cancer recurrence	Two selected items on a 7-point Likert scale [76].	b		x		
	Causal attributions	One self-conceptualized open answer question that translates to: "What do you consider as the cause of your fatigue?"	b		x		

[a]Baseline assessment T0 consists of 3 time-points: T0a: before eligibility check, T0b: after inclusion, and T0c: after randomization. T0c' is assessed after preferential allocation.

[b]Mi and Mi' = assessments at week (i=) 1, 2, 3, 4, 6, 9 of the intervention

[c]All physical activity measurements are blind except for the experimental activity feedback condition at M3, M6, and M9. In the second semester, M3', M6', and M9' do not include a physical activity measurement in the mindfulness condition.

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Table 3. Other assessments.

Demographics, medical history, and control factors	T0[a]	T1/T1'	T2/T2'	T3
Age, gender, education, family status, nationality, time since diagnosis, time since previous treatment, fatigue duration, psychological counseling in the past, comorbidity.	a			
Cancer type, cancer treatment, perceived life threat of cancer (7-point Likert scale), known heredity of cancer (yes/no/don't know), former experience with attention focusing exercise (yes/no), religious beliefs, perceived social support (Multidimensional Scale of Perceived Social Support [77]: 12 items on a 7-point Likert scale).	b			
Medication use, substance use (caffeine, nicotine, alcohol, drugs), quality of life (1 item on a 0-10 NRS).	a	x	x	x
Pain intensity and limitations by pain (2 items on a 7-point Likert scale), body mass index.	b	x	x	x
Life events since previous assessment, professional help received for fatigue outside the scope of the study protocol.		x	x	x
Perceived effectiveness of the intervention (5 items of which 1 item 0-10 NRS and 2 yes/no questions), perceived social support in following the intervention (1-10 NRS).		x		
Social desirability: 6 selected items from the Balanced Inventory of Desirable Responding [78] on 5-point Likert scale.			x	

[a]Baseline assessment T0 consists of 3 time-points: T0a: before eligibility check; T0b: after inclusion; and T0c: after randomization.

Mediating Factors

Several categories of mediators will be considered: intervention-specific mediators for either eMBCT (eg, mindfulness, catastrophizing, and fear of cancer recurrence) or AAF (eg, physical activity, perceived physical activity, and self-efficacy on physical activity), and generic mediators (eg, sleep quality, sense of control over fatigue, credibility, expectancy, working alliance, and causal attributions). Furthermore, a distinction is made between primary and secondary mediating factors: primary factors are assessed at multiple occasions during the intervention in order to study the timely development of those factors; secondary factors are not assessed during the intervention. A complete overview of all assessments on mediating factors is given in Table 2.

Demographics, Medical History, and Control Factors

Several other factors are assessed, including demographics, medical history, and control factors. All are listed in Table 3.

Analysis Plan

Overview

SPSS software will be used for data management and Mplus [79], which is a latent variable modeling program, for the subsequent analyses. The exact versions of the software used will be reported in the future papers.

Pre-Analysis

Power Analyses

The sample size for analyses for data relating to the primary objective has been calculated for a repeated measures analysis of variance: based on an alpha of .05, a minimal detectable effect size of f2=.15, and a power of .80, a total number of 55 participants [80] is required in each group to answer the primary research question of this study in a statistically valid manner.

We expect to be able to include 330 eligible participants within a period of 2 years, based on a mean of 3.7 intakes per week for the eMBCT of the Helen Dowling Institute in 2011. An estimated attrition of 30% of the participants during both experimental interventions and 15% during the minimal intervention control condition [51] would leave us with 77 participants in each experimental group and 94 participants in the control group at T2. Again, we expect a dropout rate of 30% during the second semester. Such a dropout would leave a total of 110 participants completing each experimental intervention. Ten percent of the participants may have to be excluded from the analyses because of recurrence or diagnosis of metastasis. That would result in 198 participants that complete the full trial. We expect that this number will be enough for testing the 6 mediating factors or effect predictors: A classical, conservative power calculation (analysis of variance for testing 6 mediators or effect predictors with an intermediate effect size (f2=.08), corrected according to Bonferroni (alpha=.05/6), and at a power of .80 [81]) would result in approximately 254 participants being needed. We expect that the actual power when including 198 participants, and not the required 254 participants, will be great enough to detect up to 6 mediators or effect predictors with the use of Bayesian statistics [76]. Bayesian statistics allow analysis on small sample sizes [76,77], as more power can be generated with the use of prior information which is incorporated in the model that is being tested. Various papers describe comparisons between traditional null hypothesis testing and Bayesian estimation [82-85]. For this study, prior knowledge is available for many parameters, such as the effects of mindfulness in cancer survivors [23,25,66,86] and the role of working alliance in online interventions [87]. Examples of these methods can be found in both applied psychology and social science articles [88-92].

Missing Data Handling

Missing data will be analyzed considering their pattern and randomness following guidelines proposed by Schafer and Graham [93]. Bias due to systematic missing data will be managed according to guidelines proposed by Asendorpf et al [94].

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Descriptives

Quantitative analyses will be conducted on an intention-to-treat basis. A flow diagram following the CONSORT guidelines will be included. Descriptive statistics will be calculated and presented. Independent samples' t-tests and χ^2 tests will be performed to check for baseline differences between the respective experimental conditions and the control condition with respect to demographic variables (eg, family status, age, gender, and level of education), time since end of treatment, and baseline levels of the outcome variables. If we find statistically significant differences in the mean of fatigue severity across baseline descriptives, dummy variables will be added to the model as covariates to control for these differences.

Core Analysis

Effectiveness

Overview

Five steps will be taken to evaluate the effectiveness of both interventions, which are explained here in a generic way. The specific hypotheses on the effectiveness of the interventions in our study are shown in Textbox 1.

Textbox 1. Hypotheses on effectiveness.

Primary outcome

In both experimental conditions:

Fatigue severity

- decreases during the intervention, and
- remains decreased after 6 months.

After 6 months, fatigue severity has decreased significantly more compared to the control condition.

After 6 months, more participants show a clinically relevant reduction of fatigue severity compared to the control condition. A patient is considered clinically improved if he or she has a reliable change index of more than 1.96, according to the reliable change index, and the end score has to be within the normal range, that is a score < 1 standard deviation above the mean of a normative group [94] (ie, a score < 30.4 on the CIS fatigue severity subscale [51]).

Secondary outcomes

For both interventions we expect that:

- After 6 months, mental health and work ability have improved more than in the control condition.
- After 12 months, fatigue severity, work ability, and mental health remain improved in both intervention groups.
- Improvements in mental health and work ability after 6 and 12 months are related to reductions in fatigue severity.

Return to work and reduced absenteeism will be studied as explorative outcomes.

Step 1

Overall effectiveness will be tested in an intention-to-treat analysis by a multiple group latent growth model [79] using data from the first semester. This technique allows individuals to have an individual growth trajectory over time and compensates for missing data in an elegant way.

Since different growth patterns are expected for the pre-intervention period, the intervention period, and the post-intervention period, we will apply piecewise growth modeling so that a slope factor will be estimated for each of the 3 periods (Figure 4). Initial intercepts will be configured to represent the T0b score. This intercept and the pre-intervention slope factor will be constrained to be equal between all 3 conditions (and this assumption will be checked), whereas the subsequent slope factors will be estimated separately for the 3 conditions.

The fit of the piecewise model will be compared with a quadratic model. In the quadratic model, the entire first semester is modeled with 1 slope factor and 1 quadratic factor for each of the 3 conditions and an intercept that represents T0b and is constrained similarly to the piecewise model.

Both models will be run both with and without using time-varying loadings in order to check whether corrections should be made for differences in timings between the questionnaires. Growth factor estimates and model fits for all 4 models will be reported (Table 5).

Neither the participants nor the researchers (FBE and MW) are blinded to allocation. Therefore, an independent statistician (RvdS) who is blind to the allocation will test the primary hypothesis.

The same procedure will be followed for the secondary outcomes, except that the initial intercept of mental health will represent T0a, rather than T0b, because T0b does not include an assessment of mental health.

Results of frequentist analyses will be reported by *P*-values (significant in case <.05) and with 95% confidence intervals. Parameter estimates of models by means of Bayesian estimators will be reported with 95% central credibility intervals.

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Figure 4. Simplified representation of a piecewise linear latent growth model, with latent intercept factor (I), latent slope factors preintervention (S(pre)), during the intervention (S(int)), and postintervention (S(post)), and 7 indicators Y. Error terms, correlation coefficients, and covariances are left out.

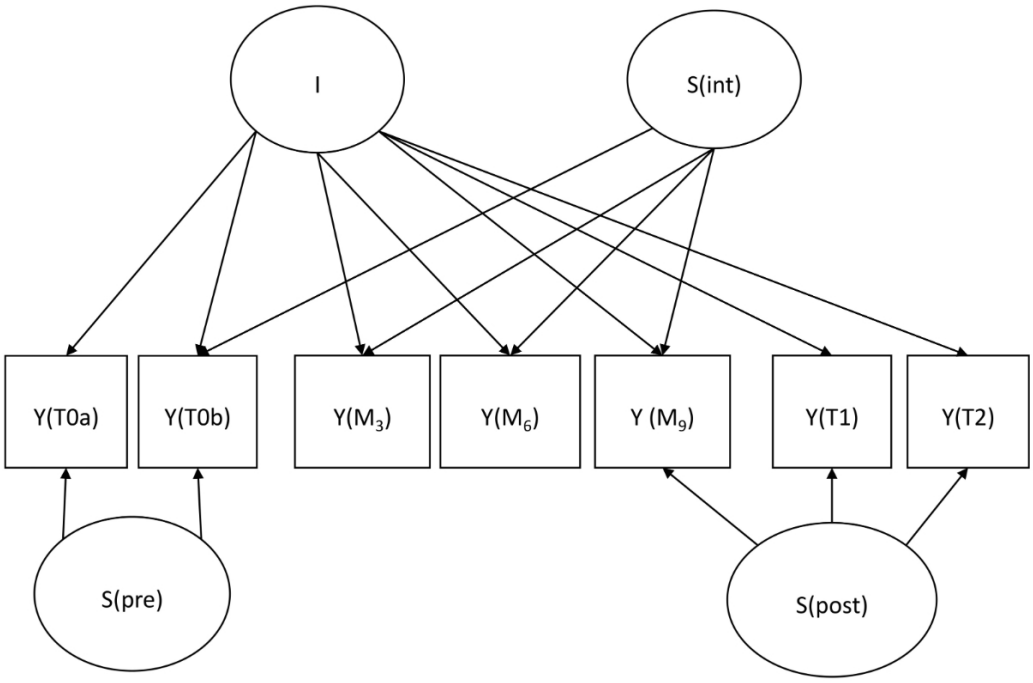

Table 5. Growth factor estimates of 4 different latent growth models.

	Fixed loadings	Time-varying loadings
Piecewise, linear	Mean: I, S(pre), S(int), S(post) Variance: I, S(pre), S(int), S(post)	Mean: I, S(pre), S(int), S(post) Variance: I, S(pre), S(int), S(post)
Quadratic	Mean: I, S, Q Variance: I, S, Q	Mean: I, S, Q Variance: I, S, Q

Step 2

The effect size of both experimental interventions will be calculated according to recommendations in Feingold (2009) [95] for both primary and secondary outcomes.

Step 3

The proportion of participants who make clinically relevant progress on the primary outcome will be calculated for all 3 conditions; again, in an intention-to-treat analysis. Percentages and standard deviations of the reliable change index will be presented.

Step 4

A latent growth model will be built of the primary outcome, in which the outcome measures that have been measured at T3 will also be included, as distal outcomes of changes in the primary outcome during the first semester.

Step 5

A growth mixture model (GMM) will be used to further explore differences between individuals, and more specifically to identify subpopulations (latent classes) with homogeneous growth trajectories of the primary outcome within the experimental groups. The Bayesian information criterion will be used for model selection [96].

If convergence considerations allow, this model will be adjusted to allow covariance of the growth factors in order to acknowledge individual variation around the estimated growth trajectories. The trace plots will be inspected to check whether the models have converged to global solutions and a set of diverse starting values will be used. For more information on these analyses, we refer to an introduction to GMM and latent class growth analysis by Jung and Wickrama [97] and examples of similar analyses in the field of Internet interventions [98] and cancer patients [41].

Mediators

Overview

The analysis of the mediators of the experimental conditions can be roughly subdivided into two steps: first analyze the primary factors individually for their longitudinal correlations with the outcome (Step 6), then combine the relevant factors in a multivariate analysis (Step 7). The specific hypothesis on the mediating factors of the interventions in this study are shown in Textbox 2.

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Step 6

For analyzing the mediators of the experimental conditions, first we want to see whether there is a correlation between the growth trajectories of our outcome parameter and the potential mediator over time. The hypotheses considering mediators are shown in Textbox 2. The combined data from the participants in the first semester and data from the preferentially assigned participants in the second semester will be used.

The following subhypotheses will be tested for each primary mediator (these are also shown in Figure 5):

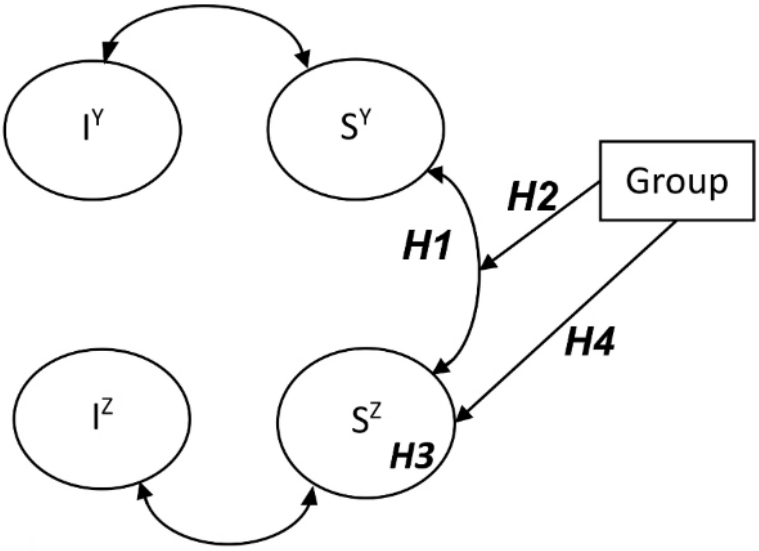
1. Is the growth of the primary outcome (Sy) for the entire study population correlated with growth of the potential mediator (Sz)?
2. Is such correlation independent of group?
3. Does the potential mediator change over time in the specific group, so is the slope factor (Sz) substantially unequal to zero?
4. Is the slope factor in the specific group substantially greater than the slope factors in the other groups?

In these 4 subhypotheses, the first is congruent with testing the "conceptual theory" in classical mediation analysis, and subhypothesis 3 with testing the "action theory." If subhypotheses 1-4 all are true, the factor will be considered a specific mediator for that intervention. If subhypotheses 1, 2, and 3—but not 4—are true, the factor will be considered a general mediator for fatigue severity. If either subhypothesis 1 (conceptual theory) or 3 (action theory) is false, the factor will not be considered a mediator.

Textbox 2. Hypotheses on mediators.

We expect that, for AAF, increasing mean cumulative daily physical activity and reductions of daily physical activity decline are specific mediators.
We expect that, for eMBCT, developing mindfulness skills is a specific mediator.
We expect that sleep quality, working alliance, sense of control over fatigue, credibility, and expectancy are generic mediators for both e-therapies.
The mediating role of the following factors will be explored: number of sessions completed, changes in causal attributions [99], decreased catastrophizing thoughts about fatigue [8], decreased fear of cancer recurrence [100,101], changes in perceived activity [102], increased self-efficacy on physical activity [103].

Figure 5. Simplified representation of a correlated growth model in which Iy and Sy represent the intercept and slope factors of the latent growth model of the outcome parameter, and Iz and Sz represent the latent growth factors of the mediator. H1-4 represent the 4 subhypotheses of Step 6. All indicators have been left out for clarity.



Step 7

The next step in studying potential working mechanisms is a single-step, multiple-mediation analysis using structural equation modeling [104-106]. By estimating such a model, we expect to obtain a comprehensive model for all the working mechanisms of the intervention. It should be noted that this model assumes that an intervention works in the same way for all participants in a particular group [107]. Again, data from both semesters will be used.

A separate model will be tested for each intervention. Each model will have the following paths (Figure 6), where X=independent variable (1/0 for specific intervention vs control group), Y=outcome variable (difference score T2-T0b of the primary outcome measure), and Z=mediator:

- a: X regressed on Z.
- b: Z regressed on Y;
- c': direct effect of X on Y.

For each experimental intervention, the starting model will consist of all the significant primary mediators of Step 6 that

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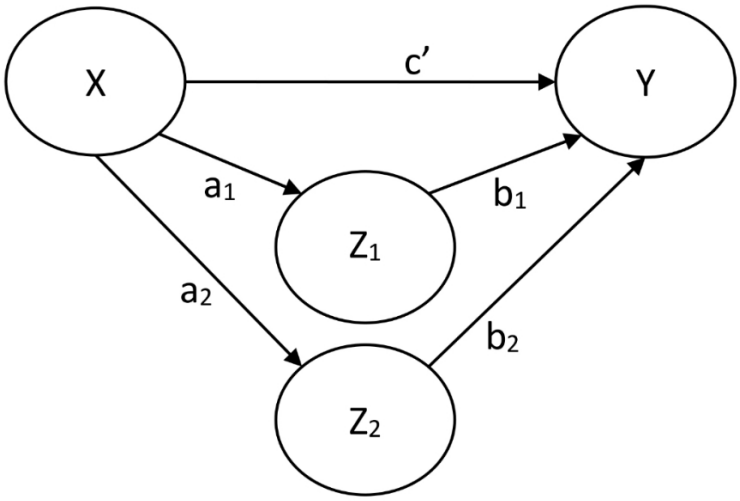
have also been assessed in the control group. In other words, the factors that have shown to be mediators in the correlated growth model will be the starting point for this model. The models will then be complemented with the secondary mediating factors described in Textbox 2. Mediating factors for which the indirect effect (a × b) is insignificant will be removed stepwise, after which a final model will be created.

Model fit, standardized path coefficients—including indirect effects—and the total effect of at least the first and final models will be reported with 95% confidence intervals.

Figure 6. Multiple mediation model with independent variable (X), dependent variable (Y), and 2 mediators (Z). Direct effect (c') and indirect effects (through a x b) are shown.



Effect Predictors

Overview

Two complementing approaches for analyzing the effect predictors are addressed in steps 8 and 9 of this analysis plan. The specific hypotheses on the effect predictors for both interventions in this particular study are shown in Textbox 3.

Textbox 3. Hypotheses on effect predictors.

We expect that for AAF, low perceived physical activity predicts reduction of fatigue severity.

We expect that for eMBCT, low perceived concentration, previous experience with mediation exercises, high perceived life threat from cancer, and a high education level predict reduction of fatigue severity.

In general, we expect that low perceived social support, longer time since last treatment, suffering from more comorbidities [108], and having strong somatic attributions [57] predict small effects on fatigue severity in both interventions. We expect that high sense of control and good sleep quality predict large effects in both experimental conditions.

Other factors will be included for explorative research.

Step 8

To find out which participants benefit most from each intervention, the final model of fatigue severity of Step 1 will be extended with potential effect predictors (Textbox 3) that load on the latent growth factors "linear slope" (the "post randomization" linear slope in case of the piecewise model) and, if applicable, "quadratic slope." As the regression coefficients of all potential effect predictors on the development of fatigue severity will be freely estimated across the 3 intervention groups, this is also called a moderation effect of intervention.

Factor loadings of all hypothesized effect predictors will be reported. Those with the highest loadings will be compared between the conditions in order to find differential effect predictors.

Step 9

To identify common effect predictors of homogeneous subpopulations within the heterogeneous population, rather than identifying effect predictors for individual growth patterns, the final step will consist of regressing predictors on latent classes. Therefore, the final model of Step 5, the GMM, will be extended. Again, several potential effect predictors will be regressed onto this model, but this time on the latent class factor, instead of on the latent growth factors. The 3-step procedure proposed by Vermunt [109] will be used for model selection. This step will be carried out separately for each experimental condition.

Factor loadings of all hypothesized effect predictors will be reported. Those with the highest loadings will be compared between the conditions in order to find differential effect predictors.

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Results

Recruitment for the trial started in March 2013 and is expected to continue until April 2015. No major changes have been made to the protocol. However, due to an error in the randomization algorithm between January 14, 2014, and July 15, 2014, allocation was dependent on the number of participants who were allocated at once. This in turn was completely random. Consequently, 10 participants were allocated directly to the AAF group; 4 other participants were divided equally between the 2 experimental interventions; and 15 accounts (of which, 1 was a dummy account) were equally divided between the 3 groups. None of the researchers were aware of this error, as this allocation could very well have simply been the result of the "roll the dice" scenario that should have been applied. How many participants were allocated at once was not the subject of the researchers' decision-making. Therefore, we argue that allocation has still been random and, accordingly, data for all considered participants will be processed as originally planned.

At the time of this writing in January 2015, 269 patients have registered at the project website. Of these, 111 have been officially included in the study, 50 were excluded from participation, and 35 withdrew before their eligibility was checked. The remaining patients are still in the enrollment phase. The main reason for exclusion so far has been a score lower than 35 on the CIS fatigue severity subscale (60%). Furthermore 11% did not meet the psychiatric stability requirement, 8% were younger than 18 at the time of cancer diagnosis, and 8% were still receiving cancer treatment.

Current group sizes as of January 2015 for participants in the first semester are 36 (AAF), 24 (eMBCT), and 32 (control). However, 19 participants have not yet been randomized. Initial responses to the primary research question are expected to be available by the end of 2015.

Discussion

Principal Findings

This paper has described the design, hypotheses and analysis plan of a randomized controlled trial in order to study the effectiveness, mediation, and effect predictors of 2 Internet-based interventions for CCRF. Although recruitment and inclusion have already started, publishing the analysis plan is of great value because it will help to prevent outcome reporting bias [110] and adds validity information to the final studies [111].

By using multiple assessments during the intervention, the proposed trial design is suitable for studying the chronological development of both potential mediators and fatigue. That has 2 main advantages. Firstly, the data will be suitable for analyses that allow for variation in the individual fatigue trajectories. We do not expect that either of the interventions that have been included in the trial will be beneficial for all participants: our study sample will be highly heterogeneous considering for example tumor and treatment types. Therefore, the analyses on individual growth trajectories can acknowledge that expectation and test that hypothesis. This will substantiate the interpretation of the results on effectiveness and will be an important first step in identifying what works for whom. Secondly, this study design enables us to use a fully longitudinal mediation analysis, at least for the most important factors, rather than using indirect effects analysis in cross-sectional mediation analysis.

Another important feature of the proposed design is that by comparing 2 different interventions with an active control group, therapy-specific elements of the interventions can be distillated from the data acquired during this trial. This advantage counts for both the effect predictors and the mediators. Knowledge about such differentiating factors can and should be used to better inform patients with CCRF and to improve allocation of patients with CCRF to suitable interventions. As a result, an increase in the overall effectiveness of relevant interventions can be established.

In this paper, we have presented the trial design, our hypotheses, and a detailed analysis plan. In accordance with good clinical practice, and to avoid outcome reporting bias, this paper was submitted before any of the data was analyzed. All methods are now openly predetermined, therefore any future publication describing this trial can be valued reliably on its quality.

Limitations

A limitation of the current paper is that for most instruments, this paper does not include information on its properties or a thorough rationale for its choice. More extensive information on the actual instruments will be reported in subsequent papers on the results of the various research questions posed in this trial.

Conclusions

Given the growing number of patients suffering from CCRF, the availability of effective Internet interventions potentially strengthens current health care for this population substantially. We have proposed a design to study 2 Internet interventions in order to gain insight into their effectiveness, mediators, and effect predictors, which fully acknowledges differences between individual patients and differences in the way they respond to each intervention. Results on the effectiveness and mediators will give useful information for improving both the quality and availability of such interventions. Also, identifying effect predictors for positive intervention effects will improve the referral of patients to relevant interventions. By presenting our hypotheses and analytic strategy before completion of data collection, this paper is a first step in carefully reporting on this comprehensive trial.

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Acknowledgments

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Authors' Contributions

Study conception and design: all authors; acquisition of data: FE and MW; analysis and interpretation of data: not applicable; drafting of manuscript: MW; critical revision: all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Picture of the ProMove accelerometer and mobile phone app with feedback.

[PNG File, 1MB - resprot_v4i2e77_app1.PNG]

Multimedia Appendix 2

Additional screenshot of the therapist Web portal for ambulant activity feedback therapy (Dutch).

[PNG File, 82KB - resprot_v4i2e77_app2.png]

Multimedia Appendix 3

Additional screenshot of the patient Web portal for eMBCT (Dutch).

[JPG File, 130KB - resprot_v4i2e77_app3.jpg]

Multimedia Appendix 4

Example of an information letter for the minimal intervention control condition (Dutch).

[PNG File, 110KB - resprot_v4i2e77_app4.png]

Multimedia Appendix 5

CONSORT E-HEALTH checklist V1.6.1 [112].

[PDF File (Adobe PDF File), 1021KB - resprot_v4i2e77_app5.pdf]

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Protocol

A Shared Mealtime Approach to Improving Social and Nutritional Functioning Among Older Adults Living Alone: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Older adults living alone are at increased risk of malnutrition as well as social isolation. Previous research has evaluated psychosocial interventions aimed at improving social support for older adults living alone. One meta-analysis in particular has suggested that multimodal psychosocial interventions are more effective than unimodal interventions. As such, it may be more effective to deliver an intervention which combines nutritional and social support together. Consequently, we designed the RelAte intervention, which focuses on shared mealtimes as a source of combined social and nutritional support for older adults living alone who are at risk of social isolation.

Objective: The objective of the RelAte trial was to evaluate the impact of such an intervention on energy intake, anthropometric measurements, and nutritional social cognitive variables among older adults living alone in the community.

Methods: There are 100 participants that will be recruited and randomized to either the treatment (n=50) or the control group. The treatment group will receive a visit from a trained peer volunteer once weekly for a period of 8 weeks. Outcomes of interest include: energy intake, social cognitive factors related to diet, abdominal circumference, body mass index, psychosocial well-being, frailty, nutritional status, and health utilities. Outcomes will be obtained at baseline, immediately postintervention (8 weeks after baseline), 12-week follow-up, and 26-week follow-up by assessors blinded to participants' randomized assignment.

Results: The Relate trial is currently active. We are currently at data analysis stage. The study started in June 2013 and will run until June 2015.

Conclusions: Results from this study will primarily describe the effectiveness of a shared mealtime intervention for older adults living alone in terms of their dietary well-being, physical health, and psychosocial well-being.

Trial Registration: Trial Registration: Clinicaltrials.gov NCT02007551; http://clinicaltrials.gov/ct2/show/NCT00102401 (Archived by WebCite at http://www.webcitation/6WptuVTtz).

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KEYWORDS

nutrition; randomized controlled trial; older; aging; intervention; social support; anthropometry; social cognitive theory

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Introduction

Socially Isolated Older Adults

Older adults who live alone independently in the community are at increased risk of becoming socially isolated, relative to those who live with others [1,2]. Social isolation, in turn, is a significant risk factor for the development of cognitive impairment, as well as increased risk of dementia, morbidity of other types, and mortality [3-5]. Since social isolation has such a significant effect on older adults, interventions are recommended. To date, there have been many attempts to design and evaluate effective and scalable interventions to improve social support among older adults. The most common form of social support intervention is the "befriending" intervention [6], whereby volunteers are trained to provide emotional support and reciprocal social support for the participant. Befriending interventions can be effective in improving psychosocial functioning and reducing depressive symptomatology [7].

Mealtime Interventions

Social isolation among older adults living alone can also increase the risk of malnutrition [8-11]. The state of malnutrition itself is associated with increased morbidity, mortality, and up to 20 times more complications at hospitalization. While studies have in the past focused on mealtime interventions, these interventions have tended to focus on institutionalized populations, or older adults with dementia [12-20]. The concept of a mealtime intervention does not appear to have been applied to a healthy independently living older population. However, the concept of a mealtime is gaining ground as a scientifically interesting topic of research [21], particularly the idea of shared mealtimes as opposed to eating alone [22]. A study of 150 older adults found that 32% never shared a meal with others [23].

It is important that interventions are designed according to a theoretical framework, to inform the research design, the content of the intervention, and to facilitate interpretation of results [24,25]. A popular theoretical framework underlying many psychosocial interventions is Social Cognitive Theory [26,27]. Interventions designed in accordance with this theory focus on the individual as learning most effectively from others, particularly when learning health behaviors. Social cognitive interventions aim to facilitate the transmission of knowledge from one individual to another, ideally between peers, so as to improve self-efficacy and ultimately change behavior. Outcome expectations, or the belief that a particular outcome will follow from a behavior, are also of interest as an outcome variable in social cognitive interventions.

A meta-analysis of befriending interventions performed by Cattan et al [28] concluded that active interventions, whereby some effort on the part of the participant was required, were more effective than those without. Furthermore, since challenges are rarely faced in isolation, Sabir et al have recommended that successful interventions should target more than one challenge at a time [29]. Combining social and nutritional support may have synergistic effects on nutritional outcomes since companionship may improve energy intake at meals [10,30]. Furthermore, social support appears to be best received if combined with a secondary leisure activity [31], presumably because incidental social contact is more acceptable to older adults than purposeful contact, which may highlight a stigmatized condition of social isolation [32]. Thus, we decided to target nutritional and social challenges faced by older adults living alone in combination, using the RelAte shared mealtime intervention. The purpose of this trial is therefore to examine the preliminary effectiveness of implementing the RelAte shared mealtime intervention for older adults living alone at risk of social isolation.

Methods

Study Design

The RelAte trial is a parallel assignment, assessor-blinded, randomized controlled trial aimed at evaluating the effectiveness of an 8-week peer-delivered social and nutritional intervention relative to text-based educational information for older adults who are living alone and at risk of social isolation. The trial protocol was registered on an Internet trial database [33]. The primary aim of the trial is to indicate the effectiveness of the RelAte intervention and its impact on social cognitive and anthropometric factors for older adults living alone independently in the community. A total of 100 participants will be recruited to the study, age 60 and over, and will be randomly assigned to the treatment or the control group based on a minimization procedure [34]. The study is a feasibility trial, and as such, our target sample size is not aimed at achieving sufficient power to make conclusive statements about the intervention effectiveness, but rather to obtain sufficient effect sizes to allow preliminary statements to be made about the impact of such an intervention, and to inform further, optimally powered, trial studies evaluating the intervention.

Participants

Participants for the current study are eligible if they are 60 years of age or older, living alone, and deem themselves to be at risk of social isolation. A phone screen will then determine whether participants are eligible for inclusion in the study according to the following criteria: that they show no sign of cognitive impairment as defined using the Telephone Cognitive Screen [35]; that they do not report a history of stroke, epilepsy, schizophrenia, bipolar affective disorder, recurrent psychotic depression, or alcohol or drug abuse within the past 5 years; that they do not report the use of anticonvulsants or antipsychotic medications; that they do not have significant hearing difficulties which are not resolved using a hearing aid; that they do not report a history of any illness which caused permanent decrease in memory or other cognitive functions; and that they do not currently have any bloodborne, airborne, or contact-borne infectious diseases which would threaten the well-being of the peer volunteer. In the original protocol plan, an additional exclusion criterion was that eligible participants must have scored as socially isolated on the Lubben Social Network Scale [36], but following the screening of the first 10 participants, it was found that this yielded only 20% eligibility from interested participants; since older adults living alone are a particularly difficult group to recruit for research without this additional criterion, it was deemed necessary to instead change

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this criterion to include participants if they themselves felt that they were at risk of becoming socially isolated.

Recruitment

Recruitment strategies include: mail-drops to sheltered accommodation areas in the greater Dublin area; presentations to senior citizens groups, active retirement groups, and other social groups for older adults; publications in national newspapers and use of national television media; published recruitment advertisements in parish newsletters; recruitment via day centers and clinics; recruitment via public health nurse networks and other allied health professionals working in the community; disseminating fliers to primary care offices and pharmacies; and word of mouth.

Informed Consent

Approval of the trial protocol and consent forms has been obtained by the School of Psychology Research Ethics Committee, Trinity College Dublin (Project, RelAte 12122-2013) prior to the recruitment of any participants. All participants must provide informed written consent prior to their involvement with the study.

Measures

All measures will be obtained at baseline, 8-weeks postbaseline (ie, immediately after the 8-week intervention period), 12-week follow-up, and 26-week follow-up, for all 100 participants. Assessments will be conducted by research assistants with qualifications in psychology, who will be blinded to the randomized assignment of the participants.

Primary Outcome Measures

Social Cognitive Variables

These variables describe the self-efficacy, self-regulation, outcome expectations, and social support related to dietary behavior for participants. The Generalised Self-Efficacy Scale [37], Nutrition Self-Efficacy Scale [38], and Health Beliefs Survey [39] will all be used to evaluate these variables across all participants, across the four measurement points.

Energy Intake

Energy intake in kilocalories will be assessed using two 24-hour dietary recalls, whereby participants are asked to recall in detail everything they ate and drank over the previous 24-hour period. The assessors will receive dietetic training in administering these dietary recalls. The dietary recalls will be converted to kilocalorie values using Nutritics software [40].

Secondary Outcome Measures

Quality of Life

Participant quality of life will be measured at each timepoint using the 19-item Control, Autonomy, Self-Realisation & Pleasure Scale [41].

Cognition

Participant cognition over time will be measured using the Montreal Cognitive Assessment [42] and the Trail Making Test [43]; premorbid cognitive function will be assessed using the National Adult Reading test at baseline only [44].

Social Connectedness

The Berkman-Syme Social Network Index will be used to measure social connectedness over time [45].

Loneliness

The De Jong Gierveld scale will be used to assess loneliness over time [46].

Psychological Well-Being

Psychological well-being will be assessed across participants over time using the Centre for Epidemiological Studies depression scale [47], the Hospital Anxiety & Depression Anxiety subscale [48], and the Ryff scale of well-being [49].

Nutrition

Nutritional health will be assessed using the Mini Nutritional Assessment [50] and the Food Enjoyment Scale [51].

Physical Health

Abdominal circumference will be measured using a measuring tape; body mass index will be measured using weight (kg) and height (cm) readings from a clinical stadiometer and body composition weighing scales. Grip strength and overall frailty will be assessed and operationalized according to the Survey of Health, Ageing, and Retirement in Europe frailty instrument [52], and overall health will be assessed using the Health Utilities Index [53].

The Intervention

The RelAte intervention is an 8-week, multicomponent peer-delivered intervention, which is delivered in the home of the participant. The intervention each week consists of a visit from a matched peer (matched based on location and gender), who decides with the participant on a recipe from the RelAte guidebook. These recipes were chosen based on the ease of preparation for one person (since the RelAte participants live alone) and for cost-effectiveness also. Each week, the participant and volunteer choose a recipe, and the volunteer brings the ingredients to the home of the participant, so that they can together prepare and share a meal. The volunteers have all received basic culinary and nutritional training and, in keeping with recommendations for active interventions, participants are advised that they must engage with all steps of the cooking process, insofar as they are able. Since the intervention is based on Social Cognitive Theory, there must be opportunities for vicarious learning (through watching the volunteer cook), social support provided by the volunteer, opportunities for skill mastery (by helping with the cooking), and facilitation of goal setting if the participant wishes. The weekly visits last for 90 minutes and, aside from the guidelines listed here, are unstructured. The participants in the control group receive the RelAte guidebook, which contains recipes and nutritional/culinary information and advice, but no visitor.

Planned Analyses

We hypothesize that engagement with the RelAte intervention will result in increased energy intake for individuals with less than ideal intake, and decreased energy intake for those with higher than ideal intake. We hypothesize that self-regulation, self-efficacy, outcome expectations, and social support relating

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to dietary behavior will all improve over time for the treatment group relative to the control group. A weighted analysis of covariance model with appropriate covariates of baseline measures and age, baseline social isolation, and gender will be used unless there are significant issues with missing data and unbalanced observations, in which case mixed models analyses will be used. All analyses will follow the intention-to-treat principle. In dealing with missing data, multiple imputation methods will be used.

Results

The Relate trial is currently active. We are currently at data analysis stage. The study started in June 2013 and will run until June 2015.

Discussion

To summarize, the RelAte trial is a two-arm, assessor-blind, parallel randomized controlled trial, which aims to evaluate the effectiveness of an 8-week combined social and nutritional mealtime intervention for older adults living alone who self-report to be at risk of social isolation. We hypothesize that engagement with the intervention, which is peer-led and modelled upon Social Cognitive Theory principles, will result in improved self-regulation, self-efficacy, outcome expectations, and social support pertaining to dietary behavior, as well as improving energy intake among older adults living alone. The study is an opportunity also to evaluate dietary behavior and intake among older adults who live alone, since this type of research has rarely been conducted with an independent Irish older population. It is expected that recruitment issues may hinder study progress, since older adults living alone are reportedly a difficult demographic to recruit for research. Furthermore, since older adults living alone are at increased morbidity risk, it is possible that the later measurement points of the study will be subject to a high attrition rate, although this is unavoidable with this population. Similarly, adherence to the weekly 8-week intervention may be poor, due to unavoidable health-related issues. Findings will not be conclusive since the sample size is not based on a power calculation; however, findings will indicate the preliminary effectiveness of a shared mealtime intervention, and hopefully elucidate future directions for research in this area.

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Authors' Contributions

JMcH wrote the manuscript, led the design, coordination, and delivery of the intervention and the trial. OL and NA facilitated the delivery of the intervention and the trial, and were involved in aspects of the design, as well as reviewing drafts of the manuscript. SB and BAL were involved in conceptualizing the intervention and trial design, and provided feedback and final approval for the current manuscript.

Conflicts of Interest

None declared.

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Protocol

Timing of High-Dose Rate Brachytherapy With External Beam Radiotherapy in Intermediate and High-Risk Localized Prostate CAncer (THEPCA) Patients and Its Effects on Toxicity and Quality of Life: Protocol of a Randomized Feasibility Trial

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Abstract

Background: Prostate cancer is the most common cancer in males in the UK and affects around 105 men for every 100,000. The role of radiotherapy in the management of prostate cancer significantly changed over the last few decades with developments in brachytherapy, external beam radiotherapy (EBRT), intensity-modulated radiotherapy (IMRT), and image-guided radiotherapy (IGRT). One of the challenging factors of radiotherapy treatment of localized prostate cancer is the development of acute and late genitourinary and gastrointestinal toxicities. The recent European guidelines suggest that there is no consensus regarding the timing of high-dose rate (HDR) brachytherapy and EBRT. The schedules vary in different institutions where an HDR boost can be given either before or after EBRT. Few centers deliver HDR in between the fractions of EBRT.

Objective: Assessment of acute genitourinary and gastrointestinal toxicities at various time points to better understand if the order in which treatment modality is delivered (ie, HDR brachytherapy or EBRT first) has an effect on the toxicity profile.

Methods: Timing of HDR brachytherapy with EBRT in Prostate CAncer (THEPCA) is a single-center, open, randomized controlled feasibility trial in patients with intermediate and high-risk localized prostate cancer. A group of 50 patients aged 18 years old and over with histological diagnosis of prostate cancer (stages T1b-T3BNOMO), will be randomized to one of two treatment arms (ratio 1:1), following explanation of the study and informed consent. Patients in both arms of the study will be treated with HDR brachytherapy and EBRT, however, the order in which they receive the treatments will vary. In Arm A, patients will receive HDR brachytherapy before EBRT. In Arm B (control arm), patients will receive EBRT before HDR brachytherapy. Study outcomes will look at prospective assessment of genitourinary and gastrointestinal toxicities. The primary endpoint will be grade 3 genitourinary toxicity and the secondary endpoints will be all other grades of genitourinary toxicities (grades 1 and 2), gastrointestinal toxicities (grades 1 to 4), prostate-specific antigen (PSA) recurrence-free survival, overall survival, and quality of life.

Results: Results from this feasibility trial will be available in mid-2016.

Conclusions: If the results from this feasibility trial show evidence that the sequence of treatment modality does affect the patients' toxicity profiles, then funding would be sought to conduct a large, multicenter, randomized controlled trial.

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Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): 15835424; http://www.isrctn.com/ISRCTN15835424 (Archived by WebCite at http://www.webcitation.org/6Xz7jfg1u).

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KEYWORDS

prostate cancer; radiotherapy; brachytherapy; external beam radiotherapy; EBRT; randomized controlled trial; RCT; Southend Hospital

Introduction

Disease Background

Prostate cancer is the most common cancer in males in the UK, affecting around 105 men for every 100,000 [1]. The role of radiotherapy (RT) in the management of prostate cancer significantly changed over the last few decades with developments in brachytherapy (BT), external beam radiotherapy (EBRT), intensity-modulated radiotherapy (IMRT), and image-guided radiotherapy (IGRT). One of the challenging factors of radiotherapy treatment of localized prostate cancer is the development of acute and late genitourinary and gastrointestinal toxicities. There are several studies and case series published in the literature assessing the toxicities developed during EBRT and brachytherapy treatment for prostate cancer.

Background for Study

EBRT and brachytherapy emerged as the mainstays of localized prostate cancer treatment in recent years. Brachytherapy can be delivered either in low-dose rate (LDR) or in high-dose rate (HDR). The low-risk, localized prostate cancers can be treated with low-dose brachytherapy or by prostatectomy, whereas the intermediate and high-risk localized prostate cancers are usually treated with EBRT alone or in combination with HDR brachytherapy (HDR-BT). HDR monotherapy in this patient group is not routinely practiced unless as part of a study. Radiation dose escalation has been proven to be effective in biochemical response and clinical outcomes in prostate cancer. However, increased toxicity limits the total dose of radiation that can be safely administered [2-4]. Combining external beam radiotherapy with a brachytherapy boost has been effective in tumor control, allowing for significant dose escalation without any change in acute and late toxicities in comparison to external beam radiotherapy alone [5].

The relative sensitivity of radiotherapy depends on the alpha/beta ratio. This ratio expresses the sensitivity to radiation fraction size and estimates the impact of the given radiation schedule on tumor control and toxicity. There is increasing evidence to support the alpha/beta ratio for prostate cancer to be as low as 1.5 Gy. The evidence indicates that a hypofractionated radiation schedule—larger dose per fraction with smaller number of fractions—would offer optimal tumor control [6-9]. As a result, the practice of combining EBRT with HDR brachytherapy is gaining momentum in clinical practice. However, the current practice across the globe differs in both radiation doses and in the timing of each modality delivered.

The recent European guidelines suggest that there is no consensus regarding the timing of HDR brachytherapy and EBRT. The schedules vary in different institutions where an HDR boost can be given either before or after EBRT. Few centers deliver HDR in between the fractions of EBRT [10].

The EBRT doses range from 37.5 Gy in 13 fractions (2.88 Gy per fraction) to 45 Gy in 25 fractions (1.8 Gy per fraction) when given with HDR. The total HDR brachytherapy dose can be delivered in fractions, however a single dose of 15 Gy is gaining acceptance across the world due to its logistical advantage [10]. The time gap between the two radiotherapy modes of delivery is generally within 21 days.

The toxicity profile of radiation therapy is dependent on the type of modality used to deliver the treatment, and whether the treatment is delivered as a combined modality or standalone treatment [11]. A randomized phase III trial where EBRT was delivered before HDR showed that the 5- and 7-year incidence for patients with any severe urinary symptom was 26% and 31%, respectively, for those treated with EBRT and HDR-BT delivered sequentially. For patients given EBRT alone, the 5- and 7-year incidence was 26% and 30%, respectively (log rank P=.5). The incidence of severe bowel events for the EBRT/HDR combination group was considerably lower—7% and 6% at 5 and 7 years, respectively (log rank P=.8) [5]. On the other hand, a single-arm phase II study was performed to determine the toxicity profile of EBRT delivering a dose of 37.5 Gy in 15 fractions that was given after a single-fraction HDR boost of 15 Gy. In this study, Morton et al found acute grade 2 and grade 3 genitourinary toxicity in 62% and 1.6% of patients, respectively, and acute grade 2 gastrointestinal toxicity in 6.5% of patients, with no grade 3 gastrointestinal toxicity [12].

Both acute and late toxicity assessments in prostate cancer patients are assessed by various tools. For example, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients (EORTC QLQ-C30), the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Prostate Cancer Patients (QLQ PR25), the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grading system, the Functional Assessment of Cancer Therapy-Prostate (FACT-P), version 4, the International Prostate Symptom Score (IPSS), the International Index of Erectile Function Scale (IIEFS), and the Expanded Prostate Cancer Index Composite (EPIC) questionnaire may be used for toxicity assessments. Furthermore, the same data collection tools are used to measure health-related quality of life.

Rationale and Risks/Benefits

There is no consensus about the timing of HDR brachytherapy when treating prostate cancer along with EBRT. The advantages of using HDR brachytherapy before EBRT are that patients

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could potentially be identified who are not suitable for brachytherapy early in the treatment process. As the patients would be radiotherapy naïve, there would be less chance of soft tissue injury during the brachytherapy process if BT is given first. However, having brachytherapy first can be logistically difficult in a busy radiotherapy unit in terms of planning and arranging delivery of EBRT within 2 to 3 weeks of BT. Moreover, if the patients develop acute urinary complications during brachytherapy they would need to continue with EBRT with a urinary catheter, which could potentially prolong the duration of the catheter in situ and cause significant patient discomfort.

On the other hand, delivering EBRT first is logistically easier to arrange and could theoretically make the hypofractionated radiation dose of brachytherapy more effective, as tumor cells could become more radiosensitive due to molecular changes having been induced by EBRT. However, normal tissue damage due to delivery of EBRT first could make the brachytherapy procedure difficult with increased risk of toxicity. It is, therefore, essential to know whether there are any significant differences in toxicities and treatment outcomes, especially acute urinary toxicity among the two treatment approaches.

This randomized feasibility study will look at the treatment arms according to the timing of HDR brachytherapy—either before or after EBRT—and their toxicity profiles. The study is called Timing of HDR brachytherapy with EBRT in Prostate CAncer (THEPCA). Assessment of acute and late toxicities and other parameters in these two arms at various time points will enable appropriate sequencing of EBRT and HDR therapy resulting in an optimal level of reduced toxicity. The treatments from both arms will be delivered with standard planning techniques. The incidence of grade 3 genitourinary toxicity is 1.6% in this cohort of patients [5]. Additionally, this feasibility study will also explore the challenges of image-guided radiotherapy planning between the two study arms. Provided a significant difference between the two treatment arms is achieved following final analysis, consideration will be made to use this to inform the development of a further pivotal study to look more deeply into the toxicity and other parameters related to the treatment.

Trial Objectives

Primary Objective

The primary objective of this study is the prospective assessment of genitourinary toxicities related to the treatment sequence of HDR brachytherapy and EBRT.

Secondary Objectives

The secondary objectives of this study are to assess treatment outcomes, including biochemical response and survival, prospective assessment of gastrointestinal toxicities according to the treatment sequence of HDR brachytherapy and EBRT, and assessment of radiotherapy planning challenges, including image-guided radiotherapy.

Primary and Secondary Endpoints

The primary endpoint of this study is the presence of grade 3 genitourinary toxicity in patients. The secondary endpoints of this study are the presence of all other grades of genitourinary toxicity (ie, grades 1 and 2), the presence of gastrointestinal toxicity (ie, grades 1 to 4), prostate-specific antigen (PSA) recurrence-free survival, overall survival, and quality of life (QoL).

Methods

Trial Design

This study will be a randomized, two-arm trial in which intermediate and high-risk prostate cancer patients are treated with both HDR brachytherapy and EBRT. In Arm A, patients will receive HDR brachytherapy before EBRT. In Arm B (control arm), patients will receive EBRT before HDR brachytherapy. The assessment of the acute and late toxicities at various time points will be carried out. The treatment should start within 3 months from the randomization date. This trial has been registered with the International Standard Randomized Controlled Trial Number (ISRCTN) registry (ISRCTN: 15835424).

Toxicity will be assessed using the following tools:

1. International Prostate Symptom Score (IPSS)

2. International Index of Erectile Function Scale (IIEFS)

3. Functional Assessment of Cancer Therapy-Prostate (FACT-P), version 4

4. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4, grading system

The THEPCA study scheme design is shown in Figure 1.

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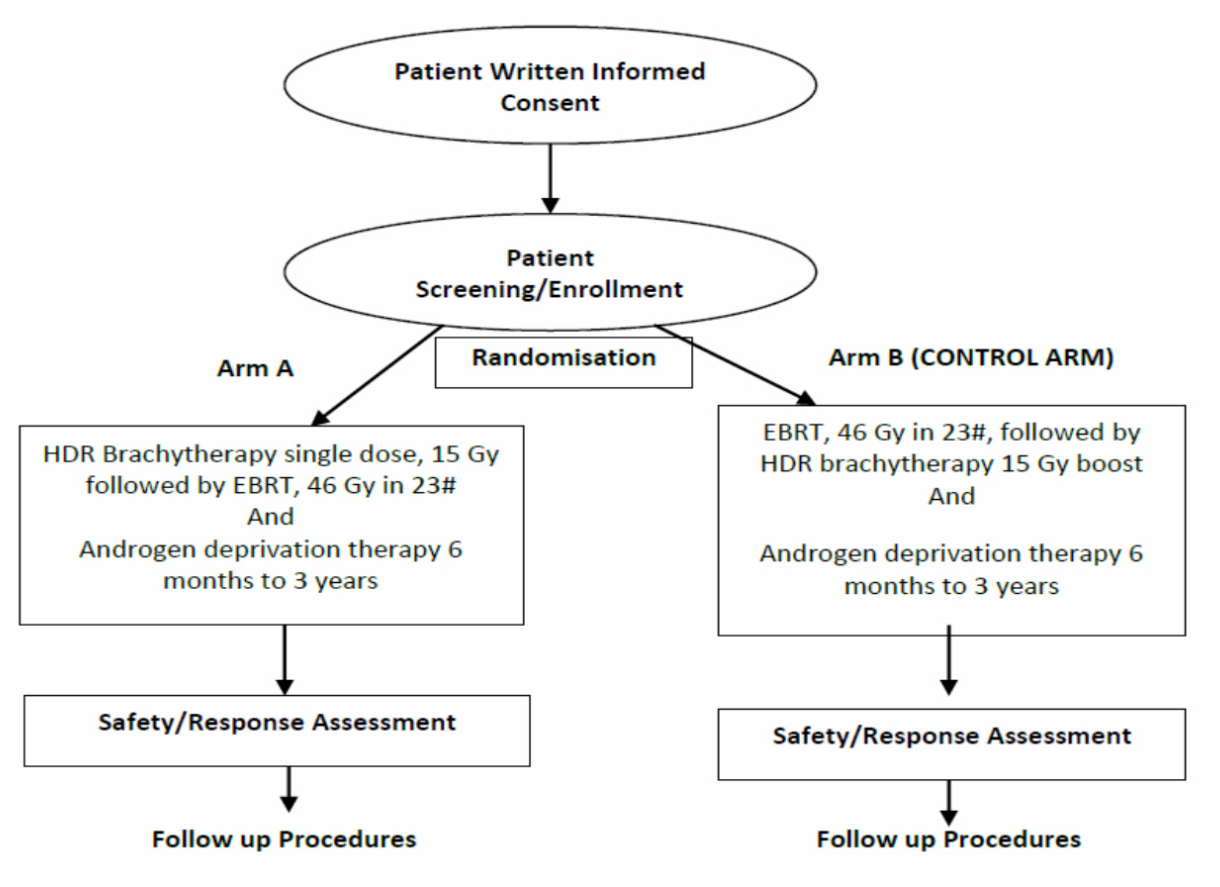
Figure 1. THEPCA study scheme design.



Number of Participants and Participant Selection

A total of 50 patients will be recruited to the whole study, which includes both arms of the study for evaluation of the outcomes. It is estimated that the dropout rate due to screen failures will be approximately 10%. Inclusion and exclusion criteria for the study are shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for the THEPCA study.

Inclusion Criteria

- 18 years of age or older
- Histologically diagnosed prostate cancer (stages T1b-T3bN0M0)
- Any Gleason score
- Any PSA level
- Patient must be able to provide consent and fill in the questionnaires

Exclusion Criteria

- Previous transurethral resection of the prostate (TURP)/holmium laser enucleation of the prostate (HoLEP) laser prostatectomy
- Any metastatic disease
- An IPSS greater than 20
- Pubic arch interference
- Lithotomy position
- Anesthesia is not possible
- Rectal fistula
- Prior pelvic radiotherapy

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Study Procedures

Screening Procedures

Patients will undergo the following procedures as per the standard of care, the results of which will be communicated to the investigator for their review prior to approaching the potential participant: tumor staging (CT/MRI/bone scans), histological confirmation of diagnosis (Gleason score), and PSA measurement.

Informed Consent and Randomization Procedures

Overview

It is the responsibility of the investigator, or an appropriately trained person (ie, trained in Good Clinical Practice [GCP]) delegated by the investigator as documented in the site delegation log, to obtain written informed consent from each participant prior to any participation-/study-specific procedures. This will follow adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

The participant will be given ample time to consider giving their informed consent for the study—for this study, 24 hours will be given during which time the consenting physician will be reachable by phone to answer any questions. The date that the Participant Information Sheet (PIS) is given to the participant will be documented within the patient's notes to ensure that sufficient time was given.

If, for some reason, the consenting physician is not accessible by phone and the participant wishes to speak with them, a second consent visit should be arranged.

The investigator, or other qualified person, will explain to the potential participant that they are free to refuse involvement with any part of the study, or alternatively may withdraw their consent at any point during the study for any reason.

If there is any further safety information which may result in significant changes in the risk/benefit analysis, the PIS and the Informed Consent Form (ICF) will be reviewed and updated accordingly. All participants that are actively enrolled in the study will be informed of the updated information and given revised copies of the PIS and ICF in order to confirm their wish to continue in the study.

Randomization

Randomization will be carried out by the clinical trials data manager within the Anglia Ruskin Clinical Trials Unit (ARCTU) at Anglia Ruskin University (ARU). ARCTU uses the Trans European Network ALEA (TENALEA) randomization service provided by the Trans European Network for Clinical Trial Services. This is an Internet-based randomization system, which will be set up for the study by ARCTU in accordance with the protocol. It will be a simple 1:1 ratio randomization, which will only be possible if a participant meets the inclusion criteria and not the exclusion criteria. The system stores the predetermined sequence of randomization—this list is not visible to the investigator or to the Anglia Ruskin Clinical Trials Unit. Once a patient has consented to take part in the trial, they will be randomly allocated to either Arm A or Arm B. The research nurse or investigator will log onto the Web browser application and enter the patient's eligibility and stratification factors into the system. The study arm allocation is then returned to the investigator and to selected members of ARCTU and the study team. Please refer to the study scheme diagram in Figure 1.

Baseline Procedures

The following baseline procedures will be performed: physical examination, measurement of vital signs, and assessment of QoL baseline (IPSS, IIEFS, FACT-P, CTCAE questionnaires), hematology, biochemistry, concomitant treatment (eg, androgen deprivation therapy [ADT]), and PSA.

Treatment Modalities

Brachytherapy Procedure

The brachytherapy procedure will be carried out at the surgical theaters in Southend University Hospital. The steps are as follows:

1. Patients will undergo prostate implantation under general or spinal anesthetic using a transrectal ultrasound-guided transperineal technique.

2. Imaging according to local practice using ultrasound, CT, and/or MRI will be undertaken.

3. The clinical target volume for prostate (CTVp) is defined by the prostate capsule and is extended to include any extra capsular or seminal vesicle disease. A volumetric expansion of 3 mm constrained to the rectum posteriorly is then added—this defines the planning target volume (PTV).

4. Catheter reconstruction and dwell time definition is then undertaken to provide a treatment plan for approval by the treating clinician.

5. Treatment is delivered once an optimized plan has been approved.

6. After completion of treatment in the brachytherapy room, the implant catheters and urinary catheter are removed—no anesthesia is required for this procedure.

7. The patient will return to the ward and may be discharged home later the same day or the following day.

Dose Prescription

A dose of 15 Gy will be given in a single treatment exposure defined at 100% isodose, which is the minimum tumor isodose to cover the PTV. PTV recommendations are as follows: the minimum dose received by 90% of PTV (D90) should be ≥15 Gy, and the volume of the target area receiving 100% of the prescribed dose (V100) should be ≥95%. See Table 1 for the risk-tolerance doses of the rectum and urethra.

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Table 1. Organs at risk-tolerance doses.

Organ	Risk-tolerance dose
Rectum D2cc[a]	12 Gy
Rectum V100[b]	0 cc
Urethra D10[c]	<17.5 Gy
Urethra D30[d]	<16.5 Gy
Urethra V150[e]	0 cc

[a]Dose to 2 cm^3(D2cc).

[b]Volume of target area receiving 100% of prescribed dose (V100).

[c]Dose covering 10% (D10) of the urethral volume.

[d]Dose covering 30% (D30) of the urethral volume.

[e]Volume of target area receiving 150% of prescribed dose (V150).

External Beam Radiotherapy

EBRT will be given to prostate and seminal vesicles only, using either intensity-modulated radiotherapy or volumetric-modulated arc radiotherapy (VMAT) to a dose of 46 Gy in 23 fractions over 4½ weeks. The dose-volume histogram (DVH) would be according to the local radiotherapy protocol. The gap between BT and EBRT, irrespective of their sequence, should not exceed 3 weeks. Therefore, the total radiotherapy treatment time should be up to 7½ weeks.

Androgen Deprivation Therapy

Patients will receive neoadjuvant and adjuvant antiandrogen therapy from 6 months to 3 years according to the risk stratification of the disease as per the standard of care.

Table 2 shows the schedule of assessments throughout the study.

Table 2. Schedule of assessments during the study.

Steps and assessments	Pretreatment time points	Treatment time points		Posttreatment time points[a]				
	Screening[b] and consent	Baseline	Start of second treatment[c]	6 weeks	3 months	6 months	9 months	12 months
Informed consent	*							
Physical examination		*	*	*	*	*	*	*
Vital signs		*	*	*	*	*	*	*
QoL, IPSS, IIEFS, FACT-P, CTCAE[d]		*			*		*	*
Hematology		*						*
Biochemistry		*						*
Concomitant treatment (eg, ADT[d])		*	*	*	*	*	*	*
Tumor staging	*							
Histological confirmation of diagnosis	*							
PSA[d]	*	*			*	*	*	*
RT[d] and brachytherapy dose				*				

[a]assessments performed after complete treatment

[b]screening procedures carried out as per standard of care

[c]start day of second treatment modality

[d]Quality of life (QoL), International Prostate Symptom Score (IPSS), International Index of Erectile Function Scale (IIEFS), Functional Assessment of Cancer Therapy-Prostate (FACT-P), Common Terminology Criteria for Adverse Events (CTCAE), androgen deprivation therapy (ADT), prostate-specific antigen (PSA), radiotherapy (RT).

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End of Study Definition

The definition of the end of the study is the point at which the last patient recruited has had the last visit at the end of the 1-year follow-up session.

Participant Withdrawal

Overview

A patient may withdraw, or be withdrawn, from trial treatment for the following reasons:

1. If the patient has to undergo urinary catheterization for relieving blockage symptoms while undergoing EBRT and should not proceed further with HDR.

2. Any other unforeseen toxicity developed during RT treatment, and as a consequence the patient is unable to finish the protocol treatment.

The withdrawn patients will be followed as per protocol up to the end of year 1 from the time of completed treatment. With ongoing consent, patients should remain in the trial and be followed up according to the protocol visit schedule.

Withdrawal of Consent

Patients may withdraw their consent to participate in the trial at any time. If the patient explicitly states their wish not to contribute further data to the study, the investigator should inform the coordinating center in writing and the withdrawal of consent should be documented by the investigator in the patient's case report form (CRF). However, data up to the time of consent withdrawal will be included in the data reported for the study.

Although the participant is not obliged to give the reason for withdrawing their consent, this information will help ascertain any trends related to trial procedures and may influence the protocol development in future projects.

Laboratory Tests

All laboratory tests will be taken as per the standard of care within the local pathology department at Southend University Hospital National Health Service (NHS) Foundation Trust. Tests include full blood count (FBC), liver function tests (LFTs), urea, electrolytes, and PSA.

The samples will be collected by the trial nurse, labelled and logged in the CRFs, processed according to the local standard operating procedures (SOPs), and the results will be recorded in the CRFs.

Pharmacovigilance

General Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by, or related to, that product. An AE can, therefore, be any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease temporarily associated with study activities.

Serious Adverse Event

A serious adverse event (SAE) fulfils at least one of the following criteria: (1) is fatal—results in death (NOTE: death is an outcome, not an event), (2) is life-threatening, (3) requires inpatient hospitalization or prolongation of existing hospitalization, (4) results in persistent or significant disability/incapacity, (5) is a congenital anomaly/birth defect, or (6) is otherwise considered medically significant by the investigator.

Investigator's Assessment

Seriousness

The chief investigator (CI) or principal investigator (PI) responsible for the care of the participant, or in his absence an authorized medic within the research team, is responsible for assessing whether an event is serious according to the definitions given above.

Causality

The investigator must assess the causality of all serious adverse events in relation to the trial treatment according to the definitions given above.

Expectedness

The investigator must assess the expectedness of all SAEs according to the definitions given above. If the SAE is unexpected and related, then it needs immediate reporting.

Severity

The investigator must assess the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on participant/event outcome criteria.

1. Mild: intensity of an event is mild if some discomfort is noted, but without disruption of daily life.

2. Moderate: intensity of an event is moderate if discomfort is enough to affect/reduce normal activity.

3. Severe: intensity of an event is severe if it causes a complete inability to perform daily activities and lead a normal life.

Notification and Reporting of Adverse Events or Reactions

If the AE is not defined as *serious*, the AE is to be recorded in the study file and the participant is to be followed up by the research team. The AE is to be documented in the participant's medical notes where appropriate, and in the CRF.

Notification and Reporting of Serious Adverse Events

Serious adverse events that are considered to be *related* and *unexpected* are to be reported to the sponsor within 24 hours of learning of the event and to the main research ethics committee (REC) within 15 days in line with the required time frame. For further guidance on this matter, please refer to Multimedia Appendix 1.

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Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial participants from any immediate hazard to their health and safety, in accordance with Regulation 30 of The Medicines for Human Use (Clinical Trials) Regulations 2004: SI 2004/1031. The measures should be taken immediately. In this instance, the approval from the licensing authority prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and main research ethics committee—via telephone—of this event immediately.

The CI has an obligation to inform the main ethics committee *in writing within 3 days*, in the form of a substantial amendment. The sponsor must be sent a copy of the correspondence with regard to this matter. For further guidance on this matter, please refer to Multimedia Appendix 1.

Annual Safety Reporting

The CI will send the Annual Safety Report (ASR) to the main REC using the National Research Ethics Service (NRES) template—the anniversary date is the date on the multicenter research ethics committee (MREC) "favorable opinion" letter—and to the sponsor.

Overview of the Safety Reporting Process/Pharmacovigilance Responsibilities

The CI has the overall pharmacovigilance oversight responsibility. The CI has a duty to ensure that pharmacovigilance monitoring and reporting is conducted in accordance with the sponsor's requirements.

Statistical Considerations

Primary Endpoint Analysis

Percentages will be compared using Fisher's exact test. This analysis will be carried out after the end of the follow-up at 12 months.

Secondary Endpoint Efficacy Analysis

For the IPSS and IIEFS scale scores, the two means at each of the follow-up assessments will be compared using a two-sided permutation *t* test, and the 95% confidence limits for the difference between the means will be calculated using a bootstrap method. There will also be an assessment of trends in the scores over time using a repeated measures analysis of variance on the four follow-up scores, with the baseline score as a covariate. Prostate-specific antigen relapse-free survival will be estimated using the Kaplan-Meier method, with a test for the difference between the survival curves using the log-rank test. Cox proportional hazards multiple regression will also be used to assess the effects of covariates on survival. For this feasibility study, this analysis will be carried out after the end of the follow-up at 12 months, whereas for a main study a longer follow-up period would be considered.

Safety Endpoints

As the primary endpoint is concerned with adverse events, this will be a central concern of the primary endpoint analysis as described above—the analyses will be carried out after the end of the follow-up at 12 months.

Sample Size

In this feasibility study, the sample size has not been determined according to statistical principles, but is the number judged to be suitable for evaluating the suitability of the processes and procedures of running the study, and for assessing the patient experience and adherence in the study. To this end, two samples of 25 patients—50 overall—will be randomized to the two treatments.

Statistical Analysis

Although the sample size will be small, there will nevertheless be attempts to analyze the data in the same way as would be the case for a main study. However, this might not always be possible depending on the pattern of the outcomes and missing values. For descriptive statistical summaries, continuous data will be summarized using means, medians, standard deviations, interquartile ranges, and ranges. Categorical data will be summarized using counts and percentages. All statistical significance testing will be at the 5% significance level. For the IPSS and IIEFS scale scores, the two means at each of the follow-up assessments will be compared using a two-sided permutation *t* test using 1,000,000 random permutations, and the 95% confidence limits for the difference between the means will be calculated using a bootstrap method using 9999 resamplings. There will also be an assessment of trends in the scores over time using a repeated measures analysis of variance on the four follow-up scores with the baseline score as a covariate.

For categorical data based on adverse events, percentages will be compared using Fisher's exact test. In this small study it will be possible to carry out the full combinatorial calculations for Fisher's exact test, whereas in a main study, 10,000 random permutations will be obtained in a Monte Carlo approach. For differences between percentages, the 95% confidence limits will be obtained using Newcombe's Hybrid Score Interval method. For the secondary analysis, prostate-specific antigen relapse-free survival will be estimated using the Kaplan-Meier method, with a test for the difference between the survival curves using the log-rank test—the *P* value will be obtained using a permutation test with 10,000 permutations. Cox proportional hazards multiple regression will also be used to assess the effects of covariates on survival, with model comparisons carried out using likelihood ratio tests. The analyses will be performed using the computer program R. All randomized participants will be included in the analyses. There are no planned interim analyses.

Data Handling and Record Keeping

Confidentiality

The investigator has the responsibility to ensure that participant anonymity is protected and maintained. He/she must also ensure that participant identities are protected from any unauthorized parties. Information with regard to study participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research

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Governance Framework for Health and Social Care and Research Ethics Committee Approval.

Study Documents

The list of study documents is shown in Textbox 2.

Textbox 2. Study documents required for the administration of the THEPCA study.

- A signed protocol and any subsequent amendments
- Current/superseded Participant Information Sheets (as applicable)
- Current/superseded Informed Consent Forms (as applicable)
- Indemnity documentation from sponsor
- Conditions of sponsorship from sponsor
- Conditional/final research and development (R&D) approval
- Signed site agreement
- Ethics submissions/approvals/correspondence
- CVs of CI and site staff
- Laboratory accreditation letter, certification, and normal ranges for all laboratories to be utilized in the study
- Delegation log
- Staff training log
- Site signature log
- Participant identification log
- Screening log
- Enrolment log
- Monitoring visit log
- Protocol training log
- Correspondence relating to the trial
- Communication plan between the CI/PI and members of the study team
- SAE reporting plan for the study

Case Report Form

Project data collection will be managed by the Clinical Trials Unit data manager who will oversee recruitment and collection of data. The responsibility for data entry rests with the research nurse who is supported by the investigator. The ARCTU uses an online data management system called MACRO to design and manage electronic case report forms (eCRFs). The ARCTU will work together with the Southend study team to design and validate the data collection tools so that they are appropriate for this study. Once a patient is enrolled in the study, the research team can access these forms remotely through the Internet portal and study data will be entered and captured for the study.

All data will be in anonymized form—patients will be identifiable only by study number. Data will be remotely monitored by the ARCTU and discussed at data monitoring committee meetings. Any inconsistencies, validation errors, or inaccuracies will be reported to the lead investigator regularly. Once data collection is complete and the data has been validated, a data lock will be performed and analysis can begin.

Record Retention and Archiving

During the course of the research, all records are the responsibility of the chief investigator and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records be kept for a further 20 years.

Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements, including, but not limited to, the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

Clinical Governance Issues

Ethical Considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the participant in addition to any advertising material, will be submitted by the investigator to an independent research ethics committee. Written approval from the committee must be obtained and subsequently submitted to the Trust's Research and Development Office to obtain final R&D approval.

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Quality Control and Quality Assurance

Summary Monitoring Plan

The ARCTU will ensure that the project is carried out in accordance with the Research Governance Framework. All research team members will have GCP training before the research commences to ensure every aspect from trial design to dissemination is carried out in line with these principles. GCP is an international quality standard that is provided by the International Conference on Harmonisation (ICH), an international body that defines standards, which governments can transpose into regulations for clinical trials involving human subjects.

Audit and Inspection

The definition for *auditing* from section 1.6 of the ICH GCP Guideline is as follows: "A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

The THEPCA study may receive an audit by any of methods listed below:

1. A project may be identified via the risk assessment process.

2. An individual investigator or department may request an audit.

3. A project may be identified via an allegation of research misconduct or fraud, or a suspected breach of regulations.

4. Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.

5. Projects may be randomly selected for audit by an external organization. Internal audits will be conducted by a sponsor's representative.

Noncompliance

Noncompliance, as described in the ICH GCP Guideline, can be defined as "a noted systematic lack of both the CI and the study staff adhering to SOPs/protocol/ICH-GCP, which leads to prolonged collection of deviations, breaches or suspected fraud."

Noncompliance events may be captured from a variety of different sources including monitoring visits, CRFs, communications, and updates. The sponsor will maintain a log of the noncompliance events to ascertain if there are any trends developing which need to be escalated. The sponsor will assess the noncompliance events and implement a time frame of actions in which they need to be dealt with. Each action will be given a different time frame dependent on the severity. If the noncompliance events are not dealt with accordingly, the sponsor will agree on an appropriate action, including an on-site audit.

Trial Committees

Trial Management Group

A Trial Management Group (TMG) has been formed comprising the chief investigator, other lead investigators—clinical and nonclinical—and members of the data centers. The TMG will be responsible for the day-to-day running and management of the trial and will meet at least three times a year by teleconference.

Trial Steering Committee

The Trial Steering Committee (TSC) has membership from TMG plus independent members, including the chair. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent chairman. The ultimate decision for the continuation of the trial lies with the TSC.

Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is the only group who sees the confidential, accumulating data from the trial. Reports to the IDMC will be produced by the Clinical Trials Unit (CTU) statisticians. The IDMC will meet within 6 months of the trial opening, with the frequency of meetings dictated by the IDMC.

Radiotherapy Quality Assurance Subgroup

The Radiotherapy Quality Assurance Subgroup developed the RT quality assurance (QA) plan and issued guidance on delivering RT in this trial.

Results

Results from this feasibility trial will be available in mid-2016.

Discussion

If the results from this feasibility trial show evidence that the sequence of treatment modality does affect the patients' toxicity profiles, then funding would be sought to conduct a large, multicenter, randomized controlled trial.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Information with regard to safety reporting.

[PDF File (Adobe PDF File), 70KB - resprot_v4i2e49_app1.pdf]

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Abbreviations

ADT: androgen deprivation therapy
AE: adverse event
ARCTU: Anglia Ruskin Clinical Trials Unit
ARU: Anglia Ruskin University
ASR: Annual Safety Report
BT: brachytherapy
CI: chief investigator
CRF: case report form
CTCAE: Common Terminology Criteria for Adverse Events
CTU: Clinical Trials Unit
CTVp: clinical target volume for prostate
D2cc: dose to 2 cm3
D10: dose covering 10% of volume
D30: dose covering 30% of volume
D90: minimum dose received by 90% of planning target volume
EBRT: external beam radiotherapy
eCRF: electronic case report form
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients
EPIC: Expanded Prostate Cancer Index Composite

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FACT-P: Functional Assessment of Cancer Therapy-Prostate
FBC: full blood count
GCP: Good Clinical Practice
HDR: high-dose rate
HDR-BT: high-dose rate brachytherapy
HoLEP: holmium laser enucleation of the prostate
ICF: Informed Consent Form
ICH: International Conference on Harmonisation
IDMC: Independent Data Monitoring Committee
IGRT: image-guided radiotherapy
IIEFS: International Index of Erectile Function Scale
IMRT: intensity-modulated radiotherapy
IPSS: International Prostate Symptom Score
LDR: low-dose rate
LFT: liver function test
MREC: multicenter research ethics committee
NHS: National Health Service
PI: principal investigator
PIS: Participant Information Sheet
PSA: prostate-specific antigen
PTV: planning target volume
QA: quality assurance
QLQ PR25: Quality of Life Questionnaire for Prostate Cancer Patients
QoL: quality of life
R&D: research and development
RCT: randomized controlled trial
REC: research ethics committee
RT: radiotherapy
SAE: serious adverse event
SOP: standard operating procedure
TENALEA: Trans European Network ALEA
TMG: Trial Management Group
TSC: Trial Steering Committee
TURP: transurethral resection of the prostate
V100: volume of the target area receiving 100% of the prescribed dose
V150: volume of the target area receiving 150% of the prescribed dose
VMAT: volumetric-modulated arc radiotherapy

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Original Paper

Contribution of Transcranial Direct Current Stimulation on Inhibitory Control to Assess the Neurobiological Aspects of Attention Deficit Hyperactivity Disorder: Randomized Controlled Trial

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Abstract

Background: The applicability of transcranial direct current stimulation (tDCS) in individuals with attention deficit hyperactivity disorder (ADHD) has not yet been investigated. This low-cost, non-invasive, and safe technique optimized to modulate the inhibitory response might be a useful treatment option for those affected by this condition.

Objective: The aim of this single center, parallel, randomized, double-blinded, sham-controlled trial is to investigate the efficacy of transcranial direct current stimulation over the prefrontal cortex on the modulation of inhibitory control in adults with attention deficit hyperactivity disorder.

Methods: A total of 60 individuals will be divided into 2 groups by block randomization to receive active or sham stimulation. Anodal stimulation over the left dorsolateral prefrontal cortex will be applied at 1 mA during a single 20-minute session. Before and after interventions, subjects will perform 2 go/no go tasks and the brain electrical activity will be recorded by electroencephalogram (EEG) with 32 channels, according to the 10-20 international EEG system.

Results: The trial began in May 2013 and we are currently performing the statistical analysis for the secondary outcomes.

Conclusions: The findings from this study will provide preliminary results about the role of prefrontal cortex activation through tDCS on ADHD patients.

Trial Registration: Clinicaltrials.gov NCT01968512; http://clinicaltrials.gov/ct2/show/NCT01968512 (Archived by WebCite at www.webcitation.org/6YMSW2tkD).

(JMIR Res Protoc 2015;4(2):e56) doi:10.2196/resprot.4138

KEYWORDS

Attention deficit hyperactivity disorder; inhibitory control; transcranial direct current stimulation

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Introduction

Attention deficit hyperactivity disorder (ADHD) presents prevalence rates in US studies of 5%-9% in childhood, especially in school age children. Of those affected, 67% continue to present symptoms in adulthood, which may compromise psychosocial, professional, and emotional development [1-5]. In a recent study, Arruda et al observed a prevalence rate of ADHD among children and adolescents of 4.4% [6]. However, despite the significant social impact, some of these patients remain undiagnosed and therefore without proper therapeutic intervention. The diagnosis, based on clinical assessment and identification of symptoms established by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), involves inattention, hyperactivity, impulsivity, and general criteria [7,8].

The clinical presentation of ADHD may arise from disorders in the prefrontal cortex and its subcortical connections [8-11]. This assumption is supported by the hypothesis that it is a neurobiological disorder, evidenced by functional deficits in neurotransmitters such as dopamine and norepinephrine, and by disorders in the frontal lobe. These disorders trigger the symptoms observed in ADHD patients including impulsivity, difficulty in inhibiting distracting behaviors, and difficulty in planning and executing tasks under focused attention and concentration [10,12]. Together, these symptoms reveal the impairment of important executive functions in individuals with ADHD [1,2,9,13].

There is evidence of a physiological association between the prefrontal cortex and inhibitory control [9,14], whereby changes in this anatomical structure may account for impairments in inhibitory control. Indeed, behavior-based actions that reflect inconsequence, unpredictability, intolerance to waiting, quick and inconsistent responses, possible exposure to hazards, and acceptance of multiple responsibilities and tasks simultaneously with consequently further withdrawals support this idea [9].This anatomical relationship between prefrontal cortex and inhibitory behavior, together with an understanding of the neurobiological mechanisms comprise a physiological framework that supports the hypothesis that activation of the prefrontal area will result in a larger and more suitable inhibitory control, minimizing the socioaffective consequences associated with this condition.

Transcranial direct current stimulation (tDCS) is a simple and well-known neuromodulatory technique [15,16] which involves applying low voltage electrical currents to increase or decrease neuronal excitability of the stimulated area [16,17]. tDCS is a noninvasive and safe approach, characterized by infrequent and mild adverse effects including local discomfort, itching, paresthesia, and/or short-lasting headaches [17].

The aim of this trial is to investigate the efficacy of tDCS over the prefrontal cortex on the modulation of inhibitory control in adults with ADHD by assessing behavioral and neurophysiological parameters. We expect that the application of this low-cost and safe technique will increase the inhibitory response in ADHD individuals what may result in a greater ability to inhibit inappropriate behaviors.

Methods

Study Design

This is a single-center, parallel, randomized, double-blinded, sham-controlled trial, conducted in the Laboratory of Functional Electrostimulation at the Federal University of Bahia (Salvador, Brazil). This study will include descriptive and analytical steps designed to investigate the neurobiological aspects of patients with ADHD, and the response of inhibitory control parameters to tDCS.

Population

Patients with ADHD will be recruited by sending letters and emails to neuropsychiatric societies and associations. Professional experts in ADHD, contacted by mail and telephone, will be invited to refer potential patients for the study. Advertisements will be published on the Internet and social networking sites, according to the inclusion criteria.

Inclusion Criteria

The inclusion criteria for the study are (1) the ability to understand and sign the informed consent form, (2) a diagnosis of ADHD according to DSM-IV-TR and the Adult Self-Report Scale (ASRS), (3) resident of Bahia, and (4) ≥18 years old.

Exclusion Criteria

Patients who meet the following criteria will be excluded (1) major psychiatric disorders such as schizophrenia and bipolar disorder, (2) inability to understand the questionnaires applied (cognitive impairment score of ≤24 on the Mini-Mental State Examination) or illiterate, and (3) abuse of psychoactive substances or alcohol, except nicotine and caffeine, during the last 12 months.

Sample Size

A sample size of 50 subjects was calculated assuming a difference in proportion between the active tDCS and sham control groups of 40% on the go/no go performance, before and after interventions. This calculation was performed using the statistical program STATA 12.0, considering an alpha of .05 and a power of 0.80, resulting in a sample of 25 subjects in each group (intervention and control). To address unexpected factors, we applied a dropout rate of 20%, reaching a total sample size of 60 individuals.

Randomization and Blinding

Individuals will be divided into two groups by block randomization aiming for a balanced distribution between the groups (30 subjects each), and considering gender and age as variables. Blocks will be composed of 10 subjects, totaling 6 blocks. Each intervention group will comprise 5 individuals from each block.

An external researcher will perform the randomization and will generate a list to allocate patients and ensure a concealed allocation.

Excluding the external researcher, investigators applying the go/no go tasks and registering the EEG, and the subjects will be blind to the intervention. Raters and researchers responsible

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for the statistical analysis will not be aware of the treatment group that the patient will be enrolled. For analysis purposes, the intervention groups will be identified as “0” and “1”. Blinding code will be known only by the principal investigator and by the person responsible for the stimulation.

Ethical Aspects

In accordance with the Declaration of Helsinki [18], this study strictly follows the ethical principles in research involving human subjects. All participants will be informed about the nature of the study and all procedures prior to enrollment. Following the resolution 196/96 of the National Health Council (Brazil), only those that will sign the informed consent form will be included. The signature of a witness will be required for the patients unable to sign the free and informed consent form.

This trial was approved on October 2012 (IRB approval number 19311) by the institutional review board of the Maternidade Climério de Oliveira-Federal University of Bahia.

Consent Procedures

Signed consent will be obtained from each participant. Only subjects capable of understanding and agreeing to the consent will be enrolled. In addition to a signed consent form and prior to any intervention, participants will receive a detailed explanation about the trial aims and procedures that will be performed. Two experienced researchers will explain that participation is voluntary and they may withdraw at anytime without losses. The trial staff also will be available to clarify any question; at the same time they will assure that subjects understood all of the steps of the study. Participants will have an indefinite amount of time to make a decision, and those that agree, will be asked to sign two copies of the informed consent form.

Assessments

Following the consent procedures, subjects will undergo a cognitive screening using the MiniMental State Examination (MMSE) [19,20], the Mini International Neuropsychiatric Interview Brazilian (MINI PLUS) [21], the Adult Self-Report Scale (ASRS) [22], the Adult ADHD Quality of Life Questionnaire (AAQoL), and an interview with a questionnaire. This evaluation script is an instrument based on the ADHD diagnostic criteria from DSM-IV-TR [7,8], and consists of epidemiological and clinical questions.

Posterior electrical brain activity will be recorded by EEG with 32 channels placed on the scalp, according to the 10-20 international EEG system. Each recording will last 5 minutes and will be performed in a resting state, with the patient's eyes open and looking for a fixed point during the first minute, and with closed eyes for the remaining four. Participants will then be asked to perform tasks on the computer: 2 go/no go tasks adapted from the original version using a fruit and a letter as the first and second target, respectively. Following the cognitive tasks, subjects will undergo the active or sham stimulation, according to the previous randomization. At the end of the intervention, subjects will perform the 2 go/no go tasks again (randomly selected to avoid learning effect), and they will undergo another EEG recording.

There will be no follow-up visits; participants will undergo a single visit of approximately two hours in duration. All subjects will be asked to abstain from caffeine, alcohol, and nicotine one day before the experiments.

Interventions

Participants of the intervention group will have the tDCS applied at 1 mA, with the anode electrode over the left dorsolateral prefrontal cortex and cathode electrode over the equivalent area on the right side. For the control group subjects, electrodes will be placed at identical positions and sham stimulation will be applied. The stimulation device will be turned on for 30 seconds so that the patient will feel the initial sensation, then will be shut down. The intervention and sham procedure will take place in one single 20-minute session to evaluate the immediate effect.

The application of tDCS and the assessment of its effects will be performed by clinical observation using a reduction of symptomatology as evaluated by the neuropsychological task, go/no go, and by neurophysiological assessment, measured by quantitative electroencephalogram (qEEG) and the reconstruction of brain networks, as parameters.

Outcome Variables

The primary outcome of this trial is the inhibitory response measured as behavioral performance by two go/no go tasks. These tests are adapted from a previous version [23], and will present as targets a fruit (version 1) and a letter (version 2). Participants will be asked to react when a target ("go" stimulus), and not when a non-target ("no go" stimulus) is presented. All stimuli will be presented in black and white ink with equal dimensions. In both versions of the go/no go tasks, one selected letter or fruit will be previously defined as the "go" stimulus and subjects will be instructed to press the left button of a computer mouse with the right finger as soon as this target is presented on the screen. Stimuli will be presented one-by-one on the computer screen during 650 milliseconds with 1000 millisecond interstimulus intervals (ISI). In each version of the task, 150 trials consisting of 80% "go" and 20% "no go" will be presented. Correct responses, impulsivity, and omissions errors will be computed separately for each version of the go/no go task, and will be the primary outcome variables.

The secondary outcome variables are power analysis of frequency bands through qEEG and the brain networks. For the EEG, data will be recorded from the 32 channels and a reference electrode (Cz) placed according to the 10-20 international EEG system with additional electrodes (FC3, FC4, CP3, CP4, FT7, FT8, TP7, TP8, and Oz). The EEG data will be filtered between 0.5-50 Hz, and analyzed through EEGLAB (The Mathworks, Inc.). Brain network reconstructions will be performed based on the EEG data.

Statistical Analysis

A 5-step statistical analysis will be conducted (see Textbox 1). These analyses will be performed using Stata, version 13.0 for Windows. Results will be considered statistically significant if $P<.05$.

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Textbox 1. The 5-step statistical analysis.

Steps

1. The socio-demographic, clinical, and epidemiological description of the groups, using the usual procedures of descriptive statistics such as calculation of frequencies, measures of central tendency, and dispersion;
2. Characteristics will be compared between groups at baseline, using a one-way analysis of variance (ANOVA) for continuous variables and a chi-square test for categorical variables;
3. Shapiro-Wilk test will be performed to assess the normality assumption of the outcome variables;
4. Analysis of paired and independent samples using a *t* test for comparisons within each group and between intervention groups, or applying equivalent non-parametric tests (according to Shapiro-Wilk test results) before and after intervention;
5. Pearson chi-square test to evaluate blinding effectiveness, comparing between groups.

Results

This trial and enrollment began in May, 2013. The statistical analysis for the secondary outcomes is currently being performed.

Discussion

The findings from this trial will provide preliminary results about the role of prefrontal cortex activation through tDCS on ADHD patients. The results of this clinical trial will allow us to evaluate behavioral and neurobiological aspects of ADHD in addition to observing the socio-demographical and clinical-epidemiological parameters of this population.

We will examine the tDCS contribution in modulating inhibitory control and neurophysiological parameters measured by neurocognitive tasks (go/no go), qEEG, and brain reconstruction network models. We also expect that the present trial will contribute scientifically to the development of neurophysiological assessment methods of ADHD, and to the evaluation of the feasibility of this low cost, non-invasive, and safe technique for optimization of inhibitory responses in ADHD patients.

One possible limitation is that we will only apply a single session of tDCS. However, since, to the present moment, there are no previous studies regarding tDCS in ADHD subjects, we opted for a conservative protocol with only one session of tDCS delivered at 1 mA to ensure safe parameters.

To the best of our knowledge, this trial will be the first study to assess the cognitive and neurophysiological effects of tDCS on ADHD patients. In the long term, we expect that our results might reinforce comprehensive programs of intervention and multidisciplinary approaches in patients with ADHD.

Authors' Contributions

CC, AB, and EPS conceived and designed this protocol, and drafted and revised the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AAQoL: Adults with ADHD Quality of Life Questionnaire
ADHD: Attention deficit hyperactivity disorder
ASRS: Adult Self-Report Scale
DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
EEG: Electroencephalogram
ICF: Informed consent form
MINI-plus: Mini International Neuropsychiatric Interview Plus
MMSE: Mini Mental State Examination
qEEG: Quantitative electroencephalogram
tDCS: Transcranial direct current stimulation

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Protocol

Normothermic Versus Hypothermic Cardiopulmonary Bypass in Children Undergoing Open Heart Surgery (Thermic-2): Study Protocol for a Randomized Controlled Trial

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Abstract

Background: During open heart surgery, patients are connected to a heart-lung bypass machine that pumps blood around the body ("perfusion") while the heart is stopped. Typically the blood is cooled during this procedure ("hypothermia") and warmed to normal body temperature once the operation has been completed. The main rationale for "whole body cooling" is to protect organs such as the brain, kidneys, lungs, and heart from injury during bypass by reducing the body's metabolic rate and decreasing oxygen consumption. However, hypothermic perfusion also has disadvantages that can contribute toward an extended postoperative hospital stay. Research in adults and small randomized controlled trials in children suggest some benefits to keeping the blood at normal body temperature throughout surgery ("normothermia"). However, the two techniques have not been extensively compared in children.

Objective: The Thermic-2 study will test the hypothesis that the whole body inflammatory response to the nonphysiological bypass and its detrimental effects on different organ functions may be attenuated by maintaining the body at 35°C-37°C (normothermic) rather than 28°C (hypothermic) during pediatric complex open heart surgery.

Methods: This is a single-center, randomized controlled trial comparing the effectiveness and acceptability of normothermic versus hypothermic bypass in 141 children with congenital heart disease undergoing open heart surgery. Children having scheduled surgery to repair a heart defect not requiring deep hypothermic circulatory arrest represent the target study population. The co-primary clinical outcomes are duration of inotropic support, intubation time, and postoperative hospital stay. Secondary outcomes are in-hospital mortality and morbidity, blood loss and transfusion requirements, pre- and post-operative echocardiographic findings, routine blood gas and blood test results, renal function, cerebral function, regional oxygen saturation of blood in the cerebral cortex, assessment of genomic expression changes in cardiac tissue biopsies, and neuropsychological development.

Results: A total of 141 patients have been successfully randomized over 2 years and 10 months and are now being followed-up for 1 year. Results will be published in 2015.

Conclusions: We believe this to be the first large pragmatic study comparing clinical outcomes during normothermic versus hypothermic bypass in complex open heart surgery in children. It is expected that this work will provide important information

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to improve strategies of cardiopulmonary bypass perfusion and therefore decrease the inevitable organ damage that occurs during nonphysiological body perfusion.

Trial Registration: ISRCTN Registry: ISRCTN93129502, http://www.isrctn.com/ISRCTN93129502 (Archived by WebCitation at http://www.webcitation.org/6Yf5VSyyG).

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KEYWORDS

pediatrics; cardiac surgery; cardiopulmonary bypass; temperature; hypothermia; normothermia; clinical trials; randomized

Introduction

Background

The treatment of many forms of congenital heart disease has continued to advance, and primary early repairs of an increasing number of defects are routinely performed (eg, atrioventricular canal, tetralogy of Fallot, transposition of the great arteries). At Bristol Royal Hospital for Children (BRHC) an average of 285 cardiac operations are performed a year, and approximately 75% (ie, an average of 210) require cardiopulmonary bypass (CPB). Despite its widespread use, there is still significant morbidity related to the nonphysiological nature of total CPB [1]. Whole body cooling (ie, hypothermia) is an integral part of congenital cardiac surgery, with most procedures being conducted between 28°C and 30°C, depending on the expected duration and type of operation. The main rationale for body cooling is to protect organs such as the brain, kidneys, and heart from ischemic injury by reducing the metabolic rate and, hence, oxygen consumption [1]. Nevertheless, hypothermia has a number of disadvantages, including detrimental effects on enzymatic function, energy generation, and cellular integrity [1]. Perfusion of the body and the brain at normal body temperature (ie, normothermia) is a potentially more physiological method to maintain the functional integrity of major organ systems, and in recent years there has been an increasing interest in normothermic CPB in adult and pediatric cardiac surgery [2-9]. The concept that normothermic systemic perfusion may confer certain advantages over hypothermic regimes arose fortuitously from adult clinical experience in which an absence of shivering, hemodynamic stability, minimum use of inotropes, and early extubation were observed when patients were not cooled [2]. This led several investigators to study the effects of systemic hypothermia and normothermic perfusion upon cellular and organ function [2,10-14].

In both adult and pediatric cardiac surgery, many of the detrimental effects of CPB on end organ dysfunction were previously believed to be mediated by activation of the inflammatory response [1,15]. One may expect that CPB-related systemic inflammatory response syndrome and multiorgan injury to be enhanced during normothermia, since most enzymatic processes occur optimally at 37°C. Supportive of this notion are clinical studies in adults [16] in which normothermic CPB (35°C-37°C) was associated with significantly elevated levels of inflammatory markers compared to hypothermic CPB (28°C-30°C). Consistent with this, previous animal data have shown that the inflammatory response is reduced by hypothermia [17,18]. However, a conflicting picture is emerging from research. Ohata et al [19] have demonstrated an attenuation of certain inflammatory mediators following warm systemic perfusion (34°C) compared to hypothermic perfusion (28°C). In a clinical study at the Bristol Heart Institute [10,20], normothermic (37°C) perfusion was also associated with attenuation of inflammatory mediator release in the postoperative period, compared to moderately hypothermic (32°C) and hypothermic CPB (28°C). In contrast, others have suggested that induction of a systemic response is not temperature dependent. Rasmussen et al have shown that the release of systemic inflammatory mediators after cardiac surgery in adults was independent of mild hypothermia (32°C) when compared to normothermia (36°C) [21]. A randomized controlled trial (RCT) in 66 children having open heart surgery, who were randomized to either moderate hypothermia (24°C) or mild hypothermia (34°C), found that neither the systemic inflammatory response nor organ injury were influenced by bypass temperature [22]. Eggum et al demonstrated that there were only minor differences in inflammatory marker concentrations between pediatric patients undergoing moderate (25°C) hypothermia and those with mild (32°C) hypothermia during CPB [23]. This evidence was supported by an RCT carried out at BRHC comparing warm (35°C-37°C) and cold (28°C) CPB on simple congenital cardiac malformations, which indicated that both whole body inflammatory response and myocardial reperfusion injury were similar between the 2 groups [24]. In addition, Caputo et al and Eggum et al demonstrated that normothermic CPB was associated with reduced oxidative stress compared with hypothermic CPB. Other researchers have studied the effect of the temperature of the cardioplegia during pediatric cardiac surgery [25,26]. Poncelet et al have taken this a step further by studying the effect of the temperature of the CPB in addition to the cardioplegia in an RCT on 47 children having cardiac surgery [27]. In this study, children were randomized to either mild hypothermia with cold crystalloid cardioplegia (CPB temperature 32°C, cardioplegia at 5°C) or normothermic with intermittent warm blood cardioplegia (CPB temperature 36.5°C). They found no significant difference in the cellular ischemic insult to the heart or in the early and late neurodevelopmental status of the patients. With conflicting evidence arising from clinical trials comprising relatively low numbers of patients and mainly simple cardiac surgery cases, it is difficult to establish whether the induction of a systemic response is temperature dependent and the impact this may have on clinical outcome. This warrants a larger study with clinical outcomes as primary endpoints.

Aim

The Thermic-2 study (Current Controlled Trials ISRCTN93129502) will compare the clinical effectiveness of

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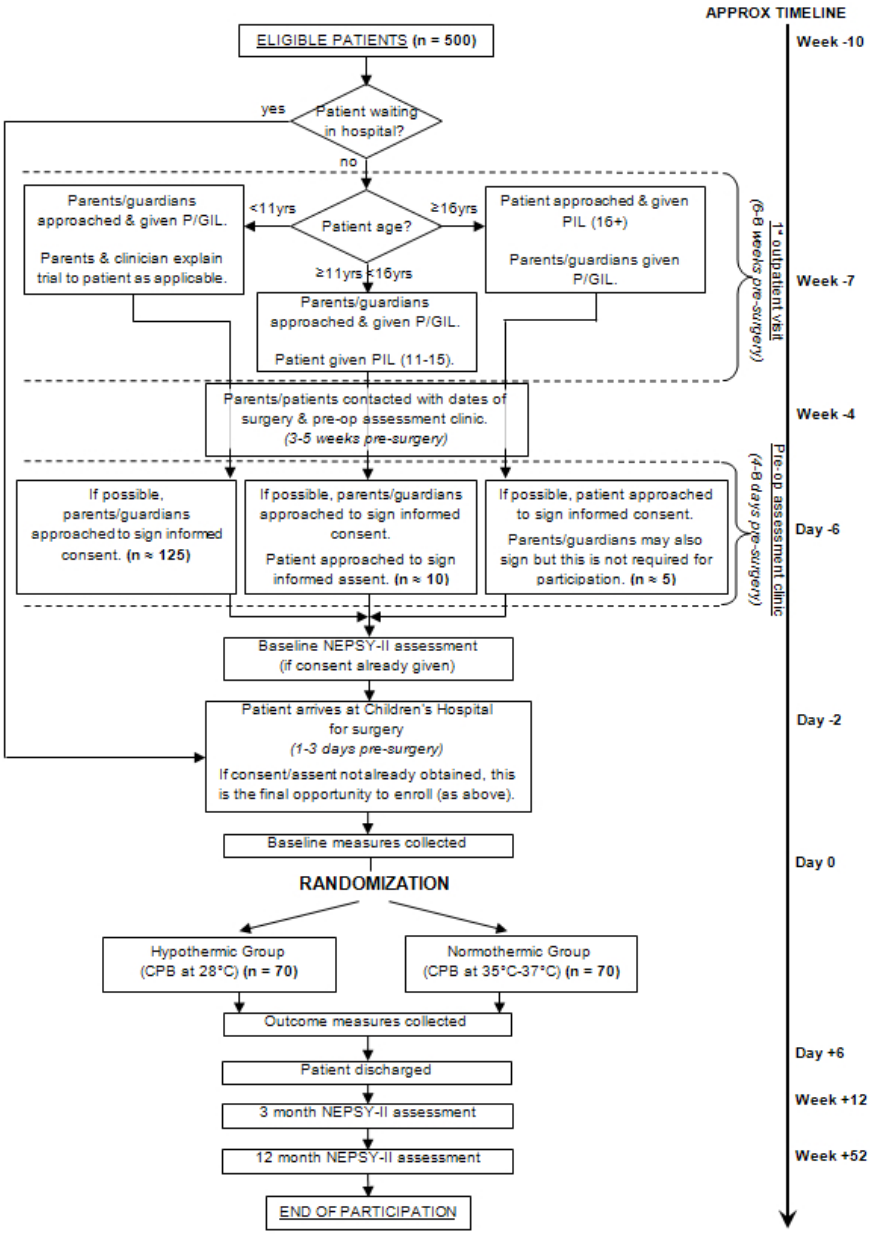
normothermic (35°C-37°C) versus hypothermic (28°C) CPB for the repair of common congenital cardiac pathologies. We will test the hypothesis that maintaining the body at 35°C-37°C (normothermia) rather than at 28°C (hypothermia) during pediatric open heart surgery reduces the whole body inflammatory response to the nonphysiological CPB and its detrimental effects on different organ functions, resulting in a better clinical outcome.

Figure 1. Study schema showing the participant recruitment pathway.



Methods

Study Design

This study is a single-center, parallel-group open RCT. The study schema is shown in Figure 1.

Research Approval

Research ethics approval was granted by the National Research Ethics Service Committee South West—Central Bristol (reference 11/SW/0122) in October 2011. The study is registered (ISRCTN 93129502).

Study Population

All pediatric patients (aged 18 years and younger) having scheduled surgery at the BRHC to repair a congenital heart defect using CPB, represent the target study population and will be screened for eligibility. Patients will be excluded from the study if either: (1) they require deep hypothermic circulatory arrest, (2) they are admitted for an emergency operation (patients with hemodynamic instability who require immediate surgical intervention), or (3) they and/or their next-of-kin do not provide

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written informed consent. We will also record specific reasons where surgeons are unwilling for the patient to be approached for the study. All reasons for ineligibility will be recorded on the study screening log.

We will aim to approach all next-of-kin (usually parents) and/or patients at preoperative clinics or on admission the day before surgery. Eligible next-of-kin and/or patients will be given a patient information leaflet (PIL), have the study explained to them, and will be given the opportunity to ask questions about the study. They will be given a minimum of 24 hours to consider the study prior to being asked to provide written informed consent if they are willing to participate in the study.

Randomization

Participants will be randomly assigned in a 1:1 ratio to either the hypothermic group or the normothermic group. Randomization will be stratified by age: 1 month or younger, 1 to 12 months, and older than 12 months. Allocations will be generated by computer using block randomization with varying block sizes. The allocation sequence will be prepared in advance of the study by a statistician independent of the study team. If a participant's surgery is unexpectedly rescheduled, he/she will retain his/her study numbers and randomized allocation. Access to the allocation will be via a password-controlled secure database. Randomization will take place as close to the start of surgery as possible.

Study Interventions

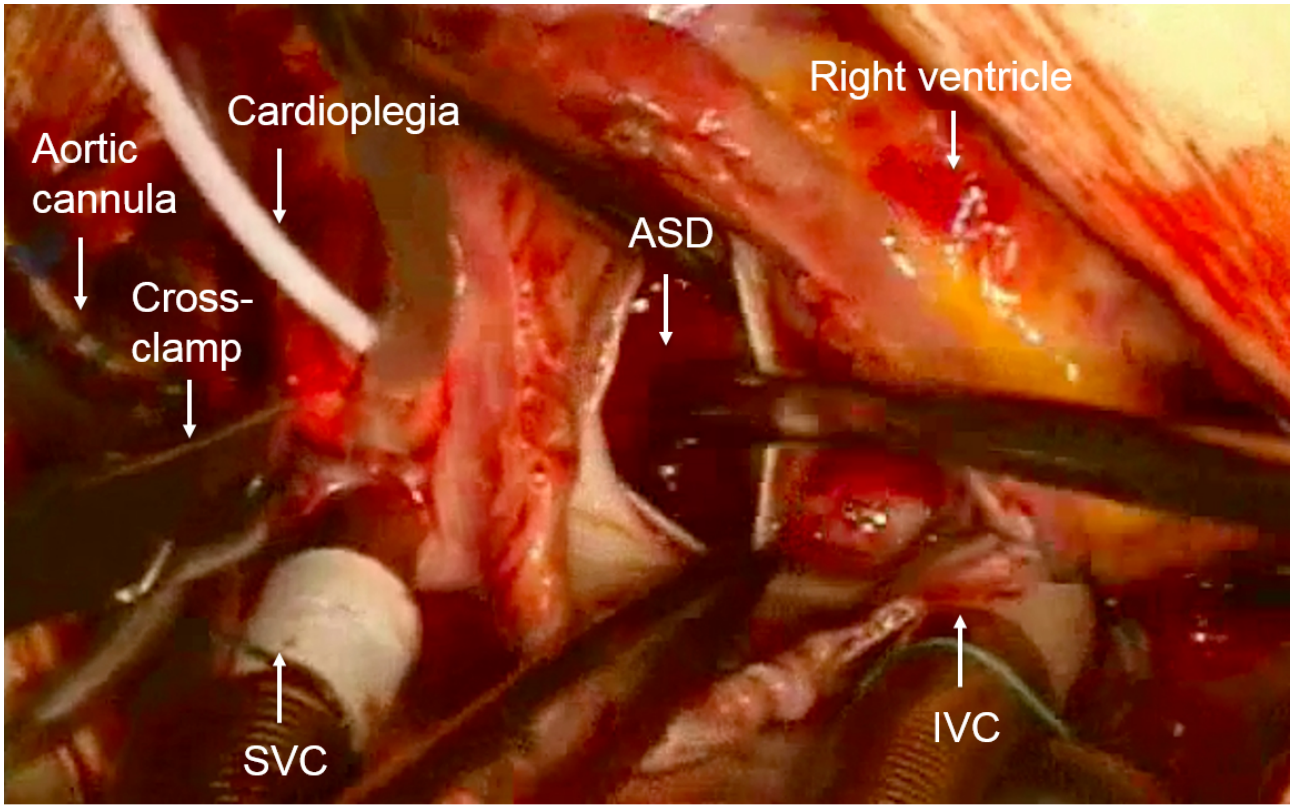
Participants will be randomized to receive either hypothermic or normothermic CPB during their surgery into the following groups:

1. Hypothermic CPB: cardiopulmonary bypass with perfusion at 28°C (control)
2. Normothermic CPB: cardiopulmonary bypass with perfusion at 35°C-37°C (experimental)

Cardiopulmonary Bypass

All operations will be performed using CPB with ascending aortic cannulation and bicaval venous cannulation (Figure 2). Cold St Thomas' I-based blood cardioplegic solution (4°C-6°C) will be used for myocardial preservation in all participants (Martindale Pharmaceuticals Ltd) with the following composition: 16 mM MgCl2, 2 mM CaCl2, 20 mM KCl, 147 mM NaCl, and 1 mM procaine HCl. Cardioplegic arrest will be achieved by an antegrade infusion of 110 ml/m^2/min for 4 minutes. Additional cardioplegia will be administered after 20 minutes of aortic cross-clamping. Intramyocardial temperature will be monitored by means of a temperature probe inserted every 10 minutes into the right and left ventricles during ischemic arrest. For all participants, concomitant rectal, nasopharyngeal, skin, and blood temperatures will be monitored throughout the operation.

Figure 2. Image showing the heart of a child born with an atrial septal defect (ASD). The heart has been emptied of blood, put on cardiopulmonary bypass (CPB), and arrested using the cardioplegia solution, which is injected into the aortic root after the aorta is cross-clamped. CPB is achieved by inserting a superior vena cava (SVC) and an inferior vena cava (IVC) cannula for the venous drainage and an aortic cannula for the arterial perfusion of the body. The right atrium is open and the ASD is clearly visible.



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Hypothermic CPB

Nasopharyngeal body temperature will be lowered to 28°C. Rewarming will commence at the completion of the anatomical correction. All participants will be rewarmed with a temperature difference of 8°C at the level of the heat exchanger between the blood and the rewarming fluid, and CPB will be discontinued only after the participant is fully rewarmed to 36°C.

Normothermic CPB

Nasopharyngeal body temperature will be maintained at 35°C-37°C. Rewarming will only take place in the normothermic group if the body temperature is <36°C and will be discontinued only after the participant is fully rewarmed to 37°C.

Anesthesia

Induction of anesthesia will be gaseous induction with sevoflurane, administration of neuromuscular blockade using pancuronium and analgesia using bolus dose fentanyl (10 mcg/kg-20 mcg/kg) pre-CPB, and morphine (0.5 mg/kg) during CPB. Maintenance of anesthesia will be with isoflurane. Alpha stat acid-base management will be adopted. Initial anticoagulation will be accomplished with 3 mg/kg to 4 mg/kg body weight of heparin and supplemented as required in order to maintain an active clotting time of ≥480 seconds.

Deviations from this standardized anesthetic technique are permissible under the following conditions:

1. Intravenous induction using ketamine, propofol, or thiopentone may be used if the anesthetist considers sevoflurane to be unsuitable for induction for the patient.
2. Where pancuronium is not available, vecuronium or rocuronium may be used instead.
3. Propofol instead of isoflurane may be used for maintenance of anesthesia where the anesthetist considers the patient to be at increased risk of awareness.

Study Center and Surgeons

Overview

All surgery will be carried out at BRHC. On average, 210 pediatric cardiac surgery procedures using CPB are performed per year at this center. All the pediatric cardiac surgeons at this center are participating in the study.

Primary Outcomes

The co-primary endpoints are (1) duration of inotropic support, (2) intubation time, and (3) postoperative hospital stay (from date of surgery to discharge from cardiac ward). These data will be collected from medical notes and hospital charts.

Secondary outcomes

Data will be collected to characterize the following secondary outcomes:

1. In-hospital mortality and morbidity rates will be recorded.
2. Blood loss and transfusion requirements will be recorded.
3. Preoperative and postoperative echocardiographic (ECG) findings will be recorded.
4. Routine blood gas and blood test results will be recorded.
5. Renal function will be measured by testing urinary albumin, urinary creatinine, retinal binding protein (RBP), N-acetyl-β-glucosaminidase (NAG), and neutrophil gelatinase-associated lipocalin (NGAL) [28-33]. All markers of renal damage will be measured preoperatively and at several time-points postoperatively.
6. Cerebral function will be measured by testing for glial fibrillary acidic protein (GFAP), a serum marker of traumatic brain injury [34,35]. GFAP levels will be measured preoperatively and at several time-points mid- and postoperatively.
7. Regional oxygen saturation of blood in the cerebral cortex will be measured at approximately 15-minute intervals during the operative period using near-infrared spectroscopy (NIRS).
8. Neuropsychological development will be assessed using the NEPSY-II psychometric tool [36]. Neuropsychological assessments will be performed on patients aged between 3-16 years old, preoperatively and at 3 and 12 months postoperatively. These tests are intended as a tool to allow the assessment of both basic and complex aspects of cognition across the following 6 functional domains: attention and executive functions, language, memory and learning, sensorimotor functions, social perception, and visual-spatial processing.
9. Cardiac tissue biopsies from heart tissue discarded during the surgical procedure and considered clinical waste will be analyzed for biochemical markers and RNA analysis on a subset of 32 patients. If available, 4 samples will be collected from each patient in this subset; 2 samples will be collected immediately after institution of CPB and a further 2 samples will be collected 10-15 minutes after reperfusion. Biochemical tests will be performed on the biopsies to determine the presence of a range of important proteins and metabolites, and transcriptional profiling by RNA extraction will be performed with the aim to help establish whether any genomic expression changes associated with hypothermia could be prevented by using normothermic techniques.

Assessment of Outcomes and Blinding

Participants and their parents/guardians will be blinded to the treatment allocation. Participants will receive the same surgical procedure as if they had not joined the study—with the exception of the temperature of the blood during CPB—and will receive the same surgical care following the procedure. At the start of the operation, the perfusion team is given the treatment allocation in a concealed envelope, asked to follow the study allocation, and record any reasons for protocol deviations. Surgeons, anesthetists, and nurses involved in the operation will be unblinded but the randomization allocation will not be disclosed until after the start of the operation. Because surgeons, anesthetists, and nurses continue to care for participants in the pediatric intensive care unit (PICU) and on the ward, it is difficult to maintain blinding in these locations. Where possible, staff will be blinded to the treatment group to which a participant is assigned. The PICU and ward nursing teams, while not being actively informed of the patient's study allocation, could become unblinded because they have access

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to the anesthetic and perfusion charts that must be stored in the medical notes. However, it is unlikely that the nursing team would check the temperature at which the operation was performed or alter the patient's after-care since the temperature during CPB would not have any implications on the postoperative management of the patient.

The primary endpoints of duration of inotropic support, intubation time, and postoperative hospital stay should all be objective outcomes and were chosen primarily as they are clinically meaningful to the patients and surgeons. While these outcomes could potentially be influenced by the clinical care team, the care team must not only adhere to strict protocols and guidelines, but there is also not a strong expectation that either arm of the study would be more beneficial to the participant; therefore, performance and detection bias are minimized.

Outcomes such as in-hospital mortality and morbidity, blood loss and transfusion requirements, routine blood gas, blood sample/test results, and regional oxygen saturation of blood in the cerebral cortex are objective outcomes and will be recorded directly from medical notes, PICU charts, and electronic records.

Preoperative and postoperative ECG findings involve some level of subjectivity and judgement; however, ECGs will be interpreted by a cardiologist blinded to treatment allocation. Renal function analysis, cerebral function analysis, cardiac tissue function analysis, and NEPSY-II test administration are not part of routine care, and assessment will be carried out by blinded researchers. Reasons for noncompletion of tests or assays will be recorded.

Data and Sample Collection Schedule

The schedule for data and sample collection is shown in Table 1.

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Table 1. Schedule of data and sample collection.

Data and samples collected	Preoperative	Perioperative				Postoperative									
		Pre-surgery	Start of CPB[a]	10m post CPB	XC[b] re-moval	XC+ 30m[c]	XC+ 2h[d]	XC+ 4h	XC+ 6h	XC+ 24h	XC+ 48h	XC+ 72h	Dis-charge	3 mo[e]	12 mo
Eligibility	✓[f]														
Consent	✓														
NEPSY-II[g]	✓													✓	✓
Baseline data	✓														
Randomization		✓													
Routine blood gases		✓			✓	✓	✓		✓	✓					
Routine blood samples		✓					✓[h]			✓	✓	✓			
GFAP		✓			✓	✓	✓		✓	✓	✓				
NIRS		✓[i]													
Urine samples		✓			✓[j]			✓		✓	✓				
Cardiac tissue biopsies			✓	✓											
Operative details		✓	✓	✓	✓[k]										
Clinical outcomes													✓		
Safety data										✓	✓	✓	✓	✓[l]	✓

[a]CPB: cardiopulmonary bypass

[b]XC: cross clamp

[c]m: minutes

[d]h: hours

[e]mo: months

[f]✓ = data/sample collected

[g]Only performed on participants eligible for NEPSY-II psychometric assessment.

[h]Routine blood samples taken on admission to PICU.

[i]As many NIRS results will be recorded as are taken in theater.

[j]Urine samples taken at cross-clamp removal/end of CPB.

[k]Operative details are recorded on cross-clamp removal and chest closure.

[l]Hospital admission questionnaire only administered if 3-month NEPSY administered.

Participant Follow-Up

All primary and most secondary outcomes are assessed while the participant is in hospital following their surgery. For NEPSY-II eligible patients, NEPSY assessments will take place at 3 months and 12 months postoperatively (Figure 1 and Table 1). Safety data will also be collected at these visits. For participants that are not eligible for NEPSY-II assessments, follow-up for safety will occur at 12 months postoperatively by postal questionnaire. Active participation for all patients will cease either at their final NEPSY-II assessment or on return of the follow-up postal questionnaire, 12 months post operatively.

Sample Size

Primary Outcomes

The geometric mean postoperative hospital stay in our institution is estimated to be 6.2 days, with standard deviation (on the logarithmic scale) of 0.4. A sample size of 100 participants per group would be sufficient to allow us to detect a clinically relevant 1 day or greater reduction in mean length of stay with 90% power, assuming a 5% level of statistical significance (2-tailed).

Using estimates for ventilation time and duration of inotropic support from our institution, a total sample size of 200 would also be sufficient to detect a 16% reduction in ventilation time (3 hours), and a 13% reduction in inotropic support (4.7 hours). All these differences represent clinically relevant reductions.

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In an earlier RCT comparing the same 2 interventions carried out at our institution (Thermic-1), 59 participants were recruited. The primary outcomes for this earlier study were biochemical markers of organ injury, but clinical outcome data were also collected. For the current study (Thermic-2), 141 participants have been recruited. The clinical data from the 2 studies will be combined for assessment of the clinical outcomes, giving a total sample size of 200 participants for analysis.

Secondary Outcomes

This sample size will also be able to detect clinically relevant differences in secondary outcomes with 90% power. For full details, see Multimedia Appendix 1.

Statistical Analyses

Plan of Analysis

Binary outcomes will be compared using logistic regression. Quantitative outcomes will be transformed if necessary to achieve approximately normal distributions and compared using linear regression and time to event variables will be analyzed using survival methods. Outcomes with repeated measures (longitudinal data) will be analyzed using mixed models, which allow for unbalanced data. Alternative correlation structures will be considered, and the sensitivity of the results to the choice of structure examined. Analyses will be adjusted for age group (stratification factor). All analyses will be carried out on the basis of intention-to-treat. Outcomes will be reported as effect sizes with 95% confidence intervals.

Specific morbidities are too infrequent for the study to be able to detect statistically significant differences between groups. Frequencies of these adverse outcomes will be tabulated, in line with guidelines for reporting adverse events in trials, and reported in accordance with International Conference on Harmonisation Good Clinical Practice guidelines.

The analysis of the microarray data for the gene expression study—including normalization, noise reduction, and analysis using, for example, unsupervised hierarchical clustering and relevance network analysis—will be performed using Genespring 7 software. Following determination of the gene expression profiles, bioinformatics data mining tools (Genespring 7) will be used to identify the gene expression profiles that are differentially significant and to cluster them by biological function. This is vital for generating hypotheses about their role. Predefined stringent criteria will be used to select candidate genes for validation; only genes with statistically significant differential expression will be considered. Patterns of change in signaling pathway networks will be explored.

Subgroup Analyses

Effect estimates for the 2 study phases (Thermic-1 and Thermic-2) will be examined by adding relevant interaction terms to the models.

Changes to the Protocol Since First Approved

After recruitment of 52 patients, an amendment was approved on August 24, 2012, which affected several secondary outcomes:

1. Markers of renal function were incorporated after new evidence emerged suggesting that normothermic CPB was associated with similar renal impairment to hypothermic CPB [31,33].
2. The marker for brain damage was changed from S100-B to GFAP and samples were taken over 48 hours rather than 24 hours. Evidence has suggested that, when measured systemically, GFAP is more specific to brain trauma and may take longer to return to baseline levels than S100-B levels, which may be elevated during an event such as CPB or when other organs are damaged or under stress and independently of whether trauma to the brain has occurred [37-42].
3. NIRS data collection was incorporated to provide insight into regional oxygen saturation of the blood in the cerebral cortex.

In addition, the list of expected adverse events was also updated to include junctional ectopic tachycardia and heart block. A second amendment was approved on September 3, 2013, in which the protocol was updated to clarify the end-of-study definition, enabling the distinction between the end of study for an individual participant and for the study as a whole.

Results

A total of 141 patients have been successfully recruited over a 2-year, 10-month period for the Thermic-2 study. The participant follow-up period will end in October 2015 and results will be published in late 2015.

Discussion

Principal Findings

While whole body cooling is still very much an integral part of pediatric cardiac surgery in the belief that it provides some degree of protection against a systemic inflammatory response and multiorgan damage, there is little evidence to demonstrate that this translates to improved clinical outcomes [22-24,31,43]. This may, in part, be due to the multifactorial nature of CPB; the clinical outcome of a patient is likely to be affected by factors including the complexity of the anatomical defect being corrected and the time spent on CPB as well as the temperature of the CPB. For instance, correction of a simple anatomical defect performed using hypothermic CPB may attenuate inflammatory responses and organ damage, however, additional time spent on CPB to cool and rewarm the patient [22-24] may offset or mask these effects. In addition, most RCTs investigating normothermia versus hypothermia do not report the length of time spent at the allocated temperature, although through randomization the times should be similar in the 2 groups. Clinically, it is not appropriate to specify how long the target temperature must be maintained since CPB time should be kept to a minimum and rewarming must commence on completion of the anatomical correction. In practice, this results in shorter, less complex operations that potentially only receive the intervention for a short time period, while the longer operations may be exposed to the intervention for a greater length of time. Furthermore, we do not know how long the target temperatures of either 28°C or 35°C-37°C need to be maintained for physiological responses to take effect. While it would be difficult to impose a specific length of time for treatment

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intervention due to the constraints and complexity of surgery, it may be useful to collect information regarding the length of time during which the target temperature was maintained and this should be considered in future study design.

RCTs in children investigating CPB temperatures have recruited relatively low numbers of participants and have included the correction of primarily simple anatomical defects [23,24,27,43]. Furthermore, there is no agreed definition in the current literature of the reference temperature for hypothermic CPB; varying from as low as 24°C to up to 32°C, making interpretation of findings and cross-referencing difficult [8,22,23,27]. The Thermic-2 study has been designed to collect data from a large patient population with varying degrees of congenital heart defect complexity. The outcomes data have been chosen based on clinical relevance and with the aim to quantify postoperative course and multiorgan injury, focusing particularly on the heart, brain, kidney, and lungs. Also, these clinical parameters have been used to compare the 2 perfusion techniques in previous studies [8,9,22,27].

Compliance

The study protocol clearly defines the target nasopharyngeal temperature during CPB to be either 35°C-37°C or 28°C. However, while the surgeon and theater team may be willing to follow the allocation, they could be faced with challenges in order to achieve strict adherence to the study temperature. The perfusion team responsible for controlling the temperature of the body throughout CPB are in charge of administering the allocation. While the perfusion equipment can be used to control temperature extremely accurately and can be set to hit an exact target temperature, the circumstances and nature of pediatric cardiac surgery can result in precise temperature control becoming a challenge; in practice, it takes time for the body temperature to change. For clinical reasons, the length of CPB should be kept to a minimum so the perfusionist must estimate how fast the body temperature will continue to drift down toward the target (eg, 28°C) prior to rewarming. This could result in either over- or under-shooting of the target temperature, and more often affects the hypothermic group, particularly on shorter cases, as the rewarming of the body is a clinically rate-limiting step, and rewarming may have to take place before the target temperature is reached. Additionally, an open chest, particularly on very small children, loses heat very quickly, and consequently the body temperature prior to starting CPB could drop and there may not be enough time to rewarm the patient in order reach the target temperature if they were allocated to the normothermic group (35°C-37°C). Finally, there may be circumstances when the surgeon may decide that, due to unforeseen circumstances, it is not clinically appropriate for the child to participate in the study. In this situation, the surgeon may dictate what temperature the CPB should be performed at and the reasons for noncompliance recorded.

Minimization of Bias

The measures outlined below have been put in place to minimize potential bias: concealed randomization should prevent selection bias; blinding all possible staff, children, parents/guardians, and researchers will minimize performance and detection biases; the majority of outcomes are based on objective criteria; the PIL; and the process of obtaining informed consent will describe the uncertainty about the effects of normothermia versus hyperthermia and, therefore ,there should not be a strong expectation that one or the other method should lead to a more favorable result; attrition bias will be minimized by making every possible effort to keep in touch with participants; the study will be analyzed on an intention-to-treat basis, and every effort will be made to include all randomized patients.

Conclusion

In summary, despite the challenges faced in delivering the temperature allocation during CPB, the study has proceeded successfully. Lessons learned from Thermic-2 should help to design and conduct future temperature-based congenital open heart surgery studies.

Study Status

The study opened to recruitment in November 2011. Recruitment has recently completed, and follow-up of study participants continues.

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Authors' Contributions

All authors have been involved in preparation of the study protocol and have read and approved the final manuscript. Specifically, MC is the chief investigator and lead surgeon on the trial, and helped conceive the trial and participated in the protocol design. CR and LC designed the protocol and reviewed the manuscript. SS and AJP were participating surgeons in the trial. KS was the lead pediatric research nurse and helped drafting and reviewing the manuscript. SB drafted and reviewed the manuscript and coordinated the trial. LE has assisted in trial coordination and review of the manuscript. CR and KP performed sample size calculations, created the statistical analysis plan and reviewed the manuscript. MTG performed sample analysis.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Sample size calculation for secondary outcomes.

[PDF File (Adobe PDF File), 46KB - resprot_v4i2e59_app1.pdf]

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Abbreviations

ASD: atrial septal defect
BRHC: Bristol Royal Hospital for Children
CPB: cardiopulmonary bypass
ECG: electrocardiogram
GFAP: glial fibrillary acidic protein
IVC: inferior vena cava
NAG: N-acetyl-β-glucosaminidase
n-GAL: neutrophil gelatinase-associated lipocalin
NIRS: near infra-red spectroscopy
PICU: pediatric intensive care unit
PIL: patient information leaflet
RBP: retinal binding protein
RCT: randomized controlled trial
REC: research ethics committee
RNA: ribonucleic acid
SVC: superior vena cava
XC: cross clamp

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Protocol

Development of an Online Well-Being Intervention for Young People: An Evaluation Protocol

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Abstract

Background: Research has shown that improving well-being using positive mental health interventions can be useful for predicting and preventing mental illness. Implementing online interventions may be an effective way to reach young people, given their familiarity with technology.

Objective: This study will assess the effectiveness of a website called the "Online Wellbeing Centre (OWC)," designed for the support and improvement of mental health and well-being in young Australians aged between 16 and 25 years. As the active component of the study, the OWC will introduce a self-guided app recommendation service called "The Toolbox: The best apps for your brain and body" developed by ReachOut.com. The Toolbox is a responsive website that serves as a personalized, ongoing recommendation service for technology-based tools and apps to improve well-being. It allows users to personalize their experience according to their individual needs.

Methods: This study will be a two-arm, randomized controlled trial following a wait-list control design. The primary outcome will be changes in psychological well-being measured by the Mental Health Continuum Short Form. The secondary outcomes will be drawn from a subsample of participants and will include depression scores measured by the Center for Epidemiologic Studies Depression Scale, and quality of life measured by the Assessment of Quality of Life-four dimensions (AQOL-4D) index. Cost-effectiveness analysis will be conducted based on a primary outcome of cost per unique visit to the OWC. Utility-based outcomes will also be incorporated into the analysis allowing a secondary outcome to be cost per quality-adjusted life year gained (based on the AQOL-4D values). Resource use associated with both the intervention and control groups will be collected using a customized questionnaire. Online- and community-based recruitment strategies will be implemented, and the effectiveness of each approach will be analyzed. Participants will be recruited from the general Australian population and randomized online. The trial will last for 4 weeks.

Results: Small but clinically significant increases in well-being symptoms are expected to be detected in the intervention group compared with the control group.

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Conclusions: If this intervention proves to be effective, it will have an impact on the future design and implementation of online-based well-being interventions as a valid and cost-effective way to support mental health clinical treatment. Findings regarding recruitment effectiveness will also contribute to developing better ways to engage this population in research.

ClinicalTrial: This study is registered in the Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12614000710628.

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KEYWORDS

well-being; mental health; young people; online intervention; apps; engagement

Introduction

Background

Positive mental health implies more than just the absence of illness, it relates to *positive symptoms* and emphasizes psychological, social, and generative dimensions such as positive affect, personal growth, social actualization, and social contribution among others [1,2]. Despite controversies surrounding the role of well-being in mental health, the concept of positive mental health is steadily gaining credibility [1]. There is evidence that people with high levels of positive mental health are physically healthier, live longer, are more productive at work, and use less health care [3].

Consistent with this reasoning, the World Health Organization defines mental health as "a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community" [4]. Promoting positive mental health can be an effective strategy to approach mental health comprehensively as it is recognized that "the alleviation of symptoms of illness does not guarantee the presence of wellness" [5]. The Complete State Model of Mental Health characterizes mental health into three stages, namely, flourishing, languishing, or moderately mentally healthy, based on symptoms of positive feeling and functioning in life [6]. Keyes and Lopez [6] have posited that positive mental health constitutes a different continuum to mental illness and although correlated, the absence of mental illness does not imply the presence of positive symptoms [1]. Keyes [3] found that people with diagnoses less than flourishing struggled as much as people with a mental illness in areas such as work, health limitations, and psychosocial functioning [1]. In addition, the absence of positive mental health is associated with an increase in risky behaviors and the potential onset of mental illness [7]. A study conducted in South Australia reported that less than half of South Australian young people (42%) aged 13-17 years had a *flourishing* diagnosis of mental health, with even lower rates reported in rural areas [7]. This means that at the time of the study, 58% of young people in South Australia had less than a complete state of mental health (flourishing), and might therefore be more vulnerable to struggle in one or more areas of their lives.

Online Well-Being Interventions

There is evidence that young people make significant use of the Internet to socialize and to find information about a wide range of issues including personal difficulties. In Australia, surveys show that the Internet is the preferred medium of support for young people after family and friends [8,9]. Specialized online mental health services for young people such as ReachOut.com have effective reach into this population group [10].

Online treatments based on a psychopathology model for a range of mental disorders such as depression and anxiety have been researched widely [11-14]. Most of these interventions are based on cognitive behavioral therapy (CBT) with specific variations such as prolonged exposure or guided relaxation, among others. These interventions have shown effectiveness in treating problems such as stress, anxiety, and depression. Other types of interventions such as general counseling and self-help approaches still show effectiveness, although to a lesser extent [11,12]

Regarding online positive psychological interventions, a number of studies in adult populations have shown positive results in improving well-being and decreasing depression. Results vary depending on the actual intervention and method of delivery [15]. Two recent trials with similar characteristics to this study demonstrated significant improvements in well-being in the general adult population, predominantly in women. Bolier et al [16] examined the effectiveness of an online self-help intervention consisting of a multicomponent, fully automated self-help online website to improve well-being. Their study investigated mild to moderately depressed adults in the general population using a waitlist control design, and found the online intervention to be effective in enhancing well-being on the 5-item World Health Organization well-being index [17] compared with a control. Small but significant effects were found for general health, vitality, anxiety, and depressive symptoms. Another study comprising a randomized, placebo-controlled, parallel-group trial with longitudinal outcome measurements used the Individual-level Wellbeing Assessment and Scoring Method to measure well-being [18]. It was found that a multimodal online intervention consisting of well-being e-mail, web- and mobile-based interventions had positive effects, with significantly improved well-being in a sample of the general adult population compared with a control.

There is a paucity of research on online positive mental health interventions in young people; however, a randomized controlled trial [19] investigated the effectiveness of a well-being website called "Bite Back" designed for young people aged 12-18 years. Using the Depression, Anxiety and Stress Scale (DASS21)[20] and the Short Warwick Edinburgh Mental Wellbeing Scale [21], the study participants were assigned to two conditions over a 6-week period. The intervention group was given access to the

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website and the control group was assigned to neutral entertainment-based websites. Results demonstrated significant improvement in clinical measures (depression, anxiety, and stress) and well-being in the participants of the intervention group who reported using the website for at least 30 minutes every week.

Online Recruitment and Engagement

Facebook, Google, and other online platforms, frequented by large number of users, have been used widely with considerable success to recruit participants for online studies [22-24]. Both Google and Facebook advertising platforms have been effective in recruiting participants with an existing mental health issue for online interventions. The average cost of recruitment is approximately AUD 12-15 for each participant, whereas contacting forums, email groups, and community notice boards are less effective and more costly [24,25]. Although social networking websites can be a promising method to recruit adolescents, the health and behavior patterns of those recruited online could differ significantly from those recruited offline [22]. The evidence for effective strategies to recruit young people for online well-being interventions is sparse. Despite the proven efficacy of Internet-based mental health interventions, they suffer from a high reuse attrition rate [26]. In fact, findings from an online smoking cessation study with a high reach showed that adherence and retention rates decrease as accessibility increases [27]. Improving adherence is a high-priority research area in Internet interventions, as higher usage rates are associated with significant improvements in well-being [19]. Periodic prompts through email, short message service (SMS) text messaging, phone, and online peers/counsellors have proven to be effective strategies in increasing login rates and the time users spend using online interventions [28].

Research has shown that in the first few weeks after engagement with a given intervention, high numbers of participants lose interest [29]. Involving users in the intervention design process can be an effective way to create person-centered innovations [30]. Participatory design is characterized by generative, experiential, and action-based methods that put emphasis on play, co-operative learning, creating visions for the future, and designing-by-doing, with the aim of involving end users in the design of services [31]. Online studies that provide useful feedback and alternative resources for the control group achieve better engagement [18].

Current Study

This study is a waitlist randomized controlled trial (ACTRN12614000710628) intended to test the effectiveness of an online intervention in improving well-being in a sample of Australian young people aged 16-25 years.

This paper provides a brief description about the Online Wellbeing Centre (OWC), outlining two different configurations for the implementation of interventions and how they were developed. It also includes a description of the methods, design of the trial, and finally a discussion with implications of this study.

Methods

Online Wellbeing Centre

The OWC was designed as a way to encourage individuals to participate in both intervention and control arms. The OWC is a virtual space where users sign up via the landing page (Figure 1), check their well-being, track their progress over time, and access different well-being resources. It has capabilities to randomize, administer study measures at different time points, and give access to tailored resources according to the assigned arms of the study. The OWC provides feedback to users in a meaningful graphic display as shown in Figure 2.

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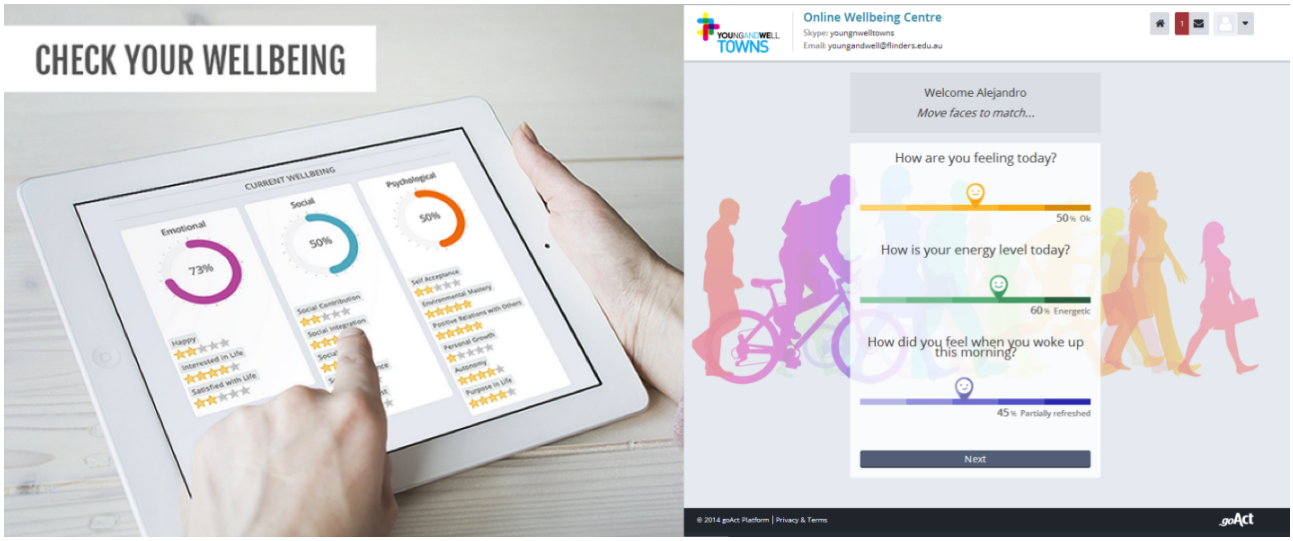
Figure 1. Screenshot of the Online Wellbeing Centre landing page.

Figure 2. Screenshots of the Online Wellbeing Centre website.



Intervention arm: "The Toolbox" by ReachOut.com

The Toolbox has been developed by ReachOut.com, with the Young and Well Cooperative Research Centre (Young and Well CRC). It houses over 50 mental health and well-being tools and apps that have been reviewed by a panel of both mental health professionals and consumers for their credibility, functionality, engagement, and aesthetics according to the Mobile Application Rating Scale developed by Queensland University of Technology [32].

The Toolbox is based on the theory of change proposed by Perugini and Bagozzi's Model of Goal-Directed Behaviour [33] as well as theories of reasoned and planned behavior [34]. The Toolbox focuses on well-being and positive functioning, and is designed to improve (1) emotional well-being (ie, positive affect and life satisfaction); (2) psychological well-being (ie, self-acceptance, personal growth, purpose in life, environmental mastery, autonomy and positive relations with others); (3) social well-being (ie, social acceptance, social contribution, social coherence, social integration, and social actualization); and (4) physical well-being [35]. In designing The Toolbox, ReachOut.com took a participatory design approach [31]. Young people were consulted at the initiation of the project and during the design phase, while also providing feedback on early prototypes. The user experience of The Toolbox is based on young people's conceptualization of well-being and what they need from an online recommendation service. Functionalities of The Toolbox website are described in Textbox 1, and

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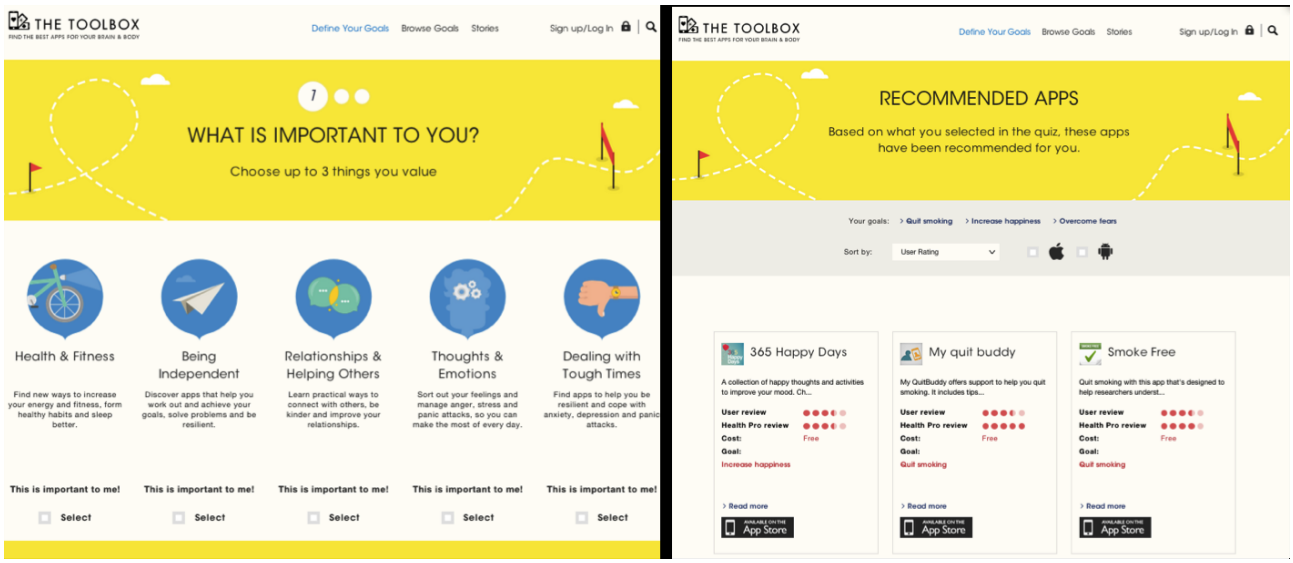
screenshots of the first 2 pages of The Toolbox website are shown in Figure 3.

Textbox 1. Functionalities of The Toolbox.

- Quiz to help participants determine their area of focus and recommend relevant apps.
- Browse apps by category. Categories include Health & Fitness, Being Independent, Relationships & Helping Others, Thoughts & Emotions, and Dealing with Tough Times.
- Read ratings and reviews by health professionals and young people. Participants can write their own review of apps including what they liked and what could be improved.
- Read stories about how others have used apps to achieve their goals and the challenges they faced. Participants can submit their own story.
- Dashboards are available in which participants can update their goals, add new apps, and view their stories.

Figure 3. The Toolbox website home page and app recommendation page.



Study Design

This is a standard parallel arm clinical trial comparing the effectiveness and cost effectiveness of control and intervention arms offered over 4 weeks. Group 1 represents the intervention arm (OWC with The Toolbox) and Group 2 represents the waitlist control arm (OWC without The Toolbox). In this study, participants in the intervention arm will be able to access the active component of the trial, The Toolbox, through the OWC straight away. Participants in the control group will gain access to The Toolbox after 4 weeks. Once participants follow the online links as described in the recruitment section, they will be directed to the project's landing page (Figure 1). Once there, they will be required to complete the steps outlined in Figure 4.

All participants will receive regular SMS and email prompts from the OWC to remind them to complete study measures. As detailed in Table 1, assessments will be administered at sign up, and at 4 weeks. In addition, participants will be prompted to regularly monitor their mood, energy and sleep.

Table 1. Assessment scales administered at each time point during the study.

Instrument	Measurement	Baseline	After 4 Wk
Mental Health Continuum Short Form	Well-being/Positive mental health	X	X
Center for Epidemiologic Studies Depression Scale	Symptoms of depression	X	X
Assessment of Quality of Life-four dimensions index	Quality of life data	X	X
Resource use questionnaire	Cost effectiveness		X
Demographics	Date of birth, gender, postcode, employment, education, cultural background, and living conditions	X	
Heuristic well-being questions	Feelings, energy, and sleep	Weekly	Weekly

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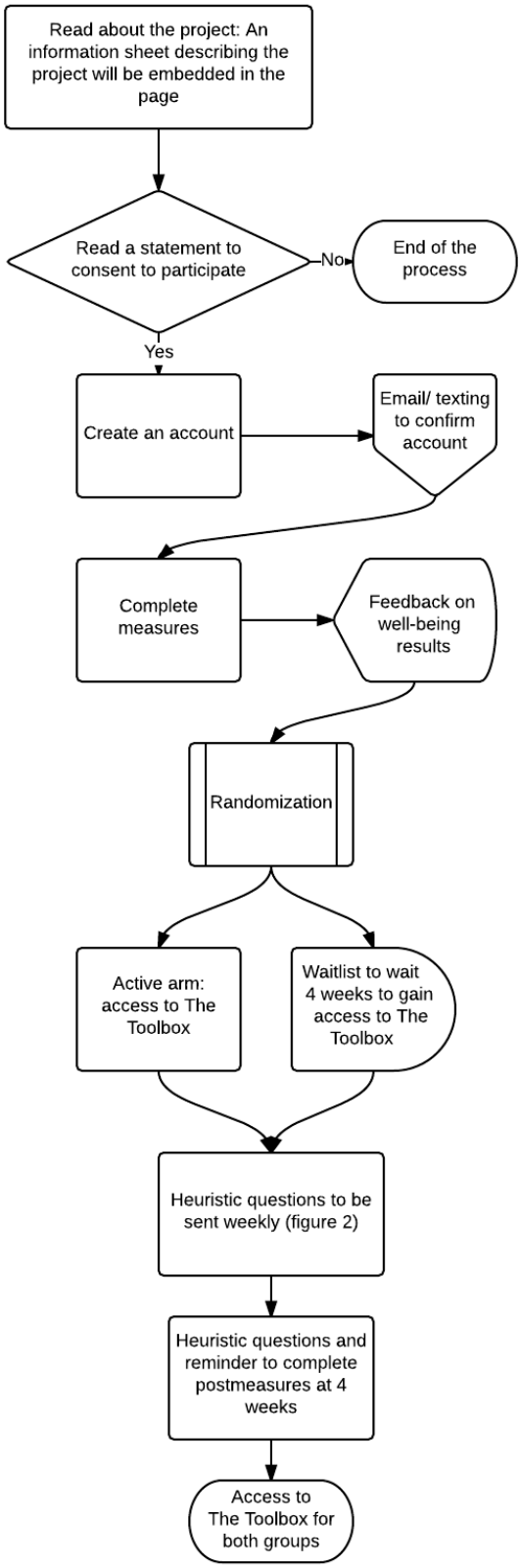
Figure 4. Online Wellbeing Centre study flow diagram.



Recruitment, Inclusion, and Exclusion Criteria

The target population is Australian young people aged between 16 and 25 years, with access to technology and the Internet (computers or smartphones). In the context of well-being theory, pre-existing mental health problems will not be considered as exclusion conditions for this study. Given that this intervention is not intended to treat any particular pathology, all participants could potentially benefit from improving well-being symptoms. Relevant links to appropriate mental health services will be

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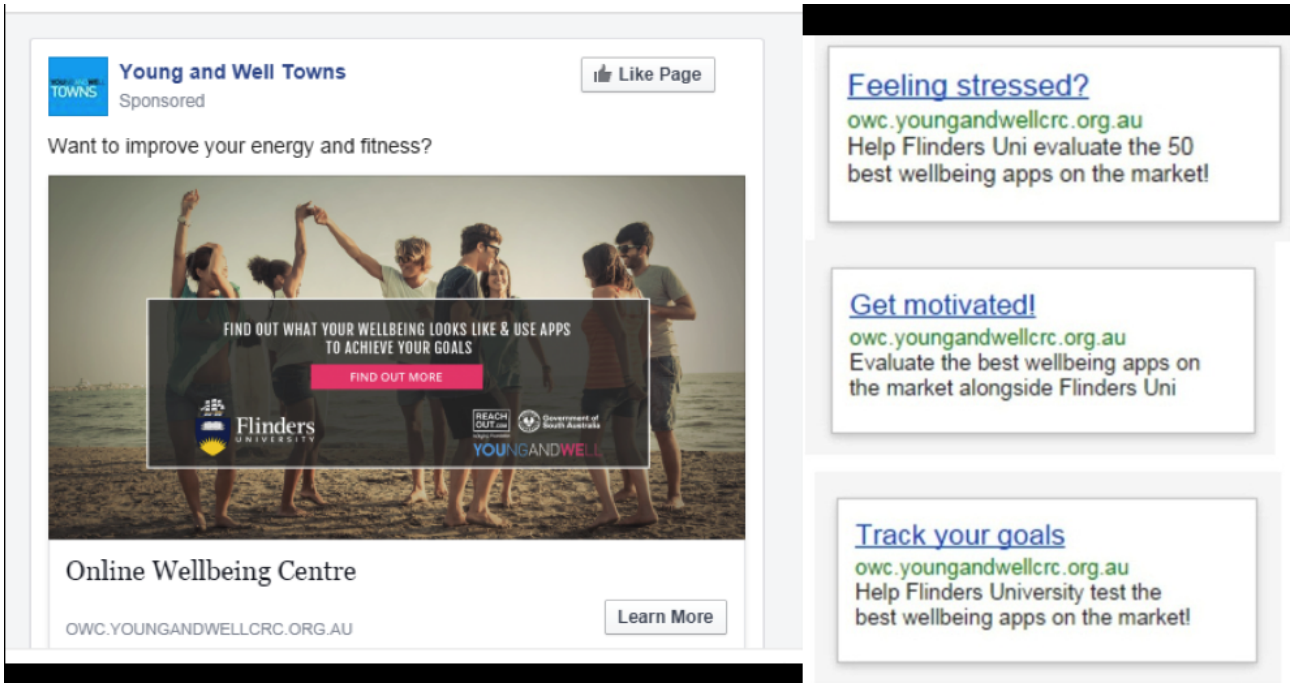
offered to participants during the trial. Online recruitment will only be targeted to participants between 18 and 25 years of age. Parental consent will be obtained for participants under the age of 18 recruited via community channels, given that we will have face-to-face contact with potential participants through schools and other organizations. People not meeting the age criteria and/or residing outside of Australia will be excluded.

Participants will be recruited using online- and community-based methods. Two platforms have been selected from the many options available to implement online paid advertising. Advertisements will be placed on Facebook and Google AdWords (see Figure 5) using keywords relevant to well-being dimensions. The keywords for the advertisements were defined in collaboration with a reference group representing the target population to ensure their validity and relevance. Examples of such keywords include *fitness*, *stress*, *relationships*, *balance*, and *goals*. Concurrently, the links to the study site will be integrated into several websites that are frequently visited by young people from different backgrounds in Australia (most notably the partner organizations of the Young and Well CRC).

The online recruitment strategy also includes changing advertisements periodically. This will be a dynamic process guided and modified by success rates of particular advertisements while they are being implemented. The wording of the advertisements and placement of links will be monitored (according to the method described in the "Recruitment Tracking" section) and periodically modified to reach the target population effectively.

Community-based organizations such as schools, universities, sport clubs, and local councils will be approached and asked to help promote the study. Promotional packages consisting of a video, information, and instructions on how to access the OWC will also be designed. These packages will be distributed to different institutions where they will be presented to potential participants. Innovative technologies (videos, Google Hangouts, etc) will be included in the recruitment packages.

Figure 5. Examples of online Facebook and Google AdWords used in recruitment for study.



Recruitment Tracking

To assess the effectiveness of the different recruitment approaches and reach of each advertisement/link, an advertisement tracking system will be implemented using the online open analytics platform *Piwik* [36]. This method involves adding a unique *campaign* and *keyword* code to the source name as a parameter at the end of each link where the advertisements, banners, and links will be embedded.

Study Hypothesis

The primary hypothesis is that the active intervention group (OWC with The Toolbox) will exhibit an increase in participant well-being [as measured by the Mental Health Continuum Short Form (MHC-SF) scores] after 4 weeks, in comparison with the control group (OWC without The Toolbox).

Primary Outcome Measure

The primary outcome is mental health (well-being), assessed using the MHC-SF [37]. This scale consists of 14 questions measuring three areas of well-being, namely, emotional, psychological, and social. The tool diagnoses mental health as flourishing, moderately mentally healthy, and languishing, consistent with the Complete State Model of Health theory. The MHC-SF has been validated with adolescents and adults in the United States, South Africa, and the Netherlands. It has an internal consistency over Cronbach alpha = .80 [38-41]. The test-retest reliability of the MHC-SF over three successive 3-month periods averaged .68, and the 9-month test-retest reliability was .65 [40]. A clinically significant change will be defined as a change in diagnostic outcome (languishing, moderately mentally healthy, and flourishing) between measures before and after the intervention in at least one of the well-being

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categories (emotional, psychological, and social). We will also consider changes in heuristic trackers as reflective of behavioral change (sleep, mood, energy).

Secondary Outcome Measures

Secondary outcomes include momentary measurements of mood, energy, and sleep using simple visual analog scales ranging from 0 (worst) to 100 (best) at weekly intervals. Changes in these scales will be correlated with the type of apps selected, goals set, and duration spent within the OWC. There is evidence that depression is a significant covariate in analyses of changes in well-being in multiple studies [16,19,42]. Participants who score below 50 for mood in the visual analog scale will be invited to undergo a screening for depression using the Center for Epidemiologic Studies Depression Scale (CESD)[43,44]. Changes in well-being of this subset will be correlated with improvement in depression. To facilitate the cost-effectiveness analysis, data on health-related quality of life will be collected using the Assessment of Quality of Life-four dimensions (AQOL-4D) index [45]. The AQOL-4D includes four dimensions, namely, independent living, mental health, senses, and relationships. Each dimension has three items and ranges from -0.04 to 1.00 with higher score indicating better quality of life. The AQOL-4D is a self-completed questionnaire that can be administered online.

Subsidiary Outcome Measures

Resource use associated with both the intervention and control groups will be collected from a sample of 50 participants at the end of the trial using a resource use questionnaire. This is a custom questionnaire developed by the funding body Young and Well CRC and includes questions corresponding to the period of the trial on participants' employment/education status, wages, their use of health services (type and duration), number of times (and duration) they accessed the OWC and other mental-health-related Internet sites, and how much they pay to access the Internet.

Sample Size

The primary outcome measure is change in well-being as measured by MHC-SF. A total of 180 completed participants (90/arm) are required to provide 80% power to detect a difference of 0.37 in improvement between arms with a two-tailed type 1 error of 0.05. This assumes an overall standard deviation of 0.63 at baseline and 0.81 at 1-month follow-up as found in Bolier et al [16], and a conservative correlation of 0 between baseline and follow-up scores. Considering the higher attrition level found by Bolier et al [16] (37.8%) this study will aim to recruit a sample of 250 participants.

Randomization

Randomization will occur in blocks of four to ensure approximately equal numbers in each arm. Participants will be asked to read the study information and give their consent online. They will then be directed to create a password-protected account to login to the OWC. After login, participants will be randomized into two groups. The intervention group will have immediate access to The Toolbox, whereas the control group will be allocated to the wait-list for 4 weeks.

Statistical Analysis

The primary analysis is based on intention to treat, and missing values from all randomized participants will be imputed with 50 samples redrawn from the original data. The primary outcome will be assessed using random effects mixed modeling, with the well-being score as the dependent variable. The independent variables are time, group, and the time × group interaction (product) term, which are clustered over age, gender, geographical location, work status, cultural background, education level, and living circumstances to account for possible correlated readings. Sensitivity analyses and secondary continuous outcomes will be assessed similarly, but also adjusted for potential confounders. All results will be reported with 95% CI and p values. A p value < 0.05 (two tailed) was taken to be significant. All analyses will be performed using Stata version 13.1 (College Station, TX, USA) [46].

Cost-Effectiveness Analysis

An economic evaluation will be conducted alongside the trial to estimate the relative cost effectiveness of The Toolbox compared with the wait-list. The evaluation will take the form of a cost-effectiveness analysis based on a primary outcome of cost per unique visit to the OWC. Utility-based outcomes will also be incorporated into the analysis allowing a secondary outcome to be cost per quality-adjusted life year (QALY) gained (based on the AQOL-4D values) [47].

The cost and outcome data will be estimated for every participant within the trial. Costs will be estimated by combining data on resource use associated with both the intervention and control groups with unit costs for each of the resource items. Resource use data will be collected using the resource use questionnaire described earlier. Unit costs (eg, staff wages or opportunity cost of time lost from work, school, or household activities) will be collected from published data sets including those from the Australian Bureau of Statistics and the Australian Government Fair Work Ombudsman. A participant-level analysis will be undertaken to determine the mean costs, increases in number of visits to the OWC, and QALYs for each trial arm. To test the robustness of the economic evaluation results, nonparametric bootstrapping and appropriate sensitivity analyses will be carried out and results will be reported in terms of incremental cost-effectiveness ratios and cost-effectiveness acceptability curves. The final results will be presented in the CONSORT format for reporting randomized trials [48] and the CONSORT-EHEALTH extension [49].

Results

This trial is funded by the Young and Well Cooperative Research Centre, Country Health South Australia Local Health Network and Flinders University. Recruitment commenced in December 2014 and final results are expected to have been analyzed by the end of 2015. We acknowledge that it may be necessary to implement personalized follow-up strategies (eg, telephone calls to ensure an appropriate number of poststudy measures).

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Discussion

Principal Findings

The current study differs from previous research in the following key areas: (1) it involves development of a well-being intervention, co-designed with young people using participatory methods; (2) it uses both community and online recruitment approaches to get a representative youth sample of the target population; and (3) it includes an assessment of effectiveness and cost–benefit analysis using a waiting list randomized controlled trial design.

The OWC has been designed as an interactive site to track well-being in a meaningful way for participants. It provides access to self-guided interventions that relate to improvements in well-being and has been designed in collaboration with final users. It is expected that these features will improve engagement rates with the study.

To our knowledge, this is one of the first online interventions designed to improve well-being using self-guided methods specifically targeted at young people. "The Toolbox" has been devised using participatory design methods with ongoing user interaction during all phases of its development. The Toolbox design enables users to choose their own goals. It then specifically recommends suitable apps, while also provides users with a space to rate apps and share their stories with other users. The Toolbox website is personalized, with active components (apps) suggested instead of imposed. It is expected that all of these elements will improve engagement and be reflected in the study outcomes.

The current study will also compare innovative ways to recruit and engage young people using either online advertisements through Facebook and Google, or community-based networks. Such a comparison of recruitment strategies for well-being interventions has not been explored before; most studies recruiting for online well-being interventions have focused exclusively on online recruitment strategies using advertisements [16,18]. The study will subsequently be able to determine whether the cohorts recruited online and offline differ in terms of their general demographic profile, as well as their response to the intervention. The approach is innovative with regard to community-based recruitment, with the intention to develop advertisement/training packages that will be deployed in community organizations using technology (videos, Google Hangouts, etc).

Another novel feature of this study resides in the fact that the intervention is not limited to a clinical population. This opens up opportunities to explore a number of variables that could be highly significant for future interventions; for example "Does well-being improve in the absence or presence of pathology?" and "What are the most effective mechanisms to recruit young people from different backgrounds and engage them with activities to improve their well-being?"

Finally, it is expected that the health economic analysis that will be conducted will determine whether improving well-being in the target population is associated with lower health care costs.

Limitations

The study has potential limitations in terms of recruitment, adherence, comparison time, and attrition levels. Although research has shown the efficacy of online networking for the recruitment of research participants [23,24], it is known that intrinsic characteristics of young people imply particular challenges regarding adherence in a study promoting well-being. To address these difficulties, recruitment methods have been co-designed with young people and service providers to ensure relevance and adequacy. We also expect to detect differences between recruitment modalities (online vs. community based).

It would have been ideal to administer the resource use questionnaire at baseline and 4 weeks but this will not be possible due to the need to avoid participant burden. The questionnaire will therefore only be applied at 4 weeks with questions focusing on resource use in the intervention and wait-list control groups corresponding to the duration of the trial. Costs will be appropriately extrapolated beyond the 4-week period.

It is not possible to determine how changes in well-being are related to using specific apps. Expected findings of this study will indicate whether accessing purposely built online resources can improve well-being. Given the nature of the study and attempting to improve recruitment and adherence, data will be obtained from just one well-being specific measure. In addition, participant compliance with secondary measures is not mandatory, or assured.

This study attempts to reach the broad population and does not focus on participants with specific profiles, including mental health background history or gender. Although representativeness is pursued mainly through community-based recruitment, it is not guaranteed.

It could be argued that 4 weeks is a relatively short time to assess intervention effects; however, based on input from the current study's youth reference group it has been found that

1. Young people are more likely to start using apps as soon as they get them and gain full mastery very quickly.
2. Typically, young people will use apps for short periods, and therefore a short intervention could improve retention of the control group.
3. Young people are transient in their interest, which implies that a brief intervention time could yield better adherence.

This study has gained ethical approval by the Social and Behavioural Research Committee of Flinders University under registration number 6478 and is registered in the Australian New Zealand Clinical Trials Registry (ANZCTR); ACTRN: ACTRN12614000710628. It has also gained ethical approval for recruitment by the Department of Education and Child Development of South Australia.

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Acknowledgments

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Conflicts of Interest

None declared.

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Protocol

Supportive Text Messages to Reduce Mood Symptoms and Problem Drinking in Patients With Primary Depression or Alcohol Use Disorder: Protocol for an Implementation Research Study

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Abstract

Background: Depression and Alcohol Use Disorders (AUDs) are two leading causes of disability worldwide and are associated with significant treatment challenges requiring new, innovative, cost-effective and technologically-based therapies including the use of supportive text messages.

Objective: To determine the feasibility and effectiveness of supportive text messages in long-term follow-up to reduce mood symptoms and problem drinking in patients with Depression or AUD respectively and to explore the usefulness of self-reports of health services utilization as an outcomes measure.

Methods: This will be a longitudinal, prospective, parallel-design, two-arm, placebo-controlled single-rater-blinded randomized clinical trial with a recruitment period of 6 months and an observation period of 12 months for each participant, with two strata based on primary diagnosis of Major Depressive Disorder or AUD. The sample size will be 120, with about 60 patients randomized from each primary diagnostic grouping. Patients in all intervention groups will receive twice-daily supportive SMS text messages for 3 months and then daily supportive text messages for the next three months. Patients will also receive a phone call every two weeks from the research assistant assigning treatment allocation to confirm that they are still receiving the text messages and to thank them for taking part in the study. Patients in the control group will receive no text messages but will also receive a phone call from the same research assistant every two weeks to thank them for taking part in the study.

Results: The study starts in April 2015 and ends in September 2016. It is envisaged that both qualitative and quantitative primary and secondary outcomes, including patient perceptions of the intervention, will shed light on the feasibility of using automated supportive text message interventions in long term for patients with Depression and AUD. This will inform a full-scale clinical trial.

Conclusions: The paradigm for behavior change using text messages as a patient-direct intervention is consistent with a cognitive behavior therapy approach and addictions counselling principles. Given the automaticity of the messages, we anticipate that if

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the intervention proves successful, it will represent a low cost strategy that will be readily available and can bring relief to patients in hard-to-reach areas with limited access to psychological therapies.

Trial Registration: ClinicalTrials.gov: NCT02327858; https://clinicaltrials.gov/ct2/show/NCT02327858 (Archived by WebCite at https://clinicaltrials.gov/ct2/show/NCT02327858).

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KEYWORDS

depression; alcohol use disorder; supportive text messages; intervention

Introduction

Background

Depression and Alcohol Use Disorders (AUDs) are leading causes of disability worldwide, associated with significant treatment challenges especially when they occur concurrently [1, 2]. Concurrent challenges include: higher rates of lifetime drug dependence [3]; worse outcomes among those entering treatment for alcohol and drug misuse [4]; higher relapse following AUD treatment among adolescents [5] and adults [6]; greater severity of suicidality in adults [7], and higher likelihood of suicide attempts [8-10] and completed suicides [11]. Given this acute disease burden, we propose a treatment strategy that takes advantage of mobile phone technology to support patients in an efficient, innovative and cost-effective manner. The ultimate aim is to restore health while reducing the combined impact of these disorders on patients, caregivers, their communities and Alberta's provincial health care provider, Alberta Health Services (AHS) [12].

In a pilot trial in Ireland, participants with concurrent depression and AUD who completed an inpatient dual diagnosis treatment program were randomized to receive twice-daily supportive text messages or a biweekly "thank you" text message for three months. Supportive text messaging improved Beck Depression Inventory (BDI) scores compared with those who received standard care. There was also a trend towards increased Cumulative Abstinence Duration (CAD) in the supportive text message group [13]. Furthermore, the majority of patients who received the supportive text messages expressed satisfaction with the support offered through the technology [14]. The pilot trial in Ireland did not explore the effects of supportive text messages on the individual disorders when they occur alone, although it would be reasonable to assume that they would benefit equally. A recent study in JAMA Psychiatry [15] randomly assigned patients leaving residential treatment for AUDs to either use of a smartphone application to support recovery in addition to standard treatment or treatment as usual. For the 8 months of the intervention and 4 months of follow-up, patients in the smartphone application support group reported significantly fewer risky drinking days than did patients in the control group. In a review of efficacy of use of text messaging as a clinical and healthy behavior intervention, Wei et al (2011) found that among 16 randomized controlled trials, 10 reported significant improvement with interventions and 6 reported differences suggesting positive trends [16]. More recently, in a meta-analysis of the results of text message interventions among 14 studies, the pooled effect size was 0.25, 95% CI (0.13-0.38), indicating that in general, text interventions have a positive effect on reducing substance use behaviors [17].

Overall Aims

To conduct a randomized controlled pilot trial to determine the feasibility, acceptability and effectiveness of supportive text messages in long-term care to reduce mood symptoms and problem drinking in patients with Depression or AUD respectively.

Specific Objectives

1. To compare mean changes in BDI scores from baseline for patients with Depression receiving standard care with supportive text messages to those receiving standard care without supportive text messages.

2. To compare the CAD from baseline for patients with AUD receiving standard care with supportive text messages to those receiving standard care without supportive text messages.

Hypotheses

Supportive text messages will:

1. Lead to a 30% better mean reduction in BDI scores at 6 months from baseline in the intervention group compared to the control group.

2. Increase the mean Cumulative Abstinence Duration (CAD) for patients with AUD in the intervention group from baseline by at least 30% over and above the mean CAD for patients in the control group from baseline.

Methods

Study Design and Setting

This will be a longitudinal, prospective, parallel-design, two arm, placebo-controlled single-rater-blinded randomized clinical trial with a recruitment period of 6 months and an observation period of 12 months for each participant with two strata based on primary diagnosis of Major Depressive Disorder or AUD. Patients with AUD will be recruited from those completing the Northern Addiction Residential Treatment program located in Grande Prairie while patients with Depression will be recruited from those assessed for wait listing onto the Cognitive Behavior Therapy (CBT) program run by the Adult Mental Health Team in Fort McMurray. The study has received ethical clearance from the Health Ethics Research Board of the University of Alberta and operational approval from the AHS. All participants will provide informed written consent prior to randomization. The study has been registered with clinicaltrials.gov

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(NCT02327858) and will be executed according to the timelines specified in the Gantt chart in Table 1.

Table 1. Gantt chart for supportive text message project.

	Year 1				Year 2				Year 3			
	Start Date-End Date				Start Date-End Date				Start Date-End Date			
Milestones	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Milestone 1: Recruiting and training of research associates												
1.1 Advertising and assembling of research associates	X											
1.2 Training of research associates and the trainee in psychiatry	X											
1.3 Writing up a bank supportive text messages in collaboration with service users and CBT and addiction counselors	X											
Milestone 2: The recruitment of study participants												
2.1 Recruitment, baseline assessment, randomization		X	X									
2.2 Assignment into intervention or control groups		X	X									
2.3 Delivery of supportive text messages to participants in the control group		X	X	X	X							
Milestone 3: Follow-up assessment of study participants and collection of administrative data												
3.1 Follow-up assessments of individual study participants (Excluding survey on the usefulness of the supportive text messages)			X	X	X	X	X					
3.2 Follow-up survey of participants in the intervention group on the usefulness of supportive text messages				X	X							
3.3 Collection of administrative data related to cost of health services utilization						X	X					
Milestone 4: Data compilation, analysis and preparation of reports, publications and presentations												
4.1 Data compilation		X	X	X	X	X	X					
4.2 Data Analysis		X	X	X	X	X	X	X				
4.3 Preparation of reports, publications and presentations								X	X			

Recruitment

All patients completing the Northern Addiction Residential Treatment program located in Grande Prairie and those assessed for waitlisting onto the Cognitive Behavior Therapy program run by the Adult Mental Health Team in Fort McMurray who fulfill the inclusion criteria below will be invited to participate. This will minimize source of referral as a confounding factor. Information leaflets will be provided and those consenting will be recruited. The Structured Clinical Interview for DSM-5 Disorders (SCID) will be used to screen and confirm the diagnosis of all study participants prior to inclusion in the study.

Inclusion Criteria

Persons aged 18 years and over who are able to provide informed consent will be eligible if they have been assessed and waitlisted for the CBT program in Fort McMurray and fulfill the DSM-5 diagnostic criteria for Major Depressive Disorder or who have completed the residential addiction treatment program located at the Northern Addiction Treatment Centre, fulfill the DSM-5 diagnostic criteria for AUD and are in the stage of change and are committed and motivated to give up alcohol. Participants must be familiar with or willing to learn how to receive text messages and be available for long-term intervention. Mobile phone handsets and top-up call credit of up to 10 dollars monthly will be provided to those who satisfy the inclusion criteria but do not have mobile phones.

Exclusion Criteria

Patients will be ineligible if they do not meet the above inclusion criteria, if they are patients with Schizophrenia, Schizoaffective Disorder, Bipolar Disorder and other psychotic disorders, or residing outside of regular cell phone connection areas.

Baseline Assessment

All study participants will undergo baseline assessments during recruitment to collect demographic and clinical data. For those with AUD, the time-line follow back (TLFB) [18] will be used to record the quantity of alcohol consumed and number of drinking days during the 90 days preceding the admission to the recovery centre. We will also record any history of alcohol-related pathology. For those with Depression, the BDI will be used to record baseline depression symptom scores. Other clinical measures will include the Obsessive Compulsive Drinking Scale (OCDS)[19] and the Alcohol Abstinence Self-Efficacy Scale (AASES) [20] that evaluates both temptation

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to drink and confidence to abstain across 20 items representing cues in the four subscale areas of Negative Affect, Social, Physical, and Withdrawal/Urges.

Functional outcome will be assessed by measuring the Health Related Quality of Life (HRQOL). The HRQOL will be measured by the Canadian version of the EQ-5D-5L instrument from all patients. The EQ-5D-5L consists of two components: a five dimensional descriptive system including mobility, self-care, usual activities, pain or discomfort and anxiety or depression with five levels in each of them, and a Visual Analogy Scale (VAS) where respondents value 'their own health today' on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). It is cognitively simple, taking only a few minutes to complete and it can also be used to calculate single index values for economic and population health studies.

Randomization and Blinding

Randomization will be stratified by primary diagnoses (Depression or AUD) using permuted blocks to ensure balance (1:1) between treatment and control groups within each condition under study. The randomization codes will be transmitted by an independent statistician via text message directly to the researcher. This will commence immediately after the participant has signed the consent form. A dedicated, password-protected phone line with a secure online backup will be used to transmit these messages.

The research assistant who sends the text messages will not be involved in the outcome assessments except to contact those receiving the supportive text messages for feedback on the benefits of the text messages. Participants cannot be blinded and treatment allocation will be made explicit to them. Outcome assessors will be blinded to treatment group allocation. To ensure this, treatment allocation will be concealed from the outcome assessor by blocking access to the database, which contains the randomization code, and all participants in the study will be asked not to reveal their treatment allocation to their assessor. Outside the assessments, outcome assessors will not participate in discussions with the participants in study forums. To test the success of blinding we will ask the assessor to guess the allocation group for each participant at 3, 6, 9 and 12-month follow-ups. Moreover, these assessors will not be involved in data analysis. After data collection is complete all data will undergo a blind review for the purposes of finalizing the planned analysis. Every effort will be taken to avoid incomplete data and methods of dealing with unanticipated missing data will be determined during the blind review of the data.

Intervention

Patients in all intervention groups will receive twice-daily supportive SMS text messages for 3 months and then daily supportive text messages for the next three months. The messages will be tailored towards improving mood, compliance with medication or targeting abstinence from alcohol in accordance with the primary aims of our study. The majority of the text messages will reflect lessons patients usually learn during CBT and addiction counseling sessions in the two recruitment sites and sent at specified times by a centralized computer program which will be set up and monitored by a research assistant. Sample text messages are outlined below.

- If you keep on going, maintaining your hope and belief that something good will happen, it generally does. One day at a time.
- Ask for help. You have lent a hand to others in need in the past. There is probably someone in your life that would be genuinely honored to help you now.
- Give yourself the time you need to recover, do not try to race ahead to where you think you should be, remember that time is a great healer.
- Think of your recovery as an opportunity to find new solutions in your life. Remember that the past is gone and what you do next is what really matters.

To safeguard patient confidentiality no identifiable patient information will be transmitted via text messages. Patients will also receive a phone call every two weeks from the research assistant assigning treatment allocation to confirm that they are still receiving the text messages and to thank them for taking part in the study. Patients in the control group will receive no text messages but will also receive a phone call from the same research assistant every two weeks to thank them for taking part in the study. The aim of this will be to help increase the retention rate for the study.

Sample Size

Consistent with the idea that this is a pilot study, the research will use the data that can be elicited from participants who can be enrolled within the existing resources [21]. The study will therefore be limited to a sample size of 120, with about 60 patients randomized from each primary diagnostic grouping.

Follow-up Assessments

At 3, 6, 9 and 12 months, a blinded researcher (a research psychologist) will contact all patients over the phone and assist them in completing a range of assessment tools relating to the primary and secondary outcome measures. The research assistant who randomized the patients will contact patients in the intervention group by telephone at 6 months to get their views on the usefulness of the supportive text messages. All patients will be similarly contacted regarding their satisfaction with their treatment using a semi-structured questionnaire. At 12 months, data related to each patient's utilization of health services and their associated costs will be compiled from AHS administrative records by the blinded research associate.

Primary Outcome Measure

1. Mean changes in the BDI scores from baseline for those with a primary diagnosis of Depression

2. CAD from baseline (since discharge from the Residential Addiction treatment program) for those with primary AUD.

Secondary Outcome Measures for Patients With Primary AUD

1. Mean units of alcohol per drinking days for participants with AUD at 3, 6, 9 and 12 months, computed from self-reports.

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2. Mean number of days to the first drink for participants with AUD, computed from self-reports.

3. Number of hazardous drinking days (drinking in excess of the safe limits) from baseline for participants with AUD at 3, 6, 9 and 12 months, computed from self-reports.

4. Mean changes in the scores on the OCDS from baseline for participants with AUD at 3, 6, 9 and 12 months.

5. Mean changes in the scores on the Alcohol Abstinence Self-Efficacy Scale from baseline for participants with AUD at 3, 6, 9 and 12 months

Secondary Outcome Measures for Patients With Either Primary AUD or Primary Depression

1. Improved EQ-5D-5L scores from baseline. Health related Quality of Life will be measured in all groups at baseline, 3, 6, 9 and 12 months using the EQ-5D-5L (Canadian version).

2. Quantitative and qualitative data will be gathered from all participants in the intervention group using the semi-structured questionnaire in Multimedia Appendix 1 to assess their perceptions about how helpful or unhelpful the supportive text messages were to the course of their recovery.

Other Exploratory Outcome Measures

1. Frequency of health services utilization at 3, 6, 9 and 12 months will be computed from self-reports and compared to the AHS administrative data on the frequency of health services utilization. We will be able to determine the usefulness and accuracy of self-report health utilization data in comparison with administrative data. Self-report data has the benefit of being available immediately.

2. The cost of health services utilization for patients in the intervention and control groups using the AHS administrative data.

3. Number of days absent from work at 3, 6, 9 and 12 months will be computed from self-reports.

Statistical Methods

Since it is unlikely that this pilot study will be powered to detect sufficiently small clinically relevant differences, the primary purpose of the statistical analysis for this pilot study will be a thorough descriptive analysis of the data, with a view to understanding the amount and mechanism for any missing data. In particular one of the goals will be to determine the feasibility of long-term impact of supportive text message treatment and follow up in this population. An analysis of missing data may help to determine how to improve follow-up and retention of patients in the full study.

A secondary goal will be to examine the patterns of the longitudinal data, which will guide the planned analysis for a full study (e.g. using a Generalized Estimating Equation [GEE] approach or a generalized linear mixed models [GLMM] approach). In particular for each outcome measure we will look at the correlation between successive time points. Analyses will be done within each diagnostic group separately.

A final goal will be to produce summary statistics for the longitudinal data, which will provide estimates for future sample size calculations. A clinically meaningful difference has already been determined as in the stated hypotheses for the full study. From this pilot study we will be able to estimate the variability in the estimates that we would expect to see, which will help to guide the sample size estimation.

Results

We expect the results for the primary, secondary and exploratory outcome measures to be available within 18 months of project commencement. It is expected that the results will shed further light on the feasibility of using automated supportive text message interventions in long-term care for patients with Depression and AUD. The results of the pilot trial will also inform the implementation of a full-scale multicenter clinical trial.

Discussion

Implementation Strategy

Overview

This research proposes a novel intervention that addresses a critical gap in care for Depression and AUD patients and their health care providers. The research seeks to test the delivery of responsive, effective, cost-efficient care that transcends geographic boundaries and makes available important psychological supports that would otherwise be inaccessible or significantly burdensome for patients to use, given their physical location or position on a waitlist. There has been excellent front-line support for this initiative during trial development. As part of an integrated knowledge translation approach [22], discussions between our team and health care practitioners (health addictions therapists, counselors, and nurses), directors, clinical leads, primary care practitioners, and others involved with the treatment of this patient population have generated important insights into the logistics and potential impact of delivering care through text messaging. The implementation plan for the research will occur in the phases described below.

Pre-Implementation Phase

The involvement of patients in the creation of therapeutic text messages alongside health care providers is a critical precursor for the intervention. Patient-direct interventions can enhance both the uptake of innovations into clinical practice [23, 24] and ensure that care is aligned with patient needs and values [25]. Ethics clearance has been received from the University of Alberta Ethics Review Board and AHS has granted operational approval for the project to proceed. Assembly and training of human resources to manage and support the study will also commence in this phase. The knowledge-to-action framework, based on planned action theory will guide the development and implementation of the research [26]. Staff working in both study centers will be recruited as research associates and trained to use assessment tools by the principal investigator who is a practicing psychiatrist.

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The study will use internet-based text messaging infrastructure; our industry partner and AHS tech will be engaged at this stage to pilot test both the system and handsets to ensure full functionality and to troubleshoot potential issues in advance of the study commencement. Text message providers will be involved in testing and troubleshooting for potential issues. Advertisement of the research project targeted to patients will start, and communication about study commencement as well as tailored dissemination of study information to health care providers (general adult psychiatrists and primary care networks), zone leadership and operations will occur. Weekly, open research team meetings will commence during this phase to facilitate exchange, and to rapidly advance the work and/or troubleshoot as the need arises. The design of CBT and addictions-focused text messages will commence immediately between patients and practitioners. The intent of the text messages is to supplement therapist-patient interaction; therefore there will be a high degree of collaboration between patients and practitioners during this activity. Once the trial infrastructure is in place, a study commencement date will be determined and the research will be executed according to the details outlined in this protocol.

Implementation Phase

Implementation will commence with recruitment of patients who will undergo study orientation, baseline assessment, and data collection. The intervention will be randomized and delivered according to the methods outlined earlier. Scheduled, open research team meetings will provide a forum for practitioners who are supporting study participants. Given that the intervention is patient-focused, key measures arising from its use will be monitored as the study data is collected and assessed by the Trial Management Committee. Ongoing, scheduled communication between the recruitment sites and research team administrators will commence during this phase to support recruitment, address any challenges arising, and to optimize implementation. Feedback will be actively solicited from health care providers, zone leaders and operations through weekly open research team meetings and supplemented by brokering activity undertaken by research team staff. As the trial moves past the mid-study mark (and should trial data suggest it effective and feasible), discussions will commence concerning the scaling up of the intervention through a full-scale, multi-site randomized trial [27, 28, 29].

Behavior Change

The paradigm for behavior change using text messages as a patient-direct intervention is consistent with a CBT approach and addictions counseling principles. These approaches will be rigorously evaluated to detect potential impact during the course of the research. We intend to have a less direct impact on practitioner behavior with the adoption of texting as we anticipate texts will be a desirable part of the suite of treatment and counseling tools available to support their work. There is a high degree of interest in this modality within the practitioner community; as such, the bulk of our interaction time with practitioners and counselors will be used to encourage bi-directional linkage and exchange between these clinicians and the research team in support of study participants. Given the automaticity of the messages, we do not anticipate the need for interventions to specifically modify practitioner behavior per se; we anticipate that our main role with respect to the practitioners will be to ensure they are well-supported with the research, appropriately apprised of all aspects of the technology and message delivery, consistent with a robust, integrated knowledge translation approach.

Commitment

We are fortunate to have excellent commitment by administrative, clinical and operational-level leaders engaged and ready to implement the intervention. The possibility of increasing patient access and support, as well as addressing unmet patient health care needs during particularly critical periods is of great interest to the practitioner communities we have engaged thus far. There exist very strong relationships among practitioners, disciplines and programs in rural and remote areas of Alberta; we perceive a high level of team presence in meeting the needs of our patient group. We look forward to continuing to build meaningful, supportive relationships between our team and health care practitioners during the course of the trial, especially among primary care physicians and alcohol detoxification and treatment centers, in order to better serve the needs of this patient group. Our success in sustaining lasting impact is directly related to the relationships we engender among these important stakeholders. Given the automatic and less visual nature of the intervention, we have gathered together committed, dedicated research team staff to help foster strong relationship-building through deliberate linkage and exchange efforts.

Training

We are fortunate to have assembled a team of research associates comprising CBT and addiction counselors and permanent staff from the study sites to execute this research in partnership with our research team. The primary intent of our team composition is to match the expertise requirements of the research and to facilitate knowledge translation through capacity and relationship building. The team was assembled to achieve an optimal mix of both content-specific and cross-content training expertise that could provide pragmatic experiences and mentorship opportunities for all involved. Our aim is to enable the kind of integrative skills development that will be required of future health services, addictions and mental health, knowledge translation, and health economics researchers. The study team will use several tools in addition to regular open research team meetings, including an access-restricted SharePoint platform (to enable intra-team interactions and to asynchronously support the sharing of study information and expertise), email interactions and the use of tele-/video-conferencing as the need arises. This study is deeply embedded within the Addiction and Mental Health Strategic Clinical Network (SCN) for Alberta, and thus has access to an extended provincial, national and international network of research expertise in the area, should any unforeseen challenges arise. The reach of the SCN network also provides an excellent opportunity for collaborators, staff involved with the study, and trainees to link and exchange with other experts with an interest in Addictions and Mental Health.

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In developing the proposal, many important zone-level linkages were established with sites and practitioners in psychiatry and primary care. The research team and supports have made these relationships a key priority to enable the research and represent a deliberate effort to establish a strong foundation for bi-directional exchange that facilitates uptake and benefits patients. The opportunity to have hands-on experience with the implementation of patient-directed, technology-enabled change is a unique aspect of this study. As such, the team will encourage enduring capacity building by engaging clinicians, staff, operations and leadership through open invitations to attend and contribute to research meetings and training/dissemination events. As part of the end of project knowledge translation plan [30] and using the guidance of health care practitioners involved with the study, key messages will be developed from study findings for dissemination among all of the participating stakeholders. Finally, the research team will leverage the networking and dissemination opportunities offered through the SCN and those offered in partnership with provincial academic institutions in a way that is consistent with the nature and strength of the research findings. At the conclusion of the study, the team will host a knowledge exchange forum with patients, key stakeholders, decision makers, health care providers, and others, to share and encourage dialogue around the findings and, should the findings allow, as a way to explore opportunities for scaling up to a province-wide trial.

Dissemination of Study Findings

We chose the highest quality design available to evaluate the intervention using a randomized control trial design. This level of evidence does not presume, but will certainly facilitate the potential to generalize study findings across Alberta. Evaluation using metrics at the patient, provider, and system (economic) level will be employed. We intend to enhance the impact of this research by targeting the dissemination of research findings at several levels (i.e. patient, practitioners, academics/researchers, as well as the health care systems, and health care economics communities). Patients involved with the research will be invited to help develop key messages arising from the work and help determine the format and modality for delivery. We will utilize existing communication channels in rural and remote areas to disseminate findings to health care practitioners on the advice of representative knowledge users on our research team. The support of the Addiction and Mental Health SCN and provincial Alcohol Networks and Detoxification Centers will be leveraged to share findings, given the broad community of stakeholders engaged through the network. Results will be shared at the annual SCN Connections meetings to encourage the consideration of technology to augment care.

We will disseminate findings to academics and researchers through peer-reviewed journals and provincial, national and international academic forums. Depending on the nature and strength of our findings, the trial is likely to be replicated in other centers because this population is ‘high needs’ and ‘hard to reach’, and accessibility, acceptability and effective care, in particular, are difficult care standards to attain.

Finally, given that we recognize the potential to transform care in a sustainable way, we believe the findings will ultimately inform and support administrative decision making with respect to scaling of the intervention within the province of Alberta and potentially beyond. To this end, we will plan a deliberate organizational engagement strategy to advance discussions about feasibility and effectiveness prior to the conclusion of the trial. This will help ensure the findings are a relevant part of decision-making processes in a way that is aligned with study findings as they emerge. We anticipate that this may help smooth the path for scaling at both leadership and operational levels, so that the potential impact of the intervention can reach patients in a timely fashion.

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Authors' Contributions

VIOA conceived and designed the study. VIOA and KM wrote the initial draft of the manuscript. VIOA, KM, VYMS, MSR, MJ, IG, JK, ML, SD, AO and AG made significant contributions to the planning and design of the study and contributed to the revision of the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared

Multimedia Appendix 1

Patient survey: SMS text message AUD/depression relapse prevention study.

[PDF File (Adobe PDF File), 66KB - resprot_v4i2e55_app1.pdf]

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Abbreviations

AASES: alcohol abstinence self-efficacy scale
AHS: Alberta health services
AUD: alcohol use disorder
BDI: Beck depression inventory
CAD: cumulative abstinence duration
CBT: cognitive behavior therapy
GEE: generalized estimating equation
GLMM: generalized linear mixed models
HRQOL: health-related quality of life
SCN: strategic clinical network

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Protocol

The Effect of Mobile App Home Monitoring on Number of In-Person Visits Following Ambulatory Surgery: Protocol for a Randomized Controlled Trial

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Abstract

Background: Women's College Hospital, Toronto, Canada, offers specialized ambulatory surgical procedures. Patients often travel great distances to undergo surgery. Most patients receiving ambulatory surgery have a low rate of postoperative events necessitating clinic visits. However, regular follow-up is still considered important in the early postoperative phase. Increasingly, telemedicine is used to overcome the distance patients must travel to receive specialized care. Telemedicine data suggest that mobile monitoring and follow-up care is valued by patients and can reduce costs to society. Women's College Hospital has used a mobile app (QoC Health Inc) to complement in-person postoperative follow-up care for breast reconstruction patients. Preliminary studies suggest that mobile app follow-up care is feasible, can avert in-person follow-up care, and is cost-effective from a societal and health care system perspective.

Objective: We hope to expand the use of mobile app follow-up care through its formal assessment in a randomized controlled trial. In postoperative ambulatory surgery patients at Women's College Hospital (WCH), can we avert in-person follow-up care through the use of mobile app follow-up care compared to conventional, in-person follow-up care in the first 30 days after surgery.

Methods: This will be a pragmatic, single-center, open, controlled, 2-arm parallel-group superiority randomized trial comparing mobile app and in-person follow-up care over the first month following surgery. The patient population will comprise all postoperative ambulatory surgery patients at WCH undergoing breast reconstruction. The intervention consists of a postoperative mobile app follow-up care using the quality of recovery-9 (QoR9) and a pain visual analog scale (VAS), surgery-specific questions, and surgical site photos submitted daily for the first 2 weeks and weekly for the following 2 weeks. The primary outcome is the total number of physician visits related to the surgery over the first 30-days postoperative. The secondary outcomes include (1) the total number of phone calls and emails to a health care professional related to surgery, (2) complication rate, (3) societal and health care system costs, and (4) patient satisfaction over the first 30 days postoperative. Permutated-block randomization will be conducted by blocks of 4-6 using the program ralloc in Stata. This is an open study due to the nature of the intervention.

Results: A sample of 72 (36 patients per group) will provide an E-test for count data with a power of 95% (P=.05) to detect a difference of 1 visit between groups, assuming a 10% drop out rate. Count variables will be analyzed using Poisson regression. Categorical variables will be tested using a chi-square test. Cost-effectiveness will be analyzed using net benefit regression. Outcomes will be assessed over the first 30 days following surgery.

Conclusions: We hope to show that the use of a mobile app in follow-up care minimizes the need for in-person visits for postoperative patients.

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Trial Registration: Clinicaltrials.gov NCT02318953; https://clinicaltrials.gov/ct2/show/NCT02318953 (Archived by WebCite at http://www.webcitation.org/6Yifzdjph).

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KEYWORDS

mobile apps; randomized controlled trial, cost-effectiveness; ambulatory surgical procedures; ambulatory monitoring; technology assessment

Introduction

Background and Rationale

Women's College Hospital (WCH) in Toronto offers specialized surgical procedures, including breast reconstruction following mastectomy for breast cancer. The goal of surgery is to restore a breast mound and improve quality of life in survivors [1-3]. Patients often travel significant distances after choosing to undergo surgery at WCH. Increasingly, telemedicine is used to overcome the distance patients must travel to receive specialized care. Telemedicine is the use of medical information exchanged from one site to another via electronic communication to improve patients' health status [4].

Several countries with large rural populations have utilized telemedicine services to improve access to care. In India, telemedicine is used to follow postoperative patients with parathyroid disease and thyroid disease. Many of these patients live more than 1000 kilometers away from the tertiary hospital [4]. In Ecuador, a mobile surgical program utilizes telemedicine to provide routine preoperative and postoperative care and demonstrated improved resource utilization through elimination of redundant examinations and superfluous travel [5]. These studies demonstrate that it is possible to improve access to necessary services with cost- and time-savings to patients and providers.

Currently, Women's College Hospital is using a mobile app (QoC Health Inc, Toronto) to replace in-person follow-up care after surgery for breast reconstruction patients. A feasibility pilot study evaluating the quality of recovery at home using this mobile device has been completed. Preliminary findings suggest that mobile follow-up care adequately detects postoperative complications and is potentially cost effective from a health system perspective [6,7].

Breast reconstruction is an underused option, despite its well-known psychosocial benefits in breast cancer patients [2,8]. Recent studies suggest that low income and nonurban residence are associated with decreased rates of breast reconstruction [9]. Telemedicine data suggest it can join patients and providers separated by physical distance at a reduced cost to society [10-12]. By reducing costs to society, of which a component represents costs borne by patients, we hope to improve access to breast reconstruction among breast cancer survivors.

Knowledge to Date

Why Is Telemedicine an Important Initiative in Ontario?

The Ontario government has devised an action plan to change health care delivery so that it meets the fiscal challenges and needs of an aging population [13]. The Ontario Action Plan identifies technology as an opportunity to reduce the growth in health care costs and eliminate the barrier of distance. The action plan states that Ontarians should have access to the right care, at the right time, in the right place. This project speaks directly to these objectives by providing breast reconstruction patients with timely contact (the right time) with their surgeon (the right care) from the comfort of their home (the right place) [13]. This technology has the potential to address wait times by freeing up specialty surgeon clinic time to see new consults and non-urgent visits to the emergency department by providing direct surgeon contact.

Why Is an Elective Ambulatory Population Suitable for Telemedicine Follow-Up?

In general, morbidity and mortality following ambulatory surgery is exceedingly low [14]. This is more apparent in an ambulatory facility where various patient selection rules result in the treatment of largely American Society for Anesthesia (ASA) class I and II patients [14]. These patients are considered healthy or with mild systemic disease, respectively. Complication rates in this subset of breast reconstruction patients are approximately 5% [15]. Low complication rates mean that postoperative intervention is exceedingly unlikely. Previous studies have found that after a tonsillectomy or adenoidectomy, telephone follow-up care with standardized questionnaires is as safe as standard follow-up care and offers considerable cost reduction and patient convenience [16]. Similar telephone follow-up has also been used successfully in elective open hernia repairs and laparoscopic cholecystectomy [17]. Others have shown that planned outpatient appointments after uncomplicated surgery are neither necessary nor cost effective [18]. A "no planned follow-up" saves money for hospitals and patients. However, postoperative follow-up is valued by patients and important for the continuity of care [18]. In this way, telemedicine follow-up care offers a middle ground between conventional in-person follow-up care and no planned follow-up care.

Why Use the QoC Health Inc Mobile App?

The QoC Health Inc mobile app allows patients to submit photos and answers to a validated quality of recovery (QoR) questionnaire and Visual Analog Scale (VAS) for the first 30 days postoperative using their mobile device [19]. A feasibility study, including 30 breast reconstruction patients, showed once daily reporting was well tolerated even in the first week postoperative period. There were high levels of satisfaction with the mobile device and app (3.9/5) and low levels of anxiety in knowing that their surgeon was monitoring their recovery [6]. One wound infection and one early dehiscence was picked up using the mobile phone app, leading to immediate intervention.

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Surgeons were able to follow patient reports on a Web portal. Post-pilot surveys reported an overall positive experience. All patients attended the standard in-person follow-up care visit at 1 and 4 weeks postoperative. Surgeons felt that at least one early follow-up clinic visit could be eliminated when using the remote monitoring technology. This was an unexpected finding [6].

The following proposed catalyst study builds on this pre-existing data by actually eliminating one or more in-person postoperative follow-ups and performs a cost-effectiveness assessment. Demonstrating cost-effectiveness in an elective ambulatory postoperative population would promote its use in similar surgical settings.

Research Question

In postoperative ambulatory breast reconstruction patients at WCH, can we avert in-person follow-up care through the use of a mobile app compared to conventional, in-person follow-up care in the first 30 days following surgery?

Methods

Design Overview

This will be a pragmatic, single-center, open, controlled, 2-arm parallel-group superiority randomized trial comparing mobile app and in-person follow-up care over the first 30 days following surgery. Permutated-block randomization will be conducted by blocks of 4-6 using the program ralloc in Stata statistical software [20].

Study Setting

All study participants will be recruited from WCH. This has been an exclusively ambulatory hospital since September 2011, meaning that all surgical patients go home the same day or the next day after surgery. The Chief of Surgery (JS) at WCH was instrumental in developing this mobile app and is a champion of eHealth interventions. Due to physician interest, the app will be adapted for use in other surgical patient populations, including arthroscopic orthopedic, thyroid, and parathyroid surgical patients. WCH has the infrastructure to support research and to participate in knowledge dissemination and uptake activities.

Characteristics of Ambulatory Breast Reconstruction Patients

This patient population is female between 18-70 years of age. Due to the limited availability of breast reconstruction in Ontario [9], patients travel from all over Ontario to receive breast reconstruction. The types of breast reconstruction performed at WCH include immediate (ie, at time of mastectomy) or delayed reconstruction using one-stage reconstruction with alloderm and implants or two-stage reconstruction using expanders that are later exchanged for implants, immediate or delayed reconstruction using a pedicled transverse rectus abdominis myocutaneous flap or pedicled lattisimus dorsi flap, bilateral breast reduction, and fat grafting.

Common indications for breast reconstruction include breast cancer surgery, prophylactic mastectomy due to familial risk factors, and breast hypertrophy qualifying for breast reduction under OHIP (Ontario Health Insurance Plan).

All patients are within the ASA class I, II, and III representing patients with good health, mild systemic disease, and severe systemic disease, respectively. The majority of patients fall within ASA classes I and II. All patients are nonsmokers with a body mass index (BMI) ≤30. Approximately 50% of breast cancer patients receive pre-operative radiation with or without chemotherapy. These factors affect complication rates and therefore determine if the groups are balanced after randomization.

Selection Criteria

The inclusion criteria are patients undergoing breast reconstruction at WCH. They must be able to use a mobile device and communicate in English. The exclusion criterion are (1) patients who are smokers, because smokers carry increased rates of complication and both surgeons have a policy to solely operate on non-smokers (minimum smoke-free period of 1 month leading to surgery). Patients must not (2) suffer from chronic pain, (3) be taking narcotic (morphine-like) medication for pain on a regular basis, and (4) have an allergy to local anesthetics or morphine-like medications. Pain ratings captured in the VAS and QoR-9 are important for judging quality of postoperative recovery. Pre-existing pain or an inability to take narcotics would compromise the reliability of these measures.

Patients with hearing or speaking impairments will be accommodated with the help of translators. The person who regularly attends visits with the patient will facilitate this, or if no such person is available, we will use a hospital translator. All patients will receive an explanation of the study and the consent form in writing. All material will be understandable by patients with a grade 6 reading level. If our patients have lower than a grade 6 reading level, we will ask them if there is a family member at home who could assist them with the use of the mobile device.

Intervention

Eligible patients will be randomized in equal proportions (1:1) between mobile app and in-person follow-up care. All patients will receive what is currently the medical standard of care in this hospital. Patients in the conventional follow-up group will have a planned clinic follow-up at 4 weeks postoperative. This is the follow-up schedule currently used by both surgeons. At these scheduled follow-ups, patients will be asked to complete the VAS to assess pain and the QoR-9.

The mobile app follow-up group will have no planned in-person follow-up at 1 week and 4 weeks postoperative. However, these visits will be replaced with surgical site examination via submitted photos, VAS, and QoR-9 questionnaire monitoring. All of this information is submitted via the mobile app (QoC Health Inc, Toronto). Patient reporting will begin following discharge from the recovery room. Since 75% of complications occur within the first 2 weeks of discharge [21], we will use daily monitoring for 2 weeks and then weekly monitoring for 4 weeks. The data entered through the mobile phone app will reach a double-encrypted server. The surgeon will then use a wireless interface to access that data and monitor the patient's

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condition (not in real time). High pain scores will be flagged in the database for quick viewing. Any red flags will prompt in-person follow-up. Physicians will summarize the clinical findings recorded by the mobile app at 1 week and 4 weeks postoperative using the prototypical subjective, objective, assessment, and plan (SOAP) note.

Primary Outcome

The total number of physician visits (including specialist, family physician, and emergency department) related to the surgery. These data will be captured at 4 weeks after surgery.

Secondary Outcomes

The total number of health care telephone calls and emails (including specialist, family physician, and emergency department) related to the surgery will be captured at 4 weeks after surgery.

We will also record and report all complications occurring within the 30-day period. This was chosen based on literature surrounding postoperative complications in the first 30 days [21]. This will be captured at 4 weeks after surgery. The complication rate within this patient population is 4%, with 1% rate of reoperation. The most common complications are superficial skin infections managed with a short course of oral antibiotics. In the pilot study, all (1/30) superficial skin infections were picked up by the mobile phone app and antibiotic prescriptions were called in to the patient's local pharmacy [6]. Rare non-serious complications include seromas and wound dehiscence. All wound dehiscence (1/30) were picked up by the app in the pilot study. These both warrant a trial of conservative (watch-and-wait) therapy. After failed conservative therapy, seroma may be drained via ultrasound guided needle aspiration. Wound dehiscence may require surgical management under local anesthetic in the clinic or, if more involved, under regional anesthetic in the operating room. Rare and potentially serious complications include hematomas. If a hematoma is small and non-expanding, it can be managed conservatively (watch-and-wait). If it is larger and expanding, it may require urgent (<24 hours) evacuation in the operating room. This type of urgent situation presents to the emergency department, not to a clinic visit.

There is no potential for clinical compromise in the telemedicine group. If anything, superficial skin infections may be identified and treated earlier. Any study participant can schedule a face-to-face postoperative visit with the surgeon at any time; however it is anticipated that the mobile phone follow-up care will eliminate the need for one or more clinic visits. Devices may be returned to the clinic in-person or by standard mail.

A societal perspective will be adopted wherein all costs are assessed irrespective of the payer [22]. This perspective was chosen based on the US Panel on Cost-Effectiveness in Health and Medicine recommendations. This recommendation is meant to improve comparability and consistency across studies [23]. Furthermore, while a broad societal perspective will be adopted, results will also be presented using a narrower health system perspective that may be of key interest to health administrators and policy decision makers. This alternative perspective focuses on costs borne within the health system and excludes external costs as well as costs borne by patients and their caregivers.

Currently, there are no validated questionnaires that capture patient satisfaction with postoperative care. We have created a post-pilot survey that captures patient satisfaction with the care and information received. All answers are recorded using a 5-point Likert scale (Multimedia Appendix 1). We will also use the QoR-9 scores and VAS recorded at 4 weeks postoperative. Psychometric properties of the QoR-9 include convergent validity and discriminant construct validity. There is also good interrater agreement and internal consistency [24]. The test-retest reliability was 0.61 (P<.001). The preferred cut-off is 0.7; however, the QoR-9 was still favored over the QoR-40 due to its ease of use (<2 minutes required to complete the survey) [24].

Sample Size

The average breast reconstruction patient attends two in-person follow-up visits within the first month after surgery. If we assume that we can avert at least one in-person visit in the mobile app arm and that we have equal number of participants in both groups, we can use the E-test for count data to generate a sample size of 64 (32 patients per group) at a power of 95% (P=.05). The E-test is more robust and more powerful than the Conditional test (C-test) originally described to compare two counts. If we assume a 10% dropout rate, we will increase our sample size target to 36 patients per group.

Informed Consent

The Research Ethics Board (REB) at WCH and the University of Toronto will review the project proposal. Amendments will be made to appease both boards.

Ethical Considerations

Anonymity and confidentiality of potential and actual participants will be ensured throughout the investigation using standard procedures in place at the WCH and the University of Toronto. All consent forms, questionnaires, data files on disks, and field notes will be stored in a locked file that will be accessed only by the investigators. No identifying information will be stored in the analytic datasets. Participants will be identified only by a study number.

Privacy

Smartphone Transmissions

Patient data collected using the mobile app was double encrypted on the server and the phone. All patients will be informed how to password protect their phone. Designed from the ground up to ensure security and privacy, the app conforms to leading health care audit and interoperability standards including Personal Health Information Protection Act (PHIPA), Health Level Seven International (HL7), Information Technology Infrastructure Library (ITIL), and Statement on Auditing Standards 70 (SAS70). Multiple layers of encryption, including resting state Advanced Encryption Standard (AES) encryption, in transmission content encryption using unique per patient public / private key pairs, and in transmission Transport Layer Security / Secure Sockets Layer (TLS/SSL) protocol encryption

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were applied to maintain the highest level of patient confidentiality as possible. Modern infrastructure design leveraging distributed infrastructure as a service (IaaS) and software as a service (SaaS) cloud computing services for seamless accessibility, redundancy, and scalability were also utilized.

Research Study Data Storage

Access is restricted to the locked filing cabinets in the investigator's office, no identifiers will be included on data sheets (only identification numbers will be used), and password-protected databases will be used. Data will be stored on a password-protected, double-encrypted, secure server. Any data stored on a mobile device (eg, universal serial bus [USB] key) will be encrypted as per WCH policies. All de-identified data will be stored for 5 years past publication and will be destroyed by shredding. The physicians will keep patient charts for the standard time period.

Risks

There are no major identified risks from participation in this study. The "risks" of using a mobile phone or tablet device are (1) the timing of diagnosis of a complication since there is a 4% risk of complication following surgery [15], and participating in mobile versus in-person follow-up care may have an impact on the timing of diagnosis of complication; (2) security issues due the risk that someone could steal and possibly break into the contents of the phone; however, the mobile phones used in this study are double encrypted and password protected, and information is transmitted in accordance with Canadian's Personal Information Protection and Electronic Documents Act; (3) the risk of injury from dropping the mobile phone on a foot or surgical wound, using the mobile phone while driving or operating machinery, distraction during other tasks, mobile phone overuse syndrome, and repetitive strain injury; however, the time required for the response is approximately 5 minutes; and (4) anxiety arising through possible complications from surgery, or possible loss of or damage to the device.

Perceived Undue Influence

Patients will be generally informed about the study by their surgeon (JS or MB). The study coordinator and researcher (KA) will be responsible for the formal study explanation and informed consent process. These two people are in no way involved in the direct care of patients. All patients will be informed that their care will be in no way compromised if they choose not to participate. All patients will be informed of their ability to leave the study at any time.

Recruitment Procedures

All patients presenting for breast reconstruction will be screened for inclusion in the study. We will consecutively approach patients to participate in the study. A member of the health care team will inform patients about the study prior to surgery. If interested in participating, a study coordinator or researcher (KA) will introduce the patient to the technology so that they can better judge what is required of them. This will include introduction to the QoR-9 and VAS score on the mobile app (see Multimedia Appendix 2). The patients will be assured of their ongoing surgical care regardless of their participation. Patients who agree to participate will review and sign the appropriate consent form. They will have the opportunity to discuss the study with the attending surgeon. Written consent will be obtained for all prospective patients. After the patient has consented to the trial, they will be randomized to the mobile app or in-person follow-up arm using the program ralloc in Stata statistical software [20].

The mobile app follow-up care stream will receive an instruction sheet detailing how to use the app. The patient will receive training on how to use the app from the study coordinator or researcher (KA). The patient will be given a mobile phone on the day of surgery and will review the use of the mobile app again at this time. This will also help the patient judge what is required of them and serve as an opt-out point.

Data Collection Overview

The QoR and VAS pain scores will be collected from all patients at 4 weeks after surgery (see Figure 1). The in-person study group will perform this via telephone interview, and the mobile app group will perform this via mobile app. Our study coordination or researchers (KA) will collect all telephone questionnaires at 4 weeks after surgery. These persons will administer the questionnaire capturing email, telephone and in-person encounters, postoperative complications (Multimedia Appendix 3), and the cost survey (Multimedia Appendix 4). They will also administer the post-pilot survey capturing patient satisfaction (Multimedia Appendix 1) at 4 weeks after surgery. The study coordinator or researcher (KA) will attempt to contact every patient four times over the 4th week after surgery.

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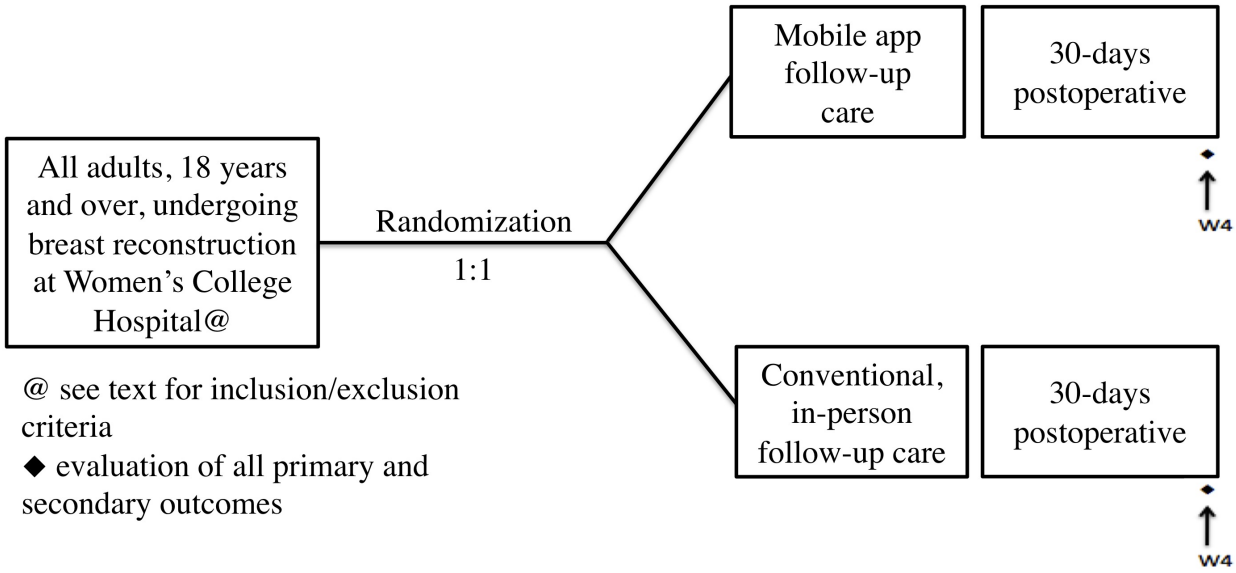
Figure 1. Data collection overview diagram.



Measuring Outcome Variables

Primary Outcome

The total number of physician visits (including specialist, family physician, and emergency department) related to the surgery will be captured at 4 weeks after surgery by the study coordinator over telephone (see Multimedia Appendix 3).

Secondary Outcomes

The total number of health care telephone calls and emails (including specialist, family physician, and emergency department) related to the surgery will be captured at 4 weeks after surgery by the study coordinator over telephone (see Multimedia Appendix 3).

All complications will be recorded including infection, seroma, hematoma, and wound dehiscence. Among patients who receive tissue expanders, deflation is another possible complication. These complications will be collected via telephone survey at 4 weeks postoperative (see Multimedia Appendix 3).

Both mobile app and conventional follow-up patients at 4 weeks postoperative will complete our cost survey (Multimedia Appendix 4). The survey will collect data necessary to conduct cost estimates (presence of caregiver at time of follow-up, overnight hotel stays prior to clinic visit, etc).

For the purposes of this study, patients will receive a managed (loaner) mobile phone; however, a bring-your-own-device model is a more scalable solution and will be represented in the cost-effectiveness data [25].

In-person follow-up costs include foregone leisure time or income for the patient and foregone income for the caregiver, travel, and overnight hotel stay and parking costs associated with follow-up visits. Our cost survey (Multimedia Appendix 4) will collect information on caregiver presence at appointments, overnight hotel stays prior to appointments, total time commitment of in-person follow-up, and return to work information. In the literature, leisure time is often valued more than foregone income because subjects are choosing to forego their income for that leisure time. We will equally weight foregone income and leisure time, as patients are not choosing to be off work. They are off work because of a medical condition. We will determine foregone income based on average Ontario wages for a given age and sex of the patient. We will determine travel costs based on distance from home postal code to WCH.

Mobile phone follow-up costs include the foregone leisure time to submit follow-up data and the cost of data submission. We will determine foregone leisure time based on questionnaire time stamps from software records. Patient training sessions are held while patients are waiting for their preoperative appointment. There are no additional patient costs associated with this time.

In-person follow-up costs related to the health care system include the overhead (lighting, heating), physician fee, staffing costs including registrars, administrative assistance, nursing, and housekeeping. Two registrars service 32 clinic rooms. One administrative assistant and nurse is assigned to each breast reconstruction follow-up clinic. A follow-up clinic generally runs for 5 hours and serves 20 patients. WCH will provide hourly overhead and staffing costs, and OHIP billing codes will provide physician fees.

Mobile phone follow-up costs related to the health care system include the start-up costs of establishing assessment questionnaires for the patient populations to be monitored. This cost is based on the number of assessment questionnaires that need to be designed based on the diversity of the surgical population (eg, orthopedic versus general surgery patient monitoring). The QoC Health Inc mobile app can be loaded onto Android or iOS (Apple) smartphone or tablet. Formal training costs include the salary of the instructor from QoC

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Health Inc and the hourly salary of 1 administrative assistant, 1 postoperative ambulatory care unit nurse, and 2 physicians being trained. All staff turnover is >5 years; therefore, these costs will be amortized over 5 years. Current e-assessment OHIP physician billing codes are limited to dermatology and ophthalmology. There is no OHIP billing code for the postoperative or surgical e-assessment. The cost of software for the physician and patient and associated technical support is $3.50 (CAD) per patient per day [7]. There is discounting for hospitals based on how many patients are enrolled. Costs associated with patient training sessions include the administrative assistants' hourly salary. The data required to send the smartphone assessment is equivalent to one email transmission.

Externally borne in-person follow-up costs include lost labor force once an individual has returned to work. In the cost survey (Multimedia Appendix 4), we will ask patients when they returned to work. We will add lost labor force costs to the in-person follow-up visits among patients who had returned to work using average Ontario wages based on the age and sex of the patient.

Patient satisfaction will be measured at 4 weeks after surgery using the post-pilot survey (Multimedia Appendix 1). The study coordinator will administer this over the telephone. The QoR-9 scores will be recorded at 4 weeks after surgery using the mobile app at home or a tablet during a scheduled clinic visit, depending on the patient's study arm.

Measuring Predictor Variables

Age impacts foregone wage estimates, and postal code impacts travel cost estimates. The type of surgical procedure, ASA classification, BMI, and preoperative radiation impacts rates of successful surgery at 30 days postoperative. Therefore, these variables are considered potential predictors of cost-effectiveness.

Timeline

Any given patient may be recruited for the study up to 2 months prior to their surgery date. They will participate in the study for a total of 1 month following their surgery. Set-up and REB approval (1-2 months); a concurrent enrollment and data collection period to attain the required study participants (4-5 months); merging, cleaning, and debugging (1 month); and development of value messages for decision-makers and knowledge dissemination activities (2 months). This study will require approximately 1 year for completion. Its precise duration depends on the patient enrollment rate.

Intervention Assignment Procedures

Randomization Strategy

All enrolled participants will be randomized to receive either the mobile app or conventional, in-person follow-up care in a ratio of 1:1 after giving informed consent for the study.

Sequence Generation

A block randomization scheme with variable block size will be generated using Stata ralloc [20]. This will ensure approximately equal sample size and that participants and study staff cannot anticipate assignment to either group. Treatments will be allocated in a 1:1 ratio. All study investigators and staff will be blinded to the block number, block size, and sequence in the block. The treatments will be assigned via pre-prepared sealed, opaque envelopes, and the envelopes will be ordered in the sequence of treatment assignments generated by the Stata code. Once eligibility for randomization has been determined, the first available allocation envelope will be assigned to the study subject. The subject will be randomized to the treatment arm indicated inside the envelope.

Allocation Concealment

As potential subjects are identified, a research assistant will be notified to assess eligibility. Once a subject is deemed eligible for enrollment, has given the necessary informed consent, has been enrolled, and has had her demographic information abstracted from her clinic records, the research assistant will issue the next in a series of sequentially numbered, sealed, opaque envelopes containing group assignment. The participant's clinic number will be written on the envelope, and the participant will be required to open and read the treatment assignment in the presence of the research assistant, who will then enter the group assignment into a database and store the envelope. If a participant is unable to read, the research assistant will read the group assignment on her behalf.

Implementation of Randomization Procedures

A biostatistician (BZ) assigned to the study from the Institute of Health Policy, Management and Evaluation will carry out randomization procedures. The biostatistician will not be involved in any other aspects of conducting the study. The sequentially numbered, opaque, sealed envelopes containing group assignment will be given to the study coordinator. The study biostatistician will retain the key to treatment assignments. The study coordinator will be on site every day to ensure compliance with the study protocol.

Results

Data Analysis Plan

Descriptive statistics (frequencies, means, standard deviations) will be calculated for all clinical and outcome variables. All data obtained in this study will be entered into Excel and analyzed using Stata 13.

Poisson Regression

We will use person-level Poisson regression to determine if there is a difference in the number of visits attended between patients in the mobile app and in-person follow-up arm.

Net Benefit Regression

We will perform a person-level net benefit regression to determine the cost-effectiveness of this intervention. We will define cost as all societal costs incurred over the 30 days after surgery. We will define effect as the rate of complication over the 30 days after surgery. We will regress net benefit (dependent variable) on study arm, age, distance from home to hospital (km), BMI, BMI^2, ASA classification, radiation status, and major or minor procedure (independent variables). Net benefit,

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age, distance, BMI, and BMI^2 are continuous variables. ASA classification is a categorical variable. Study arm, radiation status, and major or minor procedure are binary variables (1=mobile app; 0=in-person and 1=yes, 0=no), where:

$nb = B0 + B1(TX) + B2(age) + B3(km) + B4(BMI) + B5(BMI^2) + B6(ASA) + B7(radiation) + B8(major/minor)$

We will perform regression diagnostics and use these diagnostics to advise on the use of parametric versus non-parametric generation of 95% confidence intervals. We will use our net benefit regression to generate an incremental net benefit (INB):

$INB = WTP * (effect_i – effect_c) – (cost_i – cost_c)$, where:

$effect_i$ = mean effect of the intervention, ie, rate of complication in the mobile app arm at 30 days

$effect_c$ = mean effect of the control, ie, rate of complication in the in-person arm at 30 days

$cost_i$ = mean cost of the intervention, ie, societal costs from baseline to 30 days

$cost_c$ = mean cost of the control, ie, societal costs from baseline to 30 days

In this situation, where willingness to pay is unknown, we assigned numerous values for willingness to pay and generated a cost-effectiveness acceptability curve (CEAC) based on these theoretical values [26]. The CEAC illustrates the probability that the intervention is cost-effective by graphing the probability that B1>0 as a function of willingness to pay (WTP) [27].

Handling Missing Data

We will generate “best” and “worst” case scenarios for the missing data to determine if there is any change in findings.

Discussion

Relevance

At Women’s College Hospital, over 5000 elective ambulatory surgeries are performed each year. These numbers are small compared to other hospitals, such as the nearby Trillium Health Center, where over 20,000 surgeries are performed annually. These numbers will continue to grow as we follow trends in the United States where currently 60-70% of the surgical procedures are performed in the ambulatory setting [28]. Smartphones are becoming ubiquitous throughout Ontario. Using such an ubiquitous technological platform to reduce health care costs for patients and providers in an already large and growing patient population is in concordance with the Ontario Action Plan. Telemedicine is identified as a way to improve access to specialty care among underserviced communities [29]. Breast reconstruction is an underused option for patients, despite its well-known psychosocial benefits in breast cancer patients [2,8]. In fact, Canada underperforms next to countries like England and the United States. Particularly, low income and nonurban residence is associated with decreased rates of breast reconstruction [9]. By reducing costs to society, of which a component represents costs borne by patients, and eliminating the barriers of distance, telemedicine can improve access to breast reconstruction among breast cancer survivors.

Telemedicine literature is often criticized for its lack of rigorous economic evaluation [28]. In assessing the cost-effectiveness of mobile phone follow-up, we will determine general parameters that are necessary to make a telemedicine postoperative follow-up program more cost-effective. Upcoming telemedicine pilot programs can model costs around these general parameters.

Knowledge Translation Plan

The study findings will yield information relevant to clinicians, hospital administrators, and decision makers regarding support and investment in telemedicine follow-up technology. If the mobile phone app (QoC Health Inc, Toronto) is demonstrated to be cost-effective, this would support its dissemination among other divisions of ambulatory surgery, including orthopedic and general surgery. It will advise policy decision makers and managers at the regional and local level regarding who are responsible for feasibility assessment, resource allocation, program design, and quality improvement. Several knowledge dissemination activities are planned. Dissemination activities will be pursued initially in the Greater Toronto Area, and eventually, nationally to ensure that the research findings reach a broad audience. To enhance knowledge dissemination, a user-friendly report will be produced using the standard 1:3:25 format recommended by the Canadian Health Services Research Foundation (1 page of key messages for decision makers; a 3-page executive summary; and a 25-page final report written in an accessible language).

Knowledge Translation Among Health Care Providers

Locally, we will submit our findings for presentation at Gallie Day at the University of Toronto. Gallie Day attracts surgeons from all fields at the University of Toronto. Surgeons who attend this event tend to have a hand in either research or hospital administration. They work at various hospitals throughout the Greater Toronto Area. And we will present our findings at the American Society of Plastic Surgery Annual Meeting. This meeting tends to draw as many Canadians as the Canadian Society of Plastic Surgery Annual Meeting, as well as American and international plastic surgeons. This is a suitable population for dissemination as most plastic surgeons perform a large quantity of elective ambulatory surgeries. We will aim for publication in *Canadian Medical Association Journal* or *JAMA Surgery*. These journals attract a breadth of readers that include plastic surgeons and other types of ambulatory surgeons.

Knowledge Translation Among Administrators and Policy Decision Makers

We will submit our findings for presentation at the Ontario Hospital Association Conference and Health Achieve conference. These conferences tend to attract administrators and policy decision makers. Findings will be further communicated nationally through use of various listservs.

To facilitate the research process and to enhance involvement, 2 or more members of the team meet weekly. Such meetings foster communication and progress. The clinicians (JS and MB)

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on our team are enthusiastic to improve ease of follow-up with telemedicine. They have indicated that they are ready to champion research results within their respective organizations by narrowing the gap between evidence and action, and they wish to be proponents of evidence-informed decision making for the system and policy environment.

Limitations

There are three main study limitations. First, the timeline of data collection is limited to the first 30 days postoperatively. This reference was based on literature around the first 30 days postoperative. Studies reveal that the 2-week period after hospital discharge is the most vulnerable time and 75% of complications show up within 14 days of discharge [21]. Complications (eg, capsular contracture) beyond 30 days represent the minority; we will minimize bias by using the same timeline of data collection in both the telemedicine and conventional follow-up group.

A second limitation lies in the potential generalizability of the findings. Study participants will be drawn from those receiving ambulatory breast reconstruction at WCH, and consequently, the findings may not necessarily generalize to patients receiving in-patient breast reconstruction (eg, bilateral deep inferior epigastric perforator [DIEP] flap). However, the populations served are quite diverse in terms of their clinical, demographic, and regional background, which may help to improve generalizability to elective ambulatory surgery patients including the majority of breast reconstruction performed in the community. In addition, because only female English-speaking participants without psychiatric condition or chronic pain syndrome will be recruited, the findings may not be generalizable to certain populations (eg, non-English speaking).

A third limitation surrounds self-reporting and estimating costs. We will rely on in-person follow-up patients to provide us with estimated time of travel from home to clinic and back to home. We will limit bias by correlating this with distance from clinic information based on postal code. We also must rely on average wage estimates from Statistics Canada and average travel costs from Canadian Automobile Association. These estimates are commonly used in cost-effectiveness literature.

Conclusion

This study will determine if mobile app technology can be used to replace in-person follow-up care after ambulatory surgery. Such replacement may have multiple secondary ramifications including cost-effectiveness and patient satisfaction.

Acknowledgments

This trial is funded by a Canadian Institutes of Health Research (CIHR) e-Health Catalyst Grant.

Conflicts of Interest

QoC Health Inc is a private innovation group that has developed the software platform used in this study. QoC Health Inc is the sole owner of the technology. JS is part owner of QoC Health Inc. Women's College Hospital is a demonstration partner/site for this project. The REB at Women's College Hospital has reviewed and made recommendations pertaining to a Conflicts of Interest Management Plan.

Multimedia Appendix 1

Post-pilot satisfaction survey capturing patient satisfaction with care and information provided for all patients, to be completed by all patients at week four.

[PDF File (Adobe PDF File), 101KB - resprot_v4i2e65_app1.pdf]

Multimedia Appendix 2

QoR9 and Pain VAS.

[PDF File (Adobe PDF File), 176KB - resprot_v4i2e65_app2.pdf]

Multimedia Appendix 3

Telephone questionnaire capturing email, telephone and in-person encounters and postoperative complications. All patients will complete this at week four.

[PDF File (Adobe PDF File), 97KB - resprot_v4i2e65_app3.pdf]

Multimedia Appendix 4

Telephone questionnaire capturing patient costs, to be completed by all patients at week two and week four.

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Multimedia Appendix 5

CIHR reviewer comments.

[PDF File (Adobe PDF File), 257KB - resprot_v4i2e65_app5.pdf]

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Abbreviations

ASA: American Society for Anesthesiologists
BMI: body mass index
CEAC: cost-effectiveness acceptability curve
INB: incremental net benefit
OHIP: Ontario Health Insurance Plan
QoR: quality of recovery
QoR-9: Quality of Recovery-9
QoR-40: Quality of Recovery-40
REB: Research Ethics Board
VAS: visual analog scale
WCH: Women's College Hospital
WTP: willingness-to-pay

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Protocol

“Everybody Brush!”: Protocol for a Parallel-Group Randomized Controlled Trial of a Family-Focused Primary Prevention Program With Distribution of Oral Hygiene Products and Education to Increase Frequency of Toothbrushing

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Abstract

Background: Twice daily toothbrushing with fluoridated toothpaste is the most widely advocated preventive strategy for dental caries (tooth decay) and is recommended by professional dental associations. Not all parents, children, or adolescents follow this recommendation. This protocol describes the methods for the implementation and evaluation of a quality improvement health promotion program.

Objective: The objective of the study is to show a theory-informed, evidence-based program to improve twice daily toothbrushing and oral health-related quality of life that may reduce dental caries, dental treatment need, and costs.

Methods: The design is a parallel-group, pragmatic randomized controlled trial. Families of Medicaid-insured children and adolescents within a large dental care organization in central Oregon will participate in the trial (n=21,743). Families will be assigned to one of three groups: a test intervention, an active control, or a passive control condition. The intervention aims to address barriers and support for twice-daily toothbrushing. Families in the test condition will receive toothpaste and toothbrushes by mail for all family members every three months. In addition, they will receive education and social support to encourage toothbrushing via postcards, recorded telephone messages, and an optional participant-initiated telephone helpline. Families in the active control condition will receive the kit of supplies by mail, but no additional instructional information or telephone support. Families assigned to the passive control will be on a waiting list. The primary outcomes are restorative dental care received and, only for children younger than 36 months old at baseline, the frequency of twice-daily toothbrushing. Data will be collected through dental claims records and, for children younger than 36 months old at baseline, parent interviews and clinical exams.

Results: Enrollment of participants and baseline interviews have been completed. Final results are expected in early summer, 2017.

Conclusions: If proven effective, this simple intervention can be sustained by the dental care organization and replicated by other organizations and government.

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Trial Registration: Trial Registration: ClinicalTrials.gov NCT02327507; http://clinicaltrials.gov/ct2/show/NCT02327507 (Archived by WebCite at http://www.webcitation.org/6YCIxJSor).

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KEYWORDS

oral hygiene; toothbrushing; dental devices, home care; dental care; communication; social support

Introduction

The Importance of Brushing Teeth Twice a Day

Dental caries is a disease with marked socioeconomic and regional disparities. In Oregon, untreated tooth decay is twice as common in low-income children than in children from higher income families (25% vs 13%) [1]. Similarly, almost three-quarters (73%) of 6 to 9 year old children in rural Central Oregon experience tooth decay, while the statewide average is 52% [1]. Dental caries can be prevented through regular toothbrushing with fluoridated toothpaste [2-5]. The American Academy of Pediatric Dentistry and the American Dental Association recommend that toothbrushing should be performed twice daily with a fluoride toothpaste and a soft toothbrush initially by the parent, and eventually by the child [6,7]. Relatively few parents and children fully follow this recommendation [8].

Successful behavioral interventions focus on helping people acquire skills and motivation to change behavior; they are sustained and comprehensive; and, they engage peers and family members to help maintain motivation [9]. Toothbrushing beginning in infancy is a good candidate behavior. It is similar to other mildly intrusive caregiving behaviors that parents accept learning, and infants grow to tolerate. Parents' confidence to carry out this behavior is the best predictor of being caries free at age 4 [10,11]. Once established, childhood toothbrushing habits persist [12,13], but need to be reinforced.

Toothbrushing promotion programs that provide advice, free toothpaste, and toothbrushes at a child health visit and/or by mail have shown positive effects on parents' behaviors, including the frequency of twice daily toothbrushing of their children [14]. When accompanied by social support and in-person instruction, toothbrushing promotion programs show decreases in childhood caries and improved oral hygiene [15-17]. A program similar to that designed for the intervention study described here led to increased frequency of toothbrushing at home [17], and a 30% reduction in tooth decay [16].

Aims and Objectives

Our aim is to design, deliver, and evaluate the "Everybody Brush!" program, a quality improvement effort of Advantage Dental Services, LLC for children and adolescents enrolled in Medicaid and their families in Central Oregon. Our primary objective is to determine if the intervention is effective in reducing restorative dental care treatment and increasing the percentage of parents who report twice daily toothbrushing of their child's teeth. This objective reflects key evidence-based recommendations of brushing teeth with fluoride toothpaste (evidence level I) twice a day (evidence level IV). Our secondary objectives are to investigate if the intervention is effective in improving oral health and oral-health related quality of life and reducing dental care costs.

This protocol follows the SPIRIT [18] and Consolidated Standards of Reporting Trials (CONSORT) statements [19] and relevant extensions [20]. The main research question is, "Does the distribution of free toothpaste and toothbrushes with behavioral psychosocial health messages and telephone support, compared with distribution of free toothpaste and toothbrushes alone or no intervention, improve home toothbrushing behavior and reduce the restorative care of children of low-income families?".

Methods

Design, Setting, and Selection of Participants

The study design is a parallel-group randomized controlled trial. The setting is three counties in rural Central Oregon (Crook, Deschutes, Jefferson).

Eligibility and Recruitment

Selection of Participants

The study population will be approximately 20,000 families who are residents of the three county study setting, whose children/members are enrolled in the Oregon Health Plan and served by a single dental care organization. Inclusion criteria will be: (1) children less than 21 years old; (2) enrollment in the public health insurance program, Oregon Health Plan (Medicaid), and served by a single dental care organization, Advantage Dental Services, LLC; and (3) children whose home address is located in the three selected counties.

Recruitment

Participants will be identified through an electronic search of the enrollment database of Advantage Dental Services. All Advantage Dental Services members meeting the eligibility criteria will be included. The intervention will be delivered to all children less than 21 years old, but the evaluation of parent-reported twice daily toothbrushing and dental caries outcomes will focus on children less than 36 months old. Advantage Dental Services decided to focus on these children because of the Healthy People 2020 objective OH-1.1 to, "Reduce the proportion of children age 3 to 5 years with dental caries experience", the belief in the lifelong benefit of establishing toothbrushing habits in early childhood, and the cost implications of providing care for children this age who experience tooth decay. Because of all this, a random subsample of parents/caregivers of children less than 36 months old and a random subsample of children less than 36 months old will be recruited. Parents/caregivers of children less than 36 months old to be interviewed will be recruited through telephone calls.

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Children less than 36 months old to be clinically examined will be recruited at community settings such as Head Start and the Special Supplemental Nutrition Program for Women, Infants, and Children. The parents/caregivers will have the quality improvement project explained to them and have the opportunity to opt out of the evaluation.

The University of Washington Institutional Review Board reviewed this study. Consistent with US Federal regulations, participants of this quality improvement project do not meet the criteria to be considered research subjects. University of Washington personnel will have access only to deidentified data.

Randomization and Blinding

Families will be randomized with equal probability to one of three study conditions using computer-generated random numbers. A biostatistician at the University of Washington using a dataset containing only family identification codes and without personal identifying information will generate the allocation schedule for random assignment. The treatment allocation for each participant will be kept in Seattle, and the biostatistician will reveal the treatment allocation to local investigators when they are ready to implement the program. Personnel involved in the delivery of the intervention and trial participants will not be blinded to group allocation. Interviewers will be blinded to group allocation.

Intervention

The goal of the intervention is that parents will brush their young children's teeth and older children and adults will brush their own teeth twice a day with fluoridated toothpaste. Our strategies to promote this behavior reflect the integrative model of health behavior of Fishbein et al [21] and expansions by Michie et al, Michie et al, and Cane et al [22-24] (Table 1). These guides to the processes that govern health behavior were proven useful in a prior small-group intervention we designed, tested, and found to be successful to increase parents' frequency of brushing their preschool-age children's teeth. In that study of 67 families, the intervention components rated most highly by parents were the provision of free toothbrushes and toothpaste for all members of the family, hands-on instruction in how to brush a child's teeth, and tips to overcome a child's resistance and make toothbrushing "fun" [25]. In the formative work that led to the intervention's design, we found parents who brushed their children's teeth twice a day were more likely to describe using specific skills to overcome barriers, have high self-efficacy for toothbrushing, and have high self-standards for establishing it as a routine. In contrast, parents who brushed their children's teeth less than twice daily were more likely to hold negative or false beliefs about the benefits of twice daily toothbrushing, report little normative pressure or social support for the behavior, have lower self-standards, describe more external constraints, and offer fewer ideas to overcome barriers [8].

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Table 1. Mapping of the components of the "Everybody Brush!" intervention to the theoretical domains, intervention functions, and behavior change techniques.

Intervention component	Theoretical domain	Intervention function	Behavior change technique
Toothbrushing supplies (kit)			
7 toothpastes and 7 toothbrushes	Environmental resources	Enablement	Adding objects to the environment
Toothbrushing supplies helpline			
Request more toothbrushing supplies by telephone	Environmental resources	Enablement	Adding objects to the environment
Toothbrushing advice helpline			
Receive advice on safety, amount, technique, how to overcome barriers and make it fun	Knowledge, physical skills, cognitive skills, beliefs about capabilities, and beliefs about consequences	Education, incentivization, and persuasion	Instruction on how to perform the behavior, information about health consequences, information about emotional consequences, goal setting, problem solving, action planning, restructuring the physical environment, and restructuring the social environment
Health promotion messages via mail and telephone			
Postcard #0 (cling sheet)			
Brush 2 times every day, a tiny smear for baby, a pea size for ages 2 years to adult, use fluoride toothpaste to prevent decay, and you don't need a lot of toothpaste to make it work	Physical skills, beliefs about consequences	Training, education	Goal setting, instruction on how to perform the behavior
Postcard #10 (thank you)			
The best way to promote oral health and prevent tooth decay is by brushing teeth with fluoride toothpaste every day two times a day. This simple step has been proven to be effective in promoting oral health and reducing tooth decay and dental care costs.	Knowledge, beliefs about consequences	Education, incentivization, coercion	Goal setting, information about health consequences, credible source, behavior cost
Message #1 (brush front and back)			
Brush the front and the back of all the teeth. Roar like a lion to reach the back of all the teeth. Say "Chee-tah!" to reach the front and sides.	Physical skills	Training	Instruction on how to perform the behavior
Message #2 (take turns)			
Take turns brushing... your child practices brushing first and then you do it to make sure all the teeth are brushed.	Cognitive skills	Training	Problem solving
Message #3 (sleepy)			
Brush in the evening after snacks before your child gets too sleepy.	Cognitive skills	Environmental restructuring	Action planning, restructuring the physical environment
Message #4 (bathtub)			
You can brush your child's teeth in the tub! It's fun!	Cognitive skills, emotion	Environmental restructuring	Action planning, information about emotional consequences, restructuring the physical environment
Message #5 (silly song)			

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Intervention component	Theoretical domain	Intervention function	Behavior change technique
Sing a favorite song while brushing!	Cognitive skills, emotion	Environmental restructuring	Distraction
Message #6 (role model)			
Brush your teeth with your child. You are the best role model.	Identity	Modeling	Identification as role model
Message #7 (party, party)			
Have a family toothbrushing party!	Emotion	Persuasion	Restructuring the social environment
Message #8 (try, try again)			
Everyday is a new day to brush... twice a day!	Beliefs about capabilities, optimism	Persuasion	Verbal persuasion about capability
Message #9 (consequences)			
Brushing makes your mouth smell fresh.	Emotion, beliefs about consequences	Persuasion	Information about emotional consequences

Test Condition

Components of the Intervention

Participants will receive all five components of the intervention: (1) a toothbrushing kit containing supplies and a single-page instruction sheet sent by mail to families' homes; (2) a toll-free telephone helpline to request more toothbrushing supplies; (3) postcards with brief messages addressing common barriers and support for toothbrushing; (4) automated calls to parents' telephones repeating these same health promotion messages; and (5) a toll-free telephone helpline to provide toothbrushing advice. Each of these components was designed in English and Spanish.

The Toothbrushing Kit

The kit contains supplies for adults and for children, specifically 7x .85 oz. tubes of toothpaste (1500 parts per million sodium fluoride), 3 adult-size toothbrushes, 1 toothbrush each for a child ages 4-24 months, 2-4 years, and 5-7 years. This quantity was chosen because the average family served by Advantage Dental Services has 3 or 4 children. In addition to the supplies, the kit includes a single-page removable "cling sheet" with instructions to brush twice a day with an age-appropriate amount of fluoride toothpaste depicted by illustration, and information about how to request additional supplies if needed. Each family receives three kits over the 9-month intervention period.

Toothbrushing Supplies Helpline

A toll-free number for requesting more toothbrushing supplies is included on all toothbrushing kits mailed to families. Bilingual, culturally competent Advantage Dental Services staff members manage the supplies helpline.

Toothbrushing Promotion Message Postcards

We created 9 health messages. The messages reflect three sets of factors known to influence health behavior: strong intention, necessary skills, and lack of insurmountable environmental constraints [21]. The messages are written at a sixth-grade (about 11 years old) reading level and do not contain medical or dental jargon. Each message, and the theoretical domains that inspired it, are in Table 1. As postcards, the messages are accompanied by simple line drawings or pictorial aids to increase visual appeal and parents' comprehension of the written words [8,26]. An example message, designed to help in restructuring the physical environment, action planning, and to provide information about natural emotional consequences is, "You can brush your child's teeth in the tub! It's fun!" The accompanying drawing is of a child in a bubble bath having his teeth brushed by an adult. The postcard messages are mailed semimonthly during the first three months, and then approximately monthly.

Toothbrushing Promotion Phone Calls

A local radio celebrity, who identifies himself by his name on the prerecorded telephone message, delivered the health promotion messages described above (Table 1). We chose this strategy to increase perceived social support from a credible source for the intervention goal. The messages were modified for telephone delivery to make them more personable, personal, and to keep them brief. For example, the recommendation, "You can brush your child's teeth in the tub! It's fun!" was revised as, "You know, you don't have to brush your child's teeth at the sink all the time. Try brushing in the bathtub for something new and fun." There are eleven telephone message calls (two repeated) that are made, semimonthly during the first three months, and then monthly.

Toothbrushing Advice Helpline

A toll-free number for toothbrushing advice is included on all printed materials mailed to families and in the prerecorded telephone messages. Bilingual, culturally competent Advantage Dental Services staff members manage the helpline. The staff have been trained by the University of Washington investigators to be familiar with frequently asked questions about brushing children's teeth and using fluoridated toothpaste, and how to offer appropriate suggestions to overcome barriers to twice daily brushing.

Active Control Condition

Participants will receive the toothbrushing kits and access to the telephone helpline for requesting additional supplies, but

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no additional health messages by postcard or telephone, and no access to the toothbrushing advice helpline.

Passive Control Condition

Participants will receive the usual Advantage Dental Services practices, which may include receiving information about dental benefits via telephone and mail. This group will be on a waiting list for the trial intervention for 9 months and will then receive one toothbrushing kit. Only children less than 36 months old and their families will be included in this control condition.

By the conclusion of the study, all families will have received toothbrushing supplies. This principle, that all eligible Advantage Dental Services members will have the opportunity to benefit, is part of the organization's mission.

Intervention Fidelity

We plan to evaluate the fidelity of the intervention by assessing the extent to which the intervention is delivered as planned. To do so, we will confirm delivery of the toothbrushing supplies, postcards, and prerecorded telephone messages. Participants' use of the telephone helpline or supply line will be documented, and the nature of these contacts will be analyzed by type of request.

Study Measures and Data Collection

Outcomes

The primary outcome for all children less than 21 years old will be restorative dental care received as a proxy for the presence of dental caries. Additionally, for children less than 36 months old at baseline, the other primary outcome will be parent/caregiver reported frequency of twice daily toothbrushing the child's teeth. Secondary and tertiary outcomes will be cost of dental care for all participants; and, only for children less than 36 months old at baseline, parent/caregiver-reported oral-health related quality of life of the child, satisfaction with the program, and dental caries (tooth decay).

Mediators and Confounders

Mediators of the effect of the intervention on the primary outcomes will be the number of toothbrushing kits and instructions (mail and telephone) delivered. Parent's age, family size, and race/ethnicity will be considered confounders and explored for effect modification. Among children less than 36 months old, potential mediators to be examined are: parent/caregiver's self-efficacy, attitudes, intention, skills, and norms in relation to brushing their child's teeth. Additionally, for this group, parental educational level and child's juice consumption will be considered confounders.

Data Collection

Data on type, amount, and cost of dental care will be collected through health information systems of the dental care organization (Enrollment and Claims Database) for all participants. For children less than 36 months old, information on the children's toothbrushing behaviors, parent-rated oral health and oral health-related quality of life of the child, child's juice consumption and frequency, parental self-efficacy, intention and attitudes regarding brushing the child's teeth, parent educational level, and their opinions about each component of the intervention will be collected through telephone interviews with parents/caregivers at baseline and at the end of the intervention. For children less than 36 months old at baseline, information on the presence of untreated dental caries (cavitated caries in permanent or primary teeth) will be collected through a clinical examination 24 months after the study start date. Fidelity information will be obtained through examination of internal records of mailings, returned mail receipts, and telephone calls.

Statistical Analysis

Sample Size

Sample size for dental care outcomes was not calculated, as the sample size of 20,000 participants was deemed sufficient to observe an effect of the intervention on the primary outcome of restorative care utilization.

Prevalence and effect size estimates for frequency of twice daily toothbrushing among children less than 36 months old at baseline was based on that reported in a study in a similar population [25]. Assuming a proportion in the passive control group of .6, alpha = .025, beta = .20, the required sample sizes for effect sizes of 50% and 40% are 39 and 66 participants in each group. We decided on a sample size of 150 participants in each group.

Untreated dental caries estimate was based on that reported in a study in a similar population [1]. Assuming a proportion of children with dental caries experience in the passive control group of .5, alpha = .025, beta = .20, the required sample sizes for effect sizes of 30% and 40% are 206 and 113. We decided on a sample size of 210 participants in each group.

Statistical Analysis Plan

Descriptive statistics (means, SD, counts, and percentages) will be calculated for all variables of interest overall and stratified by age group. Difference in difference models will be used to evaluate changes in frequencies and rates for pre versus post intervention effects within the intervention groups and for passive control versus active control versus test effects. Linear regression will be used to evaluate continuous outcomes and logistic regression will be used to evaluate binary outcomes. The primary hypothesis for all participants is that the test intervention group will have a lower number of restorative dental care procedures received than the active control group during the 18 months post intervention start date. For children less than 36 months old, the primary hypothesis is that the test intervention will increase toothbrushing frequency more than the active control intervention and no change in passive control group will be observed 10 months post intervention start date. Secondary hypotheses are that member satisfaction and oral health-related quality of life of the participants will be greater and that dental care costs and dental caries will be lower in the test intervention and active control than in the passive control.

Data Management and Quality Assurance

Advantage Dental Services staff members will collect the data. Interview responses will be entered in a secure and US Health Information Portability and Accountability Act of 1996 compliant database with range checks for data values.

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Ethics and Dissemination

The results from the trial will be published regardless of the outcome. Reporting of this trial will adhere to the relevant and most up-to-date CONSORT statement [19] and its relevant extensions [20]. The investigators will ensure that the trial is conducted in compliance with this protocol and federal regulations.

Results

Timing of Recruitment, Intervention Delivery, and Follow-Up

Participants were recruited in June 2014, and the intervention is being delivered from August 2014 through April 2015. The toothbrushing supply kits were sent in August and November 2014 and February 2015. Postcards and telephone messages are being delivered to the test intervention group from August 2014 through April 2015. The helpline and other telephone services to request additional supplies are available throughout the intervention period, from August 2014 through April 2015.

Baseline interviews with the subsample of 450 parents/caregivers of children less than 3 years old have been conducted in June and July 2014, and final interviews will be conducted in May 2015. Dental claims data for all participants will be extracted in August 2015. Clinical examination of the subsample will be conducted in July 2016.

Trial Status

Participants were selected (N=21,743 families, 2857 with children less than 36 months old at baseline) and randomly assigned to the test (n=10,797), active control (n=10,796), and passive control (n=150 families with children less than 36 months old) conditions. A random sample of parents/caregivers of children less than 36 months old was interviewed (n=450, 150 for each test, active, and passive control conditions). The program has been deployed.

Discussion

The 9-month intervention described in this report, “Everybody Brush!”, builds on our previous work and presents a sizeable challenge to promote twice daily toothbrushing and test the effectiveness and acceptability of health promotion strategies to reach thousands of children and their families. It is a quality improvement project designed to shift the allocation of resources of a dental care organization from restorative dental services to preventive home care practices, specifically toothbrushing with fluoridated toothpaste. The focus of the evaluation on the oral health of the youngest members is because toothbrushing habits established during childhood persist [12,13], and because of the high costs associated with care of young children with rampant dental caries.

The program is being delivered as a universal preventive intervention to all eligible members served by the dental care organization within the three county study setting. There are pros and cons to this decision. A benefit of a universal approach is that it can build wide community recognition and public support for the program. A disadvantage is that it is more costly than including only families with children perceived to be at high risk for tooth decay. While this selective approach would save costs, choosing a subset of families could stigmatize the program and lose the support of even those in need. On the other hand, oral hygiene is a personal and sensitive issue. Parents may have defensive, unfavorable views of the program and report it is not needed.

This quality improvement project is being rigorously evaluated. It assesses impacts on the member-participants as well as costs. The results of the evaluation will be used to determine if the complex intervention with intensive instruction and social support is needed or could be eliminated. In addition, the evaluation will inform if the program should be sustained and expanded. If proven effective, this simple intervention can be sustained by the dental managed care organization and replicated by other organizations and government.

Acknowledgments

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Authors' Contributions

JCC wrote the protocol and drafted the first version of this manuscript. PM contributed to the protocol and edited the manuscript. RMS contributed to the protocol. CEH contributed to the protocol and revisions of the manuscript. SL and GA contributed to the operational aspects of the protocol. JAS was the primary author of the statistical section of the protocol.

Conflicts of Interest

RSM, SL, and GA are employees of the Sponsor. The other authors declare that they have no competing interests.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials

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Protocol

The Use of Virtual World-Based Cardiac Rehabilitation to Encourage Healthy Lifestyle Choices Among Cardiac Patients: Intervention Development and Pilot Study Protocol

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Abstract

Background: Despite proven benefits through the secondary prevention of cardiovascular disease (CVD) and reduction of mortality, cardiac rehabilitation (CR) remains underutilized in cardiac patients. Underserved populations most affected by CVD including rural residents, low socioeconomic status patients, and racial/ethnic minorities have the lowest participation rates due to access barriers. Internet-and mobile-based lifestyle interventions have emerged as potential modalities to complement and increase accessibility to CR. An outpatient CR program using virtual world technology may provide an effective alternative to conventional CR by overcoming patient access limitations such as geographics, work schedule constraints, and transportation.

Objective: The objective of this paper is to describe the research protocol of a two-phased, pilot study that will assess the feasibility (Phase 1) and comparative effectiveness (Phase 2) of a virtual world-based (Second Life) CR program as an extension of a conventional CR program in achieving healthy behavioral change among post-acute coronary syndrome (ACS) and post-percutaneous coronary intervention (PCI) patients. We hypothesize that virtual world CR users will improve behaviors (physical activity, diet, and smoking) to a greater degree than conventional CR participants.

Methods: In Phase 1, we will recruit at least 10 patients enrolled in outpatient CR who were recently hospitalized for an ACS (unstable angina, ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction) or who recently underwent elective PCI at Mayo Clinic Hospital, Rochester Campus in Rochester, MN with at least one modifiable, lifestyle risk factor target (sedentary lifestyle, unhealthy diet, and current smoking). Recruited patients will participate in a 12-week, virtual world health education program which will provide feedback on the feasibility, usability, and design of the intervention. During Phase 2, we will conduct a 2-arm, parallel group, single-center, randomized controlled trial (RCT). Patients will be randomized at a 1:1 ratio to adjunct virtual world-based CR with conventional CR or conventional CR only. The primary outcome is a composite including at least one of the following (1) at least 150 minutes of physical activity per week, (2) daily consumption of five or more fruits and vegetables, and (3) smoking cessation. Patients will be assessed at 3, 6, and 12 months.

Results: The Phase 1 feasibility study is currently open for recruitment which will be followed by the Phase 2 RCT. The anticipated completion date for the study is May 2016.

Conclusions: While research on the use of virtual world technology in health programs is in its infancy, it offers unique advantages over current Web-based health interventions including social interactivity and active learning. It also increases

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accessibility to vulnerable populations who have higher burdens of CVD. This study will yield results on the effectiveness of a virtual world-based CR program as an innovative platform to influence healthy lifestyle behavior and self-efficacy.

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KEYWORDS

cardiac rehabilitation; cardiovascular diseases; eHealth; telemedicine; Internet; health behavior

Introduction

Underutilization of Cardiac Rehabilitation

Coronary artery disease (CAD) has become a pandemic as the leading cause of death worldwide [1]. CAD accounts for over two-thirds of cardiac-related deaths in the US and is associated with significant morbidity [2]. According to the 2014 Heart Disease and Stroke Statistics, an estimated 635,000 Americans suffer from an acute coronary event per year with approximately 300,000 recurrent events in CAD survivors [1]. Targeting behavioral risk factors including poor nutrition, smoking, and physical inactivity as well as conditions such as hypertension, hyperlipidemia, diabetes, and obesity is of utmost importance in order to significantly reduce CAD-associated morbidity and mortality [3-6]. Cardiac rehabilitation (CR) is an essential component of the mainstay therapy for patients following an acute coronary syndrome (ACS), such as acute myocardial infarction, for facilitation of recovery and secondary prevention of further events [7]. Evidence has consistently demonstrated that the comprehensive focus of CR on healthy lifestyle change reduces all-cause and cardiac-related mortality [8-10], and improves exercise capacity, psychosocial well-being, and quality of life [5,11]. However, despite its proven benefits, CR is greatly underutilized, especially among groups that need it most such as ethnic minorities, rural residents, the elderly, and the economically disadvantaged [12,13]. Many of the cited barriers to participation are both personal and systems-related including employment/time conflicts, lack of transportation, geographical accessibility, and financial constraints [12-14].

Call for Innovation

The American Heart Association (AHA) Presidential Advisory board has recently issued a call for innovative reengineering of the traditional CR model towards approaches to improve adherence and effectiveness in cardiac patients [15]. Novel methods for reaching underserved populations who have the highest prevalence of cardiovascular disease (CVD) are crucially needed to assist in alleviating the burden and disparities within these groups. More Americans are embracing the digital world, with many accessing the Internet for health-related information [16,17]. The use of technology to deliver personalized medicine through mobile and Internet-based interventions has shown promise in improving user's knowledge, health behaviors, and clinical outcomes [18]. There is recent evidence to suggest the effectiveness of Internet-based CR, termed virtual CR or eRehabilitation through the provision of health promotion programs at the user's convenience [19-24].

Study Purpose

Virtual world technology has emerged as a potentially powerful tool for the delivery of lifestyle interventions in the management of chronic diseases including diabetes [25] and obesity [26]. Virtual world environments are unique from Internet-based applications in that they are inherently immersive, engaging, and allow for "real world" interaction though personalized avatars or online personas [27,28]. Users of virtual world are provided with a more synchronous experience allowing for collaborative and experiential learning, skill-building, and "what if" hypothetical scenarios; all core concepts of CR [27,28]. We propose the use of a virtual world interaction as an extension to traditional face-to-face CR as a means for overcoming barriers to CR participation, and for positively impacting cardiac risk factors given its affordances of accessibility, social interactivity, and self-motivation. This virtual world interaction approach could potentially assist in widening access to and participation in CR among the US population as a whole while narrowing the gap in exemplary health outcomes among underserved groups. Our pilot study consists of the following two phases: (1) feasibility and (2) a comparative effectiveness, randomized clinical trial of virtual world based adjunct CR against conventional CR.

Methods

Study Setting and Participants

We will recruit patients who were recently hospitalized for an ACS (unstable angina, ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction), or who recently underwent elective percutaneous coronary intervention (PCI) at Mayo Clinic Hospital, Rochester Campus in Rochester, MN with at least one modifiable, lifestyle risk factor target: sedentary lifestyle (<3 hours of physical activity per week), unhealthy diet (consumption of <5 servings of fruits and vegetables daily), and current smoking (>1 year). All patients must have regular high-speed Internet access (either home, work, or community). Patient exclusion criteria will include less than 18 years of age, enrolled in a current CR program, and non-fluent in English. The feasibility research protocol was reviewed and approved by the Mayo Clinic Institutional Review Board and the randomized controlled trial (RCT) will be registered. We include details of the design and methods of both the feasibility study and the proposed RCT as Phases 1 and 2, respectively.

Phase 1: Feasibility Study

Hypothesis

We hypothesize that a virtual world-based CR program can be successfully implemented as an extension of a face-to-face conventional CR program. We plan to evaluate a priori how patients utilize a virtual world-based program for CR and secondary CVD prevention by conducting a 12-week feasibility study. Our goal is to apply the evaluation information obtained

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from Phase 1 towards the design of a patient-driven and centered virtual world platform prototype (*Destination Rehab*) with high usability, understandability, and credibility.

Recruitment

Eligible patients (approximately 10) will be invited to participate from the Mayo Clinic outpatient CR enrollment listings by the study cardiovascular nurse. Evidence supports that at least 5 participants are sufficient to assess usability of Web-based applications [29,30].

Intervention

We plan to hold a series of weekly, one-hour sessions over three months on a secure virtual world platform via an established Mayo Clinic infrastructure, Linden Lab's Second Life, covering relevant cardiovascular health topics including CAD, hypertension, hyperlipidemia, and diabetes (see Textbox 1 and Figure 1) [31]. The sessions will be led by a cardiovascular diseases specialist and a cardiovascular nurse educator both trained in motivational interviewing and the Second Life application. Technical support staff will assist with any virtual world technology technical issues and troubleshooting. We will also hold live "ask-the-expert" group chat sessions on diet and exercise from a dietician and exercise physiologist, respectively. Participants will engage in virtual activities including grocery store and restaurant tours (to discuss healthy food choices, portion control, and nutrition label reading), as well as a variety of fitness activities (see Figures 2-4) [32-34]. Peer discussion forums will be available at all times to the participants. A few of our intervention preparation techniques were adapted from those endorsed by Rosal et al as established processes for virtual world interventions [25]. Participants will receive hands-on training and support including an overview of the virtual world platform, creating a Second Life account (including avatar), and navigation of the *Destination Rehab* prototype. Participants will also be provided with an instructional manual including step-by-step screen shots to support their independent home use. Upon training completion, participants will be provided with a personal laptop for use during the study, complete with required software to access the virtual-world platform and CR program materials, as well as a personal headset with microphone to facilitate communication in virtual world.

Textbox 1. Comparison of virtual world adjunct versus conventional cardiac rehabilitation program curricula.

Comparison of program curricula

- Virtual world
  - Managing heart disease risk factors (hyperlipidemia, hypertension, diabetes, obesity, and tobacco use)
  - Stress management and relaxation after cardiac events
  - "Ask-the-expert" group chat sessions on nutrition and physical activity with dietician and exercise physiologist
  - Virtual grocery store and interactive restaurant tour with dietician (selecting healthy foods, proper portion sizes, nutrition label reading, etc.)
  - Medications after a cardiac event
  - Sexuality after a cardiac event
  - Peer group "social hour" discussions
- Conventional
  - Managing heart disease risk factors (hyperlipidemia, hypertension, diabetes, obesity, and tobacco use)
  - Stress management and relaxation after cardiac events
  - Dietician nutrition counseling (hints for grocery store shopping, dining out, healthy seasoning, etc.)
  - Cooking demonstration
  - Physical activity counseling with exercise physiologist (personalized exercise program/prescription)
  - Medications after a cardiac event
  - Sexuality after a cardiac event
  - Support groups

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Figure 1. Mayo Clinic conference center virtual world platform in the Second Life application.

Figure 2. Example of virtual grocery store tour.

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Figure 3. Example of interactive restaurant tour.

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Figure 4. Example of virtual fitness center.

Measures

We plan to evaluate utility and usability, as well as user satisfaction for each user. Application usage statistics for each participant will be collected to report the frequency and duration of each interaction with the virtual world platform. Furthermore, assessments of participant-to-participant and participant -to-speaker communication during sessions will allow for an appreciation of the participant's sense of immersion and engagement. Feedback on the site usability and utility will be measured by survey and interview consisting of questions from previously validated tools [22,35-38]. The usability questions will include participant impressions of the graphical interface, as well as opinions and attitudes towards the visual appeal (ie, application was designed with the user in mind), content (ie, information was complete), navigation (ie, steps required to complete a task were logical), informational architecture (ie, visual layouts were logical), and interactive features. User satisfaction will be assessed by open response questions to allow participants to provide feedback on likes, dislikes, or concerns about the virtual world platform, and sections to provide recommendations for changes to the program. At Phase 1 completion, study participants will complete a final evaluation survey assessing their willingness to use a similar virtual world platform for CR. Results of this formative evaluation process will inform changes and adjustments to our virtual world program for Phase 2.

Phase 2: Randomized Controlled Trial

Hypothesis

We hypothesize that virtual world CR users will improve behaviors (physical activity, diet, and smoking) to a greater degree than conventional CR participants.

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Recruitment

Potential participants hospitalized for an ACS or those undergoing elective PCI procedures will be identified from the Division of Cardiovascular Diseases Hospital service census (coronary care unit, general and ischemic ward services, interventional service) by the study team cardiovascular clinical nurse specialist. Each patient will be approached prior to dismissal as part of CR discharge planning during which time they will be provided with pertinent information on the purpose and requirements of the study. Following eligibility screening by the nurse specialist, they may choose to provide written informed consent at the time of recruitment or at another convenient time (ie, baseline visit). Furthermore, eligible patients will be recruited from the Mayo Clinic outpatient CR enrollment listings. Efforts will be implemented to increase priority population (ethnic minorities, rural residents, elderly, and economically disadvantaged) accrual including community-based strategies, clinician-initiated recruitment, advertisements, and medical record review.

Baseline Visits

All participants will undergo an outpatient, baseline assessment for collection of sociodemographics, medical history, prescribed medications/adherence [39], smoking status, surveys for heart disease knowledge [40], diet quality [41,42], physical activity patterns [43,44], self-efficacy [41,44,45], social support/influence [46], and physical and mental health-related quality of life [47] utilizing validated instruments after obtainment of written informed consent. Clinical assessments including anthropometrics (height, weight, body mass index, waist circumference, and blood pressure) and laboratory studies (lipid panel, blood glucose, and hemoglobin A1c) will be obtained by standard protocols and/or extracted from participant medical records from their ACS index hospitalization or follow-up medical visits. As a part of the standard clinical CR intake process, all participants will undergo an oxygen consumption exercise treadmill test (ETT) to assess for heart rate and blood pressure responses and exercise capacity. All participants will attend an in-person computer and device training session similar to that carried out during the feasibility study and will receive a personal laptop and headset for use during the study (both control and intervention groups for standardization). Participants will also receive a personal activity tracker (Fitbit™) as a tool to accurately assess free-living physical activity [48]. Participants will be asked to wear the activity trackers on a daily basis and to upload their data to a secure webserver at least once weekly. Each participant will receive a binder of education materials (including slide presentations) relevant to their respective assignment.

Design and Randomization

The study will consist of a 2-arm, parallel group, single-center RCT. Patients will be randomized at a 1:1 ratio by a computer software-generated list (nQuery advisor) at their baseline outpatient CR visit to adjunct virtual world-based CR with conventional CR or conventional CR only. Randomization will be stratified by block sizes of four.

Control Conventional Cardiac Rehabilitation Program

The control group will enroll in a standard center-based CR program, which at Mayo Clinic Rochester consists of 36 sessions over a duration of 12-16 weeks. The comprehensive program includes supervised exercise, cooking demonstrations, didactic lectures, video presentations, group support, and stress management sessions. Participants will have face-to-face access to the medical directors, registered dietician, exercise physiologist, case manager, and stress management specialist. The curriculum course topics and sessions developed according to national standards of care for secondary prevention are outlined in Textbox 1 [49,50].

Enhanced Virtual World-Based Intervention

In addition to standard center-based CR, the intervention group will have access to an interactive healthy lifestyle community, *Destination Rehab*, delivered through a virtual world platform on Second Life. The platform will provide specialized educational tools on CVD secondary prevention including information on nutrition, physical activity, smoking, medication adherence, etc. Specific program components will include interactive 3D spaces (ie, grocery store, fitness center, restaurant, virtual library, and human heart tour), and live Mayo Clinic health professional-led education sessions and peer discussion forums (ie, social support groups) (see Figures 1-4) [31-34]. The platform design has the intention of encouraging healthy lifestyle behaviors by participant avatars with the goal of transferring these behaviors to the real world (ie, Proteus effect) [26,28, 51]. The platform features were informed by valuable input from the Mayo Clinic patient and family advisory group (One Voice) at focus groups in January and February 2014, and will be further developed from Phase 1 study results. Weekly education sessions, including slide presentations, will last for 60-90 minutes and allow for interaction between the facilitators and participants through voice chat and text message features (see Multimedia Appendix 1). A summary of the proposed education sessions including key patient-centered elements for promotion of healthy lifestyle change is provided in Textbox 1 [49,50].

Measures

The primary outcome is a composite including improvement of at least one of the following 3 cardiac risk factors at baseline, 3, 6, and 12 months (1) physical activity (at least 150 minutes per week), (2) diet (consumption of five or more fruits and vegetables daily), and (3) smoking (complete cessation for baseline smokers, maintained nonsmoking status for baseline nonsmokers). Secondary outcomes will include improvement in all 3 cardiac risk factors, intention and self efficacy to achieving lifestyle change [41,44,45], change in exercise capacity by peak oxygen uptake (VO_2), change in weight (≥5% weight reduction for patients with baseline BMI >30 kg/m^2), blood pressure optimization (blood pressure <140/90 mmHg, <130/80 mmHg for diabetics), diabetes control (hemoglobin A1c<7%), hyperlipidemia control (low-density lipoprotein <100 mg/dL), medication adherence [39], social support/influence [46], physical and mental health-related quality of life [47], heart disease knowledge [40], and user evaluation of the virtual world platform (satisfaction, usability, and utility) [22,35-38].

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Physical activity will be assessed by the International Physical Activity Questionnaire (IPAQ) which determines physical activity patterns (vigorous-intensity, moderate-intensity, and leisure) over the previous seven days [43]. Furthermore, free-living physical activity data will be obtained from personal activity trackers as number of steps per day [48]. All patients will undergo a symptom-limited ETT with oxygen consumption testing to assess for peak VO_2 [52,53]. Continuous blood pressure and heart rate measurements, as well as electrocardiograms will be obtained during exercise and recovery periods. A brief dietary recall by a food frequency questionnaire will allow for diet evaluation [42]. Mayo Clinic laboratories will process and analyze all fasting blood specimens including lipid panel (total cholesterol, triglycerides, high density lipoprotein cholesterol, and low density lipoprotein cholesterol), blood glucose, and hemoglobin A1c. Physical examination measures including height, weight, body mass index, waist circumference, and blood pressure will be obtained according to standard guidelines and Mayo Clinic protocols [54-55]. The baseline questionnaires and clinical assessments will be repeated at 3, 6, and 12 months (study completion).

At program completion, we also plan to have semi-structured focus groups to solicit feedback on the intervention and control rehabilitation programs. We anticipate holding at least two sessions (one for each study group) with at least 20 participants per session. We will collect information on participant experiences, attitudes, and beliefs on healthy lifestyle change through open-ended intervention questions developed by the research team. Incentives for participating in the program and for completion of follow-up surveys will be provided to participants (proposed gift certificates and the Mayo Clinic Healthy Heart for Life book).

Data Management

The data collected from survey materials will be entered and stored electronically on a secure (password-protected) database system (REDCap™) for the duration of the data collection and analysis (estimation one year), and only specified study coordinators/collaborators will have access to the surveys and monitor the data accordingly for research purposes only.

Sample Size Estimation and Power Calculations

Power analysis for a priori sample size was performed with equivalence testing for two proportions in a randomized design using the program nQuery advisor. Using data on previous research, we estimated that 45% of patients receiving conventional CR, and 74% of patients attending *Destination Rehab* with conventional CR would have at least one correction of a cardiovascular behavioral risk factor at 12 months [29]. Therefore, to discover a clinically-relevant difference of this size between the groups at a 0.05 alpha level with 80% power, we will require 50 participants per group. Assuming a drop-out rate of 10%, we aim to recruit a total of 120 patients for the RCT.

Statistical Analysis

Quantitative Data

For normally distributed variables, simple arithmetic means and standard deviations will be calculated. For categorical variables, frequencies and proportions will be calculated. For clinical endpoints, we plan to calculate changes in measures by comparing differences in change from baseline to follow-up interval. We will include sensitivity analyses with the inclusion of patients with complete data only. Analyses will be performed using commercial software (SAS version 9.2, SAS institute), and a two-tailed value of $P<.05$ as statistically significant.

Qualitative Data

Focus group interview data will be recorded, transcribed, and coded by a qualified audio typist and analyst according to a qualitative analysis approach [56]. Descriptive codes by constant comparison methods will then be merged to thematic categories and conceptual frameworks to provide insight to further the enhancement of both CR modalities [57] and barriers towards achieving ideal cardiovascular health. To ensure rigor and accuracy, separate transcription and coding will be conducted by independent analysts from the study team. All data will be processed and analyzed using the NVIVO software package.

Discussion

Embracing Virtual Word Technology

Telemedicine and mobile health are rapidly emerging as novel methods of the “virtualization” of healthcare delivery [58]. These technologies may serve as portals to overcome critical barriers to receipt of optimal cardiovascular care among underserved communities including the racial/ethnic minorities, the economically disadvantaged, and elderly who are disproportionately affected by CVD. Virtual world health interventions may offer a solution to this “treatment paradox” by increasing access to those who crucially need evidence-based therapies such as CR [**59]**. Further robust evidence is needed to demonstrate the effectiveness of these interventions in stimulating patient empowerment towards healthy lifestyle behavioral change. Our study will attempt to fulfill this need by assessing the feasibility and clinical effectiveness of CR delivered in a virtual world environment in comparison to standard site-based CR.

Study Strengths and Limitations

Our study has several strengths mainly given that it is the first study, to our knowledge, assessing the use of virtual technology for CR. Furthermore, it is the only virtual world-based study focused specifically on lifestyle behavior change in patients with ischemic heart disease, the leading cause of morbidity and mortality worldwide [59]. Our study will be conducted at a designated medical center of excellence with inherent patient-centric, comprehensive, and standardized CR services. The development of the program curriculum was guided by the core components and competencies for patients and health professionals as established by the AHA and the American Association of Cardiovascular and Pulmonary Rehabilitation which could facilitate widespread adaptation and insurance

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reimbursement if deemed effective [49,50]. Our study will randomize study participants to a virtual world intervention as an adjunct to standard CR versus standard CR to ensure receipt of gold standard care by all participants. We will also provide all required hardware, software, and requisite computer training to both study groups. Finally, our study includes both feasibility and comparative analysis components with quantitative and qualitative assessments to ensure scientific rigor and validity.

We recognize that our study has its limitations primarily due to our small sample size, which may limit the generalizability of our results. However, this is justified as this is a feasibility and pilot study using a new method for CR delivery in cardiac patients. Another possible limitation is our provision of a laptop computer to all participants, which may not be practical or sustainable in wide-spread implementation. However, we want to ensure access to all participants and not bias our inclusion criteria by excluding those without a virtual world technology-enabled device.

Conclusions

It is crucial that we embrace the use of novel technologies to assist cardiac patients in achieving and maintaining healthy behavioral change for secondary prevention. Virtual world technologies may fulfill this need as it has demonstrated effectiveness in improving self-efficacy for chronic disease self management even in socioeconomically disadvantaged populations [25]. We are optimistic that our proposed study of the use of virtual world-based CR will glean informative results on patient acceptability, adaptability, and ultimately empowerment toward de facto cardiovascular risk factor reduction and secondary CVD prevention.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Virtual world adjunct versus conventional cardiac rehabilitation program for Phase 2 randomized controlled trial.

[PDF File (Adobe PDF File), 51KB - resprot_v4i2e39_app1.pdf]

Multimedia Appendix 2

CONSORT-EHEALTH checklist V1.6.2 [60].

[PDF File (Adobe PDF File), 79KB - resprot_v4i2e39_app2.pdf]

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Abbreviations

ACS: acute coronary syndrome
AHA: American Heart Association
CAD: coronary artery disease
CR: cardiac rehabilitation
CVD: cardiovascular disease
ETT: exercise treadmill test
IPAQ: International Physical Activity Questionnaire
PCI: percutaneous coronary intervention
RCT: randomized controlled trial
VO_2: oxygen uptake

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Protocol

Mobile Phone and Tablet Apps to Support Young People's Management of Their Physical Long-Term Conditions: A Systematic Review Protocol

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Abstract

Background: The prevalence of long-term or chronic conditions that limit activity and reduce quality of life in young people aged 10-24 years is rising. This group has distinct health care needs and requires tailored support strategies to facilitate increasing personal responsibility for the management of their condition wherever possible, as they mature. Mobile phone and tablet mobile technologies featuring software program apps are already well used by young people for social networking or gaming. They have also been utilized in health care to support personal condition management, using condition-specific and patient-tailored software. Such apps have much potential, and there is an emerging body of literature on their use in a health context making this review timely.

Objective: The objective of this paper is to develop a systematic review protocol focused on identifying and assessing the effectiveness of mobile phone and tablet apps that support young people's management of their chronic conditions.

Methods: The search strategy will include a combination of standardized indexed search terms and free-text terms related to the key concepts of young people; long-term conditions and mobile technology. Peer-reviewed journal articles published from 2003 that meet the inclusion and exclusion criteria will be identified through searching the generated hits from 5 bibliographical databases. Two independent reviewers will screen the titles and abstracts to determine which articles focus on testing interventions identified as a mobile phone or tablet apps, and that have been designed and delivered to support the management of long-term conditions in young people aged 10-24 years. Data extraction and quality assessment tools will be used to facilitate consistent analysis and synthesis. It is anticipated that several studies will meet the selection criteria but that these are likely to be heterogeneous in terms of study design, reported outcomes, follow-up times, participants' age, and health condition. Sub-group analyses will be undertaken and where possible meta-analyses will take place.

Results: This review will synthesize available knowledge surrounding tablet and mobile phone apps that support management of long term physical health conditions in young people. The findings will be synthesized to determine which elements of the technologies were most effective for this population.

Conclusions: This systematic review aims to synthesize existing literature in order to generate findings that will facilitate the development of an app intervention. The review will form the first phase of development and evaluation of a complex intervention

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as recommended by the United Kingdom Medical Research Council. The knowledge gained from the review will be verified in subsequent phases, which will include primary qualitative work with health professionals and young people with long term conditions as research participants. Young people living with long-term conditions will be involved as co-researchers and consumer advisors in all subsequent phases to develop and evaluate an app to support the management of long-term physical health conditions.

Trial Registration: PROSPERO International prospective register of systematic reviews: CRD42014015418; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014015418#.VRqCpTpnL8E (Archived by Webcite at http://www.webcitation.org/6XREcWqQY).

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KEYWORDS

mobile app; mobile phone; protocol; smartphone; tablets; young people; long-term conditions; chronic conditions; management; systematic review

Introduction

Young People With Physical Long-Term Conditions

Globally, the pattern of illness in young people aged 10-24 years (hereafter referred to as young people) has shifted from acute episodes, to long-term or chronic conditions that will potentially affect them across the life course [1]. At least 12% of young people have a long-term or chronic condition, but the actual number with one or more conditions is unknown [2]. A long-term or chronic condition is defined as a health condition that, at the time of diagnosis, is predicted to last longer than 3 months [3] (hereafter described as a long-term condition). However, there is an increased prevalence of long-term conditions that are severe enough to limit activity and delay normal developmental milestones, thus reducing young people's quality of life and that of their parents/carers and families [4].

Survival rates for this group have improved due to better screening, earlier detection, and improvements in the delivery of specialized care [4,5]. However, there is growing evidence to suggest that young people with long-term conditions have distinct health needs when compared to other groups [6]. Effective support from the health sector is, therefore, paramount, especially during the transition from pediatric to adult health services, and particularly if adult services are not designed specifically to meet the needs of young-people [7]. This process of health transition as young people grow up requires them to develop clinical skills and knowledge in order to ultimately take responsibility for and competently manage their personal health where appropriate [2,8,9].

Delivering safe and timely health care that is accessible and tailored to the individuals' needs and preferences is a central feature of international health care strategies [6]. Additionally, government policies highlight the need for services to support self-care, for example, the UK Department of Health and Department for Education are working to support young people with complex health needs in making the transition to adulthood [10].

A recent systematic review of self-care support interventions for children and young people found that effective interventions included those that used the Internet and text messaging for delivery, although none of the reviewed studies were reported to use mobile phone or tablet apps [11]. However, contemporaneous reports indicate that utilizing modern mobile electronic technologies in health interventions for adults of all ages [12,13] and young people [14] may be a suitable way to address self, shared, or joint care in a manner that is resource efficient.

The potential of mobile technologies in this area is increasingly recognized as being significant. For example, health management behaviors can be integrated with other daily activities by technologies that are capable of tracking information whilst "on the go". An emerging body of literature on the use of mobile technologies in a health context makes a systematic review timely, to collate and build on lessons learnt as well as prevent duplication of research effort.

In this current review, young people are defined as those aged 10-24 years who are undergoing key elements of development, particularly brain development, which continues until the early 20s [1,15-17]. As increasing numbers of young people with long-term conditions are transitioning to adult-centered care, significant declines in treatment adherence have been observed during the transition period [18]. Interventions to enhance medication adherence found that education interventions alone are insufficient to promote adherence, but adding behavioral interventions such as monitoring and goal setting, reinforcing medication taking with rewards, contingency contracting, problem solving, and linking medication taking with established routines may enhance outcomes [19,20]. However, the small treatment effects of recent adherence-promoting interventions reflect the methodological limitations of the included studies and the need to reexamine the delivery and mechanisms of adherence-promoting interventions. Therefore, this is arguably a crucial time for the rigorous development, evaluation and implementation of interventions that promote shared and self-management skills and knowledge, and for the promotion of health-promoting behaviors.

Mobile Phone and Tablet Apps to Support Management of Long-Term Conditions

The new generation of inexpensive, powerful, hand-held computers (mobile electronic devices) were first described in 1987 [21]. While the potential of these devices for patients and clinicians to collect field data more easily and reliably was quickly identified, limitations in terms of expense, responsiveness, connectivity, and evidence of their effectiveness,

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has affected their integration into practice. A Cochrane review in 2009 of Interactive Health Communication Applications (computer-based, usually Web-based, information packages for patients that combine health information with social support, decision support, and/or behavior change support) concluded that the mode or site of delivery is not important but did not report any studies involving mobile phones or tablet apps [22]. However, mobile phones and tablets now form the new generation of mobile electronic devices, chiefly different to previous generations in that they are a consumer product as opposed to primarily a business product [23]. Mobile phones and tablets have the additional feature of extending their function with custom software programs called apps, which technologically, allow the development of condition specific and patient tailored software. Additionally, mobile phones and tablets are primarily communication devices; whereas traditional Web-based apps have as their main foci information provision and/or gatekeeping to wider social networks. Mobile technologies and mobile phones in particular are personal devices, adapted by the user to reflect their specific needs. This personal nature of mobile devices (as opposed to a desktop or laptop computers), as well as the technology underpinning mobile apps, allows for adaptive, responsive, confidential, and targeted channels of communication and alerts.

In a recent review of the effectiveness of mobile health technology-based health behavior change or disease management interventions for adults, only 6 of the 49 disease management interventions used apps and none of these involved young people with long-term conditions [13]. Another recent integrative review of mobile phone interventions for long-term health management of chronic disease in patients aged 18-73 years [24] concluded that there are limited mobile apps available and recommends that more be developed. A review of the top 500 medical apps in the Italian health care android market showed that the majority were designed for health care professionals [25]. Since the potential of mobile technologies in health care is significant, a rapidly growing body of literature is currently emerging on the use of apps to support patients' management of long-term conditions and a review of the evidence is timely.

In a recent commentary, Wu and Hommel [26] described current and potential technologies; such as text messaging, mobile phone apps, electronic monitors of adherence, and illness-specific medical devices to promote pediatric adherence to prescribed medical regimens. The reported uses included: delivering and collecting information, facilitating communication between patients and professionals, social networking, capturing real-time data, monitoring bodily functions, automated feedback, guidance and clinical alerts, and smart decision-making tools. However, despite the significant potential and increased use of these technologies, to our knowledge there has not been a synthesis of studies reporting on their effectiveness of these mobile technologies in the management of physical long-term health conditions in young people.

There are barriers to the use of mobile technologies by young people, including the disparity of access to mobile devices and the potential for habituation, suggesting that the use of IT to address health issues may be limited or even harmful to young people [27,28]. In addition, parents/carers play a significant part in promoting the development of young peoples' self-management skills in long-term condition management [29], but parents may be less confident than young people in using technology [30]. Furthermore, in view of the relatively underdeveloped area of adolescent health services, it can be difficult for those health professionals who are unfamiliar with mobile phone and tablet apps to engage effectively with young people via these media [31,32]. Therefore, there is a need for well-designed trials of mobile phone and tablet app interventions that may be feasibly transferred into real-life settings and which involve parents, health professionals and young people in their development and evaluation.

Nevertheless mobile apps are widely acceptable to young people living in an increasingly technology-rich environment with good access to mobile phones and tablets in their day-to-day lives [33]. In the United Kingdom, children and young people aged 5-15 years are frequent users of mobile technologies: 62% of 12-15 year olds own a mobile phone, and the use of tablet computers by 5-15 year olds tripled between 2012 and 2013 with 42% using tablets in 2013 [23]. These trends are expected to continue and have the potential to engage young people in their personal health care. New technologies are emerging drivers in adolescent health with potential for both positive and negative impact [6].

In 2013, the UK National Health Service (NHS) Commissioning Board unveiled a library of NHS reviewed health apps [34]. Although this review focused on clinical safety rather than clinical effectiveness, it acknowledged that the computing capability contained within mobile technologies offers a legitimate platform for medical and public health practice. That said, the (IMS Health)-Institute of Healthcare Informatics [35], reported that the lack of evidence regarding the effectiveness of mobile apps acts as a barrier to physicians prescribing them. The IMS identified a pressing need for credible evidence of the value of health apps, which in many cases are being used without a thorough understanding of their associated risks and benefits or a rigorous, evidenced based approach to their development, evaluation, and validation [36]. Therefore, the review protocol presented in this paper will focus on assessing the effectiveness of mobile phone and tablet apps for young people's management of long-term conditions.

Methods

The Systematic Review

Mobile phone and tablet applications can be used in a host of ways to support the management of physical long-term conditions. Namely, these apps seek to define and refine the practices and procedures required for behavioral change; which in turn are anticipated to improve clinical and psychosocial outcomes.

Management of long-term physical health conditions involves 5 core skills: problem solving, decision making, resource utilization, forming patient-health care professional relationships, and taking action [37]. Apps can support these

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skills as well as knowledge development by providing and collecting information in a manner more accessible and convenient than that which existed previously, as well as having the additional advantage of interactivity.

For example, interventions delivered through a mobile phone or tablet app could include: an electronic diary which would serve as a medication or appointment reminder, a symptom monitor, a meaningful way of displaying clinical data to patients, educational materials tailored to individual patients' needs and preferences, and/or a way of enabling patients to choose whether or not to share their data with health professional(s) for more meaningful consultations [38].

This systematic review will synthesize the evidence on all types of mobile phone and tablet apps that are used to support the management of physical long-term conditions in young people. Metaanalyses will be performed where possible. This systematic review will follow the methods described in the Cochrane Handbook for Systematic Reviews of Intervention [39], and be reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [40].

Search Strategy

Eligible studies will be identified through a comprehensive literature search of 5 bibliographical databases (MEDLINE, CINAHL, EMBASE, PsycINFO, and the Web of Science). The search strategy has been developed in consultation with an information scientist.

The search strategy uses a combination of standardized indexed search terms and free-text terms that relate to the three key concepts (young people; physical long-term conditions and mobile technology). The search includes British and North American terms and spellings. The search strategy was initially devised in MEDLINE and then adapted to the other databases (see Multimedia Appendix 1 for supporting information). The Web of Science does not employ any indexed search terms and the other databases did not employ them in a standardized fashion. Free-text terms have been used consistently throughout.

In addition to testing search sensitivity, those journals associated with the most retrieved citations will be hand-searched from 2009 to 2014. Supplementing the search with hand-searching decreases the likelihood of missing relevant studies. The production of any studies additional to those we have already identified from hand-searching will also allow us to comment on the rigour of the search strategy and the quality of indexing in the said bibliographic databases. This would be particularly useful in the relatively new domain of mobile technology. Also, due to the emerging nature of mobile technology, the search will include conference abstracts published in peer-reviewed journals, and authors will be contacted requesting additional related published or unpublished work.

Screening and Selection Criteria

Overview

Two reviewers will independently screen all titles and abstracts retrieved by the search using a screening tool with study inclusion criteria as a prompt (see Textbox 1). Two reviewers will then independently screen full articles of the abstracts still included, using the same screening tool. Whenever disagreement in interpretation arises between the two reviewers, the rest of the team members will be asked to consult the relevant materials to enable a discussion until a consensus is reached, thereby minimizing bias in the interpretation of findings. Team meetings will be held regularly for the purpose of discussing articles and for discussion of complications or challenges.

Inclusion Criteria

Criteria for included studies are in Textbox 1. The Cochrane Collaboration states that a typical metaanalysis ought to exclude non-randomized controlled trials due to their greater bias. In spite of this, we have chosen to include studies of various designs to systematically collect a broad overview of the evidence. However, decisions on which studies to include in a metaanalysis will only be made after quality assessments are undertaken and risk of bias is ascertained.

Textbox 1. Summary of inclusion criteria.

Population:

Young people aged 10-24 years old (WHO definition 2001 [1]) diagnosed with a long-term physical condition in any setting.

Intervention:

Any application for a mobile phone or tablet that can be considered a management intervention (or a component of an intervention) in terms of content and/or delivery. This judgment will be based on the 5 core management skills for long-term physical health conditions, as outlined by Lorig [34].

Comparisons:

Intervention versus usual care OR intervention variant versus intervention variant OR pre and post.

Outcomes:

Any physiological, attitudinal, behavioral or knowledge outcomes.

Study design:

Randomized controlled trial OR controlled clinical trial OR cohort analytic OR case-control OR cohort OR interrupted time series.

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Exclusion Criteria

While international literature will be included, non-English language publications will be excluded from the review due to resource limitations. Interventions using mobile phone technology only in the context of delivering/receiving text messages or phone calls will also be excluded. Given the review focus, the technology context is considered key so we will apply a publication start date of 2003. This is the year when 3G networks (required by apps) were launched in the United Kingdom [41]. The nature of modern technology means that this date is arguably internationally applicable. Studies that focus on young people with mental health problems, learning disabilities, and cognitive impairment will be excluded from this review, although at a later date we will undertake a review of studies involving such young people to determine whether apps are effective in supporting their particular skill and knowledge development.

Date Extraction

For every included study, two reviewers will extract relevant data independently. A tool based on the Data Extraction Template for Cochrane reviews [42] has been developed to facilitate consistent data extraction and prevent important information from being overlooked. This tool will be pilot tested, based on which, detailed instructions will be developed to make the process more objective. Any disagreements between reviewers will be resolved by discussion with the rest of the research team. The tool includes information regarding the study method (eg, study aim, intervention aim, study design, recruitment, participation criteria, ethics, funding, statistical methods used, and consumer involvement); participants (description, location, setting, and demographics), intervention (eg, theoretical basis, control/usual care/cointervention, delivery, providers and integrity), outcomes (primary and secondary outcome measures, how assessed and timings of follow-up), and results. Where required, authors will be contacted for clarification or additional information. Completed electronic extraction sheets will be kept as part of the audit trail, should they be required at a later stage to enable data checking.

Quality Assessment

The evidence and quality of the papers included in the systematic review will be assessed using a recognized tool [43]. A motivation for selecting this tool for quality assessment is that it is suitable for interventions of various study designs, which may be considered for inclusion in this review. As with the data extraction stage, studies will be scored independently by two reviewers, and any disagreements will be resolved through discussion with the other team members.

Data Synthesis

It is anticipated that there will be several studies that have focused on the effectiveness of mobile phone or tablet apps to facilitate the management of long-term physical conditions in young people. There are expected to be various outcome measures at various time-points for different conditions.

Where there is sufficient homogeneity amongst trials, metaanalyses will be undertaken with the RevMan software as used by the Cochrane Collaboration (RevMan v 4.2.8, Cochrane IMS). Levels of homogeneity can be determined using the chi-squared statistical test. Similar outcome measures will enable a pooled effect size and confidence intervals to be calculated as well as establishing level of publication bias through the use of funnel plots.

Based on the review's broad inclusion criteria, it is likely that interventions will be implemented at different time points and at various stages of an individual's illness trajectory. Moreover the population will likely be different age groups living with various physical long-term conditions. To counter this, the following categorizations will be considered for the synthesis: different age categories of young people; interventions developed to facilitate self-management and shared/joint management; whether or not interventions have a theoretical underpinning; short-term and long-term, based on whether any differentiation was made on length of time patient had lived with the condition. Wherever appropriate, pooled estimates will be created and sensitivity analyses will be used to assess the appropriateness of this.

Results

This systematic review aims to determine whether mobile phone and tablet apps are effective in young people's management of physical long-term conditions. Currently, the reviewers are screening papers meeting the search strategy. It is anticipated that by synthesizing included studies, the systematic review results can comment on what components of interventions are most associated with their effectiveness. The completion date for the review is projected to be early-mid-2015.

Discussion

Significance of Findings

Health care advancements mean young people living with long-term physical conditions have improved survival rates [5,44]. However, they have distinct health needs as they transition into adulthood for which regular and appropriate support is paramount [6,45]. While there is evidence suggesting that interventions in the form of mobile phone and tablet apps have great potential [13] and reasonable uptake [25], to our knowledge there has not been a synthesis of studies reporting on their effectiveness in the management of physical long-term health conditions in young people. Therefore, this review will synthesize relevant studies so as to make a definitive statement on the current evidence as well as to illuminate a clear evidence-based direction for future research.

We have an established multidisciplinary team of experts including health care professionals, consumer representatives, and researchers to take this project forward and ultimately develop evidence-based mobile phone and tablet apps for young people with physical long-term conditions. The consumer representatives on the research team have previously undertaken an online survey of 11-19 year olds with Juvenile Idiopathic Arthritis (JIA), which confirmed the need for an app that is codeveloped by people with experience of JIA (personal communication S Stones and S Douglas, 2013). This echoes

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other reports of young people calling for Web-based interventions to support self-management [46].

A particular strength of this review is that it aims to identify what interventions exist for a variety of long-term conditions (as opposed to condition specific reviews, for example in asthma [38]), which interventions are effective, and with what level of user involvement they were developed and evaluated [47]. In addition to disseminating these findings in a stand-alone review, they will be used as discussion aids in future qualitative studies with young people when developing and evaluating mobile apps. We will adapt the design and methodology of previous work (where members of the current team developed and evaluated an interactive Web app to support parents' home-based management of their childrens' long-term conditions [46,47]) to develop an evidence-based app that is effective in meeting the needs and preferences of young people with JIA. By working in collaboration with consumer representatives this app could potentially act as a template, with elements that could be transferred to other conditions. We anticipate our findings will have demonstrable benefit internationally for young people living with physical long-term conditions.

Conclusions

As yet, the effectiveness of mobile phone or tablet apps to support young people living with long-term conditions is unknown. With the emphasis on limited resources and technology, it is imperative to wholly understand the existing evidence base. This knowledge will serve those considering developing, using or recommending health care apps. Ultimately therefore, this systematic review aims to identify the existing evidence and evaluate the effectiveness of mobile phone and tablet apps for the management of physical long term conditions in young people.

Moreover, by identifying existing evidence and examined current apps, the review's results will form the first phase of the Medical Research Council (MRC) framework for developing and evaluating complex interventions [48]. The next phase will require the theoretical understanding developed from the review to be supplemented with primary research. We anticipate undertaking focus groups with young people to confirm and further illuminate the findings from the review. Apps identified from the systematic review will be used as discussion aids within the focus groups. Subsequent stages of the MRC framework will focus on designing, developing, and evaluating an app for the management of specific long-term conditions in young people. This will be undertaken in collaboration with young people living with long-term conditions. As well as using the review results as the basis of further research, the research team will disseminate the findings at international conferences and in a prestigious, peer-reviewed journal..

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Example search strategy for Medline Database: Ovid MEDLINE 1946 to January Week 2 2014.

[PDF File (Adobe PDF File), 84KB - resprot_v4i2e40_app1.pdf]

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Protocol

Hepatitis C Virus Disease Progression in People Who Inject Drugs: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Most hepatitis C virus (HCV) infections in the United States occur following non-sterile injection drug use. However, the majority of people who inject drugs (PWID) with chronic HCV are not currently receiving care.

Objective: This paper presents our protocol for the systematic review and meta-analysis of data on the natural history of HCV among PWID and will inform modeling of the impact and cost-effectiveness of HCV management among this population. This study is conducted as part of the HCV Synthesis Project, which is funded to develop recommendations for HCV control strategies in the United States.

Methods: This protocol describes the methods used for a systematic review and meta-analysis of published and unpublished data on the natural history of HCV among PWID including viral clearance, fibrosis progression, and the incidence of compensated cirrhosis (CC), decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), and liver-related mortality.

Results: Final results are anticipated by December 2016.

Conclusions: Methods used for the synthesis of data on disease progression among HCV mono-infected PWID are presented. Data from the systematic review and meta-analysis will be used to inform simulations of the natural history of HCV and to model the effects of prevention and treatment strategies to reduce disease burden and the associated costs to society and individual patients.

(JMIR Res Protoc 2015;4(2):e68) doi:10.2196/resprot.4518

KEYWORDS

hepatitis C; people who inject drugs; HCV disease progression; fibrosis; hepatocellular carcinoma; cirrhosis; systematic review

Introduction

In high-income countries, most cases of hepatitis C virus (HCV) infection are attributable to non-sterile drug injection [1,2]; the majority of chronically infected people who inject drugs (PWID) are not currently receiving care for their HCV infection [3]. Characteristics of both the virus and the population (PWID) complicate the diagnosis and management of chronic HCV infection [4]. Early infection with HCV is frequently asymptomatic, with the majority (75-85%) of those infected going on to develop chronic HCV infection [5,6]. The incubation period of HCV may last decades with symptoms only appearing after irreversible liver damage has occurred. The asymptomatic nature of HCV hampers early diagnosis, especially among those with limited or inconsistent access to health care, those uninsured or incompletely insured, and marginalized populations including PWID [7,8]. While new treatments for chronic HCV offer shorter treatment regimens with fewer side effects, high costs and concerns about reinfection after treatment limit the use and availability of these drugs.

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An additional challenge to the study of the natural history of HCV is the disease's long course towards clinically apparent liver sequelae and symptoms [9]. Disease outcomes may be underestimated because of competing mortality from events like drug overdose or co-morbidities like HIV [10,11]. Because disease duration often is estimated assuming that infection occurred at onset of drug injection rather than by observing the date of seroconversion, rates of disease progression also are underestimated [12,13]. Factors known to synergistically increase the rate of hepatic injury due to HCV—such as alcohol use—are difficult to systematically collect and often are not reported in studies on HCV natural history [13-16]. Finally, due to the challenges of outreach to a largely "hidden population" of PWID, study samples often are drawn from hospitalized patients and therefore may be biased toward greater disease severity [17].

Understanding HCV disease progression among PWID is critical to planning and allocating resources to control the HCV epidemic within this group. This paper presents our protocol for the systematic review and meta-analysis of data on the natural history of HCV among PWID and will inform modeling of the impact and cost-effectiveness of HCV management among this population. This study is conducted as part of the HCV Synthesis Project (see Hagan, Neurer, Jordan, Des Jarlais, Wu, Dombrowski, Khan, Braithwaite, and Kessler, 2014; Jordan, Des Jarlais, and Hagan, 2014) [18,19], which is funded to develop recommendations for HCV control strategies in the United States.

Methods

Design and Scope

The objective of this systematic review is to synthesize published and unpublished data on the natural history of HCV among PWID. HCV disease progression will be examined via the following outcomes: viral clearance, fibrosis progression rates, and the incidence of compensated cirrhosis (CC), decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), and liver-related mortality. Factors contributing to progression towards each outcome (eg, the role of infection with genotype 3 in DC incidence) also will be examined.

Criteria For Considering Reports

Inclusion and Exclusion Criteria

Reports will be included if: (1) the study sample is composed of participants who are chronically infected with HCV and report current or previous injection drug use; (2) original data on disease progression is presented; (3) at least 90% of the study sample is comprised of PWID; (4) findings are published or available after January 1, 1990; and (5) the study is conducted in upper-middle- or high-income countries (to insure comparability based on similar routes of infection, diagnosis, and treatment). Reports will be excluded if participants are co-infected with HIV, have received HCV treatment, or have undergone liver transplantation. Reports that include both mono- and co-infected participants will be accepted only if data from the HCV mono-infected sample is disaggregated.

Exposure Measures

The primary exposure of interest in this systematic review will be acute or chronic HCV infection. Adopting the European AIDS Treatment Network (NEAT) recommendations [20], the *preferred criteria* to measure acute exposure will be observed seroconversion, positive HCV antibody, and positive HCV RNA, or positive HCV RNA with a documented negative HCV RNA result in the previous 12 months. The *alternative criterion* for measuring exposure will be a single test result positive for anti-HCV antibody. The *preferred criterion* to measure chronic HCV infection will be documented persistent HCV RNA for at least 6 months [21]. The *alternative criterion* will be a statement in the report that all participants are chronically infected.

Outcome Measures

Primary outcomes examined will be the incidence and prevalence of spontaneous viral clearance, fibrosis, CC, DC or HCC, and liver-related mortality. To measure clearance of infection, the *preferred criterion* will be two or more consecutive undetectable HCV RNA test results separated by at least 6 months. *Alternative criterion* for clearance measurement will be a single negative RNA test result or an undetectable viral load.

The *preferred criterion* for measuring fibrosis and cirrhosis will be a liver biopsy staged according to the METAVIR, Ishak, Knodell, or Scheuer scoring systems, however, classification of cirrhosis using alternate diagnostic criteria or symptomatology also will be accepted. Data on fibrosis progression from noninvasive procedures such as FibroSURE and FibroScan will not be accepted. The criteria for measuring DC and HCC will include symptoms such as ascites, esophageal varices, and hepatic encephalopathy, and testing such as ultrasound.

To account for the underreporting of HCV as the underlying cause of death, the scope of the mortality outcome will include both HCV- and liver-related deaths among participants who have chronic HCV infection [22]. The *preferred criteria* for measuring liver-related mortality will be records from hospital databases and death registries.

Search Strategy

Electronic searches will be conducted for literature published beginning January 1, 1990 using the following electronic databases: Ovid, Proquest, PubMed, and Web of Science. Search filters will include publication date, language (English only), and type of document (journal article). Manual searches of the reference lists of eligible reports, pertinent reviews and meta-analyses, and methodological papers will be reviewed. Abstracts from scientific conferences and presentations from study cohorts will also be screened for eligibility.

Screening and Data Collection

Reports retrieved through the search strategy will be imported into Endnote X6 and duplicates will be removed. Two research assistants will perform the screening of abstracts and the extraction of data. Every abstract will be screened to determine its eligibility for inclusion in this study. Abstracts with any mention of PWID and any outcome of interest will be considered for inclusion, and the full-text report will be reviewed. For all

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potentially eligible reports, the full-text report will be reviewed by both research assistants to discern eligibility for inclusion. Reports meeting eligibility criteria will be coded. Reasons for exclusion will also be recorded.

Each research assistant will independently code the included reports using a coding tool that will be adapted from previous systematic reviews led by the principal investigator [23,24]. Coded data will be subsequently entered into a Microsoft Access database. The coding tool will include the following domains: citation information; study cohort, period, and location; study design; sampling, recruitment, testing, and statistical methodology; incidence or prevalence of spontaneous viral clearance, fibrosis, CC, DC, HCC, and liver-related mortality; rates of fibrosis progression; and, participant demographics, particularly risk factors associated with accelerated liver disease progression such as sex, race/ethnicity, and alcohol use. In the case of missing or inconsistent data in a report, the corresponding author will be contacted for additional information or clarification.

Quality Assurance

Overview

Both of the research assistants involved in the project have graduate-level training in research methodology as well as additional training in HCV epidemiology and the methods of systematic review and meta-analysis. Pilot screening and coding tests will be conducted with and under the direction of the project director and principal investigator to assess inter-coder reliability and refine procedures for data extraction. The project director will evaluate all full-text reports excluded by the research assistants to corroborate their ineligibility. The research assistants will meet weekly during the coding process to compare their independent coding results. When consensus between the research assistants is not reached, the principal investigator and project director will be consulted; they will also review all coding to ensure accuracy and completion. Weekly staff meetings will provide a forum to discuss and resolve issues with data extraction. A study manual will guide the process and provide ongoing documentation of special cases and their resolution.

Report Quality and Critical Appraisal

All reports included for the systematic review will be assigned quality ratings based on an adapted version of the Quality In Prognosis Studies (QUIPS) tool [25]. The QUIPS tool will be modified to evaluate cross-sectional studies in addition to cohort studies and will be tailored to assess potential sources of bias in the included studies. Ratings of *high* (2), *moderate* (1), or *low* (0), will be assigned to judge the degree to which each study controls selection bias, confounding, and misclassification.

To account for the threat of selection bias, we will assess whether participant selection (eg, recruitment method or study location) is likely to alter the likelihood of observing the outcomes of interest. Comparability will be assessed in relation to the extent to which measures of association between prognostic factors and outcome appropriately adjust for the effects of confounding. Classification bias related to exposure and outcome will be evaluated including consistency in methods used to ascertain date of infection (eg, observed seroconversion vs date of first injection) and disease status. Misclassification of exposure (eg, acute vs chronic infection) will be evaluated by the criterion previously discussed.

Data Analysis

This review will synthesize aggregate (report-level) data. Analysis will begin with an assessment for homogenous subsets within each outcome-specific set of reports. Given the expected variability in estimates across the reports, we will evaluate heterogeneity using the measures of Cochran's Q (Der Simonian and Laird) and I^2, at each step of the analysis to distinguish between true variation of effects and variation due to other factors [26-28]. Data-based methods will be used to select covariates in multivariate models [29]. Effect size estimates will be combined using standard meta-analytic techniques in the form of pooled odds ratios and their 95% confidence intervals [30]. We will use random effects calculations whenever possible [31]. Potential moderator effects will be tested using meta-regression [32,33].

We anticipate having to modify the collected data in three different ways during data synthesis. First, effect measures reported as hazard ratios, risk ratios, or relative risks will be transformed into odds ratios using standard methods. Second, all data on fibrosis progression (including calculated fibrosis progression rates) will be standardized by converting all classification systems (eg, Ishak, Knodell or Scheuer) to METAVIR units [34]. If a report does not provide a progression rate, a progression rate of the stage-constant linear form will be calculated using one of two methods [35]: (1) for reports with participant-level data, the ratios of each participant's METAVIR score to duration of infection in person-years will be summed, and the resulting mean will be used as the fibrosis progression rate [34,35], or (2) for reports with sample-level data, the fibrosis progression rate will be calculated as the ratio of participants' cumulative METAVIR units to the estimated disease duration in person-years for the entire sample. Third, disease duration will be estimated using two different approaches: (1) infection starting from the date of first injection drug use, and (2) an adjusted duration calculated as 2 years after the date of first reported injection drug use. This second calculation is consistent with a prior meta-analysis of time to HCV infection among PWID [36].

Results

The final results of this systematic review and meta-analysis are expected by December 2016.

Discussion

This article presents a protocol for the systematic review and meta-analysis of disease progression among PWID with HCV mono-infection. Synthesized data on disease progression will be used to inform simulations of the natural history of HCV and to model the effects of prevention and treatment strategies to reduce disease burden and the associated costs to society and individual patients. This systematic review comes at a crucial time as new, better-tolerated, and more effective drugs become

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available to treat HCV infection. As the high cost of these new treatments spurs debate over resource allocation, it is crucial to understand the natural history of HCV disease among PWID, the largest population of HCV-infected persons in the United States.

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Authors' Contributions

JC wrote the first draft of the manuscript. AEJ, HH, JC, and DS were responsible for conception and design, and critical revision of the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Reviewer Comments.

[PDF File (Adobe PDF File), 121KB - resprot_v4i2e68_app1.PDF]

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Abbreviations

CC: compensated cirrhosis
DC: decompensated cirrhosis
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
PWID: people who inject drugs
QUIPS: Quality in Prognosis Studies tool

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Protocol

The Effectiveness of Technology-Based Strategies to Promote Engagement With Digital Interventions: A Systematic Review Protocol

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Abstract

Background: Digital interventions provide effective and potentially cost-effective models for improving health outcomes as they deliver health information and services that are widely disseminated, confidential, and can be tailored to needs of the individual user. Digital interventions have been used successfully for health promotion, mental health, and for enabling self-management of long-term conditions. However, their effectiveness is limited by low usage rates, with non-engagement a major challenge. Hence, it is crucial to find effective strategies to increase user engagement with digital interventions.

Objective: This systematic review will aim to evaluate the effectiveness of technology-based strategies to promote engagement with digital interventions.

Methods: We will follow Cochrane Collaboration guidelines on systematic review methodology. The search strategy will be executed across seven e-databases (including MEDLINE, EMBASE, PsycINFO, CINAHL) using the concepts "digital intervention" and "engagement", limited by study type (randomized controlled trial). Grey literature and reference lists of included studies will be searched. Titles and abstracts will be independently screened by 2 authors. Then the full text of potentially eligible papers will be obtained and double screened. Data from eligible papers will be extracted by 1 author and checked for accuracy by another author. Bias will be assessed using the Cochrane bias assessment tool. Narrative synthesis will report on all included studies, and where appropriate, data will be pooled using meta-analysis. All findings will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Sources of heterogeneity will be further investigated if required.

Results: Our research is in progress. The final draft of the systematic review is being written and will be submitted before the end of 2015.

Conclusions: The review findings will inform researchers and digital intervention providers about optimal use of technology-based strategies to promote engagement with digital interventions.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews: CRD42014010164; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014010164#.VTZmmiFViko (Archived by WebCite at http://www.webcitation.org/6XxQC8fT8).

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KEYWORDS

systematic review; Internet; computers; Web-based interventions; engagement; adherence; attrition; usage

Introduction

Digital Interventions

Digital interventions (DIs) are programs that provide information and support (emotional, decisional, and/or behavioral) for physical and/or mental health problems via a digital platform (ie, website, computer) [1]. DIs have been developed and used for numerous health issues including improving self-management of long-term conditions [2] (eg, diabetes [3] and asthma [4]), health promotion for sexual health [1], reducing excessive alcohol consumption [5-7], smoking cessation [8,9], increasing physical activity [10,11], and mental illness (eg, depression [12]). DIs can potentially provide a convenient gateway for patients to access and receive tailored and private health information and services [1,5]. Numerous systematic reviews have confirmed the potential effectiveness of DIs in improving health behaviors and health outcomes [1-5,7-14]. However, overall, effect sizes tend to be small and many reviews have noted substantial heterogeneity. A common problem for DIs is lack of engagement, or attrition from the intervention [15].

Engagement With Digital Interventions

Research suggests that the effectiveness of a DI can be mediated by the user's level of engagement, and there appears to be a dose-response relationship [13,16-18]. For example, one randomized controlled trial (RCT) found that users of a smoking cessation DI had better quit outcomes if they had a higher number of logins (OR 1.19, 95% CI 1.08-1.31) [19]. In another RCT of an intervention to increase vegetable and fruit intake, there was a positive association between usage of the intervention and increased intake of fruit and vegetables [20]. Further, a descriptive systematic review exploring the relationship between engagement and DI outcomes found a positive association between engagement with the intervention and outcomes for interventions targeting physical health [21]. Although this association could be due to reverse causality, where users who make most change (for other reasons) ascribe this change to the DI and hence engage with it, it is not unreasonable to suggest that non-use or suboptimal use of a DI is likely to limit its effectiveness [15,22]. Hence, there is considerable interest in methods of improving user engagement with DIs.

The Use of Prompts to Engage Digital Intervention Users

One potential strategy for improving engagement that has been explored is the use of prompts or reminders [15,23,24]. An early meta-synthesis of DIs for behavior change found that use of text messages, phone calls, and email prompts had a significant enhancing effect on behavior change: effect size (d+)=0.81, CI 0.14-1.49; 0.35, CI 0.09-0.61; and 0.18, CI 0.07-0.29, respectively [25]. A systematic review also found that periodic email and phone prompts used for behavior change were effective compared to control groups either receiving non-technological prompts or no prompts [26]. However, neither of these reviews focused primarily on promoting engagement with the intervention. Both had a primary aim of determining the overall effectiveness of digital interventions for behavior change. Brouwer et al (2011) undertook a review of literature published between 1995 and 2009 to explore which strategies have been integrated into interventions to improve engagement, and what the relative effectiveness of these strategies were. This review found considerable heterogeneity but suggested that regular contacts by email or phone appeared to result in greater number of logins [27]. Human contact (eg, regular phone calls) may considerably add to the cost of delivery of digital interventions and may therefore undermine one of the potential benefits of digital interventions, namely the low marginal cost per additional user [28].

To our knowledge, there have been no reviews focusing specifically on automated or technological methods of promoting engagement with digital interventions. This review addresses this gap.

Aim and Objectives

Our overall aim is to evaluate the effectiveness of technology-based strategies to promote engagement with DIs.

Specific objectives are (1) to describe technology-based strategies to promote engagement with DIs, (2) to assess the effectiveness of technology-based strategies in promoting engagement with digital interventions, (3) to explore whether different characteristics such as timing, frequency, duration, content, sender, mode of delivery, or use of theory are associated with differential effectiveness, and (4) describe the cost of technology-based strategies to promote engagement with digital interventions.

Methods

Design

This study is a systematic review of RCTs and quasi-RCTs following Cochrane methodological guidance [29]. A structured approach has been used to build the eligibility criteria, using PICOS (Participants, interventions, comparisons, outcomes and study designs) [30].

Definitions

The systematic review was designed to be comprehensive and inclusive, thus the following definitions were used:

- Digital interventions are programs that provide information and support (emotional, decisional, and/or behavioral) for physical and/or mental health problems via a digital platform specifically a website or a computer [1]. The definition was chosen because it includes offline and online interventions and specifies the purpose of the DI without limiting it by listing specific characteristics [31].
- Engagement has been defined in the literature by its outcome measures such as the number of logins/visits, number of modules used, duration of time spent on DI or

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number, and type of pages viewed and visited [17,32,33]. This way of defining engagement usually depends on the characteristics of the DI; for example, if the DI consists of modules, then engagement will be defined by the number of completed modules. In addition, engagement has been categorized into three phases: (1) visiting the DI for the first time, (2) prolonging the first visit, and (3) revisiting the DI [34], which depends to some extent on the goal of the DI and whether it has to be used once or repeatedly. In this systematic review, the third phase of engagement will be targeted, the user's regular interaction with part or all of the DI. The most appropriate measures for this definition are the number of participants who visited the DI (logged-in to the website) and/or the number of visits/logins, as they bridge the gap between the engagement strategy and users interacting or accessing the website [27,35], but other measures will be considered depending on the included papers.

- It is important to differentiate between disengagement from a DI (non-usage attrition), and disengagement from an online trial of a DI, that is, loss to follow-up (dropout attrition) [15]. For example, one study of a DI for workplace health promotion reported higher non-usage attrition in controls compared with intervention participants (who received regular emails) but higher dropout attrition in the intervention group than the control group [36]. Similarly, another study examined the relationship between dropout attrition and disengagement from a DI and found that the relationship between these two is complex and that factors associated with greater adherence to a trial or better engagement to a DI were not similar [23].
- Based on the definition of engagement above, technology-based engagement promoting strategies will be defined as digital and analogue technology methods used to promote the user's regular interaction with all or part of the DI, including but not limited to landline phone calls, cell phone calls, text messages, multimedia messages, emails, automated voice calls, or faxes. Examples of interventions that will be included are a computerized treatment program with cell phone text messages that remind the user to visit the program or a blood pressure self-monitoring website that sends email prompts to users to enter their pressure readings on the website.

Data Sources and Search Methods

A comprehensive search strategy has been developed to ensure we identify all potentially relevant studies. The strategy was developed by the lead author together with an information specialist and reviewed by the entire team. The strategy was informed by previous search strategies for reviews of DIs available in the literature. It combined the two concepts of digital interventions and engagement, limited by study type (RCT).

Hand searching was done to pilot the electronic database search strategy. Issues from last 2 years (2012-2013) of the *Journal of Medical Internet Research (JMIR)* were searched to find related articles and test whether the articles were identified and the search strategy was adjusted accordingly. The validity of the search strategy was also assessed by taking seven known RCTs of technological strategies to promote engagement with DIs and checking to see if they were identified in a MEDLINE search using the strategy (see Multimedia Appendix 1).

The Medline thesaurus Medical Subject Headings (MESH) terms were refined for each database, and unpublished data will be sought in the form of conference proceedings (Conference Proceedings Citation Index, formerly ISI Proceedings). References of the included studies and issues of key journals such as JMIR will be hand searched, and any papers citing included or key papers will also be screened.

The following databases will be searched from inception with no language restrictions: the Cochrane Central Register of Controlled Trials (CENTRAL); General international health care electronic bibliographic databases: MEDLINE and EMBASE; and social science, education, psychology and nursing electronic bibliographic databases: ISI Web of Science, Education Resources Information Center (ERIC), PsycINFO, and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

Articles Screening and Selection

All citations identified by the search strategy will be downloaded to the reference manager EndNote X5 and de-duplicated. Studies will be independently double screened. Full text manuscripts for potentially eligible articles will be obtained, and authors will be contacted directly for articles that were not retrievable through library sources. The full text articles will be assessed for eligibility by 2 authors (GA and EM). Any disagreement will be resolved by discussion with reference to the inclusion and exclusion criteria or if necessary with input from a third reviewer (FH). Justification for exclusion will be recorded, and a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart will be constructed to show search, screening, and selection results (see Figure 1).

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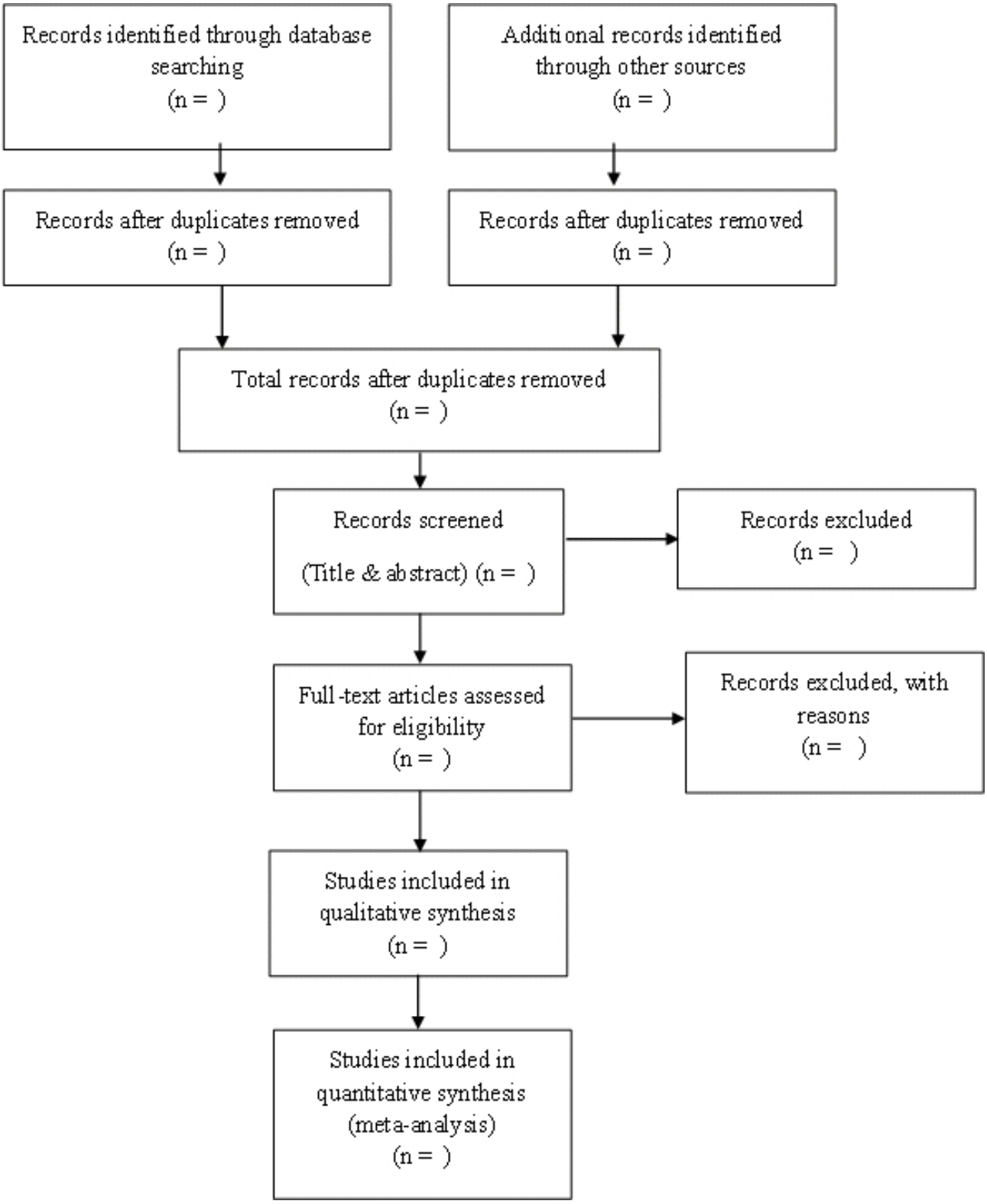
Figure 1. PRISMA flow diagram.



Inclusion Criteria

Participants

Participants will be all adults, aged 18 years old or over. There will be no limitations on gender, socioeconomic status, ethnicity, or health status. Participants may use the intervention in any setting.

Interventions

The intervention of interest is technology-based strategies to promote engagement with digital interventions. The interventions have to meet the definition of the strategies described above.

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Comparisons

We will include three groups of comparators: (1) minimal or inactive comparators, such as no strategy, (2) non-technological strategies such as printed materials or face-to-face contact, and (3) alternative technology-based strategies (eg, where the effects of email prompts are compared to the effects of text-message prompts). This third comparator will be used to explore relative effectiveness of the different strategies.

Outcomes

Primary Outcomes

The primary outcome will be engagement with the DI, which may be recorded as the number of logins/visits, number of pages visited, number of sessions completed, time spent on the intervention website, and number of DI components/features used. To simplify interpretation of the outcome measures, they will be categorized into dichotomous and continuous engagement outcomes, for example:

- Dichotomous engagement outcome: any dichotomous measure of how participants engaged with the DI such as proportion of participants who visited the DI, or proportion of participants who completed a pre-specified number of modules.
- Continuous engagement outcome: any continuous measure of how participants engaged with the DI such as number of visits or page views.

Secondary Outcomes

Two types of secondary outcomes will be selected: (1) adverse outcomes such as users feeling frustrated and bothered by engagement prompts, users experiencing a loss of self-esteem due to not being able to engage with the DI, users receiving prompts with wrong information or links to the DI, and exclusion for users who are not able to receive the engagement prompt, and (2) economic outcomes, which are costs associated with strategies promoting engagement to inform future cost-effectiveness analysis. All outcomes measured in the studies that meet our inclusion criteria will be included whether they are objective or self-reported.

Study Designs

Studies of RCTs or quasi-RCTs will be included. Trials can either be trials of DIs that used strategies promoting engagement or they can be trials evaluating strategies specifically. Economic evaluation will be included if they were conducted alongside the main trial.

Exclusion Criteria

Exclusion criteria will comprise the following: (1) interventions targeted exclusively at health professionals (eg, computer-based decision aids to assist health professionals in making decisions with regards to treatments), (2) trials where attrition from trial and attrition from intervention are non-distinguishable, and (3) trials where the effect of the DI components cannot be separated from the effect of the engagement promoting strategy; for example, when trials where the DI is not compared to another DI (eg, a website to lose weight with email prompts compared with dietitian face-to-face sessions with emails from the dietitian) or when a DI with an engagement strategy is compared to a different DI without engagement strategy (eg, an enhanced version of the DI with email prompts compared to a basic version without engagement prompts).

Data Abstraction

Data will be extracted using an adapted version of the Cochrane Consumers and Communication Review Group data extraction template. The data extraction form will be piloted and changes will be documented. Standard information will be collected including study references, design, aims and objectives, funders, setting, health condition/health behavior, population details, exclusion and inclusion criteria, digital intervention, analytical methods, follow-up duration and rates, results, and risk of bias. In addition, we will extract full details of the engagement strategy, including timing, frequency, duration, content, sender, mode of delivery (eg, email, text message), and use of theory. We will apply a taxonomy of behavior change techniques (BCT) developed for use with digital interventions [37] to describe and codify the content of the engagement strategies. Data will be extracted from the included studies by 1 review author (GA), and a second review author (FH) will independently verify the extracted data. Application of the BCT taxonomy will be undertaken by the lead author (GA) and checked by a second author with experience using this taxonomy (RW).

Disagreement will be resolved by discussion between the 2 authors. If no agreement can be reached, a third author (EM) will decide and reasons for the decision documented. If any information is missing or needs to be clarified, authors will be contacted.

Data Analysis and Synthesis

Measurement of Treatment Effect

The appropriate effect measure will be determined depending on the type of data. For the primary outcome, website metrics will either be continuous or dichotomous. For dichotomous outcomes, odds ratio or relative risk and their 95% confidence intervals will be used. For continuous outcomes, mean difference with 95% confidence intervals or standardized mean difference will be used.

Unit of Analysis Issues

It is anticipated that most studies will have randomized DI users to either intervention or control groups, therefore the unit of analysis will be the individual.

Dealing With Missing Data

As primary outcomes measures (ie, website metrics) are automatically generated during a DI, it is anticipated that missing data will most likely be in secondary outcomes. Where missing data present a clear bias to the study outcomes, it will be noted and discussed with the research team and the authors will be contacted directly for clarification. Where the risk of bias cannot be mitigated, studies will be included only in the narrative part of the systematic review.

Data Analysis

Results will be reported according to the PRISMA guidelines [30]. Data from included studies will be tabulated to allow for

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narrative description of the results. This also allows for assessment of heterogeneity in terms of participants, DI and strategy, outcomes, comparator, study design, and quality of studies (risk of bias). Where appropriate, data will be summarized statistically by meta-analysis according to Cochrane systematic review methodology. Data will be pooled using fixed effects and random effects model. The results will be presented for three comparator types: minimal or inactive comparators, non-technological strategies, and alternative technology-based strategies.

Where possible, we will use the number of participants who visited the DI (logged-in to the website) or the number of visits/logins, as these are the most appropriate indicators for engagement [27,35]. The longest follow-up period available will be chosen, as it is important to demonstrate sustained change.

Due to the variable nature of the interventions, heterogeneity is expected and it will be assessed using the I^2 statistic to quantify the amount of variation in results across studies beyond that expected from chance [30]. Sensitivity analysis will be conducted according to the Cochrane handbook recommendation by excluding trials with poor quality to determine their effects on the meta-analysis. Reporting bias will be assessed through visual inspection of funnel plots.

Data on characteristics of engagement strategies, and adverse and economic outcomes will be described narratively and summarized statistically if possible.

Critical Appraisal Techniques

An assessment of risk of bias will be done based on the Cochrane risk of bias assessment tool [29]. The following criteria will be used:

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated interventions adequately prevented during the study (blinding)?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?
- Was the study free of other problems that could put it at a risk of bias? Including but not limited to differences in baseline characteristics between groups, validity and reliability of outcome measures, sample size, and power.

Studies will be categorized as low risk of bias, high, or unclear. A risk of bias graph and summary table will be generated. The bias assessment will be done by 1 author (GA) and will be checked by another author (FH). Any discrepancies will be resolved by a third author (EM).

Consumer Participation

If possible, developers, researchers, individuals, or groups interested in the review will be asked whether the protocol addresses priorities and if they can help in interpretation of data synthesis and to inform the discussion and conclusion of the systematic review.

Results

Our research is in progress. The final draft of the systematic review is being written and will be submitted before the end of 2015.

Discussion

This review will present an unbiased and detailed summary of the current and available evidence regarding technological strategies that promote engagement with DIs. Results of this review will enable researchers and DI providers to make optimal use of technological prompts to enhance engagement with DIs.

Acknowledgments

Ruth Muscat, Knowledge Resources Librarian, from University College London, London, UK, assisted with developing the search strategy. GA is a PhD student at UCL, funded by the Saudi Cultural Bureau.

Authors' Contributions

GA developed the protocol, which was revised and approved by all authors. GA will conduct search strategy, screening, extraction, analysis, and writing with support and contribution by all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1

MEDLINE search strategy.

[PDF File (Adobe PDF File), 91KB - resprot_v4i2e47_app1.pdf]

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Abbreviations

DI: digital intervention
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial

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Protocol

The Effect of Health Information Technology on Health Care Provider Communication: A Mixed-Method Protocol

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Abstract

Background: Communication failures between physicians and nurses are one of the most common causes of adverse events for hospitalized patients, as well as a major root cause of all sentinel events. Communication technology (ie, the electronic medical record, computerized provider order entry, email, and pagers), which is a component of health information technology (HIT), may help reduce some communication failures but increase others because of an inadequate understanding of how communication technology is used. Increasing use of health information and communication technologies is likely to affect communication between nurses and physicians.

Objective: The purpose of this study is to describe, in detail, how health information and communication technologies facilitate or hinder communication between nurses and physicians with the ultimate goal of identifying how we can optimize the use of these technologies to support effective communication. Effective communication is the process of developing shared understanding between communicators by establishing, testing, and maintaining relationships. Our theoretical model, based in communication and sociology theories, describes how health information and communication technologies affect communication through communication practices (ie, use of rich media; the location and availability of computers) and work relationships (ie, hierarchies and team stability). Therefore we seek to (1) identify the range of health information and communication technologies used in a national sample of medical-surgical acute care units, (2) describe communication practices and work relationships that may be influenced by health information and communication technologies in these same settings, and (3) explore how differences in health information and communication technologies, communication practices, and work relationships between physicians and nurses influence communication.

Methods: This 4-year study uses a sequential mixed-methods design, beginning with a quantitative survey followed by a two-part qualitative phase. Survey results from aim 1 will provide a detailed assessment of health information and communication technologies in use and help identify sites with variation in health information and communication technologies for the qualitative phase of the study. In aim 2, we will conduct telephone interviews with hospital personnel in up to 8 hospitals to gather in-depth information about communication practices and work relationships on medical-surgical units. In aim 3, we will collect data in 4 hospitals (selected from telephone interview results) via observation, shadowing, focus groups, and artifacts to learn how health information and communication technologies, communication practices, and work relationships affect communication.

Results: Results from aim 1 will be published in 2016. Results from aims 2 and 3 will be published in subsequent years.

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Conclusions: As the majority of US hospitals do not yet have HIT fully implemented, results from our study will inform future development and implementation of health information and communication technologies to support effective communication between nurses and physicians.

(JMIR Res Protoc 2015;4(2):e72) doi:10.2196/resprot.4463

KEYWORDS

interdisciplinary communication; health information technology; computer communication networks; hospital communication systems

Introduction

Background

While more information and communication technology (ICT) will be deployed in the next 10 years than ever before, these developments do have risks to patients, leading some to call this a "dangerous decade" for health information technology (HIT) [1]. Poor communication between physicians and nurses is well known as one of the most common causes of adverse events for hospitalized patients [2-4] and a major root cause of all sentinel events [5]. HIT is often promoted as offering potential solutions to the problems uncovered by root cause analyses, including a variety of media that physicians and nurses are rapidly adopting to communicate with each other: the electronic medical record, computerized provider order entry, email, and pagers. While there is no doubt that increasing use of ICT will change the way nurses and physicians communicate, there is already evidence that communication technologies can contribute paradoxically to more [3,6], not fewer [7] communication difficulties. Thus, it is critically important to understand how communication technology is being used in health care and when it is most likely to achieve the goals of better communication and safer care [6].

The purpose of the study we outline here is to describe, in detail, the ways in which health information and communication technologies facilitate or hinder communication between nurses and physicians with the ultimate goal of identifying optimal ways to support effective communication. Effective communication is the process of developing shared understanding between communicators by establishing, testing, and maintaining relationships [8]. While this study is designed to provide generalizable lessons about the use of ICT in a rapidly changing health information technology environment, our description is designed to provide a framework and an exemplar for smaller investigations within single institutions that are seeking to understand and improve their communication culture.

As the use of newer communication technologies increases, physicians and nurses who previously came together frequently at the point of care delivery to discuss a patient face-to-face, are now increasingly separated by location and time and use a variety of technologies to transmit their discussions [9]. This change may improve the efficiency with which communication occurs but could also increase message ambiguity [6] and contribute to more adverse events [10], especially when complex situations arise [11]. Communication practices that consist of sending messages solely through a single medium, such as a pager, ignore the fact that a message sent via pager will differ from the same message sent verbally because content conforms to the medium in which it is presented [12].

Theoretical Model

A theoretical framework allows researchers to empirically test relationships among concepts of interest, facilitating accumulation of knowledge and progression in the field. Our theoretical model provides a plausible explanation for both why and how technologies may influence communication. The theoretical model for this study explains how health information and communication technologies might meet the demand for more information through better alignment between technology and the message to be conveyed. Our theoretical model, depicted in Figure 1, posits that through communication practices and work relationships, health information and communication technologies contribute to alignment or mismatch between the technology and the message which, in turn, can affect communication.

Communication practices and work relationships form the context in which communication technology is situated. Communication practices are influenced by the use of rich media and the location and availability of computers. Media richness is defined as a characteristic of a communication medium that facilitates the ability of information being sent through that medium to change understanding [13]. Classification of media as rich or less rich is based on a medium's capacity for immediate feedback, number of cues and channels used, personalization, and language variety [13]. Physician and nurse communication practices may or may not include a consideration of the richness of the media available to them. Media richness theory suggests that people should choose rich media such as face-to-face conversations or telephones to communicate about complex issues with lots of ambiguity. Rich media reduce ambiguity by enabling communicators to overcome different frames of reference and by providing the capacity to process complex messages. Less rich media provide fewer cues, restrict feedback, and tend to be impersonal but are effective for processing well understood messages and standard information [13]. Computer applications (eg, physician and nursing notes on electronic medical records (EMRs), computerized provider order entry (CPOE), electronic text) fall at the less rich end of the spectrum; computer applications are impersonal when they have very little opportunity to personalize the documentation or use a variety of language options.

The location and availability of computers influences communication practices by disrupting the development of distributed cognition [9,14], the notion that knowledge about a patient's illness and treatment is distributed among the

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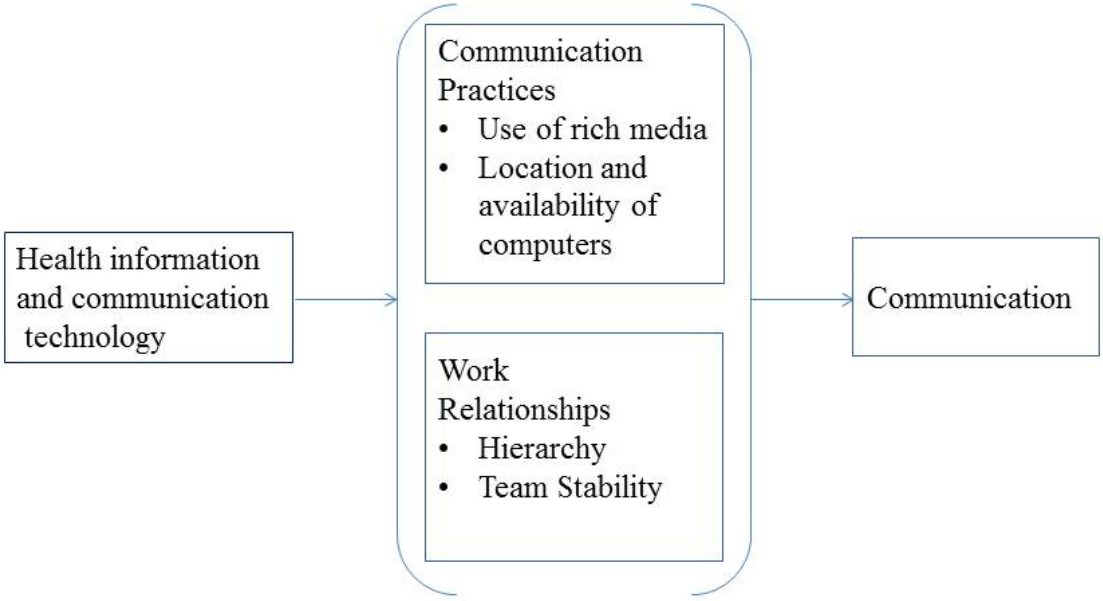
physicians and nurses (and other disciplines) who are providing care [15]. When physicians and nurses are dispersed to several far-flung locations to use communication technologies instead of being co-located, opportunities for sharing knowledge from differing perspectives are diminished [16], so the meaning of a message pertaining to the understanding of a situation is open to misinterpretation.

Work relationships affected by hierarchies within a health care team and team stability also influence how health information and communication technologies affect communication. Physicians and nurses must communicate with each other to solve patient care problems which require input from multiple disciplines for successful resolution [17]. Communication in these situations needs to facilitate consensus building that may be difficult to achieve for many reasons, but we have identified two in our theoretical model. First, the hierarchical nature of the relationship between physicians and nurses can hinder consensus building if nurses do not speak up about a patient care issue because they fear being embarrassed or censured by physicians [18]; nurses' silence possibly contributes to adverse outcomes [19]. Thus, collaborative rather than hierarchical relationships are recommended to help to assure that all perspectives are brought to bear on a complex problem and arrive at consensus. Second, team stability may be especially relevant to the connection between communication technology and communication [20]. Team stability is defined as the same individuals who come together to work on collaborative tasks [20]. Team stability is important because it allows the development of relationships necessary to facilitate understanding of varying perspectives [21]. Individuals who communicate more with each other become more similar as they increasingly share their beliefs and knowledge [22]. Stable physician presence on the health care team makes it easier for clinicians to find common ground (shared knowledge between two communicators [23]) and construct a shared reality [24].

Figure 1. Theoretical model.



Methods

Study Overview

We will use a sequential, mixed-methods study design [25], beginning with a quantitative survey and using those results to inform a two-part subsequent qualitative phase [25]. Mixed-methods blend the strengths of both qualitative and quantitative research, generating additional data and enhancing insights to provide a robust view of the phenomenon under investigation. We will integrate multiple forms of data, mixing methods through an approach known as connecting data, which involves using information gained through one method to inform subsequent data collection using another method [25]. Our purpose in using mixed-methods is to provide a contextualization of communication technologies being used in medical-surgical units [25], and to develop a more complete understanding of how health information and communication technologies facilitate or inhibit understanding between physicians and nurses when they communicate. Information gained through the quantitative survey will inform subsequent data collection using qualitative methods. Specifically, stratified purposeful sampling will be applied to results from the surveys to identify sites that vary in their use of communication technologies for the qualitative phase of the project. Textbox 1 provides an overview of our study design.

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Textbox 1. Overview of study design.

Design

- Quantitative phase
  - Administer survey to Chief Nurse Executives, or other designated personnel
  - Use Healthcare Information and Management Systems Society's (HIMSS) model to categorize survey results
  - Analyze survey data
- Qualitative phase
  - Part 1
    - Select cases from the survey for semi-structured interviews based on maximal variation in communication technologies
    - Collect telephone interview data from 8 hospitals
  - Part 2
    - Select hospitals for intensive investigation based on information about communication practices and work relationships gained from telephone interview data
    - Collect data using ethnographic methods in 3-4 hospitals
    - Analyze data from parts 1 & 2 using thematic techniques

Aim 1

The first aim of our study is to identify the range of health information and communication technologies used in medical-surgical units.

Study Sample

The National Nursing Practice Network (NNPN) will be used as a sampling frame for this study. The NNPN is a consortium of 108 acute care agencies committed to the use of evidence-based practices. The majority of member organizations in NNPN are in the Midwest, but there are NNPN member organizations in 29 contiguous states, Hawaii, Alaska, and Puerto Rico. NNPN facilities range from academic medical centers in urban areas to small rural hospitals, single hospitals, and multi-hospital systems. Almost one quarter of NNPN members are part of the Veterans Health Administration, the largest integrated health system in the United States [26] and the health system with the most mature electronic medical record [27]. Given the wide range of adoption of electronic medical records nationally [28], we expect that the use of communication technologies within hospitals across our sample will also vary widely.

Survey Development

Questions asked in the American Hospital Association annual hospital survey's Information Technology supplement (AHA IT) related to communication technology (electronic clinical documentation, CPOE, decision support) were used as the starting point for our survey. The AHA IT supplement identifies both minimum functionalities hospitals need to label a system an electronic records system as well as comprehensive functionalities considered advanced with regard to electronic records systems [29]. While the AHA IT supplement asks questions about some electronic functionality related to communication, such as clinical documentation (ie, physician progress and discharge notes, nursing assessments) and order entry (ie, CPOE), it does not ask about other functionalities, such as characteristics of the paging system in use or computer-mediated communication between physicians and nurses. We added questions about these other functionalities (ie, pagers, computer-mediated communication devices such as email, cellular phones, tablets, electronic white boards) and grouped them according to categories of media richness. Information gathered through the AHA IT supplement is not available the same year it is collected, creating a lag time and possibly out-of-date information. Thus, we included key AHA IT questions to gather the most current information about communication technology through our survey. In pilot testing the preliminary survey took 10-20 minutes to complete. The survey will be administered via the web to contain costs and increase the efficiency and accuracy of data collection. We will follow recommendations for web survey visual appearance [30].

Data Collection

Procedures

We will follow web survey implementation procedures as outlined by Dillman and colleagues [30] to increase response rates and use a multi-mode survey method. The Chief Nurse Executives (CNEs) of all 108 members of the NNPN will be invited to participate in the study. We will send a postal letter of invitation to the CNE of each hospital at his/her institutional affiliation address since contact via post is associated with higher response rates [30,31]. The postal mail letter will introduce the study and include a survey link with a personal access code that will be assigned to each respondent. Assigning a unique identification number or personal access code allows the respondent to complete the survey without further contact, prohibits the same respondent from completing the survey more than once, and allows us to link a particular survey with a specific hospital. The postal mail letter will serve as the first of three contacts, since multiple contacts using different modes is

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the most effective method of increasing response rates, and does not increase measurement error [30]. We will include a "fact sheet" highlighting key study strengths and advantages to participation as well as a $20 gift card in the letter as an advance incentive to complete the survey. Advance financial tokens are one of the largest contributors to improved response rates [30,32], but have limited success when sent electronically. The CNE will be instructed to work with an informatician, physician, or other appropriate personnel as needed to complete the survey. Thus, we will not know who completed the survey, which helps to protect the anonymity of responses.

Next, we will send an email reminder to identified respondents using email addresses provided by the NNPN. Email requests to complete the online survey will be sent within a week of sending the postal mail letter, although the optimal timing sequence for web surveys has not been determined [30]. In this email reminder we will resend the "fact sheet" in case the earlier mailing was misplaced. Using a combination of postal and email contacts has been associated with response rates of ≥50% [30]. Then we will send out a second email reminder about 1 week later, varying the message and its appearance, which has also been shown to increase response rates. Because of the success we [33,34] and others [35,36] have had with the Dillman method, we anticipate a response rate of >50%, sufficient for the purposes of this study.

Remaining Data Needs

The survey will ask questions to identify the use of hospitalists on medical-surgical units and hospital characteristics (ie, size, urban/rural location, teaching status) because certain characteristics are associated with more or less adoption of technology. This information will allow us to stratify our sample for aim 2.

Data Analysis Plan

The analytic plan for aim 1 will be quantitative, using descriptive statistics to characterize the range of health information and communication technologies used at participating hospitals. We will stratify survey responses into two broad categories of hospitals, those that have few and those that have more health information and communication technologies based on their location on the Healthcare Information and Management Systems Society's (HIMSS) electronic medical record (EMR) adoption model. The primary unit of analysis will be the hospital unit. Since aim 1 is descriptive, we did not conduct a power analysis.

We will use descriptive statistics to describe the distribution, dispersion, and central tendency of each concept in our survey. We will calculate ranges and mean values for certain concepts. For example, it will be possible to determine that on average 65% of physicians and nurses frequently engage in face-to-face communication (more than once a week). This information will provide the context for understanding communication practices and work relationships in aims 2 and 3.

Using media richness categories to stratify our sample into hospitals that have more or less health information and communication technologies will not be possible since technology is only classified on the media richness spectrum. We will use the HIMSS model to stratify survey responses into two broad categories of hospitals that have more or less technologies. The HIMSS model uses an 8-step scale (0-7) to identify hospitals' trajectories towards a fully paperless environment, which is stage 7 [28]. Hospitals below stage 4 will be considered to have a low likelihood of many health information and communication technologies while hospitals at stage 4 or above will be considered to have a high likelihood of these technologies. Stage 4 will be the cutoff because physicians and nurses communicate through CPOE, and miscommunication through CPOE is associated with increased errors [6]. The most recent data (fourth quarter, 2014) indicate that 68% of 5467 surveyed hospitals are at stage 4 or above [28], thus from the entire NNPN network of >100 hospitals there will be sufficient variation in HIT needed for this study. Table 1 compares information on technology functions as identified through the study survey (based on questions from the AHA IT supplement) with the HIMSS model [28].

Once our sample has been stratified into low and high health information and communication technologies, we will describe each stratum, guided by our theoretical model. The 2 groups, high and low communication technology hospitals, will be used as the starting point for aim 2.

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Table 1. A comparison of survey information and the HIMSS EMR adoption model.

Survey information (from AHA IT supplement)	Corresponding placement on HIMSS model	EMR adoption model
	Stage 0	All 3 ancillaries not installed
Results viewing	Stage 1	Ancillaries (lab, radiology, pharmacy) installed
	Stage 2	Clinical data registries (CDR), controlled medical vocabulary, clinical decision support (CDS), may have document imaging; health information exchange capable
Clinical decision support (CDS): error checking only	Stage 3	Nursing/clinical documentation (flow sheets), clinical decision support (error checking)
CDS: error checking and clinical protocols	Stage 4	CPOE, clinical decision support (clinical protocols and error checking)
Computerized provider order entry	Stage 4	
	Stage 5	Closed loop medication administration
Electronic clinical documentation	Stage 6	Physician documentation (structured templates), full CDS (variance & compliance), full radiology picture archiving and communication system (R-PACS)
	Stage 7	Complete EMR; continuity of care document (CCD) transactions to share data; data warehousing; data continuity with emergency departments (EDs), ambulatory, outpatient (OP)

Aim 2

The second aim is to describe communication practices and work relationships between physicians and nurses that may be influenced by health information and communication technologies in medical-surgical acute care units.

Sampling and Study Setting

We will use the results of aim 1 to divide a sub-sample of hospitals into 2 groups. We will use purposive sampling [37] based on high/low use of health information and communication technologies, and stratify by hospital type and the use of hospitalist physicians on medical-surgical units. Each case will represent a prespecified combination of concepts thought to influence communication practices and work relationships [19,38,39]. Answers to demographic-type questions on the survey will allow us to sort surveys into 1 of 8 categories (bottom row in Figure 2) [37]. Our goal will be to recruit informants from 8 hospitals for telephone interviews.

Figure 2. Sampling plan for aim 2.

Few health information and communication technologies in use				More health information and communication technologies in use			
Community hospital		Teaching hospital		Community hospital		Teaching hospital	
H[a]	NH[b]	H	NH	H	NH	H	NH

[a]H: Hospitalist program in use on the medical-surgical unit to be the focus of study
[b]NH: No hospitalist program in use on the medical-surgical unit to be the focus of study

Recruitment

Our recruitment will begin with the CNE using a snowball sampling technique to recruit up to 3 informants at each participating hospital.

Data Collection: Telephone Interviews

A semi-structured interview guide will be developed by the research team based on our conceptual model and insights gained from pilot studies (on the topic of communication between physicians and nurses) and survey results. The guide will focus on understanding communication practices and work relationships in each medical-surgical unit, and how these have influenced the health information and communication technologies in use. The guide will also be designed to encourage ideas or concepts not included in our conceptual model to surface. Interviewees will be asked to validate survey information on technologies in use on medical-surgical units, in case new technologies were deployed since the survey was completed. Telephone interviews will continue until informational redundancy has been reached at each facility (ie, no new information is being collected) or all potential participants have been exhausted. We anticipate that each interview will last 30-40 minutes.

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Data Analysis Plan

The analytic approach for aim 2 will consist of qualitative and quantitative components. First we will qualitatively analyze telephone interview transcripts using a directed content analysis approach [40], and approach the data with analytic categories (ie, codes) derived from our theoretical model, also looking for other analytically relevant categories in the data. Once qualitative analysis is complete we will triangulate qualitative results with survey results. For example, through triangulation we will be able to compare communication practices and work relationships (qualitative data from telephone interviews) between a medical-surgical unit in a hospital that reported using only paper-based patient medical records on the survey with communication practices and work relationships in a medical-surgical unit in another hospital where patient medical records are 100% computer-based. Through triangulation we will begin to understand potential relationships between variation in health information and communication technologies, communication practices, and work relationships to inform our choice of sites for ethnographic study.

Aim 3

The third aim will explore how differences in health information and communication technologies, communication practices, and work relationships between physicians and nurses influence communication.

Sampling and Study Setting

Our theoretical model and emerging themes generated through analysis of telephone interviews will guide our choice of hospitals. We will purposefully choose up to 4 hospitals from the sub-sample of 8 hospitals that provided informants for telephone interviews.

Data Collection

Hospital visits will be sequential to allow time for data analysis between site visits, so that we can use knowledge gained from one hospital to inform our approach to subsequent site visits in other hospitals.

Direct Non-Participant Observation

To “kick off” the ethnographic portion of the study, two research team members will travel to each hospital to meet with key personnel (ie, Chief Nurse Officer, Chief Medical Officer, nurse manager, and medical director of medical-surgical unit). The purpose of the kick-off is to garner support for the study, discuss logistical issues, provide entrée for research assistants, and establish buy-in. During meetings we will gather information on the roles and responsibilities of nurses and physicians, which will be validated when research assistants conduct general observation. We will establish buy-in by soliciting input from key personnel, to engage them more thoroughly and demonstrate shared ownership of the project, important strategies for success [41,42].

Immediately after the kick-off, a pair of trained research assistants will be deployed to the medical-surgical unit selected for observation and engage in direct non-participant observation. We anticipate that research assistants will be at each site for about 2 weeks. Using the procedure most acceptable to all, the research assistants will observe physicians and nurses in the hallway, nursing station, physician team room, and public spaces on each unit, to unobtrusively observe communication events between physicians and nurses as they occur in these spaces. Research assistants will observe the general flow of work and document their observations of health information and communication technologies, including the use of rich as well as less rich media for communication purposes.

Observations will be conducted in 4-8 hour blocks of time during different shifts but weighted primarily towards the hours of 07:00-20:00 which is when the bulk of patient activities (and communication between physicians and nurses about patients) occur. Through observation we will capture different situations and different communication uses in those situations. Research assistants will also use informal interview techniques in situations where they do not understand a certain practice, allowing us to better describe communication practices that are in use. All observations will be captured in field notes. De-identified field notes and summaries will be entered into NVivo and coded using codes that we developed in aim 2. New emerging codes will be included as well.

Shadowing

Research assistants will shadow nurses and physicians in 4-hour blocks of time on the medical-surgical unit. We will recruit up to 7 nurses and 7 physicians to be shadowed, purposively recruiting nurses with a variety of experience, and physicians at varying stages of their career (eg, intern, 3rd year resident), and different specialties (eg, internist, general surgeon). Research assistants will shadow physicians and nurses independently. These specific observations will center on each individual’s daily interactions with all paper, computer, pager, telephone, and oral patient-related communications and record keeping activities. During shadowing we will gain deeper understanding about how physician roles and responsibilities influence communication with nurses.

To better understand why physicians and nurses use a specific health information or communication technology (eg, CPOE, pager, email), as part of their communication practice we will use a specific interview technique known as *think-aloud* in combination with shadowing. The think-aloud technique takes place during the course of action and involves asking participants what they are thinking and feeling as they communicate about patient care. This method provides the meanings behind the actions that are otherwise difficult to obtain, and will give us greater insight into communication practices and work relationships. Research assistants will record the length of conversations between physicians and nurses, and will take field notes during the shadowing experience, to be treated the same as observation field notes and summaries described above.

Focus Groups

The purpose of gathering data through focus groups is to provide validation for what we observe and to develop greater understanding of communication practices and work relationships from the perspective of physicians and nurses. Focus group questions and probes will be identical for both groups, having been used in a pilot study where we found that

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physicians and nurses described how a specific technology influenced the content of the message. We will invite up to 9 nurses to participate in one focus group (about 3 from each shift) and a similar number of physicians to participate in a separate focus group to better understand communication and organizational issues from each group and derive greater understanding of differences between the groups [43]. Nurse characteristics such as age, experience, and shift most often worked have been significantly linked to communication in previous studies [44]. Physician characteristics such as specialty and level (ie, attending, fellow, resident) may influence communication with nurses and physician attitudes towards hierarchical differences [45]. Focus groups will be audio recorded and transcribed verbatim.

Artifacts

Artifacts are a key source of data in ethnographic studies [46] and are useful organizational resources which provide guidance and support in the conduct of work [47]. Research assistants will collect documents such as policies and procedures (eg, policies on processing STAT orders), incident reports, and any other documents related to health information and communication technologies, communication practices, or work relationships. We will use artifacts to compare formal guidelines for communication with communication practices that actually occur, and to determine from incident reports if communication or technologies were at the root cause of the event. Deployment of health information and communication technologies are regulated by policies and procedures but frequently not useful in clinical practice, leading to workarounds with potentially deleterious consequences for patients [48]. We will abstract corresponding physician and nursing notes from a small sample of patient medical records to determine concordance on the plan of care. Absence of similar themes between physician and nursing notes would suggest lack of shared understanding and ineffective communication. We will conduct preliminary data analysis after observation, shadowing, and focus groups have been completed at each site.

Follow-Up Site Visits

Follow-up site visits will be conducted as a form of member checking. We will travel to each site to present findings and have key personnel put findings into context. We will ask questions about observed processes or acquired artifacts that may lead to additional insights about communication practices and work relationships at each hospital. For example, we may observe variable understanding in a policy regarding how to communicate STAT orders, or implement a bundle to prevent health care associated infections, but not understand the genesis of that variability until we talk with key leaders.

Data Analysis Plan

The data analysis plan for aim 3 will be similar to and build on analysis done to meet aim 2. We will use directed content analysis on all data gathered through aim 3 to look for themes generated earlier as well as themes consistent with concepts in our theoretical model. We will then combine qualitative data from aims 2 and 3 using content analysis and merge the qualitative data set with the quantitative data set from aim 1 to triangulate the data and conduct final data analysis of the study. Developed codes and themes from aim 2 will be used in aim 3 to better draw out the key commonalities and differences across the study sites. We will explore common and divergent themes [49] by asking questions consistent with our theoretical model such as (1) how did communication practices contribute to patient event X only in this hospital, although all hospitals used the same communication technology? and (2) how did work relationships lead to hospitals coming up with such different policies related to the same health information technology process (ie, process for STAT orders)? Once the qualitative data have been fully analyzed, the two datasets (quantitative and qualitative) will be merged using concurrent data analysis. This requires triangulating the data to develop a more complete picture of the findings [50]. This approach ensures that the study aims are fully explored and all findings are weighted equally.

Results

This 4-year study is well-aligned with the Agency for Healthcare Research and Quality's (AHRQ) interest in the nature of clinical expertise in individual and team decision making. Health care work is information sensitive [8], and information must be understood before it can be acted upon [51]. Study results will provide a rich understanding of the many factors that influence communication so that strategies to promote improvements can be developed and tested. Current health information and communication technologies do not facilitate knowledge building required to solve complex patient care problems, nor do we know the best way to configure them to improve their functionality. Work relationships and communication practices influence what technologies will be used, and may offer insights into how to improve the use of health information and communication technologies, but have rarely been studied in context.

Discussion

The ability to capture a range of contexts in which communication occurs is a strength of our methods and this study. Authentic work relationships are visible only through direct observation, semi-structured interviews, and focus groups. Comparing face-to-face with technology-mediated communication will provide insight into how clinical meanings are negotiated for mutual understanding and agreement on action. Insights into the various communication practices will illuminate what types of information get communicated, how and when they are communicated, and what the resulting activities are because of these exchanges. This study will also provide insight and reason into how miscommunication can occur and possible ways to improve communication so that patient care is not adversely affected. Our approach is deliberately open-ended so that non-verbal communication events which are not well-captured in quantitative surveys will be more accessible and documentable. These "hidden" communications are necessary to understand the full scope of communication practices and to capitalize on those processes that work and those that need improvement.

There are several challenges associated with this project. The first challenge will be to get hospitals to agree to participate in

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the survey portion of the study. We will use the Dillman approach and provide advance incentives to increase study participation as described in the methods for aim 1. A related challenge will be to get physicians and nurses to participate in observation and shadowing. We will post flyers explaining the study and inviting participation in each unit. In the nurse/physician communication pilot study we found that having the support of the physician director of the unit was helpful in enlisting physician participation. Nurses and physicians may have to come in on a day off or take time away from direct patient care; each nurse and physician will receive a $40 gift card as a token of appreciation. The introduction of observers could be uncomfortable for some individuals. We will use strategic integration to gradually acclimatize study participants to observer/research assistant presence. We will not observe any potential subject who prefers not to participate. Observations might interfere with the orderly conduct of patient care. This risk will be offset by having unobtrusive, well-trained observers. No identifying information on staff will be gathered.

In summary, a fuller understanding of clinical work in context is essential if interventions aimed at improving interdisciplinary communication and using technology to do so will be realized. This study will identify those health information and communication technologies that support mutual understanding between nurses and physicians and those that are more prone to misunderstanding, so that prior communication failures do not haunt future communication strategies which in the 21st century will depend heavily on technology.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

NIH Review summary statement.

[PDF File (Adobe PDF File), 181KB - resprot_v4i2e72_app1.PDF]

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Abbreviations

AHA IT: American Hospital Association Information Technology
CNE: Chief Nurse Executives
CPOE: computerized provider order entry
EMR: electronic medical record
HIMSS: Healthcare Information and Management Systems Society
HIT: health information technology
ICT: information and communication technology
NNPN: National Nursing Practice Network

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Original Paper

Delivering a "Dose of Hope": A Faith-Based Program to Increase Older African Americans' Participation in Clinical Trials

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Abstract

Background: Underrepresentation of older-age racial and ethnic minorities in clinical research is a significant barrier to health in the United States, as it impedes medical research advancement of effective preventive and therapeutic strategies.

Objective: The objective of the study was to develop and test the feasibility of a community-developed faith-based intervention and evaluate its potential to increase the number of older African Americans in clinical research.

Methods: Using a cluster-randomized design, we worked with six matched churches to enroll at least 210 persons. We provided those in the intervention group churches with three educational sessions on the role of clinical trials in addressing health disparity topics, and those in the comparison group completed surveys at the same timepoints. All persons enrolled in the study received ongoing information via newsletters and direct outreach on an array of clinical studies seeking participants. We evaluated the short-, mid-, and longer-term effects of the interventional program on clinical trial-related outcomes (ie, screening and enrollment).

Results: From 2012 to 2013, we enrolled a balanced cohort of 221 persons in the program. At a 3-month follow-up, mean intention to seek information about clinical trials was higher than baseline in both treatment (mu=7.5/10; sigma=3.1) and control arms (mu=6.6/10; sigma=3.3), with the difference more pronounced in the treatment arm. The program demonstrated strong retention at 3-month (95.4%, 211/221) and 6-month timepoints (94.1%, 208/221).

Conclusions: The "Dose of Hope" program addressed an unmet need to reach an often overlooked audience of older African Americans who are members of churches and stimulate their interest in clinical trial participation. The program demonstrated its appeal in the delivery of effective messages and information about health disparities, and the role of clinical research in addressing these challenges.

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KEYWORDS

health disparities; clinical trials; churches; study recruitment; African Americans

Introduction

Older-Age Racial and Ethnic Minorities Underrepresented in Clinical Research

Underrepresentation of older-age racial and ethnic minorities in clinical research is a significant problem in the United States, as it impedes medical research advancement of effective preventive and therapeutic strategies [1]. In the United States, older minorities (age ≥ 60 years) suffer from greater morbidity and mortality stemming from chronic illnesses (eg, cancer, congestive heart failure, obesity, diabetes, and dementia), as well as from infectious diseases (eg, pneumonia, influenza, and septicemia) [1-6]. Recent studies have corroborated that health disparities arise from attributable differences in socioeconomic status, resulting in an increased burden of illness and disability among African Americans over the age of 65 years [7]. These inequalities in access to care and treatment, a lack of health-supporting social networks, and lack of knowledge about prevention interventions and clinical treatments are also known challenges to the achievement of health equity[8].

Demographic trends point to a significant increase in the both the burden of disease among African Americans in the United States, as well as the proportion of the population that will be African American by 2030 [5]. Older African Americans remain severely underrepresented in clinical trials, despite this population suffering greater prevalence of many diseases than the white population, including greater prevalence of some cancers, cardiovascular disease, diabetes, influenza and pneumonia, obesity, and other conditions such as dementia [9-14]. For example, among the 39,574 patients observed from 17 studies included in a meta-analysis of clinical trial participation for prostate cancer from 1993 to 2011, only 5.3% of participants in the US studies were African American [15]. Older African Americans have similar participation rates (9.9%) in Alzheimer's disease trials [9]. In two other randomized controlled trials for influenza vaccines, older African American participation was as low as 2.5% (N=48) to 4.9% (N=450) [16,17].

The US Centers for Disease Control and Prevention (CDC) advocates the importance of expanding access to clinical trials and providing information to community members to facilitate study participation by older minorities for whom new prevention and treatment options may be beneficial [4,18]. The 1994 National Institutes of Health mandate specifying the inclusion of women and minorities in federally sponsored studies also underscored the importance of recruiting and retaining diverse racial and ethnic groups to ensure that social justice and scientific aims are achieved through the conduct of research [19]. Enrollment of older persons, including racial and ethnic minorities, in clinical trials is of national interest in effectively addressing health disparities and Healthy People 2020 objectives [1,5,6,20].

The call to increase racial and ethnic minority participation in clinical research has invigorated efforts to identify effective community engagement and recruitment approaches, yet very few interventions have been subjected to rigorous scientific assessment [21-24]. We therefore tested the feasibility of a community-developed faith-based intervention to increase ethnic diversity in clinical research. A "Dose of Hope" engages one of the most powerful forces for community and personal behavioral change in the South, African American communities of faith. The church is a trusted institution in African American communities and has partnered with other organizations to address a variety of health disparity concerns [25-27]. The churches selected for this project had histories of successful partnerships with state and local health departments, local college and universities, and service-oriented community-based organizations, among others.

Study Implementation and Training

To operationalize this faith-based intervention, we assigned three churches to host the "Dose of Hope" intervention, which included an initial half-day program for congregation members at baseline, followed by two subsequent two-hour small group sessions at three and six months for follow-up. Consensus on program topics and presenters was achieved by holding multiple meetings with pastors, other faith leaders, content area experts, and community advisory board members. Through this approach, content areas selected for delivery included topics such as "Health Disparities in our Community", "Why Bother with Clinical Trials?", "The Role of the African American Church in Clinical Research and Human Protections", "Clinical Trial Updates", as well as specific health condition presentations (eg, influenza, human immunodeficiency virus/acquired immune deficiency syndrome [HIV]/[AIDS], stroke, and hypertension). For each of these topics, we included background on the issue, its relevancy to the population, direct and indirect health effects, and how community members can get involved to address the concerns. Each session also included time for questions, answers, and up to 10 minutes of group discussion.

As faith leaders were involved in developing and delivering some components of the intervention, they were invited to a small group content development/planning meeting and a separate program delivery training session prior to implementation. We created preliminary slide decks for each session and conducted a crosswalk discussion on standardized talking points. Presenters then rehearsed their talks with study leaders (Principal Investigator, program director, other content area faculty). Prior to delivery at the designated session(s), we followed up with the presenters to ensure that they had adequate training with presentation equipment and educational spaces to ensure that speakers did not experience unnecessary challenges with these logistics.

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Process Evaluation

We sought to identify the factors contributing to intervention success and our participants' satisfaction in the program. To achieve this, we conducted a comprehensive program evaluation to assess qualitative (eg, attitudes, self-efficacy and empowerment, and network opinions) and quantitative (demographic, housing and insurance status, health care utilization, provider trust, etc) elements contributing to clinical trial enrollment and moderation of the intervention effect. The program evaluation enabled our team to discover the factors that contributed to the program's success. Understanding what specific program components were effective including messages conveyed, along with the recruitment and retention processes, enabled us to develop "best practices" for community engagement in clinical research.

We implemented an evaluation strategy informed by the CDC framework for public health program evaluation, along with principles drawn from Utilization-Focused Evaluation [28,29]. The CDC framework enabled us to develop our program theory and assess how interdependent components and underlying processes contribute to impact [28] (Table 1).

Table 1. CDC evaluation framework for study protocol [28,29].

Step 1: Engaging stakeholders	Through our ongoing work with faith leaders and community partners, we solicited advice on our study instruments to ensure that they were culturally appropriate, and that they elicited important contextual, communication, and network factors that may contribute to clinical trial outcomes. During the project, we also scheduled ongoing discussions with faith leaders at the churches to maintain strong engagement.
Step 2: Describing the program	We developed a "program description" during the first study quarter that included the need for the project, expected effects, activities, resources, stage of development, context, and logic model. This model described the hypothesized mechanism for change underscored by our theoretical orientation, and its potential overall impact on the realization of increased participation in clinical research.
Step 3: Focusing the evaluation design	This aspect focused on assessing "Dose of Hope's" feasibility for wider dissemination, describing its implementation successes and challenges, and final assessment of the program's effects.
Step 4: Gathering credible evidence	We collected data on program attributes throughout the intervention period to strengthen the credibility of program findings. Table 1 highlights some of the process indicators relating to participation rates and intervention effects that were collected during the intervention period to bolster the project's credibility and utility.
Step 5: Justifying conclusions	The final evaluation products, including manuscripts, presentations, reports, and newsletters, reflected the values and efforts of all stakeholders involved in the process. The evidence was continuously synthesized and interpreted with partner agency input, and recommendations are being made on the program's future via consensus. This process builds on our previous experience with the "Dose of Hope" program evaluation in which we considered its format, delivery, sustainability, and potential for scale-up expansion.
Step 6: Ensuring use and sharing lessons learned	The evaluations for the "Dose of Hope" pilot endeavors were very useful for identifying problems and implementation challenges, along with opportunities and advances. In addition to our planned internal use, we intended to broadly disseminate the findings from this program to others who could benefit from the lessons learned from our community-participatory research model.

Methods

Community Based Participatory Research Approach

The "Dose of Hope" program utilized the Community Based Participatory Research approach to develop the intervention. Our project incorporated "best practice strategies" including building trust with the community, hiring community members as lead staff, and delivery of cultural competency training to reinforce the knowledge and skills necessary to work with this special group [8].

Protocol Aims

The study addressed two major aims. First, we examined the effect of the educational intervention on clinical trial recruitment of older African Americans by tracking screening and enrollment outcomes for 24 months following the pilot study. Within this scope, we explored the pathways through which individual and network factors operated to shape enrollment differences. We also sought to characterize participants' health-supporting network linkages.

To evaluate the feasibility and potential effectiveness of "Dose of Hope", we used a cluster randomized controlled trial design to test whether delivery of a three-session group intervention increased the proportion of older African Americans who enroll in an array of chronic and infectious disease-related clinical trials. The sampling frame of about 20 churches was identified via ethnographic observation and key informant interviews. Given our intervention's goal of increasing clinical trial participation rates among older African Americans, eligibility for the project venues was restricted to: (1) faith organizations with congregation membership of ≥ 30% African Americans ages ≥ 50 years, and (2) faith organizations situated within one of the 22 counties comprising metropolitan Atlanta. Prospective venues were matched by denomination and estimated congregational membership. From the 20 in the sampling frame, six churches were randomly selected to participate in the study using matched-pair randomization.

Using random selection, one church in each pair was allocated to the intervention condition (Intervention Group 1) and the

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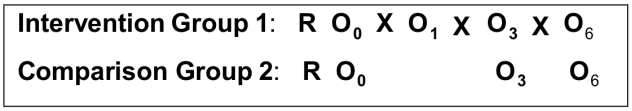
matched pair was assigned to the control condition (Comparison Group 2). Figure 1 shows the study design.

Participants completed intermediate assessments at 3 months and 6 months, and were followed longitudinally for 24 additional months. Through monthly telephone and email outreach, all participants from both intervention and control arms were notified of local study opportunities and screened for specific clinical trials by recruiters. “Dose of Hope” partnered with 23 other studies/clinical programs in 2013 and 2014 to provide recruitment and referral opportunities to program participants. The studies that participants were referred to addressed a variety of health disparities to encourage “Dose of Hope” participants to join studies of great interest to them. These included clinical studies on how the brain controls head movements; sleep, memory, and ageing; urinary symptoms; vaccine trials including those for influenza (H7N9), yellow fever, cholera, and pneumonia; Alzheimer's disease; experiences of intimate partnership violence; treatment for trauma from domestic/interpersonal violence; post traumatic stress disorder; HIV risk factors; treatment of fatigue related to breast cancer treatment; the effect of high blood pressure medication on thinking ability and brain activity; insomnia and blood pressure; language processing; and heart failure and memory.

Figure 1. Delivering a "Dose of Hope” study design.



(Continuous assessment of clinical trial screening and enrollment rates from baseline visit through 24 months)

Legend:	O_0 = pretest/baseline questionnaire
R = Randomization Cluster	O_1 = posttest
O = Observation	O_3 = 3-month questionnaire
X = Intervention Session	O_6 = 6-month questionnaire

Church Sampling Strategy

We drew a list of all prospective churches from those that agreed to participate as either intervention or control sites. All sites on the roster were enumerated. We then drew from this enumerated sampling frame of nearly 20 churches, choosing the 6 churches that ultimately participated as sites for this study. For each site selected, we also identified one back-up church in the event that the selected church was no longer able to participate. The three denominations represented were the American Methodist Episcopalian (AME), Baptist, and Seventh-Day Adventist (SDA) practices. Following venue randomization, we worked with faith leaders to identify specific days of the week and time blocks that were ideal for producing an adequate pool of potential participants that could be recruited from the selected churches. We worked directly with the churches to outreach to target populations within their church, drawn from elders’ groups and bible study groups, and via direct outreach via flyers, presentations at church gatherings, and other activities. We then worked directly with the church contacts assigned to our study to conduct research activities at each location; it was during those specified times that we conducted our research activities with their approval.

Participant Recruitment

Within the selected churches, we screened and enrolled persons recruited through outreach conducted by pastors, health ministers, and other congregational leaders. Church members included those who regularly attend services, tithe, may be active on church committees, and attend church-related social gatherings. Eligibility requirements for the study included: (1) self-identified race/ethnicity as black or African American; (2) age 50 or older; (3) residing in the 22-county metropolitan Atlanta region; (4) plans to reside in Atlanta for 12 months following recruitment; (5) no previous history of participation in clinical research studies; (6) church-confirmed congregant status; and (7) ability to read and write English.

Our initial aim was to enroll a minimum of 105 participants on each arm, of whom 35 were to be selected from each intervention site. However, given the potential for significant attrition among an older cohort, we determined that oversampling the cohort would retain sufficient power to evaluate the primary endpoint of clinical trial enrollment in the event of a ≥20% loss of participants during the course of the study. Thus, the recruitment efforts resulted in 11 more persons than the original target of 210 persons (final N=221 participants).

Study team members screened all participants for eligibility. Screened members of intervention churches who were not eligible based on personal criteria were given the opportunity to attend the sessions and given the same program materials as enrolled participants, but they did not complete questionnaires at the sessions. Those who were ineligible from control churches were provided with information about clinical research study opportunities; they did not complete any questionnaires. All persons deemed eligible to participate underwent the informed consent process prior to the start of the first session.

Intervention Groups

The program for intervention participants included initial breakout sessions facilitated by faith leaders and clinical researchers that covered the following issues specified in the facilitator’s guidebooks: “Myths about Clinical Trials”,

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"Challenges to Research Involvement", "Benefits and Rewards to Involvement in Clinical Trials", and "Hope in the Community". Subsequent to the half-day seminar hosted at each intervention church, two follow-up small group sessions (one hour each) were scheduled with 12-20 persons to occur at 3- and 6-month timepoints. Disease-related topics included HIV/AIDS, influenza vaccination, stroke, diabetes, hypertension, diet and nutrition, and others. Participants also discussed structural determinants of health such as the role of violence, incarceration, food availability, health care access, housing, employment, discrimination, and transportation. Session leaders also engaged study participants in deep discussions about the lack of community participation in prevention and treatment studies, navigating social support influences, and safeguards to ensure participant safety and well-being. All elements of the sessions were determined prior to implementation to ensure standardized delivery of the program at all locations. A program manual and standard operating procedures was developed to ensure fidelity.

Control participants did not receive any type of study intervention, but completed the study questionnaires at baseline, 3-month, and 6-month timepoints. We invited control participants to attend other events such as community health fairs, screenings, and educational presentations on health topics unrelated to clinical trials (eg, mammography screening). Both control and intervention participants received quarterly newsletters informing them about the study activities, preliminary results and study findings, and clinical trial opportunities.

Measures

The three key endpoints are captured by screening, enrollment, and referral pattern tracking of all participants with data provided by study coordinators who are following our cohort. Additionally, we gathered self-reported data from surveys at all three timepoints as longitudinal measures of intention to screen and enroll in clinical studies, and at 3- and 6-months asked participants to report any studies that they had screened and enrolled in so that we could conduct verifications of these events with study coordinators. We also tracked the number of persons who screened (captured as an outcome), but were determined to be "medically ineligible" for specific studies due to comorbidities and health conditions. These events enable us to understand "screen failures" within the cohort due to specific conditions and other study enrollment placement. Thus, people are consistently referred to a number of studies to capture screening and enrollment rates. With multiple referrals made to studies, this often resulted in multiple screening and enrollment events.

This study built upon our previous theoretical research drawing upon micro and macro-theoretical approaches to understand community engagement in clinical research [30-32]. We targeted three major outcomes from this program: clinical trial screening, enrollment, and promotion/diffusion of participation messages. We also focused on reinforcing positive social norms and attitudes toward clinical trial participation, as is consistent with the major components of the Theory of Reasoned Action. We created an expanded Theory of Reasoned Action (TRA), which incorporated Diffusion of Innovations (DOI) constructs [33,34]. The key domains of TRA (ie, attitudes and social norms) were addressed in all aspects of the program [30,35]. For example, facilitators engaged participants in an interactive discussion on attitudes and beliefs toward clinical trials (ie, "Why Bother with Clinical Trials?"), dealing with negative social appraisal of involvement (ie, "Inspiration, Information, and Motivation to Act"), and forming behavioral intentions (ie, "Clinical Trial Update: Progress in Drug Development and Prevention Research"). The "breakout sessions" enabled a deeper level of conversation, as we targeted attitudes and behavioral beliefs, along with social norms, with this intervention. We built upon TRA to promote more favorable attitudes toward clinical trial participation by reinforcing positive norms toward community engagement in health research.

In addition, our measures drew upon DOI to explore the dimensions of social networks to understand how certain ideas and behaviors become socially acceptable, and therefore become more commonplace in communities [33]. We incorporated social network analyses to elicit underlying social network processes driving clinical research participation (ie, homophilous or heterophilious communication among caregivers, social support systems, and others). These measures enabled our team to explore the impact of interconnectedness on trial-related outcomes. This effort ultimately advanced our understanding of the intersection of networks and community-level factors that influence participatory outcomes [36-39].

Table 2 details questionnaire domain measures for all participants. Our measures were reliable and valid [32,40]. Given the large volume of survey data collected at each timepoint, we used self-administered pen-and-paper surveys developed at a sixth-eighth grade reading level. We believe this also reduced interviewer bias. In addition, up to 10 participants were asked to do intercept interviews which are typically ≤ 10 minutes to gauge what they learned, what they intend to do as a result of their participation, and their satisfaction with the program.

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Table 2. "Dose of Hope" measures.

Variables		
Baseline		
Sociodemographics:	Gender, age, educational attainment, marital and sexual orientation status, employment and housing status, income level, health care utilization and insurance status	Behavioral/community characteristics/indicators (TRA and DOI) [30-35,40] Faith and place of worship affiliation, community affiliations, group memberships, mono and polymorphic network opinion leadership, network linkages, volunteerism experience, previous clinical trial experiences and knowledge, recent volunteer health behaviors (eg, organ donation in past 12 months), health research and clinical trial attitudes, social support indicators (eg, RAND social health battery) and personal network interactions, trust in provider, health research organization, and clinical research involvement scales (measured by CRIS)
Follow-up (3- and 6-month)		
Sociodemographics:	Employment and housing status, health care utilization, and insurance status (3-month recall)	Behavioral/community characteristics/indicators (TRA and DOI) [30-39] Health and clinical trial information and media consumption, modes of network communication, community affiliations and group memberships, network linkages, opinion leadership, clinical trial interest and knowledge, Emory clinical research experience, recent volunteer health behaviors (eg, organ donation in past 3 months), health research and clinical trial attitudes, perceived social support for clinical research involvement (personal network support), social activism congruence, trust in provider scale (measured by CRIS)
Clinical trial variables (24-months post baseline)		Clinical trial variables (tracking screening and enrollment database) Date of clinical trial site contact, date of screening, date of enrollment, reasons for study exclusions, recruitment source/venue

Three- and Six-Month Follow-Up Questionnaires

The three-month and six-month follow-up questionnaires included measures repeated from the baseline survey to explore longitudinal changes. We also planned to randomly select up to 20 persons to participate in 30-45 minute interviews on their experiences in the program and intentions and behaviors post intervention. These interviews enabled us to gather information on their knowledge, attitudes, beliefs, intentions, and screening and enrollment behaviors. We concluded interviews as soon as the data were determined to be saturated, meaning that no new content was arising as a result of these discussions. This resulted in a total of 31 persons interviewed during and after the program.

All data, including personal identification numbers, from participants that enroll in Emory clinical studies were linked back to their previous questionnaires. The information contained in the clinical trial database includes sociodemographics, contact data, recruitment source, motivations for participation, and enrollment outcomes including reasons (if known) for exclusion (eg, health reason and age).

Data Analysis

Based on our past experience with trial enrollment, we assumed a baseline trial enrollment rate of 6% in the control group. We sought a minimal sample size of 210 individuals (105 in each arm) by sampling 3 clusters with at least 105 subjects in the intervention group and 3 clusters with 105 subjects in the control group. This would enable us to achieve 80% power to detect a difference between the group proportions of at least 15% (ie, 21% of individuals in the intervention group) using the two-sided Z test (unpooled) at a 5% significance level. Sample size estimates were adjusted for expected intracluster correlation and an expected retention rate of 80%.

We examined differences in demographic and behavioral variables across the intervention and control groups with a combination of *t* tests, chi-square, and linear mixed models. In addition to bivariate models, multivariate analyses were performed adjusting for demographic, behavioral, and contextual variables. These analyses included calculation of the increase between timepoints in mean scores for intention to seek information about clinical trials and intention to join clinical trials. We selected the linear mixed model approach as most appropriate for the longitudinal analyses, as they account for clustered design. In addition, the study protocol enabled us to assess the impact of the study intervention on clinical trial enrollment events using Poisson regression. For the primary analysis, incidence rate ratios included counts of individuals enrolled in clinical trials during the 24-month follow-up period from the intervention arm compared to the counts of enrolled individuals who were recruited from the control arm. All models

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account for clustering at the church level, and therefore robust confidence intervals are most appropriate.

Results

Early Descriptive and Longitudinal Study Results

Early descriptive and longitudinal results from this ongoing study indicate successful recruitment of the “Dose of Hope” cohort (Table 3). The two study arms were well balanced (n=109 in control and n=112 in intervention), as was denominational participation. Participants were primarily female (78.2%, 173/221), though men were also represented. Ages ranged from 50 to over 90, with nearly half of the participants’ ages 60 to 69 (48.8%, 108/221). The distribution of age differed significantly between the intervention and control group (Mann-Whitney *U* test; *P*=.03). Almost half were currently married or living with a domestic partner (46.1%, 102/221), yet many were divorced or separated (26.6%, 59/221) or widowed (15.8%, 35/221). Only a few persons had never been married (10.9%, 24/221).

Participant Sociodemographics

We recruited an educated population. The majority of participants had attained a technical or associate's degree (29.9%, 66/221) or high school/GED or less (35.7%, 79/221) as their highest level of educational attainment. Most participants were retired or unemployed (67.0%, 148/221), and one-quarter had annual household income less than twenty thousand dollars per year (27.6%, 61/221). Half of the participants were insured through managed care or a combination of private insurance and managed care (50.2%, 111/221), one-third used private insurance only (33.0%, 73/221), and 10.0% were uninsured (22/221). The intervention and control groups did not vary significantly with respect to any of the other variables presented in Table 3 (chi-square test; *P*>.05).

Participant Retention

We observed a very strong retention rate over time. The program had better-than-expected 3-month (95.4%, 211/221) and 6-month retention rates (95.0%, 208/220, accounting for the loss of one person who died during the project from a nonrelated study cause). We believe that the qualitative and evaluative data will provide insight on what components of the program participants felt were most valuable and deserving of their dedicated time in the sessions. The social network analyses may also provide additional perspective on the extent of social cohesion experienced by participants in this program as a motivator to continue participation, and will help determine whether the social-educational nature of the program may have fostered its strong retention.

Early Results

Early results assessing intentions to seek clinical trial information, screen, and enroll reflect a moderate amount of change over baseline. Participants' self-reported intentions to seek information about and to join clinical trials are summarized in Tables 4 and 5. At baseline, participants expressed relatively neutral opinions about their likelihood to contact researchers about clinical trials, balanced in both the intervention (mu=5.7/10; sigma=2.9) and control (mu=5.5/10; sigma=2.9) arms. Yet at 3 months, mean intention to seek information about clinical trials was higher than baseline in both treatment (mu=7.5/10; sigma=3.1) and control arms (mu=6.6/10; sigma=3.3), with the difference more pronounced in the treatment arm. Mean intention to seek information decreased slightly at 6 months in both arms. A similar trend is present in participants' intention to join a clinical trial, though less pronounced than with intention to seek information about clinical trials.

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Table 3. Sociodemographic characteristics of study participants (N=221).

Sociodemographic characteristics		n	%
Study arm			
	Control	109	49.3
	Intervention	112	50.7
Church denomination			
	AME	60	27.1
	Baptist	78	35.3
	SDA	83	37.6
Gender			
	Male	48	21.7
	Female	173	78.3
Age (years)			
	50-59	62	28.1
	60-69	108	48.9
	70-79	41	18.6
	80-89	5	2.3
	90+	2	0.9
	Missing	3	1.4
Marital status			
	Single/never married	24	10.9
	Married/domestic partner	102	46.2
	Divorced/separated	59	26.7
	Widowed	35	15.8
	Other	1	0.5
Educational attainment			
	High school/GED or less	79	35.7
	Technical associate’s degree	66	29.9
	Bachelor’s degree	37	16.7
	Master’s/doctorate	39	17.6
Employment			
	Unemployed or retired	148	67.0
	Employed (part-time and full-time)	65	29.4
	Missing	8	3.6
Annual household income (US dollars)			
	Less than 20,000	61	27.6
	20,001-40,000	49	22.2
	40,001-60,000	36	16.3
	60,001-80,000	20	9.0
	80,001-100,000	19	8.6
	More than 100,000	13	5.9
	Missing	23	10.4
Medical insurance policy			
	No insurance/other	22	10.0

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Sociodemographic characteristics		n	%
	Private insurance plan	73	33.0
	Managed care/combination plan	111	50.2
	Missing or don't know	15	6.8

Table 4. Intention to contact Emory about clinical trials in next 6 months (N=221).

	Mean intention to seek information[a]		
	Baseline	3-month[b]	6-month[b]
Intervention	5.7	7.5	7.1
Control	5.5	6.6	6.5

[a] measured on 10-point Likert scale

[b] Participants who had screened at 3 or 6 months were given an intention score of 10 (5 at baseline, 14 at 3-month, 15 at 6-month).

Table 5. Intention to join a clinical trial in next 6 months (N=221).

	Mean intention to join trial[a]		
	Baseline	3-month[b]	6-month[b]
Intervention	5.8	6.2	6.3
Control	5.8	5.9	5.7

[a] measured on 10-point Likert scale

[b] Participants who had screened at 3 or 6 months were given an intention score of 10 (5 at baseline, 14 at 3-month, 15 at 6-month).

Participant Intent to Enroll in Clinical Trials

Self-reported initiation of contact and joining of clinical trials at the 3- and 6-month timepoints is summarized in Tables 6 and 7. After 3 months, a relatively large proportion of participants reported contacting researchers about clinical trial participation, including a large proportion of both the intervention (37.5%, 42/112) and control (32.1%, 35/109) arms. A slightly smaller proportion indicated current contact with researchers at the 6-month timepoint (30.6%, 34/111 in the intervention arm and 26.6%, 29/109 in the control arm). A smaller proportion of participants passed through the study screening stage to be deemed eligible to participate in clinical trials. After 3 months, (6.2%) 7/112 of the intervention and (1.8%) 2/109 of the control participants had joined clinical trials, moving up to (9.0%) 10/111 of intervention and (2.8%) 3/109 of control participants after 6 months.

Table 6. Participants contacting researchers about clinical trial participation (3-month total = 221; 6-month total = 220).

	Number of participants/arm n (% of arm)	
	3-month, n (%)	6-month, n (%)
Intervention	42/112 (37.5)	34/111 (30.6)
Control	35/109 (32.1)	29/109 (26.6)

Table 7. Participants joining clinical trials (3-month total = 221; 6-month total = 220).

	Number of participants/arm n (%)	
	3-month, n (%)	6-month, n (%)
Intervention	7/112 (6.2)	10/111 (9.0)
Control	2/109 (1.8)	3/109 (2.7)

Discussion

Community Engagement in Clinical Trials

Community engagement involves multidirectional communication for the overarching purpose of enhancing the public's trust in the effort. Evidence-based methods include consultation, dialogue, and collaboration with communities [41] to develop shared understanding and meanings associated with the research programs [2]. This process also fosters the community's voice in research endeavors and develops a sense of community empowerment [3]. These methods are vital for reaching minority communities and women to sustain their

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involvement in medical research studies [4,5,8,9,12], and to promote favorable health outcomes in the population [10,11].

Therefore, the role of community engagement in clinical research figures prominently in addressing salient concerns among diverse groups. Previous findings related to clinical trial recruitment of African Americans suggest differences exist among men and women from diverse communities in their motivations for participation [42,43]. The early results from this study suggest the value of a strong researcher-participant relationship, particularly for female participants, in which study volunteers are made to feel comfortable, are treated well, and share rapport and good communication with the study team members [42]. Moreover, women appreciate notification of research conducted in their locales, and of its importance and relevance to their communities. The results from this study suggest that the program, which was successful in recruiting a cohort comprised of mostly women, successfully created a positive environment aligned with these factors.

Researcher involvement in the local community also is a significant motivator in clinical trial participation [43]. This is an important factor that merits commentary for this protocol. Not only was the research team comprised of health scientists and physicians deeply committed to the project, but they also had histories of working on other projects with the selected churches. Given the ill-fated history of the Tuskegee syphilis study involving African American men, and its resonance with older African Americans, we were conscientious of the potential for lower levels of trust in their assessment of health care providers and health care systems [44,45]. Moreover, we recognized that negative experiences and perceived bias in this population's previous health care encounters likely influenced their trust of us as part of the medical establishment [46,47].

To address these concerns, we set out to build a community-based participatory action model that would enable participants to have direct experiences with the "Dose of Hope" providers in the sessions. By leveraging the role of the church in its ability to send persuasive "social cues", we were able to build greater trust in providers and medical entities involved in the program [41,44,48]. Although there are similarities observed across studies, clinical trial perceptions vary greatly among African American communities. Variations may be due to socioeconomic status, access to care, health service utilization patterns, insurance provision, and interpersonal dynamics of patients and physicians [44,47]. With this assemblage of factors, interpersonal and perceived socioenvironmental normative messaging may have had an influential effect on clinical trial decision-making.

With the 1994 National Institutes of Health (NIH) mandate specifying inclusion of women and minorities in research, greater emphasis has been placed on recruiting and retaining these populations. Although minorities are not participating in health research at a level equal to whites [41,43,48,49], it is important to recognize that knowledge of and access to health research activities may have a favorable impact on willingness to participate in health research [18]. In a large scale review study of 70,000 persons, minorities were found to be more willing to participate in clinical and surgical studies than whites [18]. These findings indicate that little difference is seen in enrollment patterns when minorities are invited to participate in health research studies [18]. With these differences taken into account, the authors conclude that underrepresentation in health research is likely due to other factors.

Recent evidence on minority participation in health research indicates a desire for information of the research activity in the community, greater demand to understand the relevance of the research efforts in addressing medical problems, and occasions to learn about clinical research entities and study volunteer participation [19,39]. Thus, the creation of opportunities to serve these needs is a necessary precursor for effective community engagement with African American communities. These aforementioned reasons provide rationale for the creation of our program.

Future Directions

We will evaluate the indirect effect of our intervention for the enrollment-related endpoint. This will be achieved by comparing the counts of individuals enrolled in clinical trials who belonged to the intervention churches, but did not attend the small group sessions versus counts of individuals enrolled who belonged to the control churches and were not included in the control arm (ie, were not included in the baseline data collection). For this analysis, an offset term comprising of the total number of congregation members in each type of church is typical. The total (ie, direct and indirect) effect of the intervention can be assessed by including all individuals belonging to either arm and by using an offset term of the total number of congregation members in each arm.

We are also conducting social network analysis per protocol. Network data were collected at the 6-month timepoint. We asked people to respond to 4 items that asked them to name the top 3 persons involved in the program (eg, health minister, pastor, study team member, and others involved) that they would turn to for advice in life, about their health, about personal crises, and with whom they socialize. This information provided us with an understanding of the extent of homophily within groups, and it helped us to determine whether network density impacted message diffusion [36,39]. By gathering name-based information, we were able to capture the extent of integration of the program "actors" (study staff, speakers) with church member participants, and the degree of reciprocity evoked by bringing information to participants and their willingness to give back in the relationship [36-38].

Conclusions

The "Dose of Hope" program is a feasible, sustainable, and engaging model for education and recruitment of older African Americans in faith-based settings. The early results of this study indicate that the program had an effect on intentions to seek clinical trial information, and in the longer term, participate in appropriate studies. Additionally, the strong retention rate of the cohort suggests that the program was well received by participants. "Dose of Hope" may therefore usher in a new model for clinical trial engagement of willing, yet overlooked, diverse participants.

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Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

NIH study section reviewer comments.

[PDF File (Adobe PDF File), 341KB - resprot_v4i2e64_app1.pdf]

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Abbreviations

AIDS: acquired immune deficiency syndrome
AME: American Methodist Episcopalian
CDC: Centers for Disease Control and Prevention
DOI: Diffusion of Innovations
HIV: human immunodeficiency virus
NIH: National Institutes of Health
SDA: Seventh-Day Adventist
TRA: Theory of Reasoned Action

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Protocol

Accuracy of Detecting Residual Disease After Cross Neoadjuvant Chemoradiotherapy for Esophageal Cancer (preSANO Trial): Rationale and Protocol

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Abstract

Background: Results from the recent CROSS trial showed that neoadjuvant chemoradiotherapy (nCRT) significantly increased survival as compared to surgery alone in patients with potentially curable esophageal cancer. Furthermore, in the nCRT arm 49% of patients with a squamous cell carcinoma (SCC) and 23% of patients with an adenocarcinoma (AC) had a pathologically complete response in the resection specimen. These results provide a rationale to reconsider and study the timing and necessity of esophagectomy in (all) patients after application of the CROSS regimen.

Objective: We propose a “surgery as needed” approach after completion of nCRT. In this approach, patients will undergo active surveillance after completion of nCRT. Surgical resection would be offered only to those patients in whom residual disease or a locoregional recurrence is highly suspected or proven. However, before a surgery as needed approach in oesophageal cancer patients (SANO) can be tested in a randomized controlled trial, we aim to determine the accuracy of detecting the presence or absence of residual disease after nCRT (preSANO trial).

Methods: This study is set up as a prospective, single arm, multicenter, diagnostic trial. Operable patients with potentially curable SCC or AC of the esophagus or esophagogastric junction will be included. Approximately 4-6 weeks after completion of nCRT all included patients will undergo a first clinical response evaluation (CRE-I) including endoscopy with (random) conventional mucosal biopsies of the primary tumor site and of any other suspected lesions in the esophagus and radial endo-ultrasonography (EUS) for measurement of tumor thickness and area. Patients in whom no locoregional or disseminated disease can be proven by cytohistology will be offered a postponed surgical resection 6-8 weeks after CRE-I (ie, approximately 12-14 weeks after completion of nCRT). In the week preceding the postponed surgical resection, a second clinical response

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evaluation (CRE-II) will be planned that will include a whole body PET-CT, followed again by endoscopy with (random) conventional mucosal biopsies of the primary tumor site and any other suspected lesions in the esophagus, radial EUS for measurement of tumor thickness and area, and linear EUS plus fine needle aspiration of PET-positive lesions and/or suspected lymph nodes. The main study parameter is the correlation between the clinical response assessment during CRE-I and CRE-II and the final pathological response in the resection specimen.

Results: The first patient was enrolled on July 23, 2013, and results are expected in January 2016.

Conclusions: If this preSANO trial shows that the presence or absence of residual tumor can be predicted reliably 6 or 12 weeks after completion of nCRT, a randomized trial comparing nCRT plus standard surgery versus chemoradiotherapy plus "surgery as needed" will be conducted (SANO trial).

Trial Registration: Netherlands Trial Register: NTR4834; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4834 (archived by Webcite at http://www.webcitation.org/6Ze7mn67B).

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KEYWORDS

esophageal cancer; neoadjuvant chemoradiotherapy; esophagectomy; surgery as needed; active surveillance policy

Introduction

Background

Cancer of the esophagus remains a highly lethal malignancy, as reflected by an average overall 5-year survival of 17% [1]. In the Netherlands, the incidence of esophageal cancer resembles the growing trend in Western countries, with an estimated incidence of 15/100,000 for men and 6/100,000 for women [2] and more than 2,500 new cases being diagnosed nationally each year.

At present, surgical resection is still considered the cornerstone of curative treatment for patients eligible with stage cT1b-4aN0-3M0 disease. The reported 5-year survival rate for patients who undergo an esophagectomy ranges from 20% to 50%, but rarely exceeds 35% [3-7]. Esophagectomy is associated with postoperative mortality rates of 1% to 5% in high-volume centers, severe postoperative morbidity, and a substantial impact on the quality of life [8-13]. In order to improve the radicality of surgical resection and the long-term survival after surgical resection, many trials have been performed to study the effect of neoadjuvant chemo and/or radiation therapy [14-17]. One of the largest trials is the recently published chemoradiotherapy for oesophageal cancer followed by surgery study (CROSS trial). This randomized trial compared neoadjuvant chemoradiotherapy (nCRT) plus surgery to surgery alone [18].

During a 5-year period, 366 patients from 5 academic and 2 nonacademic high-volume teaching hospitals in the Netherlands were included in the CROSS trial. Results showed that the addition of nCRT (carboplatin AUC2, paclitaxel 50 mg/m^2, and 41.4 Gy of concurrent radiotherapy) to surgery significantly increases long-term survival as compared to surgery alone. Median overall survival of patients who received nCRT plus surgery was 49 months, compared to 24 months for those who received surgery alone, and the 3-year overall survival was superior in the nCRT arm (hazard ratio (HR) = 0.66; 95% confidence interval (CI) 0.50-0.87; *P*=.003). Therefore, nCRT plus surgery is now considered the therapy of choice in the Netherlands and several other countries for potentially curable esophageal cancer (cT2-3N0-3M0 and cT1N1-3M0, according to the UICC TNM classification [19]). In subsequent analyses of secondary endpoints of the CROSS trial an interesting observation was made. In the nCRT arm, 49% of patients with a squamous cell carcinoma (SCC) and 23% of patients with an adenocarcinoma (AC) had a pathologically complete response (pCR) in the resection specimen (ie, no viable tumor cells were found, neither at the site of the primary tumor nor in the resected regional lymph nodes, as determined by conventional histological examination) [18]. Therefore, these results provide a rationale to reconsider and study the timing and necessity of standard esophagectomy in patients after application of the CROSS regimen.

Objective

We propose a "surgery as needed" approach after completion of nCRT for carcinoma of the esophagus. In this surgery as needed approach, patients will undergo active surveillance after completion of nCRT. Surgical resection would be offered only to those patients in whom a locoregional recurrence is highly suspected or proven, in the absence of any signs of distant dissemination. Such an organ-preserving strategy would clearly have great advantages. Postoperative mortality and severe morbidity (grade ≥3 according to the Clavien-Dindo classification [20]) after esophagectomy in the Netherlands is 5% and 60%, respectively. Thus, a nonsurgical treatment strategy in patients with a clinically complete response after nCRT, theoretically saves 5% mortality and 60% severe morbidity in this patient group. Moreover, this approach might improve quality of life and might lead to a reduction in health care costs. However, this surgery as needed approach is only favorable if long-term survival would be comparable to that of the trimodality approach comprising nCRT followed by standard surgery. Before a surgery as needed approach can be tested in a randomized trial, we aim to determine the feasibility of accurate detection of residual disease after chemoradiotherapy through a surgery as needed in oesophageal cancer patients study (preSANO trial).

The aim of this present prospective, multicenter, and diagnostic preSANO trial is to determine the accuracy by which we can detect the presence or absence of residual disease after nCRT. The results of this trial will inform us about the percentage of patients with a clinically complete response after nCRT and

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will help to estimate the number of patients needed for a subsequent randomized controlled trial. The future so-called "SANO trial" will randomize patients into 2 strategy groups: (1) nCRT plus surgery, and (2) nCRT followed by an active surveillance.

Methods

Study Design

The preSANO trial is a prospective, multicenter, diagnostic trial including 120 patients, using a single arm. Five high-volume centers in the Netherlands are currently participating in this study: Erasmus Medical Center, Rotterdam; Academic Medical Center, Amsterdam; University Medical Center, Utrecht; Catharina Cancer Center, Eindhoven; and Atrium Medical Center, Heerlen. The study has been approved by the medical ethics committee (MEC) of the Erasmus Medical Center (MEC2013-211) and has been registered in the Netherlands Trial Register (NTR4834).

Study Population

We plan to include individuals from a population of operable patients with potentially curable SCC or AC of the esophagus or esophagogastric junction. All patients who are planned to undergo nCRT according to the CROSS regimen [18] followed by surgical resection are eligible to participate. Patients with dementia or altered mental status prohibiting the understanding and giving of informed consent will be excluded from participation in this study. Patients will undergo conventional pretreatment selection (including at least a "partial body" F18-FDG positron emission tomography-computed tomography (PET-CT) to assess the avidity of the primary tumor process; Figure 1 and Table 1).

Table 1. Study algorithm.

Parameter	Pretreatment	First clinical response evaluation (CRE-I)	Second clinical response evaluation (CRE-II)
History, physical examination	X	X	X
Performance status	X	X	X
Hematology[a]	X		
eGFR	X		
Biochemistry[b]	X		
Endoscopy + (random) biopsies	X	X	X
Radial EUS[c]	X	X	X
Linear EUS (+FNA)[d]	X		X
CT of neck, thorax, abdomen, and pelvis	X		
PET-CT	X "partial body"	X[g]"whole body"	X[h]"whole body"
Pulmonary function tests	X		
Bronchoscopy[e]	X		
ECG	X		
Toxicity[f]	Baseline		

[a]Hematology: CBC, differential

[b]Biochemistry: serum protein, albumin, magnesium, electrolytes, serum creatinine, bilirubin, alkaline phosphatase, AST, and pregnancy test if indicated at baseline only

[c]Radial EUS: with measurement of maximum tumor thickness and area

[d]Linear EUS: with FNA of any suspected lymph nodes

[e]Bronchoscopy: when tumor is located above the carina and when there is suspicion for invasion of the tracheobronchial tree

[f]Toxicity: to be evaluated after each cycle (incidence and grade according to CTC toxicity scale)

[g]PET-CT: during CRE-I, after EGD and EUS, only for clinically noncomplete responders to exclude disseminated disease

[h]PET-CT: during CRE-II, prior to EGD and EUS, for all patients (all were clinically complete responders during CRE-I) to guide EGD and EUS in targeting suspected locoregional lesions and to exclude disseminated disease

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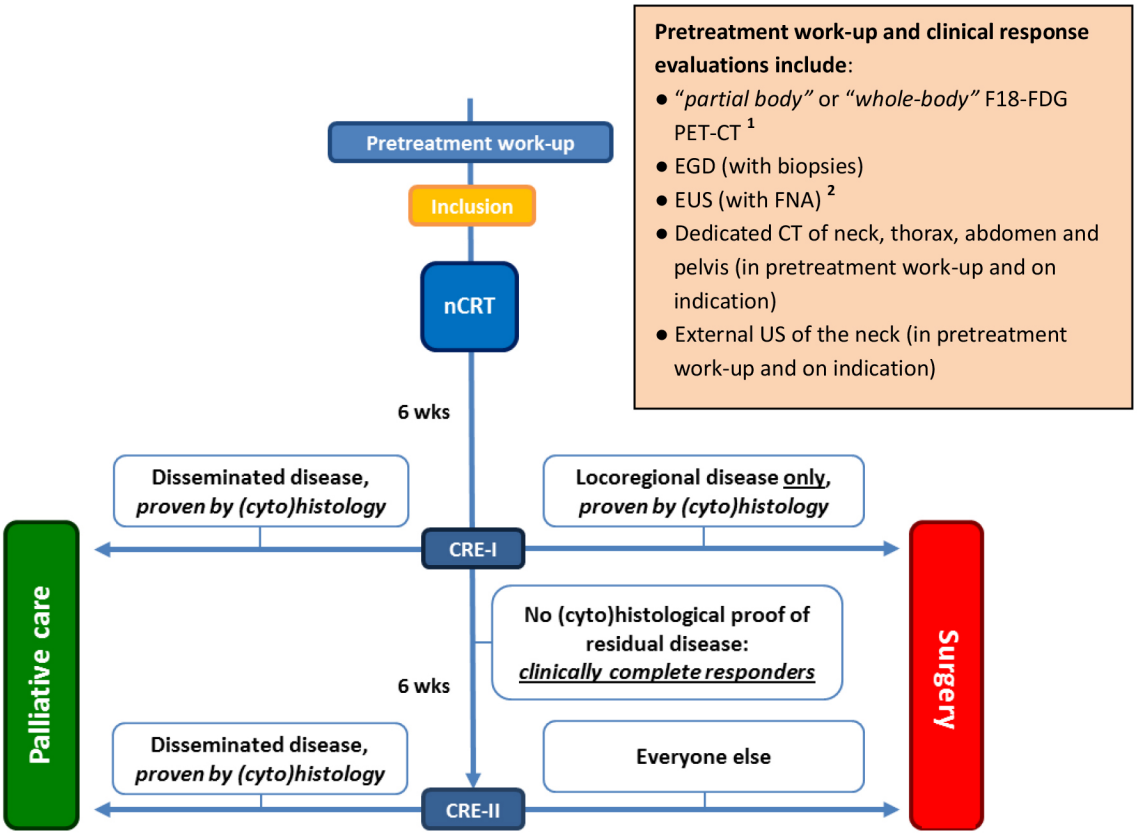
Figure 1. Study algorithm. 1. During the pretreatment workup, it suffices when a "partial body" F18-FDG PET-CT of the esophagus will be performed (to test for avidity of the primary lesion); if it is preferred to make a "whole-body" PET-CT not only after, but also before the neoadjuvant chemoradiotherapy in order to detect distant metastases at an earlier stage, the indication for performing an external US with FNA of the neck can be limited to those patients who have a suspected lymph node on the PET-CT [23]. In the period after neoadjuvant therapy, 1 whole-body F18-FDG PET-CT will be performed either at CRE-I (for the clinically noncomplete responders) or at CRE-II (for the clinically complete responders at CRE-I). 2. EUS with FNA of suspected lymph nodes only during CRE-II, not during CRE-I. CRE: clinical response evaluation; CT: computed tomography; EUS: endoscopic ultrasonography; FNA: fine-needle aspiration; nCRT: neoadjuvant chemoradiotherapy; EGD: esophagogastroduodenoscopy; PET: positron-emission tomography; US: ultrasonography.



Study Algorithm

Overview

All included patients will receive nCRT according to the CROSS protocol (carboplatin, paclitaxel, and concurrent radiotherapy) [18]. Patients will be reevaluated either once or twice before undergoing surgical resection during clinical response evaluations (CRE). The aim of these CREs will be to identify those patients in whom residual and/or disseminated disease is present.

CRE-I

The first CRE (CRE-I) will be performed 4-6 weeks after completion of chemoradiotherapy (Figure 1). During CRE-I, all patients will undergo esophagogastroduodenoscopy (EGD) with registration of endoscopic images for future reference and biopsies of any suspected lesions, including mucosal biopsies at the site of the primary tumor (1 regular biopsy per centimeter in each of the 4 quadrants), radial endoscopic ultrasonography (EUS) for measurement of maximal tumor thickness and area, and linear EUS. Patients with histological evidence of locoregional residual disease, but without evidence of disseminated disease, will be offered immediate surgical resection. These patients have no clear benefit from postponement of surgical resection and should therefore have no delay according to current recommendations. Patients without histological evidence of locoregional residual disease and without disseminated disease will be considered to be *clinically complete responders* and will be offered a postponed surgical resection. In these patients a surgical resection will be postponed for an additional 6-8 weeks, allowing patients more time to reach a better condition for surgery.

CRE-II

In the week preceding the planned postponed surgical resection, a second clinical response evaluation (CRE-II) will be scheduled. CRE-II will be performed only in patients who were considered to be clinically complete responders (ie, no viable tumor found) at CRE-I. CRE-II will consist of a PET-CT (standard for all patients at CRE-II and only for tumor-positive patients at CRE-I), an EGD with registration of endoscopic images for future reference, and biopsies of any suspected lesions, including (random) mucosal biopsies at the site of the primary tumor, radial EUS for measurement of maximal tumor thickness and area, and linear EUS plus fine-needle aspiration (FNA) of PET-positive lesions and/or suspected lymph nodes.

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An important difference between CRE-I and CRE-II will be that during CRE-I clinically complete responders will be offered a postponed surgical resection, whereas after CRE-II both locoregionally complete and noncomplete responders will be advised to undergo a surgical resection (Figure 1). In other words, all patients who are considered clinically complete responders at CRE-I and are therefore allowed to postpone their surgery by an additional 6-8 weeks, will undergo CRE-II followed by the postponed surgical resection, irrespective of the locoregional findings during CRE-II. The diagnostic results from CRE-II will later be compared with results from both CRE-I and the final pathological analysis of the resection specimen. However, patients with (cyto)histological evidence of disseminated disease during CRE-I or CRE-II will be excluded from further curative therapy and will be referred for palliative care.

If after CRE-II the planned operation is postponed for more than 4 weeks (eg, because the patient has not yet sufficiently recovered from the nCRT), a CRE-III (comparable to CRE-II) will be performed 1 week before the (further) postponed operation.

Surgery

Surgical resection will be attempted immediately after CRE-I only in those patients who present at CRE-I with histologically proven residual disease after completion of nCRT, without any signs of disseminated disease. All other patients will undergo surgical resection after CRE-II in the absence of distant metastases.

A transthoracic esophageal resection or a transhiatal approach can be performed, depending on both patient characteristics and local expertise and preference. Both open and minimally invasive techniques are allowed.

A wide local excision including the regional lymph nodes is carried out in both techniques, including a standard dissection of the lymph nodes around the coeliac axis. The continuity of the digestive tract will preferably be restored by a gastric tube reconstruction or, if required, by a colonic interposition.

At least 15—but preferably 23 or more—lymph nodes should be aimed to be removed in every patient since it has been shown that long-term survival is maximized with the removal of at least 23 nodes [21]. Moreover, the risk of understaging the tumor in these patients should be minimized. If an insufficient number of nodes is removed, the patient might be erroneously staged as ypN0, while in fact ypNpos nodes have been left in situ (stage migration).

Pathology

All resection specimens will be revised centrally by 2 independent expert pathologists, using a standard protocol. In case of a discordant outcome, the specimens will be reviewed by a third independent expert pathologist. A final diagnosis will be made only if at least 2 pathologists agree. Also, all the CRE-II biopsies of patients who were considered negative at CRE-II, but who had more than 10% residual tumor in their resection specimen will be revised centrally following the same strategy. In these specimens special attention will be given to the effects of the preoperative chemoradiation (ie, tumor reduction and therapy effects). The lymph node dissection should contain at least 15—but preferably 23 or more—nodes derived from both mediastinum and upper abdomen, which are essential for correct ypTNM staging. The resection margins, especially the circumferential margin, will be evaluated with a 1 mm cutoff point for vital tumor. This implies that the tumor-free margin should be larger than 1 mm in order to be classified as R_0. If vital tumor is present at 1 mm or less from the surgical resection margin, it is considered microscopically positive (R_1).

Interim Analysis

An interim analysis will be performed by an independent safety committee after a total inclusion of 60 patients in order to carefully monitor serious complications during CRE-I and CRE-II and to assess the achieved radicality of the performed operations.

Main Study Parameter/Endpoint

The main study parameter in this study is the correlation between the clinical response assessment during CRE-I and CRE-II and the final pathological response in the resection specimen as measured by the modified tumor regression grading (TRG) system of Chirieac [22]: no residual carcinoma (TRG1), 1%-10% residual carcinoma (TRG2), 11%-50% residual carcinoma (TRG3), 51%-100% residual carcinoma (TRG4) [22].

We propose that in this study TRG2 residual tumors may be missed as long as we expect them to be detectable reliably as soon as they have outgrown from TRG2 to TRG3-4 during follow-up. The risk that TRG2 residual tumors will lead to irresectability in the short-term is likely to be small/negligible. However, we do propose that TRG3 and TRG4 residual tumors should be detected without further delay in order to prevent short-term loss of resectability and to minimize the risk of long-term distant disease dissemination. The validity of these assumptions can only be determined in a future SANO trial, in which an active surveillance strategy will be compared with standard surgery in all patients after nCRT.

Statistical Analysis

Sample Size Calculation

As was seen in the previous CROSS trial approximately 40% of the included patients will have TRG3 or TRG4 residual tumor in the resection specimen [18]. With a total inclusion of 120 patients, approximately 45 patients will have TRG3 or TRG4 residual tumor. We consider 45 patients a sufficiently large sample for determining the accuracy of individual and/or combined diagnostic tests. In order to estimate the distribution of 120 patients planned to be included, data were used from the CROSS trial as indicated in Figure 2. Furthermore, several assumptions were made:

- We assume that during CRE-I clinically complete responders will comprise patients with TRG1 or TRG2 (as taken from the pathological response data of the CROSS trial), whereas clinically noncomplete responders will be patients with TRG3 or TRG4.

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- The percentage of patients with SCC and AC with TRG1 or TRG2 in the CROSS trial was 78% and 57%, respectively. This means that approximately 60% of included patients are expected to have negative (cyto)histology at CRE-I.
- In a trial by Blom et al [23], approximately 10% of patients who were reevaluated by PET-CT after completion of nCRT had newly discovered disseminated disease. We assume that there will be fewer newly found disseminated disease with positive (cyto)histology at CRE-II because a number of these patients are expected to be discovered during CRE-I.
- We assume that approximately 25% of clinically complete responders will refuse to undergo the postponed resection and choose to undergo an active surveillance strategy if no alarming results are found during CRE-II.

These calculations indicate that approximately 60 patients will show a clinically complete response after combined diagnostic investigations during CRE-I and CRE-II (including EUS-FNA with tumor thickness measurements and PET-CT). Of these, approximately 15 patients will refuse to undergo surgery and will undergo active surveillance and approximately 30 patients will have a pCR (TRG1). The 15 remaining patients are expected to have residual disease, of whom approximately 12 patients will have TRG2 residual tumor and approximately 3 patients will have TRG3 or TRG4 residual tumor. As we proposed above, TRG2 residual tumors may be missed. Therefore, we expect that approximately 3 patients with clinically relevant residual disease (TRG3 or TRG4) will be missed.

In case of unexpected aberrant distribution of patients in the preSANO trial that leads to decreased TRG3 and TRG4 rates, results of the first 120 patients will be analyzed following the present protocol. If these results are promising but do not reach statistical significance, possibly due to a lack of power, inclusion of extra patients will be considered. If inclusion of extra patients is desirable, the protocol will be amended and assessed by the medical ethics committee.

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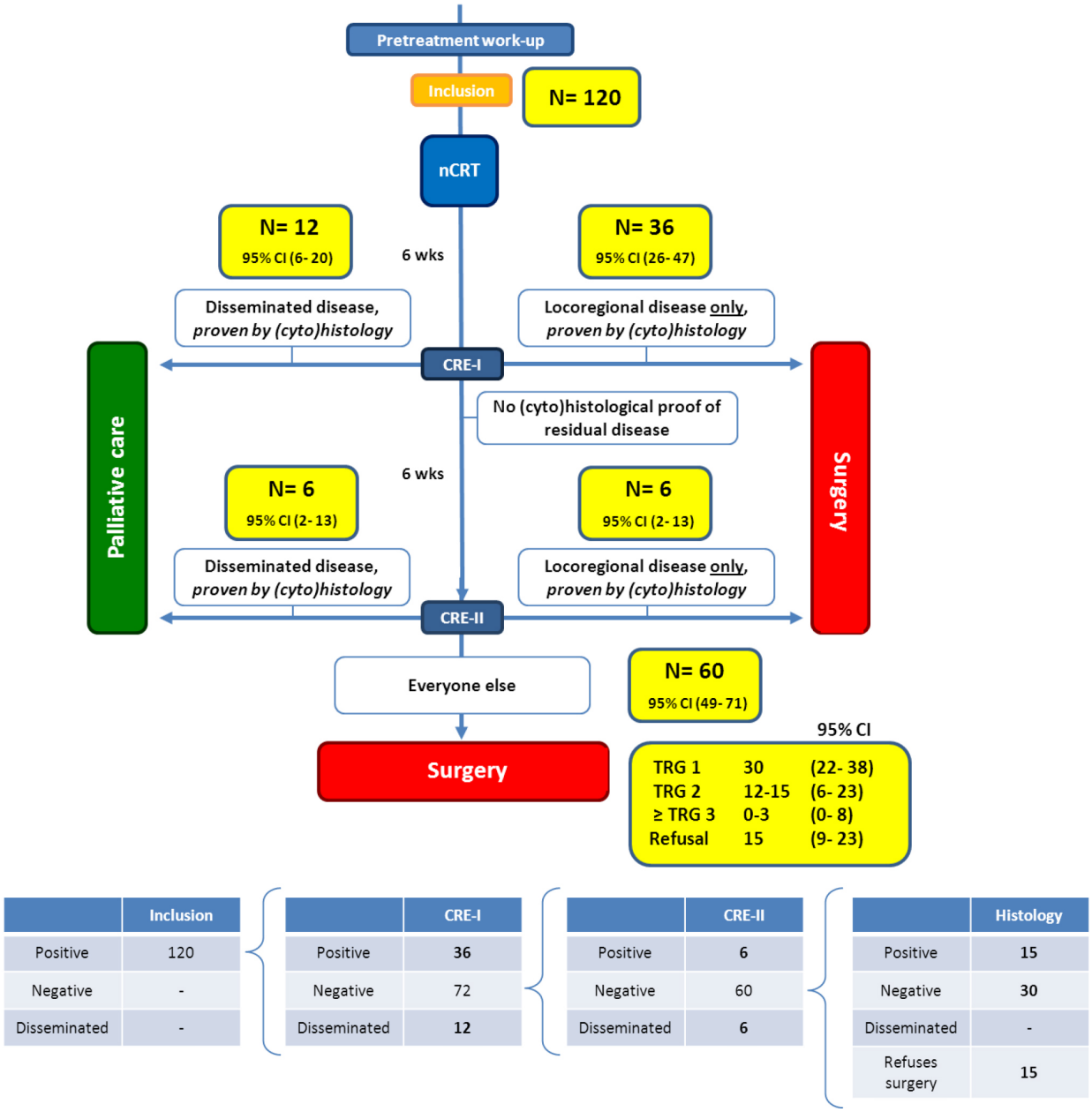
Figure 2. Expected distribution of patients (based partly on CROSS trial data). All numbers are based on an inclusion of 120 patients. CI: confidence interval; CRE: clinical response evaluation; nCRT: neoadjuvant chemoradiotherapy; N: number of patients; TRG: tumor regression grade, as measured by the modified TRG system of Chirieac. Of the 45 patients who will undergo a postponed resection following CRE-II, 15 patients are expected to have a pathologically incomplete response (at least TRG2).



	Inclusion
Positive	120
Negative	-
Disseminated	-

	CRE-I
Positive	36
Negative	72
Disseminated	12

	CRE-II
Positive	6
Negative	60
Disseminated	6

	Histology
Positive	15
Negative	30
Disseminated	-
Refuses surgery	15

Data Analysis

The clinical response evaluation will consist of different diagnostic modalities. Results of each diagnostic modality will be presented as categorical or continuous data, depending on the outcome measure of each diagnostic modality. These results will be correlated to the (categorical) tumor regression grading in the resection specimen using a Chi-square-based test (categorical-categorical) or a 1-way ANOVA test (continuous-categorical) with post-hoc testing.

Results

The first patient was enrolled on July 23, 2013, and results are expected in January 2016.

Discussion

The uniqueness of this study lies in the prospective evaluation of a sufficiently large number of patients, using multiple diagnostic modalities on different time points. Although (cyto)histological assessment of biopsies and/or FNAs is the most objective parameter, several studies have shown that the response to nCRT is reflected by tumor size or volume as

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assessed by EUS [24-27]. The rationale to include a second clinical response evaluation before a planned surgical resection is to allow for a comparison between multiple measurements and to increase the chance of detecting residual and/or disseminated disease. It is expected that during CRE-II (due to an extended time period from the end of nCRT) the F18-FDG PET-CT signal will have a more favorable signal-to-noise ratio than has been described previously [28-33] because after 12 weeks the artefacts due to radiation-induced inflammation are expected to have largely dissolved. This allows for identification of suspected lymph nodes to be targeted by FNA during CRE-II.

The reason to include patients with SCC as well as patients with AC in the preSANO trial is that the CROSS regimen has been shown to be effective in both groups of patients. The pCR rates of 49% in patients with SCC and 23% in patients with AC in the CROSS trial provide a rationale for a SANO approach in both histological subtypes. Furthermore, together with the low frequency of toxic effects of the CROSS regimen (91% received the full treatment regimen of nCRT), these high pCR rates advocate the use of the relatively low dose of 41.4 Gy radiotherapy [18].

Although we have not yet clearly shown that we are able to detect a clinically threatening residual cancer 4-6 weeks after nCRT, there are several arguments why it is not deemed necessary to do so before we delay the planned surgical resection with an additional 6-8 weeks. Recently, it was shown that prolonged time to surgery after nCRT up to at least 12 weeks had no effect on disease-free and overall survival (HR=1.00 and HR=1.06 per additional week, *P*=.976 and *P*=.139, respectively). Moreover, prolonged time to surgery increased the probability of pCR in the resection specimen (odds ratio = 1.35 per additional week of time to surgery, *P*=.0004) [34]. Comparable results have been published by other groups [35,36].

Postoperative mortality and severe morbidity (grade ≥3 according to the Clavien-Dindo classification [20]) after esophagectomy in the Netherlands is 5% and 60%, respectively. Thus, a nonsurgical treatment strategy in patients with a clinically complete response after nCRT theoretically saves up to 5% mortality and 60% severe morbidity in this patient group. Moreover, this approach might improve quality of life and might lead to a reduction in health care costs. Therefore, we will consider this study as successful when the results of the combined diagnostic modalities lead to a maximum percentage of clinically false-negative TRG3 and TRG4 tumors of twice the postoperative mortality (ie, 10%). If more than 10% of TRG3 or TRG4 tumors are missed, the SANO trial will be reconsidered.

If the preSANO trial shows that TRG3 and TRG4 residual tumor can be predicted reliably, a randomized trial comparing nCRT plus standard surgery versus chemoradiotherapy plus surgery as needed in oesophageal cancer patients (the SANO trial) will be conducted. Hopefully, this SANO trial will result in an organ-preserving treatment strategy for a selected group of patients and therefore reduce treatment related morbidity and mortality, improve quality of life, and lead to a reduction in health care costs.

Acknowledgments

The preSANO trial is funded by the Koningin Wilhelmina Fonds Kankerbestrijding (KWF, Dutch Cancer Society) and Stichting Coolsingel Rotterdam (Coolsingel Rotterdam Foundation).

Conflicts of Interest

None declared.

Authors' Contributions

BN participated in the study design and drafted the manuscript. JS, MS, KK, HL, MB, GN, RH, MS, and ES participated in the study design and critically revised the manuscript. BW initiated the trial and critically revised the manuscript. JL initiated the trial and supervised the drafting of the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Multimedia Appendix 1

The trial is funded by amongst others the Koningin Wilhelmina Fonds Kankerbestrijding (KWF, Dutch Cancer Society) and has been reviewed by external reviewers from the KWF. They assigned the study an A-status, indicating that funding of this project is of the highest priority.

[PDF File (Adobe PDF File), 567KB - resprot_v4i2e79_app1.pdf]

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Abbreviations

AC: adenocarcinoma
CI: confidence interval
CRE: clinical response evaluation
CROSS: chemoradiotherapy for oesophageal cancer followed by surgery study [18]
CT: computed tomography
EGD: esophagogastroduodenoscopy
EUS: endoscopic ultrasonography
FNA: fine-needle aspiration
HR: hazard ratio
MEC: medical ethics committee
nCRT: neoadjuvant chemoradiotherapy
NTR: Netherlands Trial Register
pCR: pathologically complete response
PET: positron-emission tomography
SANO: surgery as needed approach in oesophageal cancer patients

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SCC: squamous cell carcinoma
TRG: tumor regression grading

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Protocol

Cognitive Impairment in Diabetes: Rationale and Design Protocol of the Cog-ID Study

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Abstract

Background: Cognitive impairment frequently co-occurs with type 2 diabetes but is often undiagnosed. Cognitive impairment affects self-management leading to treatment-related complications.

Objective: The aim of this study is to develop a stepped diagnostic procedure, consisting of a screening test complemented by an evaluation by a general practitioner (GP), to detect undiagnosed cognitive impairment in older people with type 2 diabetes.

Methods: The accuracy of two self-administered cognitive tests, the "Test Your Memory" (TYM) and "Self-Administered Gerocognitive Examination" (SAGE) alone, and in combination with an evaluation by a GP will be assessed. A diagnosis of mild cognitive impairment (MCI) or dementia at a memory clinic will serve as reference standard. This cognitive impairment in diabetes (Cog-ID) study will include 513 people from primary care facilities aged ≥70 with type 2 diabetes. The participants will first fill out the TYM and SAGE tests, followed by a standardized GP evaluation for cognitive impairment, including a mini mental state examination (MMSE). Subsequently, participants suspected of cognitive impairment (on either test or the GP assessment) and a random sample of 15% (65/435) of participants without suspected cognitive impairment will be referred to the memory clinic. At the memory clinic, a medical examination, neuropsychological examination, and magnetic resonance imaging (MRI) of the brain will be performed. Participants will also fill out questionnaires assessing health status and depressive symptoms at baseline and after 6 and 24 months.

Results: This research obtained funding and ethical approval. Enrolment started in August, 2012, and all study-related activities will be completed in September, 2016.

Conclusions: With the results from this study, physicians will be able to detect cognitive impairment affecting type 2 diabetes patients through case-finding, and can use tailored care to reduce associated complications. Additionally, the results may stimulate discussions about cognitive impairment and whether early recognition is desirable.

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KEYWORDS

type 2 diabetes mellitus; cognitive impairment; diagnostic procedure; screening; dementia; elderly

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Introduction

Background

Patients with type 2 diabetes have an increased risk of cognitive impairment and a doubled risk of dementia compared to people without diabetes [1,2]. Cognitive impairment often remains unrecognized by physicians, even when patients or their relatives express complaints [3,4]. This is an important problem since in patients with type 2 diabetes, cognitive impairment is associated with impaired self-management and an increased incidence of diabetes-related complications [5,6]. Early recognition of cognitive impairment could assist the general practitioner (GP) in taking appropriate, personalized measures in diabetes management to prevent complications [7].

Routine screening for cognitive impairment in elderly patients with type 2 diabetes has been advocated [8]. The American Diabetes Association advises to individualize diabetes treatment and to adjust management to the preserved capacity of patients, thereby specifically taking into account cognitive functioning [9]. However, compared with other potential complications and co-morbid conditions of type 2 diabetes, the diagnostic evaluation of diabetes-associated cognitive impairment is underdeveloped. While screening algorithms have been established for microvascular complications, such as retinopathy or nephropathy, there is no established method to detect undiagnosed cognitive impairment. The ideal procedure for the assessment of possible disturbances of cognitive functioning should be easy and quick to perform. The procedure should readily identify people who require further, more elaborate and time consuming, evaluations by the GP or possibly referral to a memory clinic. Unfortunately, administration of most cognitive tests already requires a lot of time from a physician, nurse, or other health care worker. In addition, currently available tests with the shortest administration times tend to cover only certain aspects of cognition, particularly those affected in Alzheimer's disease. Moreover, these tests are much less accurate in identifying people with other conditions, in particular vascular cognitive impairment [10].

These issues may be resolved by the recent introduction of self-administered cognitive tests, such as the Test Your Memory (TYM) [11] and the Self-Administered Gerocognitive Examination (SAGE) [12] tests. In a memory clinic setting, these tests have been shown to measure a broader range of cognitive domains than the mini mental state examination (MMSE) and they were also able to detect mild cognitive impairment (MCI) [11-13]. Therefore, in our view, these self-administered cognitive tests could be promising tools for the detection of cognitive impairment in type 2 diabetes in primary care.

The ultimate goal of a diagnostic procedure for cognitive impairment is to improve clinical outcomes and patients' quality of life. However, before the effect of a diagnostic procedure can be evaluated, which specific tests to include must be determined. The latter is examined in this cognitive impairment in diabetes (Cog-ID) study. Here, we aim to establish a reliable, valid, and efficient stepped diagnostic procedure to detect cognitive impairment in patients ≥70 years of age with type 2 diabetes, starting with the TYM and the SAGE tests. It is unknown which of these two tests is best suited for application in a primary care setting; therefore we will assess the accuracy and feasibility of both. In addition, we will describe how early detection of cognitive impairment affects treatment and quality of life in an observational study that is part of the main study. Together, the results will help shape future studies with the goal of answering the unresolved, but increasingly relevant and heavily debated question [14], whether early recognition of cognitive impairment in patients with type 2 diabetes will help the GP to take appropriate measures in disease management, and ultimately prevent treatment-related complications. Future studies are needed to assess the effect of the established diagnostic procedure on clinical outcomes in a randomized controlled trial.

Objectives

Our overall aim is to establish a reliable, valid, and efficient stepped diagnostic procedure to detect undiagnosed cognitive impairment in patients ≥70 years of age with type 2 diabetes. The procedure will consist of a self-administered cognitive test and an evaluation by a GP. Additionally, we will describe how early detection of cognitive impairment affects treatment and quality of life in participating patients in a parallel observational study. The specific objectives of the study are (1) to assess the validity of two self-administered cognitive tests (TYM and SAGE) in detecting undiagnosed cognitive impairment in elderly patients with type 2 diabetes in a primary care setting and to select the best instrument, (2) to assess the diagnostic accuracy of a standardized evaluation by a GP in detecting undiagnosed cognitive impairment in patients with type 2 diabetes, (3) to estimate the accuracy and efficiency of the best cognitive test(s) combined with the evaluation by the GP, and (4) to describe the effect of the diagnostic procedure on several aspects of diabetes care (ie, treatment targets and appointment schedules) and patients' quality of life.

Methods

Study Participants

General practitioners (GPs) in the surroundings of Utrecht, the Netherlands, will be asked to select patients with type 2 diabetes mellitus ≥70 years of age. Exclusion criteria include a diagnosis of dementia, previous investigation at a memory clinic, and the inability to write or read in Dutch. Patients with a disorder that might influence cognitive functioning, like substance abuse or a psychiatric or neurological disorder, but without a diagnosis of cognitive impairment are not excluded as we are interested in the presence of unknown cognitive impairment regardless of the cause. Eligible patients will receive a letter from their GP with information regarding the study. Patients will be asked to return the response form on which they can mark whether or not they are willing to participate. In the case of non-response, one reminder will be sent.

Screening Tests

Test Your Memory Test

The TYM is developed to test a range of cognitive functions and consists of 10 tasks [11]. It is a self-administered test and

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takes a patient around 5 minutes to complete. The tasks include orientation (10 points), ability to copy a sentence (2 points), semantic knowledge (3 points), calculation (4 points), verbal fluency (4 points), similarities (4 points), naming (5 points), visuospatial abilities (2 tasks, total 7 points), and recall of a copied sentence (6 points). The ability to complete the test without help is an 11th task (5 points); because of our study design all patients will receive these 5 points. The maximum score is 50 points. A score of ≤39 is suggestive of dementia [11]. The TYM was translated into Dutch and then translated back to English by a bilingual native English speaker, which resulted in a version almost identical to the original.

Self-Administered Gerocognitive Examination

The SAGE measures cognitive functioning in the domains of orientation (4 points), language (4 points), memory (2 points), executive function (4 points), calculations (2 points), abstraction (2 points), and visuospatial abilities (4 points) [12]. Furthermore, the SAGE includes several questions on demographic information, medical and family history, and current status. The maximum score is 22 points. A score of ≤14 is suggestive of dementia [12]. Like the TYM, the SAGE was translated into Dutch and then back into English, which resulted in a version almost identical to the original.

The Diagnostic Strategy

Part 1: Home Visit

Participants will be visited at home by a research physician (a trainee GP). The home visit will take about 1 hour. The participant will be asked to fill out the TYM, SAGE, and a questionnaire assessing health status and depressive symptoms, including the Short Form Health Survey (SF-36)[15], EuroQol (EQ)-5D and EQ-VAS [16], and the Center for Epidemiologic Studies Depression Scale (CES-D) [17]. The research physician will be blinded for the scores on the TYM and the SAGE, and will not provide any assistance in filling out the questionnaires. Following the questionnaires, the research physician will administer a standardized diagnostic interview based on the Dutch guideline for case finding of dementia by GPs to both the participant and (if possible) a close informant [18], representing the evaluation by the GP. The interview will include demographic variables, educational level, and living conditions, as well as a medical history and a list of cognitive complaints (Table 1). After the interview, the MMSE will be administered. The MMSE consists of 11 tasks including the domains orientation in time (5 points), orientation in space (5 points), registration of three words (3 points), concentration and calculation (5 points), recall of three words (3 points), language (8 points) and visuospatial abilities (1 point). The maximum score is 30 points with a higher score indicating a higher level of cognitive functioning. A score of ≤24 is suggestive of dementia.

Based on the history taken, the research physician will decide whether the participant should be classified as "suspected of cognitive impairment" or "no cognitive impairment" according to the criteria for MCI and dementia [19,20]. If the MMSE score is ≤24, the participant will always be classified as "suspected of cognitive impairment".

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Table 1. List of questions about acquired cognitive symptoms for the participant and informant.

Questions	Patient[a]	Informant[a]
Do you have memory problems?		
Do other people think you are forgetful?		
Do you forget names of relatives or peers?		
Do you often lose things?		
Do you have to write more things down to remember it than you were used to?		
Are there activities you stopped doing in the past five years (and why)?		
Do you visit friends or family less often?		
How does cooking, grocery shopping and the household go?		
Do you have trouble managing your finances?		
Do you have trouble driving a car or using public transport?		
Do you need help getting dressed?		
Do you sometimes forget what month or year it is?		
Can you independently manage your medication?		
Can you follow the news in the paper or on television?		
Do you have problems with walking or holding your balance?		
Did you lose weight unintentionally in the past years?		
Has your smell or taste changed in the past years?		
Are you depressive?		
Can you still have pleasure in things?		
Do you have problems with hearing or vision?		
The following 3 questions to be completed by the informant		
Do you think his/her personality has changed?		
Did you take over tasks from the participant (and why)?		
Does he/she repeat things often?		
Observational points	**Yes**	**No**
Inability to find the correct words		
Many repetitions or hesitations		
Often does not understand the question		
Head turning sign		
Inconsistencies or confabulation		
Poor grooming		

[a]input fields to be filled in with the answers

Part 2: Selection Criteria for Memory Clinic Visit

After the home visit, an independent physician, not involved in the home visit or in the memory clinic, will determine whether the participant will be selected for a visit to the memory clinic of the University Medical Centre Utrecht. To minimize the influence of the increasing experience of the research physician because of the growing number of home visits during the study period, the research physician who visited the participant at home will not be informed about the results of the memory clinic. The following 3 criteria will be used to decide whether a participant will be invited to the memory clinic (1) a classification of “suspected of cognitive impairment” by the research physician, (2) a score of ≤39 on the TYM, and (3) a score of ≤14 on the SAGE. When a participant scores positive on one of these criteria, the participant will be invited to the memory clinic. In addition, a random sample of 15% (65/435) of participants with negative scores on all 3 criteria will be invited to the memory clinic (see sample calculation below and Figure 1).

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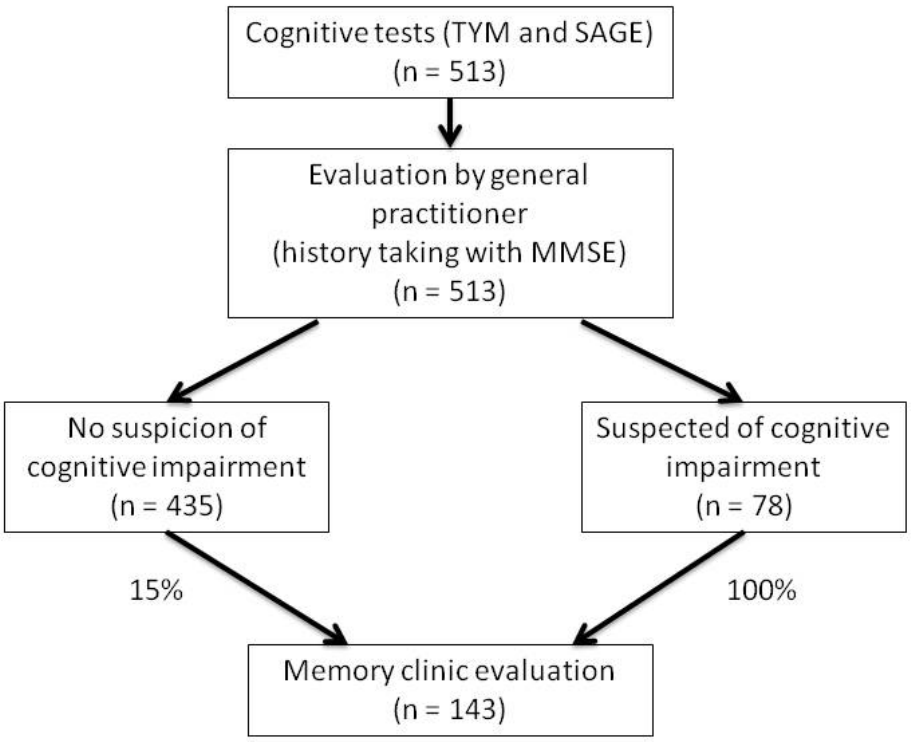
Figure 1. Study flowchart.



Part 3: Memory Clinic Visit

All professionals involved in the memory clinic will be blinded to the results of the TYM and SAGE. The visit to the memory clinic will take half a day and will consist of a standardized memory clinic workup.

Medical Examination

Participants will be examined by a (trainee) neurologist who will perform a diagnostic interview and a neurological examination, administer the Cambridge Cognitive Examination (CAMCOG) [21], and measure body weight, height, and blood pressure. Body mass index (BMI) will also be calculated. In addition, the Disability Assessment for Dementia (DAD) [22] and the Neuropsychiatric Inventory (NPI) [23] will be administered to a caregiver to measure functional abilities of daily living and to assess the presence of neuropsychiatric symptoms.

Neuropsychological Assessment

A neuropsychologist will administer a 90-minute standardized neuropsychological assessment examining memory, information processing speed, attention and executive functioning, and visuoconstruction. The division in cognitive domains will be made a priori, according to standard neuropsychological practice and cognitive theory [24]. The domain "memory" will be assessed by the subtest Digit Span of the Wechsler Adult Intelligence Scale -Third edition (WAIS-III) , the Rey Auditory Verbal Learning Test (RAVL), and the delayed recall of the Rey-Osterrieth Complex Figure Test (ROCF). The domain "information processing speed" will be assessed by the trail-making test (part A), the Stroop Color-Word Test (parts 1 and 2), and the subtest symbol digit substitution of the WAIS-III. The domain "attention and executive function" will be assessed by the trail-making test (part B; ratio score), the Stroop color-word test (part 3; ratio score), the visual elevator test, a letter fluency test using the letters ‘N’ and ‘A’, and category fluency (animal naming). The domain "visuoconstruction" will be assessed by the copy trial of the ROCF, the Judgment of Line Orientation (JLO), and the *Visual Object and Space Perception Battery* (VOSP). Furthermore, the premorbid level of intelligence (intelligence quotient (IQ)) will be estimated by the Dutch version of the National Adult Reading Test (NART). Educational level will be recorded in seven categories and subsequently translated into years of education. Frailty will be examined with the Short Physical Performance Battery (SPPB).

Additional Examinations

MRI data will be acquired on a Philips 3.0 Tesla scanner using a standardized protocol and consisting of a T2-weighted scan (48 continuous slices, reconstructed voxel size: 0.99 × 0.99 × 3.00 mm^3), a 3D T1 scan (192 continuous slices, reconstructed voxel size: 1.00 × 1.00 × 1.00 mm^3), a fluid attenuated inversion recovery (FLAIR) scan (48 continuous slices, reconstructed voxel size: 0.96 × 0.95 × 3mm^3), and diffusion-weighted MRI

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data using a single-shot spin echo planar imaging sequence (48 contiguous slices, acquired isotropic voxel size 2.50 mm, 45 isotropically distributed diffusion-sensitizing gradients with a b value of 1200 s/mm^2, and one b=0 s/mm^2).

Venous blood samples will be drawn to determine non-fasting blood glucose, HbA1c, blood count, lipid-levels (HDL, LDL, total cholesterol, triglycerides), thyroid function, liver functions, and kidney function.

Cognitive Impairment Diagnosis

Within two weeks of the visit to the memory clinic, a multidisciplinary team meeting will be planned with a neurologist, the neurology resident, and the neuropsychologist to establish the diagnosis. Cognitive impairment (ie, MCI or dementia) is our primary outcome. For the diagnosis of dementia, the DSM-IV criteria will be used [19]. In short, dementia will be defined as memory impairment and impairment in at least one other cognitive domain, including aphasia, apraxia, agnosia, and executive functioning, that significantly affects social or occupational functioning compared to the previous level of functioning, and that is not caused by a delirium. MCI will be diagnosed according to the criteria by Winblad et al, and defined as not normal, not demented, with cognitive complaints that can be objectified by a neuropsychological assessment and/or evidence of decline over time, and preserved basic activities of daily living [20]. In addition, the presumed etiology of dementia will be specified (eg, Alzheimer's disease).

Guided by the diagnosis, tailored treatment advice will be given to the participants' GP regarding management of the diabetes treatment and cognitive impairment. Advice for the diabetes treatment will consist of re-evaluation of the proper glycemic target and the risk of insulin treatment. As well, advice evaluating the need for extra support for participants unable to meet treatment goals or in need of tools, for example a memory aid for appointments or medication, will be provided.

After the Diagnosis

The results of the visit to the memory clinic and the treatment advice will be sent to the GPs who will discuss the results with the participant. Subsequently, the GP and the participant will decide together what actions will be taken. Further support by the memory clinic will be available if considered desirable by the GP and the participant.

Follow-Up

Following the home visit (6 months), participants will receive a follow-up questionnaire, including the SF-36, EQ-5D, EQ-VAS, and the CES-D to evaluate the course of their health status, quality of life, and depressive symptoms. A questionnaire asking whether and how many hypoglycemic events, visits to emergency services, and hospital admissions they experienced will also be included. In addition, participants will be asked whether they regret their participation in the study and whether they would again participate in the study. A second follow-up questionnaire with the same questions will be sent after 24 months.

After the home visit (6 months), the medical records of the participants will be examined to obtain information on the medical history, values of recent diabetes controls (HbA1c, lipids, creatinine, weight, height, blood pressure), complications (hypo- or hyperglycemic events), and visits to emergency services and hospital admissions in the year before and six months after participation in the study.

To further assess the impact of the study on participants' treatment, GPs of participants that attended the memory clinic will receive a questionnaire 6 months after the evaluation at the memory clinic to assess whether the study led to new insights and whether it changed their treatment plan (Textbox 1).

Textbox 1. Follow-up questions for the general practitioner (GP).

1. Did the result come as a surprise to you or did you expect it? And why?
2. Do you agree with the result of the memory clinic? And why?
3. Did you adjust your diabetes treatment or management because of the results? And why?
4. Did the results have consequences for your overall medical treatment of the patient? And why?

Statistical Analysis

The diagnosis of cognitive impairment (MCI or dementia) at the memory clinic will be used as the reference standard. To address the first two objectives, participants will be classified as true positive, false positive, false negative, or true negative separately for the evaluation by the GP, TYM, and SAGE.

Not all of the patients in our study will receive the reference standard, which could lead to partial verification bias [25]. However, if only patients with the reference standard were included in the analysis (complete case analyses), the results would be biased because the selection of the patients with the reference standard will not be at random [25]. A reliable method to reduce this bias is to impute the reference standard [25]. A cognitive impairment diagnosis (yes or no) in the memory clinic will, therefore, be imputed for patients who did not attend the memory clinic. Imputed databases (N=10) will be generated with the predictors TYM, SAGE, MMSE, GP evaluation, as well as age, gender, educational level, living situation, and score on the domain mobility of the EQ-5D. The latter two are chosen because they can influence why some patients did not attend the memory clinic. With these imputed numbers, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) will be calculated.

The extent to which the cognitive tests and the evaluation by the GP discriminate between participants with and without cognitive impairment will be determined by the area under the receiver operating characteristic (ROC) curve. Next, the optimal

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cutoff values of the tests for this population will be determined according to the best combination of corresponding sensitivity and specificity assessed with the Youden index. The Youden index measures the effectiveness of a diagnostic marker and enables the selection of an optimal cutoff point [26]. By means of the ROC curve and the best combination of diagnostic values, the optimal instrument will be selected.

For assessing the accuracy and efficiency of the diagnostic procedure (ie, the cognitive test combined with history taking; objective 3) the results of the best cognitive test and the evaluation by the GP will be combined. This should reflect the future implementation of the stepped diagnostic procedure, in which a GP will only evaluate those patients with a positive test result. Participants will be categorized in the “test positive” group when both the best cognitive test and the evaluation by the GP are positive. This combination will likely have a higher PPV than the cognitive test or the evaluation by the GP alone, leading to a more efficient diagnostic procedure. The added value of the GP’s evaluation will be assessed by calculating the adjusted ROC curve and the net reclassification index [27].

The fourth objective of this study will be addressed by comparing the difference in health status and depressive symptoms between those with and without a diagnosis of cognitive impairment, both at baseline and at the 6- and 24-month follow-up, taking into account potential baseline differences of relevant parameters. In addition, we will describe the changes that were made in diabetes care by comparing the diabetes management before and after study participation (ie, changes in treatment, number of hypo- or hyperglycemic events, emergency and hospital visits).

Sample Size Calculation

For our sample size calculations, we assumed a prevalence of undiagnosed cognitive impairment of 8%. Since little quantitative information is available on the prevalence of undiagnosed cognitive impairment, we based this assumption on four considerations. The first assumption is the prevalence of dementia in the Dutch population >65 years of age is around 16% [28].The prevalence of cognitive impairment will be even higher if MCI is also considered. The second is that around half of all patients with cognitive impairment are undiagnosed. The third is the prevalence of cognitive impairment is higher in people with diabetes. And the fourth is the oldest old, in whom dementia prevalence is highest, are least likely to participate in research projects.

In previous research in adults aged ≥59 years recruited from geriatric and memory clinics and facilities for seniors, the SAGE had a PPV of 64%, a NPV of 95%, a sensitivity of 79%, and a specificity of 95% with regard to diagnosing cognitive impairment [12]. In a memory clinic population, the TYM had a specificity of 95%, a sensitivity of 81%, a PPV of 64%, and a NPV of 98% at a cutoff score of 39 points for Alzheimer's disease. In our view, a new cognitive test should have a PPV comparable with that of the most commonly used instrument, the MMSE, which has a PPV of 53.6% for the diagnosis of dementia in primary care [29]. Therefore, for our sample size calculation, we set the lower margin for the estimated PPV at 53% (ie, 11% below the previously established PPV of 64%). With this margin and an alpha of 5% and one-sided testing (we are only interested in the lowest 5% of cognitive scores), 52 participants with a positive test result ($0.11=1.65*\sqrt{(0.64*(1-0.64)/n)}$) are needed to have reliable, interpretable results. To achieve this number of test positive participants, given an assumed prevalence of 8% and a sensitivity of 79%, 513 participants are required. Given the test features of the TYM, this sample size should also be sufficient to determine the accuracy of the TYM. As participants will be referred to the memory clinic based on the results of all 3 tests (TYM, SAGE, and evaluation by the GP), and the results of the tests will probably not completely overlap, the group "suspected of cognitive impairment" will be larger than the group that will be tested positive on the SAGE alone. We estimate that the former group will be 50% larger than the SAGE-positive group (ie, 78 people are estimated to be in the group “suspected of cognitive impairment”). All these 78 participants will be invited to attend the memory clinic in order to establish the true and false positive rates of each of the tests. In addition, a sample (14.9%, 65/435) of the participants in which all 3 tests are negative (the screen-negatives) will be invited to the memory clinic to establish the true and false negative rates of each test. Hence, 143 participants in total will be evaluated at the memory clinic (Figure 1).

Because of uncertainty on the actual prevalence of undiagnosed cognitive impairment in our cohort, an interim analysis is planned after the inclusion of 80 participants. During this interim analysis, only the proportion of participants classified as "suspected of cognitive impairment" will be checked without unblinding the test scores or the findings at the memory clinic. If the proportion deviates significantly from our assumptions we will adjust the sample size of the study population accordingly.

Regulation Statement

This study will be conducted according to the principles of the declaration of Helsinki and in accordance with the Dutch law on Medical Research Involving Human Subjects Act (WMO).

Ethics Committee Approval

The cognitive impairment in diabetes (Cog-ID) study was approved by the medical ethics committee of the University Medical Centre Utrecht, the Netherlands. Written informed consent will be obtained from all participants.

Results

Funding was obtained through the EFSD/Lilly Mental Health and Diabetes Program in 2012. Participant enrolment started in August, 2012. All study-related activities will be completed in September, 2016. The first results are expected to be published in 2015.

Discussion

This cognitive impairment in diabetes (Cog-ID) study will provide a stepped diagnostic procedure to identify patients with type 2 diabetes and undiagnosed cognitive impairment, which can be readily implemented in daily practice. This is essential

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to improve the care for this vulnerable patient group. We will have information on the diagnostic accuracy of two new cognitive tests, the TYM and the SAGE, and whether these tests can be used in a diagnostic procedure (ie, combining a cognitive test with history taking by a GP) to detect cognitive impairment in primary care. In addition, we will collect observational data on the impact of such diagnostic procedures on several aspects of patients' lives (health status, depressive symptoms, complications, and diabetes treatment) after 6 and 24 months. Physicians often assume that informing the patient about a diagnosis of cognitive impairment will negatively influence their health status, quality of life, and depressive symptoms [30]. However, one could also argue that undiagnosed cognitive impairment might cause a reduced quality of life and depressive symptoms, because it is likely to impact patients. If these aspects of patients' lives are affected by undiagnosed cognitive impairment, and could be ameliorated by informing the patient, then the tailoring and possibly the adjustment of treatment and/or organizing support could be another argument as to the importance of detecting cognitive impairment at an early stage.

A potential bias in diagnostic studies in which not all patients receive the reference standard is partial verification bias [25]. However, we will try to reduce this verification bias by imputing the reference standard in participants that do not visit the memory clinic. This method has been shown to give reliable estimates of missing reference data [25].

With the information from this study, we can advise GPs on how to assess cognitive functioning in their patients so they can adjust diabetes treatment to the preserved capacities of their patients, as advocated by the American Diabetes Association, and consequently might prevent treatment-related complications. In addition, the results will form a base for future discussions on whether the early recognition of cognitive impairment in patients with type 2 diabetes with a case-finding strategy is desirable.

Acknowledgments

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Authors' Contributions

PSK, GJB, LJK, and GEHM designed the study. PSK coordinates the study. PSK, JJ, and MK manage the study and data collection. PSK, JJ, MK, GJB, and EvdB are involved in data collection. PSK wrote the first manuscript. All authors read, commented, and approved the final draft of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Confirmation of grant approval.

[PDF File (Adobe PDF File), 38KB - resprot_v4i2e69_app1.pdf]

Multimedia Appendix 2

Confirmation of ethical approval.

[PDF File (Adobe PDF File), 46KB - resprot_v4i2e69_app2.pdf]

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Abbreviations

CES-D: Center for epidemiologic studies depression scale
Cog-ID: Cognitive impairment in diabetes study
EQ-5D: EuroQol 5 dimensions
EQ-VAS: EuroQol visual analogue scale
GP: General practitioner
MCI: Mild cognitive impairment
MMSE: Mini-mental state examination
NPV: Negative predictive value
PPV: Positive predictive value
ROC: Receiver operating characteristic
SAGE: Self-Administered Gerocognitive Examination
SF-36: Short form health survey 36
TYM: Test Your Memory test

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Original Paper

Diet Quality of Young Adults Enrolling in TXT2BFiT, a Mobile Phone-Based Healthy Lifestyle Intervention

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Abstract

Background: Young adulthood is associated with poor dietary habits and vulnerability to weight gain. Population studies have revealed that inadequate fruit and vegetable intake, excessive sugar-sweetened beverages, and frequent takeaway food consumption are dietary habits requiring intervention.

Objective: The aim was to examine the dietary patterns and diet quality of overweight young adults on enrollment into a mobile phone–based healthy lifestyle (mHealth) intervention, TXT2BFiT.

Methods: Baseline diets were analyzed using the online Dietary Questionnaire for Epidemiological Studies version 2. The Healthy Eating Index for Australians (HEIFA) based on the 2013 Dietary Guidelines, was used to rate individual diets according to intake of core foods and deleterious nutrients including sugar, sodium, saturated fat, and alcohol. Findings were compared with the 2011 Australian National Nutrition and Physical Activity Survey (NNPAS). Gender differences were assessed with *t* tests and chi-square tests. ANOVA models were used to determine linear trends of core and noncore food intake and nutrients across quartiles of HEIFA scores. Associations between HEIFA score, sugar-sweetened beverages, and takeaway food consumption were assessed using linear regression analysis.

Results: Diets of 230 participants (females: n=141; males: n=89; body mass index: mean 27.2, SD 2.5 kg/m^2) were analyzed. The mean diet quality score was 45.4 (SD 8.8, range 21.7-77.0) out of 100 points, with no significant difference between genders. Compared with the NNPAS data for adults aged 19-30 years, this cohort had a lower intake of some core foods and higher intake of alcohol and saturated fat. Better quality diets were associated with higher intakes of fruits, vegetables, and wholegrains (P<.001). Takeaway food (P=.01) and sugar-sweetened beverage consumption (P<.001) were negatively associated with diet quality.

Conclusions: Overweight young adults had poorer diets compared with the reference Australian population within the same age group. This study reinforces that gender-specific interventions are required, as is the current practice in TXT2BFiT, with a need to reduce sodium and alcohol intake in males and sugar intake in females. It also confirms the need to increase fruit and vegetable intake and reduce takeaway food consumption in this population, with additional focus on saturated fat and wholegrain intake.

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KEYWORDS

food habits; young adults; overweight; mHealth; eHealth; telemedicine

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Introduction

It is widely recognized that poor diet quality and physical inactivity can increase the risk of becoming overweight and developing chronic diseases [1,2]. In developed countries, reduced levels of incidental activity combined with a changing food supply consisting of many energy-dense, nutrient-poor (EDNP) options, also known as discretionary or noncore foods, may have contributed to the rising prevalence of obesity [3,4]. Young adults are at the greatest risk of increasing body weight as they transition to independence, become responsible for their food choices, and are more likely to develop poor eating habits [5-7]. Data from the latest Australian Health Survey revealed that young adults have the lowest fruit and vegetable intake and obtain a greater percentage of their total energy from discretionary foods and sugar-sweetened beverages [8].

Despite the poor dietary habits and vulnerability of this population to weight gain, prevention initiatives targeting this age group are lacking [9,10]. Additionally, the number of Australian studies investigating the dietary patterns of overweight young adults is limited [11,12]. The existing research indicates that the diet quality of overweight or obese young adults varies from those within the healthy weight range [12]. As weight gain in young adulthood tends to persist throughout adulthood [13], examining the diets of this population will inform age-appropriate strategies to prevent weight gain and reduce the risk of chronic disease in later life.

Diet quality indexes are a commonly used methodological approach in exploring the dietary patterns of populations [12,14,15]. They are designed to compare dietary intakes with current healthy eating guidelines and recommendations. The outcome is a summary measure of overall diet quality that represents a collection of scores applied to intake of dietary components deemed to be in-line with the guidelines. This holistic approach to diet characterization is considered superior to alternative methods which explore individual nutrients because it is the whole diet which impacts health, not just specific foods, food groups, or nutrients [16,17].

The TXT2BFiT mobile phone–based (mHealth) intervention uses technology to provide an easily accessible and convenient lifestyle program aimed to prevent weight gain in young adults aged 18-35 years. This population provides the opportunity to study food intakes of overweight young adults seeking assistance to change.

The primary objective of this study was to classify the quality of the baseline diets of TXT2BFiT participants using a modified version of the Healthy Eating Index for Australians (HEIFA) [18]. The secondary objective was to compare the dietary patterns (core, noncore food, and micro- and macronutrient intake) of overweight young adults to the nationally representative sample of adults aged 19-30 years who participated in the National Nutrition and Physical Activity Survey (NNPAS). Finally, this study sought to explore the amount of sugar-sweetened beverages and the frequency of takeaway food consumption among this cohort, while examining how this varies with diet quality.

Methods

Participants

Materials and methods of the TXT2BFiT Randomized Controlled Trial were approved by the University of Sydney Human Research Ethics Committee (approval number 13698). Baseline dietary data were collected from 250 young adults enrolled in the TXT2BFiT healthy lifestyle program. TXT2BFiT is tailored to address the health-related beliefs, barriers, and sociocultural norms of young adults aged between 18 and 35 years. In combination with telephone counseling and website and mobile phone app use, participants received text messages targeting behaviors such as inadequate fruit and vegetable intake, physical inactivity, and excessive sugar-sweetened beverages, alcohol, and energy-dense takeaway food consumption. Participants were recruited from the greater Sydney area in New South Wales, Australia [19,20]. They completed a baseline survey and a food frequency questionnaire (FFQ). The baseline survey included questions on frequency of sugar-sweetened beverages, water, and takeaway food consumption. Details of the specific information collected are published elsewhere [19]. Participants who did not complete the baseline survey (n=2) or made “serious” errors in their responses on the FFQ (n=3) were excluded, as well as those determined as over- and underreporters (n=15), defined as energy intake basal metabolic rate (BMR) of <0.5 or >2.0 (BMR was calculated using the Schofield equation based on body weight, age, and gender) [21,22].

Dietary Assessment

Baseline self-reported dietary intake was measured online using a FFQ known as the Dietary Questionnaire for Epidemiological Studies version 2 (DQESv2) created by the Cancer Council Victoria [19,23]. This 74-item questionnaire was used to gather the respondent’s usual consumption of food and alcohol in the last month. Although this tool was originally designed to measure intake over the preceding 12 months, it was previously validated against 5-day weighed food records to measure intake over 1 month for Australian young adults. It was found that the DQESv2 is a valid measure of all nutrients studied at the group level and has good reproducibility [24,25]. Because the DQESv2 does not measure sugar-sweetened beverage intake, a single-item question that asked respondents “On average how much sugary drinks do you usually drink per week” was used to determine consumption of sugar-sweetened beverages. Respondents were asked to consider intake of soft drinks, energy drinks, sport drinks, cordials, vitamin waters, and iced teas, but not diet, low joule, or artificially sweetened drinks for which a separate response category was provided. The reproducibility and reliability of this question was tested previously against weighed food records using interclass correlations and weighted kappa statistic. Analyses revealed that the short question is a valid tool for classing intake into categories at the population level and has good reproducibility allowing for variation in sugar-sweetened beverages overtime to be detected (unpublished results).

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Diet Quality Scoring Using the HEIFA

A modified version of the HEIFA (Multimedia Appendix 1) based on adherence to the most recent Dietary Guidelines for Australian Adults 2013 (DGAA) and The Australian Guide to Healthy Eating 2013 (AGHE) [26], was used to determine the diet quality of participants based on data from both the online DQESv2 and the baseline questionnaire. Because there is currently no agreement on how EDNP foods should be defined [27,28], the AGHE was used to classify foods as either core or noncore [26].

The modified HEIFA presented in Multimedia Appendix 1, assessed 11 components: the 5 food groups, consumption of discretionary (noncore) foods, and intake of water, alcohol, fats, total sugars, and sodium. The maximum score was awarded to participants who met the specified criteria based on the guidelines. Prorated scores were given to intakes below the recommendation. Points were awarded for choosing a variety of fruit and vegetables and for consuming low-fat dairy. The total score ranged from zero to 100, with higher scores reflecting better adherence to the dietary guidelines.

Statistical Analysis

All statistical analyses were conducted using SPSS version 22 for Windows (IBM Corp, Armonk, NY, USA). The normality of the distribution of diet quality scores was assessed before analyses. As the data was found to be normally distributed, no transformations were required. The number of participants who attained the maximum score on each dietary component assessed by the HEIFA was tallied to determine the percentage of participants meeting each guideline. Quartiles of HEIFA scores were then created for the overall cohort, in which quartile 1 (Q1) indicated a diet least consistent and quartile 4 (Q4) represented a diet most consistent with the DGAA. The mean diet quality score and individual dietary component score was determined for the cohort and across quartiles. A *t* test and chi-square test for proportions was used to examine differences between genders. A polynomial 1-way analysis of variance (ANOVA) was used to identify linear trends in intakes of core foods, noncore foods, and selected nutrients across quartiles. Macronutrient and core and noncore food intakes were calculated as the mean percent of total energy intake for both genders. The calorie content of core and noncore foods selected were calculated as the mean of all brands presented in the Australian Food and Nutrient Database (AUSNUT 2011-2013) [29]. Intake of core foods, noncore foods, and nutrients were compared to corresponding data from the representative sample of adults age 19-30 years who participated in the NNPAS [8,30]. Finally, linear regression analyses were employed to explore the associations between diet quality, sugar-sweetened beverage intake, and frequency of takeaway food consumption.

Results

Participants

The data from 141 females and 89 males (N=230) were included in the analyses. These participants were aged between 18-34 years, with a mean age of 27.7 years (SD 4.9). The mean body mass index (BMI) was 27 kg/m^2 (SD 2.5) with 20.4% (47/230) of participants classed as obese and 63.5% (146/230) as overweight. The mean total energy intake per day was 2123 kcal (SD 865) and 1706 kcal (SD 630) for men and women, respectively. This was lower than that of the mean total energy intakes of the NNPAS population (2632 kcal/day for males and 1881 kcal/day for females).

Diet Quality

Overview

In this population of young adults, the mean diet quality score was 45.4 (SD 8.8, range 21.7-77.0), with a slightly higher average score in males than females (males: mean 46.6, SD 9.2, range 26.8-77.0; females: mean 44.6, SD 8.5, range 21.7-65.9). There was minimal variation in the individual dietary components of HEIFA between genders, with the exception of sodium, sugar, and alcohol intake (Table 1). As seen in Table 1, a greater proportion of women met the dietary guidelines for sodium ($P<.05$) and alcohol ($P<.01$), whereas a greater proportion of males met the guidelines for sugar ($P<.01$). Overall, there were no dietary guidelines that were well met by the study population. The highest individual component score attained was for meats and meat alternatives. The percentage of the sample scoring zero in a category was highest for saturated fat (76.1%, 175/230) and vegetable variety (94.3%, 217/230).

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Table 1. The number (%) of participants meeting each dietary guideline.

Dietary component	Cohort (n=230)		Males (n=89)		Females (n=141)		*P*
	Score, mean (SD)	Met guideline, n (%)	Score, mean (SD)	Met guideline, n (%)	Score, mean (SD)	Met guideline, n (%)	
Discretionary foods[a]	4.3 (3.1)	0 (0.0)	4.6 (3.1)	0 (0)	4.0 (3.1)	0 (0.0)	>.99
Vegetables[a]	1.0 (1.1)	0 (0.0)	1.0 (1.1)	0 (0)	1.1 (1.1)	0 (0.0)	.30
Fruit[a]	5.2 (3.6)	73 (31.7)	4.9 (3.6)	26 (29)	5.3 (3.7)	47 (33.3)	.59
Breads & cereals[a]	4.8 (2.8)	14 (6.5)	5.1(2.8)	8 (9)	4.7 (2.9)	7 (5.0)	.20
Meat & alternatives[a]	6.7 (3.3)	87 (37.8)	6.7 (3.5)	39 (44)	6.7 (3.1)	48 (34.0)	>.99
Dairy & alternatives[a]	5.6 (3.0)	15 (6.5)	5.3 (3.0)	5 (6)	5.8 (2.9)	10 (7.1)	.17
Water[b]	2.1 (1.3)	13 (5.6)	2.2 (1.3)	7 (8)	2.0 (1.3)	6 (4.3)	.42
Fat[a]	1.8 (2.2)	2 (0.9)	1.5 (2.1)	0 (0)	2.1 (2.3)	2 (1.4)	.15
Sodium[a]	3.9 (4.0)	51 (22.2)	2.8 (3.5)	11 (12)	4.6 (4.0)	40 (28.4)	<.05
Total sugars[a]	5.1 (4.0)	75 (32.6)	6.6 (3.7)	42 (47)	4.2 (4.0)	33 (23.4)	<.05
Alcohol[b]	3.8 (2.1)	176 (76.5)	3.4 (2.4)	60 (67)	4.1 (1.9)	116 (82.3)	<.01

[a] Scored out of 10.

[b] Scored out of 5.

Intake of Core and Noncore Foods

Tables 2 and 3 compare the total mean intakes of core and noncore foods of TXT2BFiT participants to that of Australians aged 19-30 years who participated in the NNPAS. Mean baseline vegetable intake in our study population was similar between genders; however, males consumed more fruit. Compared to NNPAS participants, this cohort consumed fewer vegetables and more fruit. The dietary guidelines recommend that mostly wholegrain cereals are consumed. This cohort's overall wholegrain intake was poor, with 33.5% (77/230) of the cohort consuming mostly (>50%) wholegrain bread and cereal products. Dairy intake was higher in this cohort with 59.1% (136/230) consuming low-fat (skim or reduced fat) milk. Overall, the current study population obtained 10% more energy from core foods compared to Australians aged 19-30 years who took part in the NNPAS. Although the TXT2BFiT participants consumed less fruit juice and sugar-sweetened beverages than the NNPAS population, they had a higher intake of alcohol. Frequency of takeaway food consumption was high with 45.7% (105/230) and 13.0% (30/230) of the cohort consuming takeaway foods 2-3 times and 4-5 times per week, respectively.

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Table 2. Mean intake (grams) of selected core foods for males and females and their mean percentage contribution to total energy intake using results from the Dietary Questionnaire for Epidemiological Studies version 2 (DQESv2), compared to the averages of Australians aged 19-30 years who took part in the National Nutrition and Physical Activity Survey (NNPAS).

Core food groups	Total		Male		Female	
	DQESv2	NNPAS[a]	DQESv2	NNPAS[a]	DQESv2	NNPAS[a]
Intake (g), mean (SD)						
Vegetables	116.8 (78.9)	172.8	119.8 (93.1)	172.9	115.0 (68.8)	173.0
Fruit[b]	209.1 (153.7)	109.5	228.3 (168.3)	106.3	197.0 (143.1)	112.9
Breads and cereals	242.5 (148.0)	171.5	272.6 (158.6)	209.3	223.5 (138.1)	132.1
Wholegrain cereals[c]	90.1 (86.0)	—	87.9 (97.4)	—	91.5 (78.2)	—
Meat and alternatives	190.1 (116.1)	221.5	233.7 (146.1)	278.2	162.5 (81.7)	162.6
Dairy and alternatives	337.3 (168.8)	242.1	335.8 (170.5)	280.7	338.2 (168.3)	201.9
Low-fat dairy[d]	172.4 (172.2)	—	164.9 (180.5)	—	177.1 (167.2)	—
% Energy, mean (SD)						
Vegetables[e]	3.6 (2.9)	7.5	3.4 (3.6)	6.8	3.7 (2.3)	8.7
Fruit[b]	5.9 (5.0)	3.1	5.6 (4.9)	2.7	6.1 (5.1)	3.6
Breads and cereals	24.4 (11.5)	16.5	24.9 (12.6)	17.0	24.1 (10.7)	15.7
Meat and alternatives[f]	21.8 (8.6)	19.4	23.3 (9.5)	20.6	20.9 (7.9)	17.2
Dairy and alternatives[g]	10.5 (7.1)	9.9	9.4 (6.9)	9.9	11.2 (7.2)	9.9
TOTAL	66.2 (15.5)	56.4	66.6 (16.1)	57.0	66.0 (15.1)	55.1

[a] National Nutrition and Physical Activity Survey (NNPAS) results for participants aged 19-30 years. Mean intake (g) obtained from data cube table 5 and mean % energy from data cube table 8 [8]. SDs not available for NNPAS data.

[b] Excluding fruit juice.

[c] Includes whole meal, rye, and multigrain bread, All Bran, Bran Flakes, Weet-Bix, porridge, and muesli. Wholegrain intake not available for NNPAS population.

[d] Low-fat dairy intake not available for NNPAS population.

[e] Including legumes.

[f] Including meat, poultry, game products and dishes, egg products and dishes, fish, seafood product and dishes, legumes and nuts.

[g] Including milk products and dishes and milk substitutes.

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Table 3. Mean intake (grams) of selected noncore foods for males and females and their mean percentage contribution to total energy intake using results from the Dietary Questionnaire for Epidemiological studies version 2 (DQESv2), compared to the averages of Australians aged 19-30 years who took part in the National Nutrition and Physical Activity Survey (NNPAS).

Noncore foods	Total		Male		Female	
	DQESv2	NNPAS[a]	DQESv2	NNPAS[a]	DQESv2	NNPAS[a]
Intake (g), mean (SD)						
Crackers	7.4 (12.5)	3.5	6.9 (13.9)	9.2	7.7 (11.7)	3.7
Sweet biscuits	8.7 (14.2)	7.8	7.5 (12.5)	3.2	9.4 (15.3)	6.3
Cake	16.2 (20.7)	17.2	15.8 (23.5)	15.3	16.4 (18.7)	19.3
Chocolate	17.6 (22.9)	6.8	13.8 (19.5)	4.6	20.1 (23.4)	9.0
Crisps	5.3 (7.6)	3.8	4.9 (6.5)	5.4	5.6 (8.3)	2.1
Jam	3.5 (6.2)	1.6	2.8 (4.5)	2.2	3.9 (6.9)	1.0
Margarine	1.3 (5.5)	1.9	1.8 (5.7)	1.8	0.9 (4.9)	2.0
Butter	3.4 (7.2)	1.6	4.1 (8.4)	1.6	3.0 (6.2)	1.6
Ice cream	11.6 (23.0)	—[c]	9.3 (10.8)	—	13.1 (28.3)	—
Sausage	8.2 (11.7)	10.2	10.7 (13.7)	13.4	6.6 (10.1)	6.8
Salami	3.5 (8.25)	—	4.2 (9.9)	—	3.1 (7.1)	—
Meat pie	14.0 (16.4)	—	14.8 (15.4)	—	13.6 (17.1)	—
Pizza	28.9 (33.9)	—	41.2 (43.7)	—	21.1 (23.2)	—
Hamburger	15.0 (20.7)	—	22.8 (25.3)	—	10.1 (15.4)	—
Hot chips	13.1 (12.5)	—	16.0 (14.4)	—	11.3 (10.8)	—
Fruit juice (mL)	113.0 (175.7)	126.8	124.7 (192.3)	149.7	66.2 (82.6)	102.8
Alcohol	13.9 (19.7)	10.8	18.9 (22.9)	14.4	10.7 (1.4)	7.0
Sugar-sweetened beverages (mL) [b]	81.5 (101.3)	309.4	71.4 (109.1)	389.9	67.9 (93.8)	225.4
% Energy, mean (SD)						
Crackers	1.5 (1.9)	0.4	1.2 (1.9)	0.4	1.7 (1.8)	0.5
Sweet biscuits	2.0 (2.6)	1.6	1.6 (2.3)	1.7	2.2 (2.7)	1,6
Cake	2.8 (3.0)	2.6	2.4 (3.0)	2.1	3.1 (2.9)	3.5
Chocolate	4.6 (5.3)	1.5	3.1 (3.7)	0.8	5.6 (6.2)	2.4
Crisps	1.4 (2.0)	0.9	1.2 (1.3)	1.0	1.6 (2.3)	0.6
Jam	0.4 (0.6)	0.2	0.3 (0.5)	0.3	0.4 (0.6)	0.2
Margarine	0.3 (1.5)	0.5	0.4 (1.4)	0.4	0.3 (1.4)	0.6
Butter	1.2 (2.5)	0.5	1.3 (2.5)	0.4	1.2 (2.5)	0.6
Ice cream	1.2 (1.4)	—[c]	0.9 (1.0)	—	1.4 (2.0)	—
Sausage	0.9 (1.2)	1.1	1.1 (1.3)	1.3	0.8 (1.0)	0.8
Salami	0.7 (1.4)	—	0.7 (1.2)	—	0.7 (1.5)	—
Meat pie	1.7 (2.0)	—	1.5 (1.4)	—	1.8 (2.3)	—
Pizza	3.7 (3.3)	—	4.6 (3.6)	—	3.1 (2.9)	—
Hamburger	1.8 (2.2)	—	2.5 (2.6)	—	1.4 (1.8)	—
Hot chips	1.7 (1.5)	2.5	1.7 (1.4)	2.7	1.6 (1.6)	2.3
Fruit juice	0.2 (1.3)	1.1	0.2 (1.0)	1.2	0.2 (1.4)	1.1
Alcohol	5.1 (7.0)	2.8	6.0 (7.1)	3.5	4.7 (6.9)	2.1
Sugar-sweetened beverages	1.5 (2.5)	3.9	1.6 (2.6)	4.5	1.4 (2.4)	3.2
TOTAL	33.2 (12.4)	35.9	33.0 (12.5)	36.4	33.5 (12.7)	35.2

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[a] National Nutrition and Physical Activity Survey (NNPAS) results for participants aged 19-30 years. Mean intake (g) obtained from data cube table 5 and mean % energy from data cube table 9 [8]. SD's not available.

[b] Excluding artificially sweetened drinks. Includes soft drink, cordials, flavored mineral water, electrolyte, energy, and fortified drinks. Measured using a single-item question not the DQESv2.

[c] Ice cream data from the NNPAS has not been included because the category of frozen milk products also measures frozen yogurt intake, limiting comparability.

Change Across Quartiles

As displayed in Table 4, the mean intake of core food groups increased as diet quality improved with the exception of dairy. Higher intake of low-fat dairy was significantly associated with higher HEIFA scores. Additionally, noncore food and sugar-sweetened beverage consumption was lowest for participants with the highest diet quality, indicating an association between lower intakes of these less desirable items and higher quality diets. Higher diet quality scores were also associated with higher intake of iron, vitamin C, zinc, and folate. Finally, negative associations between HEIFA score, takeaway food consumption (P=.01), and sugar-sweetened beverage intake (P<.001) were found (not displayed in table).

Table 4. Mean diet quality (Healthy Eating Index for Australians, HEIFA) scores across quartiles and the associated mean intake of core and noncore foods.

Dietary component	Quartile				P [a]
	1	2	3	4	
HEIFA score, mean (SD)	34.0 (4.1)	42.4 (1.6)	48.1 (2.0)	56.4 (4.9)	
Energy (kcal/day), mean (SD)	1865 (852)	1886 (660)	1747 (621)	1970 (868)	
Core foods, mean (SD)					
Vegetables (g)	77.3 (55.9)	107.9 (68.2)	125.4 (65.7)	154.7 (99,4)	<.001
Fruit (g)	126.2 (87.0)	176.8 (118.4)	240.6 (174.2)	289.0 (167.2)	<.001
Breads and cereals (g)	182.8 (88.0)	211.5 (127.1)	278.0 (159.3)	295.3 (173.9)	<.001
Wholegrains[b] (g)	61.6 (56.7)	72.7 (62.9)	96.2 (83.6)	128.8 (114.0)	<.001
Meat and alternatives (g)	149.5 (85.9)	176.6 (96.7)	216.8 (154.8)	215.5 (102.7)	<.001
Dairy and alternatives (g)	322.7 (181.2)	336.6 (195.5)	336.1 (142.9)	353.0 (153.5)	.42
Low-fat dairy (g)	125.7 (181.3)	171.0 (173.2)	170.6 (159.7)	219.8 (166.0)	.006
Noncore foods, mean (SD)					
Discretionary foods[c] (g)	64.6 (55.2)	70.8 (59.3)	65.0 (69.7)	58.2 (36.2)	.004
Sugar-sweetened beverages (mL)	109.7 (118.2)	84.7 (107.7)	81.1 (94.5)	51.4 (73.9)	<.001
Nutrients, mean (SD)					
Iron (mg)	10.4 (4.0)	11.9 (5.5)	12.5 (5.0)	13.3 (4.6)	<.001
Vitamin C (mg)	60.4 (28.3)	77.9 (32.1)	104.7 (74.1)	105.7 (49.8)	<.001
Zinc (mg)	10.2 (4.2)	11.2 (4.9)	12.7 (6.5)	12.4 (4.5)	.008
Folate (µg)	185.5 (66.5)	223.0 (92.5)	240.9 (97.5)	263.9 (91.7)	.02
Calcium (mg)	818.2 (348.3)	856.6 (363.3)	891.0 (318.3)	890.1 (312.1)	.31

[a] P for linear trend.

[b] Includes whole meal, rye and multigrain bread, All Bran, Bran Flakes, Weet-Bix, porridge, and muesli.

[c] Includes all noncore foods measured by the DQESv2.

Macronutrient Distribution

As displayed in Table 5, the mean percentage intake from protein was within the acceptable macronutrient distribution range (AMDR). The mean percentage intake from total fat fell on the upper limit of the AMDR (mean 35%), with a high percentage derived from saturated fats. The cohort's intake of carbohydrates (40%) was below the AMDR (45%-65%). Despite this, the highest percentage of energy in the diet was derived from carbohydrates (40%), with a high percentage from sugars (17.5%). There were no large variations in macronutrient intake between males and females; however, males exceeded the maximum recommended percentage energy from alcohol. The cohort's intake of fiber was lower than the NNPAS population, with females meeting 65% and males meeting 54% of the recommended daily intake.

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Table 5. The mean % energy intake from carbohydrates, fat, protein, and alcohol, and the mean (SD) fiber intake (g) of the cohort using data from the Dietary Questionnaire for Epidemiological studies version 2 (DQESv2) compared to National Nutrition and Physical Activity Survey (NNPAS) data with corresponding recommendations.

Dietary component	Recommendation	Total, mean (SD)		Male, mean (SD)		Female, mean (SD)	
		DQESv2 (N=230)	NNPAS[a] (N=1592)	DQESv2 (n=89)	NNPAS[a] (n=739)	DQESv2 (n=141)	NNPAS[a] (n=853)
% Energy							
From carbohydrates	45%-65%[b]	40.5 (7.4)	45.3	39.3 (8.7)	45.0	41.2 (6.4)	45.5
From total sugars	<15%	17.6 (5.4)	19.8	15.5 (5.3)	19.1	18.8 (5.1)	20.5
From starch	N/A[c]	22.7 (6.1)	24.7	23.7 (6.5)	24.9	22.1 (5.8)	24.5
From protein	15%-25%[b]	19.8 (3.3)	18.1	20.3 (3.6)	18.5	19.5 (3.1)	17.7
From fat	20%-35%[b]	35.2 (5.5)	31.2	35.0 (5.6)	30.5	35.4 (5.4)	31.9
From saturated fat	<10%	14.3 (3.2)	11.7	14.0 (3.3)	11.4	14.5 (3.2)	12.0
From monounsaturated fat	N/A	12.8 (2.3)	12.0	12.9 (2.5)	11.9	12.7 (2.2)	12.0
From polyunsaturated fat	7%	4.9 (1.5)	4.9	4.8 (1.5)	4.7	4.9 (1.6)	5.1
From alcohol	<5%	5.1 (7.0)	2.8	5.9 (7.1)	3.5	4.6 (6.9)	2.1
Intake (g)							
Fiber	28-38 g/day[d]	19.2 (8.5)	23.7	20.6 (10.1)	24.8	18.3 (7.2)	

[a] NNPAS results for participants aged 19-30 years. Mean percentage energy for macronutrients obtained from data cube table 2 [8]. SDs not available for NNPAS data.

[b] Acceptable macronutrient distribution range (AMDR) [31].

[c] N/A, not available.

[d] Lower range for females, upper range for males.

Discussion

This study shows that diet quality was generally poor among overweight young adults with an average score half of the maximum achievable. The participant's diets were worse than the Australian population sample of adults aged 19-30 years with lower intake of vegetables and higher intake of alcohol, noncore, and takeaway foods. This finding is consistent with previous studies showing poor diet quality in individuals with a higher BMI [13].

Although diet quality scores were very low among the study participants, this is a common trend observed when scoring diets against national guidelines [12,14,15]. Participants with diets higher in core foods and that incorporated more fruits, vegetables, and wholegrain cereals were of better quality and more nutrient-dense. This finding is consistent with prior research that found higher diet quality scores are associated with higher intakes of fruits, vegetables, iron, folate, and vitamin C in men and women [15].

Contrary to prior research [14,32], overall diet quality varied little among these overweight men and women. Further diet analyses based on core and noncore food intake did, however, reveal some differences. Males consumed greater amounts of meats and meat alternatives and females obtained a greater proportion of their total energy from dairy foods. Males also reported a higher intake of savory takeaway foods, such as pizza, hamburgers, and hot chips, whereas females favored sweet treats such as chocolate, ice cream, and sweet biscuits. Considering that savory and meat-based dishes are typically higher in salt, whereas dairy products and desserts contain more sugar, it is evident why fewer men met the guidelines for sodium and fewer women met the guidelines for sugar.

This group of young adults consumed less than a quarter of the amount of sugar-sweetened beverages reported by NNPAS participants aged 19-30 years. A high proportion of participants reported to consume no sugar-sweetened beverages or artificially sweetened versions only (23.5%, 54/230 and 17.4%, 40/230, respectively), which likely contributed to the lower mean group intake. Although sugar-sweetened beverage consumption was lower than expected, alcohol intake was high with a significantly greater proportion of men exceeding the dietary guidelines for alcohol. The link between weight management and alcohol consumption is not clearly defined; however, research has demonstrated a positive correlation between alcohol intake and obesity irrespective of the type of alcohol consumed [33,34]. These results emphasize the importance of targeting a reduction in alcohol intake as part of healthy lifestyle intervention, especially for young males who are consuming amounts substantially higher than the recommendations.

Also of concern in this group is the high intake of saturated fat. Although low-fat dairy was consumed by 59.1% of participants, butter was favored over margarine and intake is twice that of the NNPAS population. It appears these young adults consume less discretionary foods than the NNPAS representative survey group, but it is important to note that there are limited

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discretionary foods included in the DQESv2 and intake may be greater than estimated. It is also possible that aspects of social desirability resulted in underreporting of discretionary foods that are perceived as unhealthy. Evidence of selective underreporting has been found in both genders [35,36] and especially among obese women [37]. Although the 24-hour recall used in the NNPAS is also subject to this bias, many more of the TXT2BFiT participants were overweight, increasing the likelihood of underreporting. Despite possible underestimation, the percentage energy from noncore foods was still substantially higher than the maximum recommended limit of 20%. These results highlight that interventions targeted at increasing core foods and limiting EDNP food consumption are essential for both healthy and overweight young adults.

This study suggests that those who consume takeaway foods more frequently have lower quality diets. These results are consistent with previous research, which indicates diet quality is negatively associated with takeaway food consumption [38]. A possible cause of the negative correlation between diet quality and commercially prepared meals is the lower nutrient content of the food. Takeaway foods usually contain more total and saturated fat, and less fiber than homemade meals [39]. In this group of young adults, frequency of takeaway food consumption was high with 46% (106/230) consuming commercially prepared meals 2-3 times per week and a further 13% (30/230) consuming them 4-5 times per week. Based on these results, it is evident that the component of the TXT2BFiT healthy lifestyle intervention that aims to reduce takeaway food consumption is appropriate.

Despite the cohort consuming twice as much fruit as the NNPAS population, their diets were lower in fiber. This can be attributed to an inadequate intake of wholegrain cereals and vegetables; mostly refined breads and cereals were consumed by this cohort. Vegetable intake was also poor with approximately 1.5 servings of vegetables consumed per day, less than the 2.3 servings consumed by the NNPAS participants. However, it should be acknowledged that validation of the DQESv2 with weighed food records in young adults found fruit was overestimated in males and vegetables were underestimated in both genders [24]. This raises some uncertainty as to whether vegetable intake may be better than indicated.

Overall, the study cohort appeared to consume diets lower in energy than the NNPAS population, suggesting they may be practicing calorie restriction. The TXT2BFiT intervention is designed to improve lifestyle patterns and differs from other electronic and mobile weight management interventions that typically use calorie monitoring to instigate behavior change. This is a significant strength of the intervention because it is evident that this cohort would benefit more from strategies which encourage healthier eating habits and improved diet quality.

A number of limitations must be taken into consideration when interpreting the data. Firstly, although comparisons were made with results of NNPAS, the different dietary assessment methods, food coding, and classification procedures restrict comparability. Furthermore, the DQESv2 dietary assessment tool is limited in the number of EDNP items, only includes certain brands of cereals, fails to distinguish between lean and fatty meats, and does not measure salt added at the table or in cooking. This may have resulted in underestimation of sodium and fiber. Among the strengths of this study is that it utilizes a comprehensive diet quality index (HEIFA) which focuses on food indicators based on the most recent DGAA.

This study identifies some of the dietary improvements necessary in this population and will help focus future nutrition interventions to generate change where it is most required. The results reveal that this cohort needs support to change their dietary behaviors to limit alcohol intake and replace refined cereals with wholegrain foods and high-fiber cereals. Although the TXT2BFiT program includes a beverage app that counts alcoholic, energy, and sugary drink intake and indicates when targets are exceeded, whether this is effective in reducing the excessive intake found in this group is yet to be demonstrated.

The findings of this preliminary study will also allow monitoring of a young adult population enrolling in an mHealth program. Intervention outcomes will allow us to assess whether dietary patterns at baseline influence weight loss results postintervention. Previous studies have shown that individuals with higher diet quality scores lose more weight postintervention than those with lower scores [11].

In conclusion, the findings confirm that in the young adult population, there is a need to increase fruit and vegetable consumption and decrease energy-dense takeaway food intake. Further attention to wholegrain cereal and saturated fat intake is also indicated. Additionally, this study reinforces that gender-specific interventions are required, as is the current practice in TXT2BFiT, with a need to reduce sodium and alcohol intake in males and sugar intake in females.

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Authors' Contributions

MAF and MMN conceived the study design. SP, KB, LH, and AW collected data. MMN, RR, and KM contributed to data analysis. MMN drafted the initial manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

The Healthy Eating Index for Australians (HEIFA) based on the new Dietary Guidelines for Australian Adults (DGAA) (2013) using an eleven-component system of 5 food groups, 4 nutrients and a measure of variety of food intake.

[PDF File (Adobe PDF File), 185KB - resprot_v4i2e60_app1.pdf]

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Abbreviations

AMDR: acceptable macronutrient distribution range
BMI: body mass index
BMR: basal metabolic rate
DGAA: Dietary Guidelines for Australian Adults
DQESv2: Dietary Questionnaire for Epidemiological Studies version 2
FFQ: food frequency questionnaire
HEIFA: Healthy Eating Index for Australians
NNPAS: National Nutrition and Physical Activity Survey

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Protocol

A National Surveillance Survey on Noncommunicable Disease Risk Factors: Suriname Health Study Protocol

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Abstract

Background: Noncommunicable diseases (NCDs) are the leading cause of death in low- and middle-income countries. Therefore, the surveillance of risk factors has become an issue of major importance for planning and implementation of preventive measures. Unfortunately, in these countries data on NCDs and their risk factors are limited. This also prevails in Suriname, a middle-income country of the Caribbean, with a multiethnic/multicultural population living in diverse residential areas. For these reasons, “The Suriname Health Study” was designed.

Objective: The main objective of this study is to estimate the prevalence of NCD risk factors, including metabolic syndrome, hypertension, and diabetes in Suriname. Differences between specific age groups, sexes, ethnic groups, and geographical areas will be emphasized. In addition, risk groups will be identified and targeted actions will be designed and evaluated.

Methods: In this study, several methodologies were combined. A stratified multistage cluster sample was used to select the participants of 6 ethnic groups (Hindustani, Creole, Javanese, Maroon, Chinese, Amerindians, and mixed) divided into 5 age groups (between 15 and 65 years) who live in urban/rural areas or the hinterland. A standardized World Health Organization STEPwise approach to surveillance questionnaire was adapted and used to obtain information about demographic characteristics, lifestyle, and risk factors. Physical examinations were performed to measure blood pressure, height, weight, and waist circumference. Biochemical analysis of collected blood samples evaluated the levels of glucose, high-density-lipoprotein cholesterol, total cholesterol, and triglycerides. Statistical analysis will be used to identify the burden of modifiable and unmodifiable risk factors in the aforementioned subgroups. Subsequently, tailor-made interventions will be prepared and their effects will be evaluated.

Results: The data as collected allow for national inference and valid analysis of the age, sex, and ethnicity subgroups in the Surinamese population. A publication of the basic survey results is anticipated in mid-2015. Secondary results on the effect of targeted lifestyle interventions are anticipated in late 2017.

Conclusions: Using the data collected in this study, the national prevalence of NCD risk factors will be approximated and described in a diverse population. This study is an entry point for formulating the structure of NCD prevention and surveillance.

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KEYWORDS

ethnicity; multistage cluster sample; noncommunicable disease risk factors; STEPwise approach to surveillance; Suriname

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Introduction

Background

A noncommunicable disease (NCD) is a medical condition or disease that has a prolonged course, and is neither infectious nor transmissible among people. Worldwide, NCDs, like cardiovascular disease, cancer, chronic respiratory disease, and diabetes are responsible for a large number of deaths. In 2013, the NCD Alliance reported that NCDs account for 60% (35 million) of global deaths and the largest burden—80% (28 million)—occurs in low- and middle-income countries [1]. NCDs and their risk factors worsen poverty, while poverty contributes to rising rates of NCDs, posing a threat to sustainable development [2-4]. It is expected that by 2030 low-income countries will have 8 times more deaths due to NCDs than high-income countries [5]. Compared with industrialized countries, NCD-related deaths occur more frequently and at earlier stages in low- and middle-income countries. In developed countries, 13% of the NCD-related deaths occur before the age of 60. This number is higher (29%) in developing countries [1].

Preventable risk factors are at the root of most NCDs. Worldwide, the leading risk factors for mortality are raised blood pressure (13%), followed by tobacco use (9%), raised blood glucose (6%), physical inactivity (6%), and overweight, including obesity (5%) [1]. Studies in developing countries focused on NCDs and their risk factors, which are important for the identification of subgroups that are at increased risk [3], development of preventive strategies, and eventually to reduce the expected burden of NCDs in the near future. The World Health Organization (WHO) has developed a simple, standardized method for collecting, analyzing, and disseminating data on its member countries: the WHO STEPwise approach to surveillance (STEPS) [6]. More than 90 countries have published their STEPS results in country reports, data books, fact sheets, journal articles, presentations, or posters [7].

Suriname

The Republic of Suriname is located in the Northeast of South America and has a population of 541638 inhabitants, which is mainly concentrated in the coastal areas [8]. The overall population density is 3.3/km^2 and ranges from 1.324/km^2 in the Paramaribo District to 0.3/km^2 in the Sipaliwini District [8]. The main economic activities in Suriname are gold and bauxite mining, crude oil drilling, agriculture, fishery, forestry, ecotourism, commerce, services, and industry [9]. The gross national income per capita is approximately US $8800/annum [10], which places Suriname among the upper-middle-income countries in the World Bank's list of economies [11].

The historical development of the country has resulted in a unique social structure, composed of a variety of cultures, religions, ethnicities, and economic units. As a former colony, Suriname has a history of changing ownership that in the end, from 1667 to 1975, remained Dutch. Throughout this period, the Dutch imported slaves from Africa and indentured laborers from China, India, and Indonesia. These groups, together with the settlers and the original inhabitants, the Amerindians, are the ancestors of the present-day population of Suriname [12,13]. At present, the descendants from India are the Hindustani and those from Indonesia are the Javanese. The descendants from Africa are culturally divided into Creoles, descendants of plantation slaves, and Maroons, descendants of refugees who escaped slavery and formed independent settlements. Nowadays, migration is a global phenomenon on the rise [14]. The present population distribution in Suriname is as follows: Hindustani (27.4%), Maroons (21.7%), Javanese (15.7%), mixed (13.4%), and other ethnicities (8.2%) [8].

Suriname's mortality data underline the burden of NCDs as observed in many middle- and low-income countries. For decades, NCD-related mortality has been reported as the main cause of death in Suriname [15-17]. Currently, the only population data available are collected by the Bureau of Public Health [15-17]. The lack of data on risk factors and morbidity is a major hurdle for the development of preventive strategies.

According to the WHO, surveillance is essential for evidence-based public health decision making and the monitoring of the success of public health interventions [18]. For NCDs, this includes the ongoing systematic collection and analysis of data to provide appropriate information about disease burden, groups at risk, estimates of risk factors, and determinants, coupled with the ability to track health outcomes and risk factor trends over time. Surveillance is critical to provide the information needed for formulation of policies and the development and management of prevention and control programs. It is also basic to measure progress made in implemented policies and programs by monitoring and evaluation [19].

Several studies have reported ethnic differences in cardiovascular disorders and diabetes [20-25]. In Suriname, a 2003 study showed that the highest prevalence of hypertension in adults has been observed in Creoles [26]. However, in another study, high blood pressure was reported to be more frequent in the adolescent Hindustani population compared with other ethnicities [27]. The 2003 study also showed that the prevalence of the combination of hypertension, diabetes, and hypercholesterolemia in adults was higher for Hindustani [26]. Furthermore, a study on 637 patients with diabetes in 12 primary health care centers reported an earlier onset of diabetes in Hindustani (44 years) compared with Creoles (53 years) [28], which indicates a difference among ethnicities.

Data collected in 2001 from 1654 persons (18-55 years) in 3 coastal districts indicated a prevalence rate of 10% for diabetes mellitus, 33% for hypertension, and 5% for both [29]. The survey also provided insight regarding lifestyle and behavioral factors with regard to NCDs: 70% were physically inactive, 30% smoked; 20% were obese, and 15% had high total cholesterol levels.

Adverse lifestyle habits have also been assessed in younger populations. The Global School-Based Student Health Survey 2009 among students aged 13-15 years showed that 73% of the respondents had less than 1 hour of physical activity/day and 81% had a high calorie intake [30]. The 2009 Global Youth Tobacco Survey reported that among students aged 13-15 years, 19.2% were current users of tobacco products. In addition, many students were exposed to "second-hand smoke": 46.7% lived

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in homes where others smoked and 53.3% were exposed to smoke outside of their homes [31]. Studies on harmful use of alcohol indicated that among students aged 13-15 years, 73.8% had their first drink before 14 years and 32.6% consumed alcohol on one or more occasions in the past month. Alcohol use was the highest in the 26-34 age group (36.8%), followed by the 35-64 age group (33.9%) [22,30].

The principal objective of this study is to provide baseline data for the monitoring of NCD risk factors. The study will determine the prevalence of NCD risk factors in the age category of 15 and 65 years of 6 ethnic groups living in different geographical areas. Main inquiries such as the national prevalence of metabolic syndrome, diabetes, and hypertension; the national prevalence of NCD risk factors such as tobacco and alcohol use; fruit, vegetable, oil, and fat consumption; physical activity and mental distress; overweight; obesity; and raised blood pressure; the national prevalence of deviating values for biochemical markers such as levels of blood glucose and blood lipids; the presence of age, ethnic, and geographical differences in NCD outcomes and risk factors will be answered. Evidence of ethnic differences in disease burden emphasizes the importance of data segregation to identify risk groups. The study will provide national baseline data on morbidity, which will enable monitoring and evaluation of public health intervention programs. Forthcoming results of this study will also be of interest in nations where similar ethnic groups are present [14].

Methods

Overall Design

A multistage cluster, household population cross-sectional design was used in this study. The research proposal for this study was approved by the Ethics Committee of the Ministry of Health of Suriname. Data were collected during the period from March 1 to September 31, 2013. Each study participant was first informed about the details of the study, and then asked to sign a consent form. Besides the aim and survey procedure, the respondent was also explained how the information gathered would be used. The informed consent form consisted of two parts: a form for Steps 1 and 2, concerning the questionnaire and physical measurements and a form for Step 3, concerning the biochemical measurements. The respondent was also explained that he or she could refuse to participate at any period of the study.

All the measures registered in Steps 2 and 3 were revised by medical doctors. All the respondents received the results of their physical and biochemical examinations in writing. The medical staff of the research team provided advice for respondents with an adverse outcome and referred them to the general practitioner.

For the estimated outcome prevalence of 0.5 for the baseline indicators, a sample of 5 10-year age groups between 15 and 65 years from each sex was chosen. For a 95% CI with a margin of error of 0.05, a basic sample requirement of 384.16 was required. With a design effect of 1.5 for the multistage cluster design and 10 sex/age groups, 5762 samples were required.

Sampling Procedure

Each of the 10 districts of Suriname served as a primary sampling unit (PSU), and for every PSU a sampling frame was created. In 9 districts, the enumeration areas (EAs) of the Census 2012 were listed [8]. The tenth district, Sipaliwini, included specific village areas (VAs; Figure 1). From the PSUs (n=10), 101 EAs and 4 VAs were selected at random. From these areas, 343 clusters were randomly selected. Within the EAs, each cluster contained 25 households and in the VAs every cluster contained 40 households. The clusters in the VAs were larger because of the high costs associated with reaching the population in this area. In each selected household, the final unit (the respondent) was selected using the Kish method [32] (Figure 1).

The sample size also needed to be adequate to separately analyze each of the 6 ethnic groups, which are as follows: the Creole group, the Hindustani or East Indian group, the Javanese group, the Maroon group, the Amerindian group, and the mixed group. Considering the population numbers, it was estimated that the sample would result in a small number of the Amerindians. Therefore, an oversample of 10 extra clusters from areas with a high density of Amerindians was drawn.

Within the 343 clusters, 8815 households were randomly selected, and 7493 were invited to participate in the study. The overall response rate was 76.75% (5751 participants). Of these respondents, only 3765 gave a blood sample for analysis. The respondents who have lived in Suriname for less than 1 year and those with health issues that rendered them incapable of participating in the study were excluded (Figure 2).

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Figure 1. Multistage cluster sample of the Suriname Health Study. FU=Final Unit; PSU=Primary sampling Unit; SSU=Secondary sampling Unit; TSU=Tertiary sampling Unit.

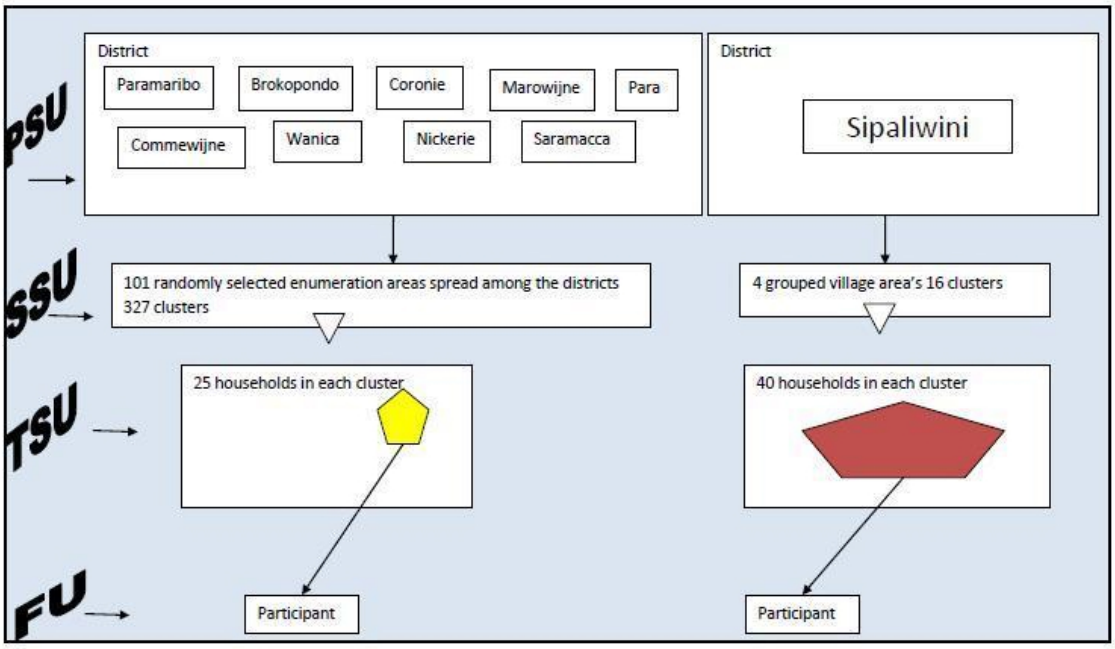
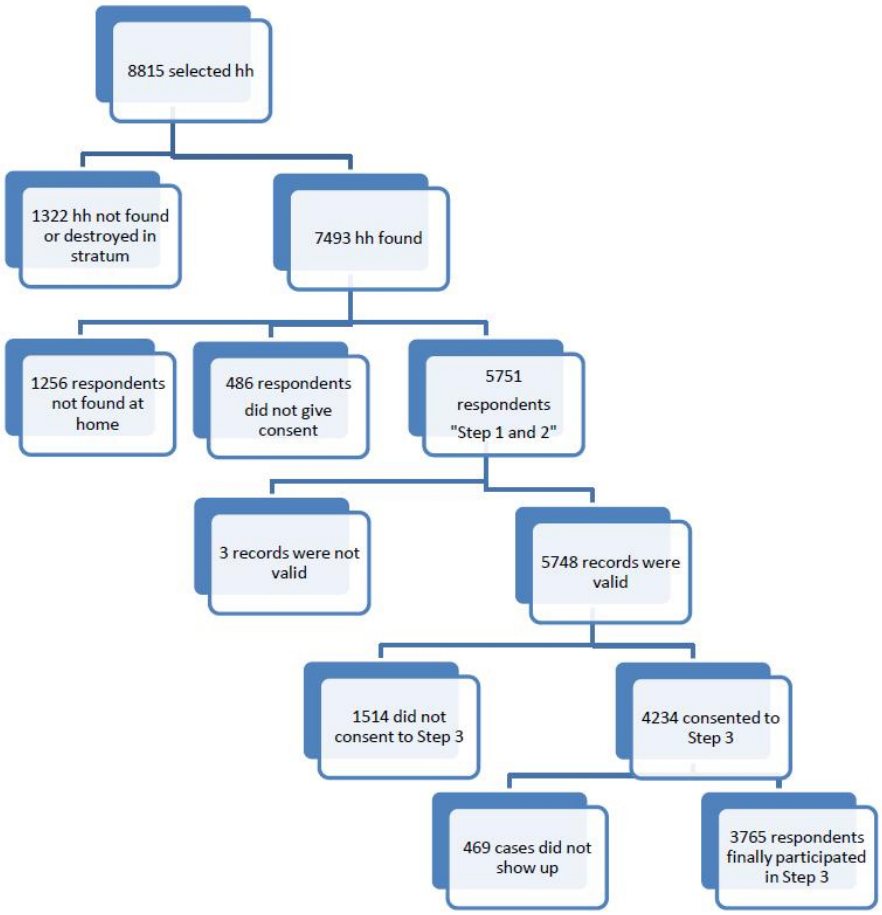


Figure 2. Sample selection flowchart. hh=household.



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Data Collection

Overview

Data were collected using the WHO STEPS to chronic disease risk factor surveillance. This method retrieves information on risk factors within a population, and includes different research tools. These tools are used in 3 levels of data collection, described as Steps 1-3 [33,34]. The following 3 steps were conducted in this survey:

STEP 1 (Questionnaire)

Information on demographics; smoking; alcohol consumption; dietary habits such as salt, fruit, and vegetable intake; physical activity; the cost of health care and loss of productivity; history of hypertension, diabetes, screening for cervical and breast cancer, injuries, and violence; mental health; and the use of health care was collected using a questionnaire. Apart from income, the other variables corresponding to these questions were composed using 5436/5748 to 5748/5748 of valid data. Only 4052/5748 of the data on income were valid (see Multimedia Appendix 1).

STEP 2 (Physiological Measurements)

Body weight and height, waist circumference, and blood pressure, were measured using specific tests and devices. The amount of valid records for these measures ranged from 5423/5748 to 5688/5748 (see Multimedia Appendix 2).

STEP 3 (Laboratory Analysis)

Levels of blood glucose, cholesterol, and triglycerides were measured by full-blood analysis. For the analysis of blood-glucose data, 3323/3765 of laboratory data provided valid data, whereas for blood-lipids on average only 3017-3030 of the total valid 3765 records could be used (see Multimedia Appendix 2).

Within the database, extreme outliers and missing data were considered invalid and were subsequently not used in the analysis. The staff participating in this study were trained extensively according to the WHO STEPS manual [35].

Residential Area and Ethnicity

Based on criteria of the General Bureau of Statistics used in the Suriname Multiple Indicator Cluster Survey on health indicators for children, residential addresses were divided into urban areas, rural coastal areas, and the rural interior according to the residential areas (Table 1) [36].

Table 1. Residential areas of Suriname. Source: Suriname Ministry of Social Affairs and Housing, General Bureau of Statistics Suriname. Suriname Multiple Indicator Cluster Survey 2010, Final Report. Paramaribo, Suriname: General Bureau of Statistics Suriname; 2013 [36].

Strata	Districts and resorts
Urban	Paramaribo, Wanica, Nickerie (resort: Nw Nickerie), and Commewijne (resorts: Meerzorg and Tamanredjo)
Rural in the coastal area	The remainder of Nickerie, the remainder of Commewijne, Coronie, Saramacca, Para, and Marowijne
Rural in the interior	Brokopondo and Sipaliwini

Ethnicity has a racial and a cultural component. Self-reported ethnicity of the individual was shown to be deficient when evaluating health components [37-40]. Thus, to determine the ethnicity of a participant both self-reported ethnicity and deduced ethnicity would be used. For deduced ethnicity, that of the grandparents will be considered. A person was categorized into a certain group if at least three of the four grandparents will be considered of ethnicity of that specific group. All others will be categorized as “mixed ethnicity.” Self-reported ethnicity will be used only for comparison with other data collected using the same method (eg, to adjust for ethnicity with regard to the census data [8]).

Physical Measurements and Equipment

Respondents were measured and weighted as described in the WHO STEPS manual Part 3 [35]. Blood pressure was measured 3 times with the Omron HEM-780 blood pressure monitor. Height was measured with the Seca 213 stand-alone stadiometer, waist with the Seca 201 measuring tape, and weight with the Tanita HS302 solar scale.

Biological Samples

We signed a contract with a commercial laboratory in Paramaribo (ISO 9001:2008 certified) for performing all the biochemical analyses. Blood samples were collected from the respondents after they fasted for 12 hours overnight. The samples were drawn at home or at a nearby place to increase response. For respondents who failed the 12-hour fasting blood test, the number of hours fasted was registered and their blood was drawn. All blood samples were collected in sodium fluoride (NaF) tubes (2 mL) and lithium heparin (LiHep) tubes (4 mL) for the analysis of glucose and cholesterol levels, respectively. Each sample was labeled with a barcode, which corresponds to the name of the respondent. In the laboratory, the LiHep and NaF tubes were centrifuged at 4100 rpm for 8 minutes at 20°C. The biological samples were analyzed using a CX9 fully automated analyzer (Beckman Coulter, Inc, Atlanta, GA).

The drawn blood was stored in a cooler with ice packs (temperature between 6 and 20°C) and transported to the laboratory within 4 hours. In remote areas, the blood was centrifuged at 4100 rpm for 8 minutes and stored between 3 and 8°C while waiting for transportation to the central laboratory. Once the samples arrived at the laboratory, they were processed and analyzed. Before performing the analysis, 1 mL of the LiHep plasma sample was pipetted into cryo vials to establish a bank of sera for this study. These aliquots were then stored at −80°C.

Interventions and Follow-Up

After data analysis, risk groups will be identified and targeted by custom-fitted lifestyle interventions, which will be

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implemented within 6 months after the basic study results are made available. The stored aliquots (from the serum bank) will be analyzed as baseline data to measure the effectiveness of interventions. The effects of all interventions will be assessed and disseminated after 2 years of implementation. For surveillance, the basic set up of this study will be repeated after 5 years.

Data Management

After data collection, all questionnaires were verified for completeness and consistency of responses. In addition, we evaluated the reliability of the interviewer by partially reinterviewing 238/4757 of the respondents at random in the coastal area. EpiData was used for data entry, which started in April 2014. Frequent quality checks were performed to detect and correct errors in data entry. The laboratory results of the biochemical analysis were added to the file of the respondent. The data entry and validation of these results were done separately. Double data entry resulted in two databases, which were crosschecked using Epi Info's data compare tool. Finally, 2 identical databases, K1 and K2, were created. Once data entry was complete, it was prepared for cleaning and analysis. The unique identification code for the variables included a code for location, which enabled us to trace each respondent. This code was used to divide the sample into rural and urban localities as presented in Table 2.

Table 2. Data by urban or rural area for Steps 1-3.

Areas	Steps 1 and 2 n (%)	Step 3 n (%)
Urban areas	2797 (48.7)	1750 (46.6)
Rural coastal areas	1959 (34.1)	1321 (35.0)
Rural interior areas	992 (17.3)	694 (18.4)
Total	5748 (100.0)	3765 (100.0)

The variables age and sex were checked and only those records containing both variables were considered valid for additional analysis because both variables are needed to analyze the survey data by age-sex groups. Records with either one of these variables missing were considered invalid. Table 3 provides an overview of respondent's sex by age group for the sample in each step of the survey, and Table 4 presents this overview for ethnicity. Outliers in the data were revised and if incorrect, they are registered as missing. Results deemed unusual, but nevertheless correct were left in the database.

Table 3. Valid data presented by sex and age group for Steps 1-3.

	Steps 1 and 2			Step 3		
Age group	Men	Women	Total	Men	Women	Total
15-24	421	670	1091	240	433	673
25-34	426	857	1283	213	581	794
35-44	493	794	1287	286	567	853
45-54	491	728	1219	318	523	841
55-64	324	544	868	203	401	604
Total	2155	3593	5748	1260	2505	3765

Table 4. Frequency of data by ethnic groups.

Ethnic group	Steps 1 and 2 n (%)	Step 3 n (%)
Creole	693 (12.1)	445 (11.9)
Hindustani	1342 (23.5)	916 (24.5)
Javanese	935 (16.4)	600 (16.0)
Maroon	1395 (24.5)	943 (25.2)
Amerindian	435 (7.6)	300 (8.0)
Mixed ethnicity	833 (14.6)	499 (13.3)
Other ethnic groups	74 (1.3)	39 (1.0)
Total	5707 (100.0)	3742 (100.0)

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Weighting of Subgroups

Collected data will be subjected to a weighting procedure so that inferences can be made to the whole population. The weights used for analysis were calculated to adjust for probability of selection, nonresponse, and differences between the sample population and target population (see Multimedia Appendix 3). The nonresponse weight was separately calculated for each district by age group (see Multimedia Appendices 4 and 5). The data will be weighted based on selection and nonresponse. These were applied for individual districts and normalized.

A quick analysis of the data showed that the variability of the response rate for Steps 1 and 2 was quite similar, but differed significantly from the variability of the response rate for Step 3. The difference in variability meant that the weights to be applied for Steps 1 and 2 are different from those to be applied for Step 3. The population data used to calculate weights were deduced from the Census 2012 report [8] (see Multimedia Appendices 6 and 7). The weights of the population size were calculated by age and sex/10-year age group.

Finally, the data will be adjusted for the distribution of the ethnic groups indicated in the research questions. The overall weight of the data is the multiplication of the sample design weight, the response weight, and the adjustment weight (see Multimedia Appendix 8).

Results

Data collection resulted in 5748 valid data for analysis. These results are anticipated in mid-2015. A report with general tables will be presented to the Suriname Ministry of Health. Results on the effectiveness of targeted lifestyle interventions are anticipated in late 2017.

Discussion

Preliminary Findings

The high mortality as a consequence of NCDs necessitates the need for data with regard to their risk factors. In response to this growing need, the WHO STEPS [33] was developed. The use of the same standardized questions and protocols by countries provides information to monitor trends within the country and make comparisons possible between countries. This study was designed to obtain data in order to represent the ethnic and geographic diversities of the Surinamese population by sex in 5 different age groups. For each of these groups, the basic sample requirement of 384.16 is needed for results within a 95% CI. For an estimated design effect of 1.5, a total of 5762 respondents were needed, and finally, 5748 valid questionnaires (99.76%) were entered into the database. Therefore, it can be concluded that this study, as designed, includes an adequate dataset. The analysis of these data, in general and in subgroups, will provide high-precision outcome measures for Steps 1 and 2. However, recall bias and, to a lesser extent, interviewer bias should be considered.

By contrast, the sample size for Step 3 is limited. For the sample size of 3742 (95% CI), no design effect can be considered. This smaller sample size is of consequence for the analysis of subgroups such as age and ethnicity. The male subgroups in Step 3 are under the size of 385 (range 203-313). In addition, the Amerindian ethnic group includes only 300 respondents in Step 3. If the CI is changed from 95% to 90%, then the basic sample requirement will become 270.67. For an estimated design effect of 1.38, however, a total of 3742 would be needed. Therefore, although the size of the sample in Step 3 will result in less-precision outcome values, they are still of considerable value for this study.

The use of normalized weights for inference of these data allows for the presentation of reliable record for the Surinamese population. Further, the results allow for comparisons between ethnicities and geographical areas of various countries. Ethnic differences have been reported in several STEPS surveys [7]. However, in this case, Suriname will be the first country that contributes results for 6 ethnic groups living within one environment. Because of the composition of the Surinamese population, the results can also be used as estimations of prevalence of immigrating ethnicities elsewhere.

Conclusions

In summary, this study reaches its purpose and presents valid and precise data of the Surinamese population by sex, age group, urban and rural localities, and ethnicity. The study design as realized allows for valid approximations of the prevalence of risk factors for NCDs. Risk groups will be identified, and targeted interventions will be implemented and evaluated. For NCD surveillance, the repetition of such a cross-sectional population survey every 5 years is recommended [6]. This will allow the following of trends; in addition, it is also necessary to evaluate, implement, and adapt health interventions.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Quality of data records for Step 1 (questionnaire).

[PDF File (Adobe PDF File), 58KB - resprot_v4i2e75_app1.pdf]

Multimedia Appendix 2

Quality of data records for Step 2 (physical measurement) and Step 3 (biochemical measurements).

[PDF File (Adobe PDF File), 50KB - resprot_v4i2e75_app2.pdf]

Multimedia Appendix 3

Survey design weight.

[PDF File (Adobe PDF File), 34KB - resprot_v4i2e75_app3.pdf]

Multimedia Appendix 4

Nonresponse weight adjustment for questionnaire and physical measurements.

[PDF File (Adobe PDF File), 46KB - resprot_v4i2e75_app4.pdf]

Multimedia Appendix 5

Nonresponse weight adjustment for biochemical measurements.

[PDF File (Adobe PDF File), 42KB - resprot_v4i2e75_app5.pdf]

Multimedia Appendix 6

Adjustment weights for age groups for each district for the questionnaire and physical measurements.

[PDF File (Adobe PDF File), 53KB - resprot_v4i2e75_app6.pdf]

Multimedia Appendix 7

Adjustment weights for age groups for each district for biochemical measurements.

[PDF File (Adobe PDF File), 53KB - resprot_v4i2e75_app7.pdf]

Multimedia Appendix 8

Adjustment weights for ethnicity for each study step.

[PDF File (Adobe PDF File), 32KB - resprot_v4i2e75_app8.pdf]

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Abbreviations

EAs: enumeration areas
LiHep: lithium heparin
NaF: sodium fluoride
NCDs: noncommunicable diseases
PSU: primary sampling unit
STEPS: STEPwise approach to surveillance
VA: village area
WHO: World Health Organization

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Original Paper

An Interactive, Bilingual, Culturally Targeted Website About Living Kidney Donation and Transplantation for Hispanics: Development and Formative Evaluation

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Abstract

Background: As the kidney shortage continues to grow, patients on the waitlist are increasingly turning to live kidney donors for transplantation. Despite having a disproportionately higher prevalence of end-stage kidney disease (ESKD), fewer waitlisted Hispanic patients received living donor kidney transplants (LDKTs) than non-Hispanic whites in 2014. Although lack of knowledge has been identified as a barrier to living kidney donation (LKD) among Hispanics, little is known about information needs, and few bilingual educational resources provide transplant-related information addressing Hispanics' specific concerns.

Objective: This paper describes the process of developing a bilingual website targeted to the Hispanic community. The website was designed to increase knowledge about LKD among Hispanic patients with ESKD, their families, and the public, and was inspired by educational sessions targeted to Hispanic transplant patients provided by Northwestern University's Hispanic Kidney Transplant Program.

Methods: Northwestern faculty partnered with the National Kidney Foundation of Illinois for expertise in ESKD and Hispanic community partners across the Chicago area. We established a Community Advisory Board (CAB) of 10 Chicago-area Hispanic community leaders to provide insight into cultural concerns and community and patients' needs. Website content development was informed by 9 focus groups with 76 adult Hispanic kidney transplant recipients, living kidney donors, dialysis patients, and the general Hispanic public. The website development effort was guided by community input on images, telenovela scripts, and messages. After initial development, formal usability testing was conducted with 18 adult Hispanic kidney transplant recipients, dialysis patients, and living kidney donors to identify ways to improve navigability, design, content, comprehension, and cultural

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sensitivity. Usability testing revealed consistently high ratings as “easy to navigate”, “informative”, and “culturally appropriate”. Bandura’s Social Cognitive Theory and Gagne’s Conditions of Learning Theory guided website design to facilitate adult learning.

Results: The website, “Infórmate: Living Kidney Donation for Hispanics/Latinos” (*Infórmate Acerca de la Donación de Riñón en Vida*), includes six sections: Treatment Options, Donation: Step-by-Step, Benefits and Risks, Financial Issues, Immigrant Issues, and Cultural Beliefs and Myths. Sections host 5-10 interactive messages that summarize important points and link to detailed explanations for users interested in learning more about specific issues. The website hosts interactive videos, multimedia testimonials, telenovelas, games, and quizzes. Photographs and videos of Hispanic living donors are shown to promote pride and ownership.

Conclusions: Our success in developing a website was driven by a development team with expertise in transplantation, social science, evaluation, instructional design, and Hispanic perspectives, and by a patient-centered approach toward content and design. Based on feedback from usability testing and our CAB, the website is sensitive to Hispanic cultural sensibilities. We have nearly completed a formal evaluation of the website’s impact on increasing Hispanics’ knowledge about LKD and will disseminate the website thereafter.

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KEYWORDS

culturally targeted; ethics; ethnic groups; eHealth intervention; Hispanic Americans; Internet; immigrants; informed consent; kidney transplantation; Latino; living donors; multimedia

Introduction

Disparities in Kidney Transplantation for Hispanics/Latinos

The shortage of kidneys for transplantation and ethnic disparities in living kidney donation (LKD) are major public health problems [1,2]. Living donor kidney transplantation (LDKT) is considered the optimal treatment for end-stage kidney disease (ESKD) because LDKT provides shorter waiting time, longer patient and graft survival, and better quality of life than deceased donor kidney transplantation (DDKT) [3-5]. Despite having a disproportionately higher prevalence of ESKD [6-10], a smaller proportion of waitlisted Hispanics received living donor kidney transplants than non-Hispanic whites in 2014: 4% versus 10% [11]. As Hispanics are the largest and fastest growing minority group in the United States with a high prevalence of risk factors for ESKD [12], the disparity in LDKT rates is likely to increase.

Hispanics’ low rates of LDKT have been attributed to cultural beliefs, lack of knowledge, and negative attitudes about living kidney donation [13,14]. Patient and potential donor knowledge about LDKT is associated with the likelihood of having a living donor [15,16], and interventions to increase knowledge about LDKT can increase donor evaluations and actual LDKTs [17,18].

The Internet can be an excellent medium for educating underserved populations with low health literacy [19]. The “digital divide”, or lack of access to computers or the Internet, has diminished to the point where Hispanics are using the Internet at comparable rates to non-Hispanic whites (76% versus 86%) [20], suggesting that Internet-based education is an accessible medium to learn about transplantation. Efforts are increasingly being undertaken to educate patients with chronic kidney disease (CKD) through digital media [21], which have been met with general interest among patients with CKD [22].

Internet-based interventions are increasingly used for health education and behavioral change. Similarly, targeting health interventions to cultural groups is gaining greater traction [23]. Interventions that are culturally targeted address “a set of values, principles, behaviors, attitudes, policies, and structures that enable organizations and individuals to work effectively in cross-cultural situations” [24]. By using the term “culturally targeted”, our intent was to use an anthropological approach to address deep-seated cultural values commonly shared among Hispanic communities. Additionally, we recognized Hispanic communities as heterogeneous and dynamic, and that the culture of biomedicine can affect patients’ health experiences [25]. Relatedly, although preferences for the terms “Hispanic” or “Latino” vary [13,26], we use “Hispanic” herein to refer to commonly shared language and cultural values and beliefs among a heterogeneous population in the United States [27,28].

While targeting websites to cultural groups has been extensively examined in business and marketing fields [29], and shown to be effective in website performance measures (eg, ease of use) among Spanish and other European consumers [30,31], such targeting has only recently been used in Web-based health interventions to facilitate effective uptake of health messages. For example, websites have been culturally targeted to Hispanics about regional health resources in Texas [32], Turkish immigrants in the Netherlands about depression [33] or hepatitis B screening [34], and American Indian/Alaska Native youth about smoking cessation and prevention [35,36].

We created a bilingual, culturally targeted website to increase knowledge about LKD, LDKT, and kidney transplantation among Hispanic patients with ESKD, their families, and the public. The website is called “Infórmate: Inform Yourself About Living Kidney Donation For Hispanic/Latinos” (*Infórmate Acerca de la Donación de Riñón en Vida)*. The website is designed to present information needed to make informed treatment decisions. This resource is especially needed because there are few websites about kidney donation and transplantation that address specific needs of the Hispanic community or that are in Spanish [37].

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This paper describes the development of *Infórmate*. We begin by presenting the theoretical approaches guiding website design and functionality. We then describe our community engagement processes and data collection efforts used to identify culturally appropriate content and design. We describe our website content and design, and usability testing, and then conclude by describing our evaluation research.

Methods

Website Development Process

Inspiration

The website was inspired by educational sessions targeted to Hispanic transplant patients that are provided by Northwestern University's Hispanic Kidney Transplant Program (HKTP), which have been shown to increase knowledge about LKD, as previously described [38]. The Director of the HKTP and co-author (JCC) implemented the HKTP in 2006 with the intent of increasing LDKT rates in Hispanics by addressing Hispanics' cultural beliefs, values, and information needs during the Spanish education sessions and by encouraging family involvement in the HKTP.

Research Team

The research team comprised a partnership between Northwestern faculty, including a medical anthropologist/ethicist with expertise in ethical issues relating to kidney transplantation and donation (EJG), health services researcher (JF), instructional design health educators (PC and JB), a Hispanic transplant surgeon (JCC), and a Hispanic research staff member (DR), and the National Kidney Foundation of Illinois (NKFI), including the former Chief Executive Officer (KO), the Hispanic community outreach staff member (MO), and the former marketing expert (JM). The NKFI was selected as a partner given their expertise in ESKD, connections to Hispanic community partners in Chicagoland, and to host the website as a neutral, unbiased information source. Two additional staff members later assisted in translation processes, for a total of five Hispanic, bilingual team members.

Community Advisory Board (CAB)

Leveraging the NKFI's community connections, we established a Community Advisory Board (CAB) of 10 Chicago-area Hispanic community leaders to provide insight into cultural concerns, community needs, and patients' needs. Hispanic community organizations represented included the Mexican Consulate, the Hispanic outreach coordinator from Gift of Hope Organ and Tissue Donor Network (the organ procurement organization serving Illinois and Northwest Indiana), Latinos por la Salud (Latinos for Health), Family Focus, Promotoras de Salud/Mano a Mano (Women Promoting Health/Hand in Hand), Juan Diego Community Center, Sinai Health Systems, Block by Block, a kidney transplant recipient, and a transplant physician researcher. The CAB was involved in several Web development and data collection activities, as discussed below.

Initial Website Content

The investigator team, with input from our bilingual clinical investigators including leaders of the HKTP, developed an outline of the most critical information needs of Hispanic patients and their families. All issues selected were based on the need to improve informed treatment decision making. The investigator team was careful to neither promote nor discourage living kidney donation. Thus, the website aimed to deliver information in a neutral, balanced tone with appropriate attention to the risks and uncertainties inherent in LKD to allow potential recipients and donors to make informed treatment decisions.

Our initial learning objectives addressed topics derived from ethical and legal standards of informed consent for treatment. We needed to provide information about the procedure of living donation, risks to the donor of donating, potential benefits to the donor, risks and benefits to the recipient, alternative options to the potential donor, as well as emphasizing the voluntariness of living donation. The team drew upon formal policies, for example, the Centers for Medicare and Medicaid Services (CMS) Conditions for Hospital Participation Guidelines [39] for specific informed consent content to address for living kidney donors. Members of the research team provided professional expertise in kidney disease and transplantation and contributed their experiential clinical knowledge about Hispanics' cultural concerns about transplantation.

The investigator team grappled with several issues in the initial content development process: (1) selecting valid sources of information, (2) determining the level of detail provided in the website, and (3) defining language commensurability of health terminology in English and Spanish. These and other issues were then taken to our community partners for discussion.

Source Materials

We drew upon government websites, such as Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS), the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK), Health Resources and Services Administration (HRSA), professional resources including the American Society of Transplant Surgeons, American Society of Transplantation, the National Kidney Foundation (NKF), and peer-reviewed publications in leading transplant journals for the most accurate, current, and credible information. We did not use material from non-professional websites such as individual donor's blogs or transplant center websites as they potentially present information in a biased fashion.

Level of Detail

We developed *Infórmate* to serve as a supplemental educational resource to formal transplant center education. There was tension between providing extensive information that would offer sufficient contextual understanding but might generate information overload versus limiting the amount of text provided to key ideas. To resolve the issue, we used a heuristic to guide our selection of information: including information that users would "need to know" versus information that is "nice to know." Considering the potentially limited health literacy level of the website users, we sought to keep the website as user-friendly as possible by limiting the amount of written text to facilitate adult learning.

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Language Commensurability of Health Terminology

We relied on terminology used by our bilingual transplant clinicians to standardize the website. Bilingual, Hispanic members of the research team engaged in forward and back translation to ensure agreement upon the alternative phrases used to convey "donor" and "recipient". We then tested these translations with Hispanic community audiences.

We encountered challenges in creating equivalence between the English and Spanish versions of the website. For example, one goal was to educate the public about disparities in LDKT rates among Hispanics to fuel interest in learning more about treatment options for ESKD. The word "disparity" does not translate easily into Spanish; other research similarly found that this term was not well understood among some Hispanics [40]. Therefore, we used visual approaches to convey the concept of "disparity". For example, inline display of multiple pie charts facilitated a quick and intuitive demonstration of the concept, without relying on ambiguous language (see Multimedia Appendix 1).

Data Collection Activities

Focus Groups

Website development research began with 9 focus groups conducted over 3 months with 76 adult Hispanic kidney transplant recipients, living kidney donors, dialysis patients, and the general public to identify Hispanics' information needs, cultural beliefs, and values about LKD [13]. Participants included individuals from diverse Hispanic countries, such as Mexico, Puerto Rico, and countries in Central and South America. Participants provided feedback on website names, preferred use of "Hispanic" or "Latino", logo designs, photographs, statistical graphs and explanations, and mission statement descriptions.

Community Advisory Board and Community Partner Outreach

The research team held a community event at the NKFI office suite for Hispanic donors, recipients, and dialysis patients from NKFI and Northwestern's patient lists, and members of the CAB to discuss the project goals, mission, and approach. CAB members and volunteers interacted with the research team over dinner and we used this opportunity to video-record additional LDKT recipient and donor testimonials as well as elicit additional feedback on website content and design.

For example, because the website was going to be evaluated for increases in knowledge, it needed to be designed in a way that would allow users quick and easy access to the most important learning points within each section, as identified by the research team. We asked participants to complete a brief survey that listed 20 facts about living kidney donation on paper surveys and asked community participants to rate how important each fact was for people to know, from "very important" to "moderately important" to "not important". We drew upon the ratings provided to inform the selection of the facts listed in the "Did you know?" column that, when clicked, transport users to the website section directly addressing that issue.

Another CAB dinner meeting was also held at the NKFI office suite to screen the initial website and obtain further input for making modifications before conducting usability testing. CAB members were organized into 4 groups of 2 to 3 members and a research team member at each computer work station as they viewed specific website sections. In addition to their initial reactions, CAB members completed a survey form rating what they liked and did not like about specific website sections.

We video-recorded interviews with donors and LKDT recipients in the Transplant Division offices at Northwestern University. We asked each donor or recipient to share his or her experiences as part of a semi-structured interview that provided short video testimonials for inclusion in the website. In addition, we asked donors and LKDT recipients to complete a brief survey that profiled their experiences as a donor or LKDT recipient to be used as captions for their website videos.

Usability Testing

After making further changes, the website was evaluated by a third party contractor, User Centric, Inc., dba Consumer Experiences GfK Custom Research, LLC, through two waves of testing, with website modifications in between. Usability testing involved 18 adult Hispanic kidney transplant recipients, dialysis patients, and living kidney donors, in either Spanish or English, as preferred. Eligible participants were recruited through an introductory letter followed by a phone call. Testing occurred in person (n=16) or remotely (n=2) for 60 minutes, and each participant was paid US $70. Usability testing aimed to "gauge overall user experience with the *Infórmate* website; inform future design iterations in terms of the overall user experience; identify user preferences and potential problem areas; understand if the website meets users' expectations and goals; and evaluate if the site communicates valuable information about living kidney donation" [41]. User Centric maintains a state-of-the-art laboratory setting that includes a two-way mirror and overhead displays of the participant's computer screen to allow the research team to unobtrusively observe and listen to each participant as he or she navigated *Infórmate*. At least 3-5 members of the research team observed each participant.

Usability testing entailed free navigation of the website followed by a series of six tasks requiring participants to find specified information on the website. The learning objectives for those tasks were determined through collaboration between the research team and User Centric staff. To illustrate, one task stated: "As you continue to learn about being a living donor for a family member, you would like to learn more about how donating will impact your daily life and activities. Show me how you would search for that information".

User Centric evaluated website usability metrics including: time needed to find sections of the website, number of clicks to find sections, and satisfaction with navigation and content. Participants' comments about their expectations of website design were recorded. Usability data for each scenario illuminated which tasks were easier or more difficult to achieve, thereby revealing website sections that required content or design modifications.

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After completing each task, participants were asked standardized survey questions to determine how our website compared to others in terms of usability. The System Usability Scale (SUS), a 10-item scale, assesses a user's overall usability [41]. Scores range from 0 to 100, with higher scores representing greater usability. Participants were also asked, "How likely are you to recommend this device?", which generates the Net Promoter Score (NPS), an 11-point scale about a user's loyalty to the website. Scores range from 0 to 10, with higher scores representing greater enthusiasm for the website. For each of the six task scenarios, participants were asked:

- "How easy was it to find what you were looking for?" to assess information findability, on a scale from 1 to 5 (range 1-5), with higher scores representing greater satisfaction.
- "How satisfied are you with the information presented in this section" to assess information satisfaction, on a scale from 1 to 5 (range 1-5), with higher scores representing greater satisfaction.
- "Rate your overall experience with this website" to assess overall website experience, on a scale from 1 to 7 (range 1-7), with higher scores representing greater satisfaction.

Website usability analysis involved descriptive statistics, for example, *t* tests to assess changes in efficiency and reduction in error between the benchmark test and re-test measures of the total usability score. User Centric provided a formal report detailing usability metrics and recommendations.

To ensure that the website met high levels of quality, we designed and modified the website using the 16-item validated instrument, "Quality Assurance Rating Tool for Internet Health Sites (Version 3)" [19]. This instrument includes metrics for website developers to assess their own website's quality such as, "Does the health Website mention the nature of audience that the site is intended for?"

Results

Design

Our website is called "*Infórmate: Living Kidney Donation for Hispanics/Latinos*" (*Infórmate Acerca de la Donación de Riñón en Vida*, which translates to "Inform yourself about living kidney donation") (Informate.org). The different name in English and in Spanish derives not from translation *per se*, but from focus group feedback that the English name should directly address the point about living donation, and that the Spanish name should present an indirect message. The website was designed using Web 2.0 design, jQuery web programming, and Articulate Storyline online training development software [42] for interactive modules according to adult learning theories and instructional design principles.

Theoretical Approaches and Applications to Content and Design

To foster cultural sensitivity and cultivate culturally appropriate user interface design, we used Resnicow's definition of cultural sensitivity. Because few well-validated theories of health education have been applied to website design or have been used to increase understanding of organ donation, we drew upon Gagne's Conditions of Learning Theory and Bandura's Social Cognitive Theory to guide website design.

Cultural Sensitivity

Our approach to website content and design entailed addressing both "surface" and "deep" cultural structures to increase cultural members' receptivity to the intervention [23]. Surface structure refers to matters of appearance by providing images of cultural expression that can be somewhat superficial in cultural meaning. For example, we used colors throughout the website that coincide with Hispanic sensibilities, such as orange, red, and turquoise [43]. To illustrate further, when referring to lifestyle changes for living donors following donation, we showed pictures of traditional Hispanic foods. By contrast, deep structure refers to the deep-seated beliefs, values, and meanings shared by members of the cultural group. Deep structure was addressed through the content and form of content delivery such as through immersive multimedia and telenovelas. *Infórmate* accommodated both surface and deep structures to be most effective in connecting with Hispanics.

Robert Gagne's Conditions of Learning is based on a hierarchy of intellectual skills necessary to facilitate learning [44,45]. The website content and presentation style adheres to the nine instructional design strategies that educational programs should use to ensure that learning will occur [44,46] in the following ways. The website gains participants' attention by using culturally sensitive design and colors, and posing questions that stimulate thought. For example, the Home Page includes a rotating banner that portrays images of Hispanic individuals engaging in healthy behaviors and enjoying family interactions. Each banner photo has a text overlay designed to gain attention with a phrase related to one of the website sections. Each banner photo is also linked to the corresponding section so a viewer can easily access that content.

The website informs users of the objectives by incorporating the learning objectives used in the instructional design phase into the introductory text of each section. In the Treatment Options section, the introductory text includes: "Find answers to questions many people ask about kidney failure and treatment options for people with kidney failure: what is kidney failure, what treatment options are there for someone who has kidney failure, what are living and deceased kidney donation, how does dialysis compare to kidney transplantation and how does living donor transplantation compare to deceased donor transplantation?" Thus, users are contextually introduced to the learning objectives of the website. The website also stimulates recall of prerequisite learning where appropriate. For example, in the Immigrant Issues section, various citizenship terms are addressed in the introduction. The user has the option of reviewing definitions of these terms in an interactive exercise. The website presents the stimulus material that engages the user in learning about living kidney donation throughout the website. The website provides learning guidance by providing cognitive processing opportunities through interaction. In the Benefits and Risks section, hovering over an interactive graphic poses a question asked by kidney donors. Clicking on this section shows current medical advice regarding the question. The website elicits the performance through the use of formative

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assessment. In the Cultural Beliefs and Myths section, a quiz assesses the user's knowledge of myths versus facts. After completion of the quiz, the exercise provides feedback about the performance correctness by stating whether or not participants got answers right or wrong and why, and assesses the performance by providing a score, for example, "You got 9 out of 10 questions correct!" Last, the website enhances retention and transfer by providing PDFs to download that summarize information about facts versus myths, and advantages and disadvantages of living donation versus deceased donation.

Bandura's Social Cognitive Theory (SCT) is based on the idea that learning occurs by observing and modeling the behaviors and attitudes of others [46-48]. Instruction can be made more efficient by modeling desired behaviors to learners and by providing situations that allow learners to use or practice that behavior to improve retention. Learning occurs by enhancing a person's (1) self-efficacy in his or her ability to engage in a behavior or understand a topic, and (2) appreciation of the benefits of that behavior or topic (by addressing knowledge, values, outcome expectations, and emotions). Efficacy beliefs can be promoted by (1) successful experiences, (2) vicarious experiences (modeling), (3) verbal encouragement, and (4) improvement in emotional states (reducing stress or negative mood) [49]. Accordingly, the website used video testimonials and telenovelas for modeling, and drag-and-drop interactive exercises with feedback to improve knowledge as applications of SCT interactive learning strategies.

Navigation and Elements

The website hosts numerous interactive features including hover-over effects, animated drop-down lists, and hyperlinks to other sections in *Infórmate* and to other websites. *Infórmate* orients users to their location on the website by showing the *Infórmate* logo on all pages, and provides a breadcrumb trail: the path followed by the individual as he or she moves from Web page to Web page. In these and other regards, *Infórmate* expresses Hofstede's uncertainty avoidance (the need for clear rules and direction, and for reassurance) [50]. The top of the website shows a row of photographs of Hispanic living donors and living donor recipients to convey the target population (see Multimedia Appendix 2).

Additionally, *Infórmate* hosts 19 living donor kidney recipient and living kidney donor video testimonials about their experiences of donating, life after donating, and relationships between recipient and donor. There are 8 video clips and 6 photographs of Hispanic transplant health care professionals addressing the benefits and risks of deceased donation and living donation and a priest addressing religious concerns about organ donation, thereby supporting Hofstede's concept of high power distance and respect for authoritative figures as knowledge sources [50] (see Figure 1 and Multimedia Appendix 3).

Infórmate hosts 9 interactive modules, 2 telenovelas, 3 drag-and-drop games, and a Myth versus Fact quiz about myths and misconceptions about LKD. The 100 photographs and images and 9 graphs and charts are used throughout. Free downloads of 3 fact sheets in English and Spanish as PDFs can help users remember and engage in future discussion about treatment options (eg, "Pros and Cons of Dialysis versus Kidney Transplantation", "Pros and Cons of Living Donor and Deceased Donor Kidney Transplantation", and "Myths and Facts about Living Kidney Donation". Sections include videos and/or up to 10 interactive take-home messages in the "Did you know?" right-hand column that, when tapped, bring users to a detailed explanation in that section. All cross-section linking includes animated scrolling and section-expanding effects, avoiding possible navigation confusion. The website footer includes the NKFI logo and contact information (see Figure 2 and Multimedia Appendix 4).

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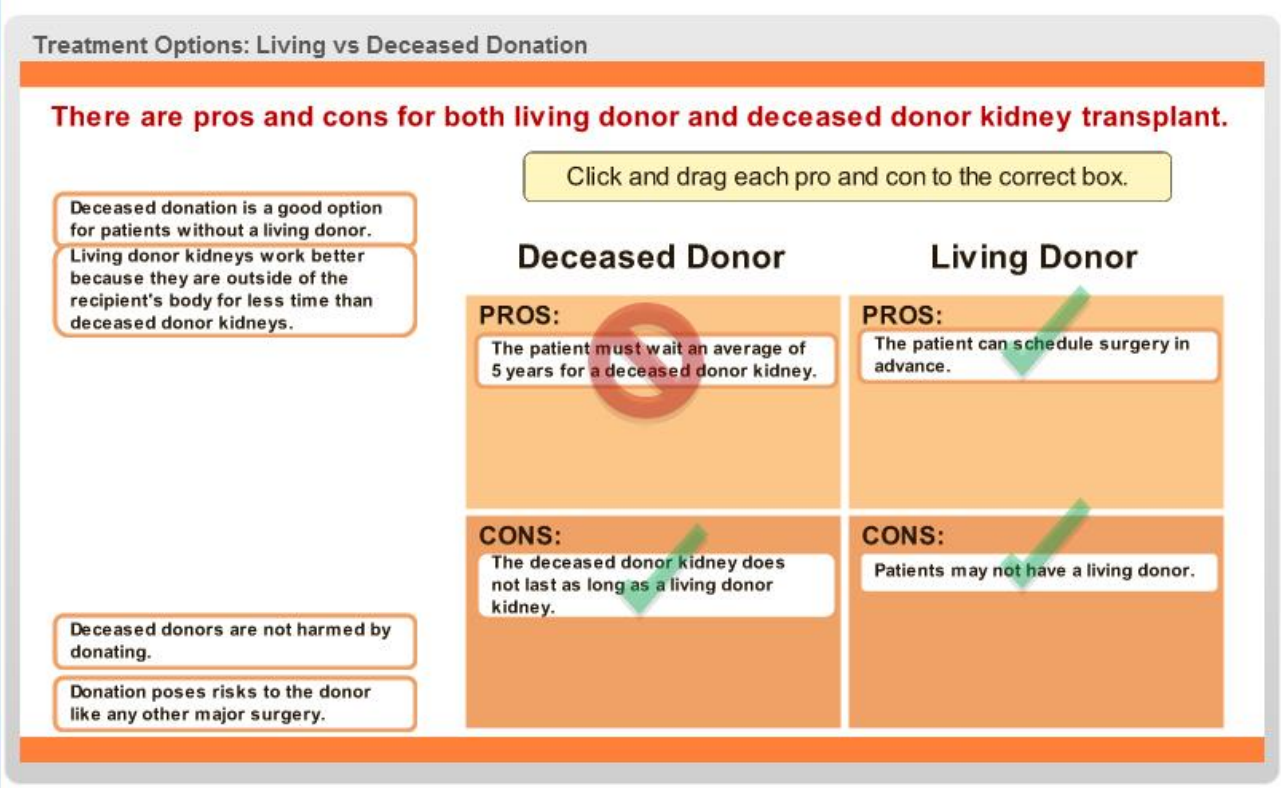
Figure 1. Screenshot of video of a priest is included to illustrate the authority figures represented.

Figure 2. Screenshot illustrating one of the drag-and-drop games.



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Structure

Infórmate includes six key sections: (1) *Treatment Options: Dialysis, Transplantation, and Donation*, which defines options, covers pros and cons of dialysis, transplantation, deceased donor and living donor transplantation, and addresses health disparities among Hispanics in kidney transplantation and LKDT, (2) *Benefits and Risks*, which presents the benefits, medical, and psychological risks, and potential living donor complications, as well as lifestyle changes for living donors. "Benefits" was intentionally placed before "Risks" because focus group members felt that users should know up front that there are few potential benefits to potential living donors, (3) *Donation: Step-by-Step*, which describes what tests and procedures potential donors undergo in the living donor evaluation process, (4) *Financial Issues*, which describes financial costs of transplantation and donation for donors and recipients, (5) *Immigrant Issues*, which explains the relationship between citizenship, insurance status, and being able to donate or receive a transplant, and (6) *Cultural Beliefs and Myths*, which addresses myths, misconceptions, and religious perspectives about LKD. Although our focus groups revealed that religious concerns are not a source of barriers to becoming a *living* donor, but are for becoming a *deceased* donor, we included religious perspectives about organ donation because religion plays an important role in the lives of many Hispanics [51] (see Multimedia Appendix 5).

The Home page provides a mission statement and welcome message that emphasize the focus on Hispanic communities. The About Us section includes the full mission statement, the backstory for developing the website, photos and biographies of the research team and CAB members, photos of developing the website, partners, bibliography of publications related to the study, and contact information. The use of proper titles, pictures, and an organizational chart of important people who were involved in website development in the About Us section corresponds with other research showing that Hispanics preferred business websites that display information about executives and biographical information [52].

The Resources section provides a link to a transplant hospital finder, listings and links to financial resources, pharmaceutical company programs that provide aid, websites on living kidney donation, religious perspectives on organ donation, support groups, donor and recipient testimonial videos, and a glossary.

Text

Our focus group participants who responded to the question expressed ambivalence as to whether they preferred to be identified as "Hispanic" or "Latino". While 44% (31/71) preferred both terms, 39% (28/71) preferred "Hispanic", and 17% (12/71) preferred "Latino". Thus, as most respondents selected both terms together, both are used throughout the website. All website text is available in Spanish and English, and users can effectively switch between two complete language versions of the website at any time. All text was written at a 5th to 8th grade reading level using the Flesch-Kincaid measure. Health literacy best practices were utilized to foster greater comprehension and simplify the presentation of written and statistical information [53-55]. For example, we used sans serif font, short sentences, active voice, plain language, second person "you" to engage viewers, posed questions as topic headers, presented frequencies with percentages, and provided diagram interpretations as titles. Further, the depth of content was layered to accommodate users with varying functional health and media literacy by providing definitions [56] (see Multimedia Appendix 6).

Images and Telenovelas

Videos and photographs represent diverse skin tones and nationalities to provide inclusive representation [52]. *Infórmate* hosts 19 video testimonials and 20 photographs of Hispanic living kidney donors and LDKT recipients. The photos and videos assure viewers that Hispanics can be living donors. Video testimonials about Hispanic living kidney donors' and living donor kidney recipients' experiences of donating or receiving a living donor kidney served as role models for users. The testimonials also give users the impression that they are talking to another person about LKD. We intentionally included testimonials and conversations because focus group living donor participants reported that they preferred to observe and listen to conversations on the website rather than to read text. Testimonials are also theoretically valuable because they increase affective reactions to the message, which facilitates greater learning [57] (see Multimedia Appendix 7).

We developed two 10-minute telenovelas as a "model of" concerns commonly raised by Hispanics about living donation so that viewers can learn what to expect and become prepared to discuss those issues, and as a "model for" [58] resolving those dilemmas. Topics derived from our focus groups. Telenovelas are like soap operas and express "dramatizations of compelling stories in Spanish" [59] Telenovelas are commonly viewed among Hispanics and embed cultural values of family, community, and storytelling. Telenovelas are a culturally accepted medium for conveying health education messages among Hispanics [60], and have been shown to improve attitudes about the use of home care services [59], increase knowledge about cardiovascular disease and breast cancer [61,62], and increase behavioral intentions for mammogram screening [61].

One telenovela, "*An Anguished Cry*" ("*Grito de Angustia*"), is about how a family decides whether the health risks of living kidney donation are worth taking, and addresses the concern about being able to have children after being a living kidney donor, which has contributed to reluctance to be a living kidney donor [13]. The telenovela "*The Decision*" ("*La Decisión*"), is about how a family decides whether the financial and other risks of living kidney donation are worth taking. It addresses concerns about job security and insurance coverage by discussing the financial impact on the lives of the potential living kidney donor and his or her family because living donors are out of work for 4 to 6 weeks or longer for recovery [13]. Both telenovelas were produced in Spanish with English subtitles to be consistent with the Spanish-language format of traditional telenovelas. The screenplays were written by the research team, with CAB input, and all actors were Hispanic (see Figure 3).

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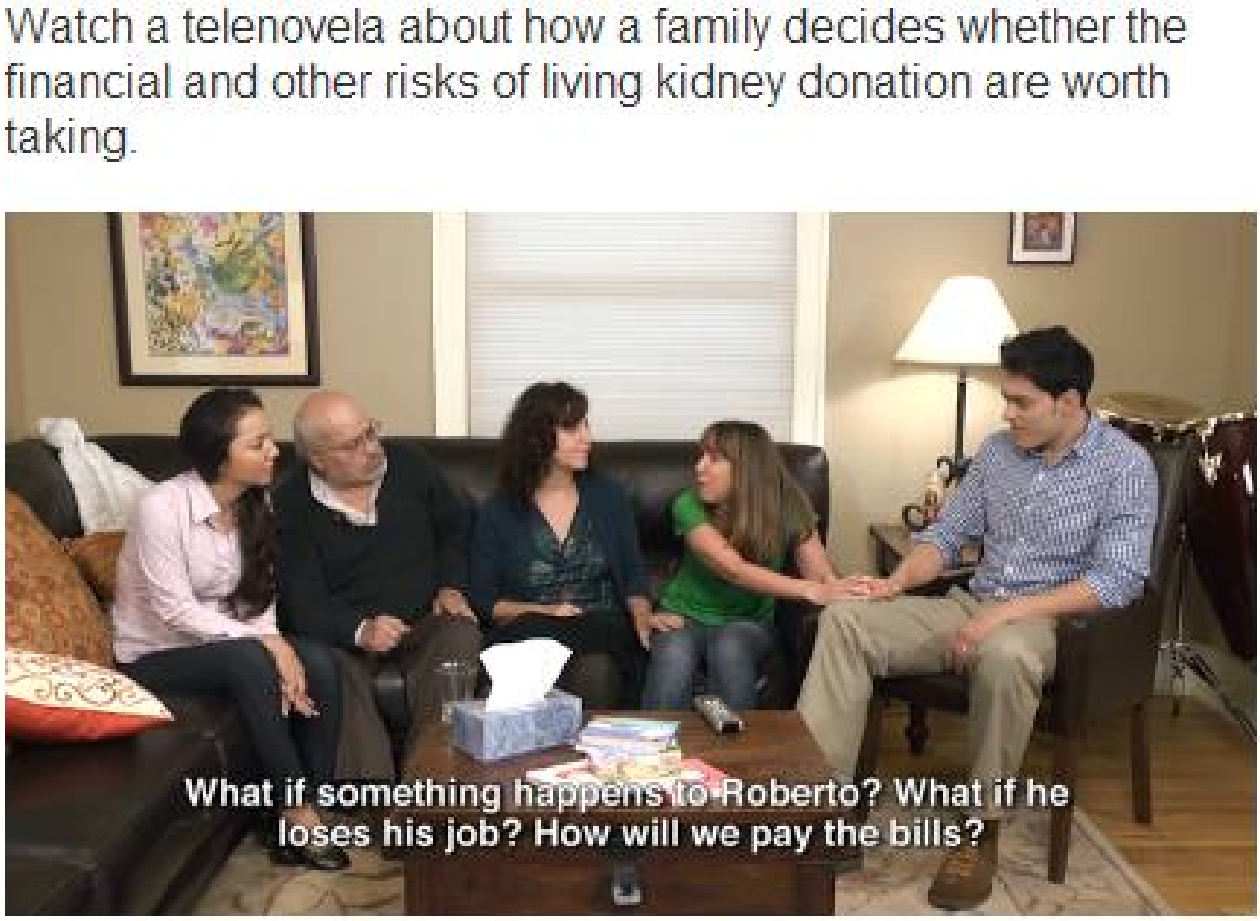
Figure 3. Screenshot from the Telenovela, "An Anguished Cry" ("Grito de Angustia").



Website Tone and Values

Infórmate conveyed a friendly tone and presented content in a polite fashion to convey respect (*respeto)* [52], by using the formal "You", as in "*¿Sabía usted?"* ("Did you know?"), and sentimental language: "*de todo corazón*", "*mejorarle la vida a un ser querido*". These approaches are based on harmony in relationships, or *simpatia*, which is commonly valued in Hispanic cultures [27].

We expressed the interrelated values of collectivism (the group and group activities are prioritized over the individual [27,63]) and familism (family loyalty and solidarity is valued more than the individual or community [64]), which are commonly shared among Hispanics, by providing pictures and videos of families, images of national identity through flags representing different Latino/Hispanic countries, and using text stating "you and your family". By showing a picture of grandparents and families on the home page, the website sought to emotionally connect [32,65].

We tapped into traditional Hispanic gender roles (eg, *machismo)* [27], in addressing cultural concerns. For example, concerns about the ability of both men and women to have children after donating were depicted by an interactive module, and concerns about potential living donors playing sports after donating were depicted by a photograph of soccer players (see Figures 4 and 5).

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Figure 4. Screenshot illustrating one of the interactive modules of a woman talking about reproduction after donation.

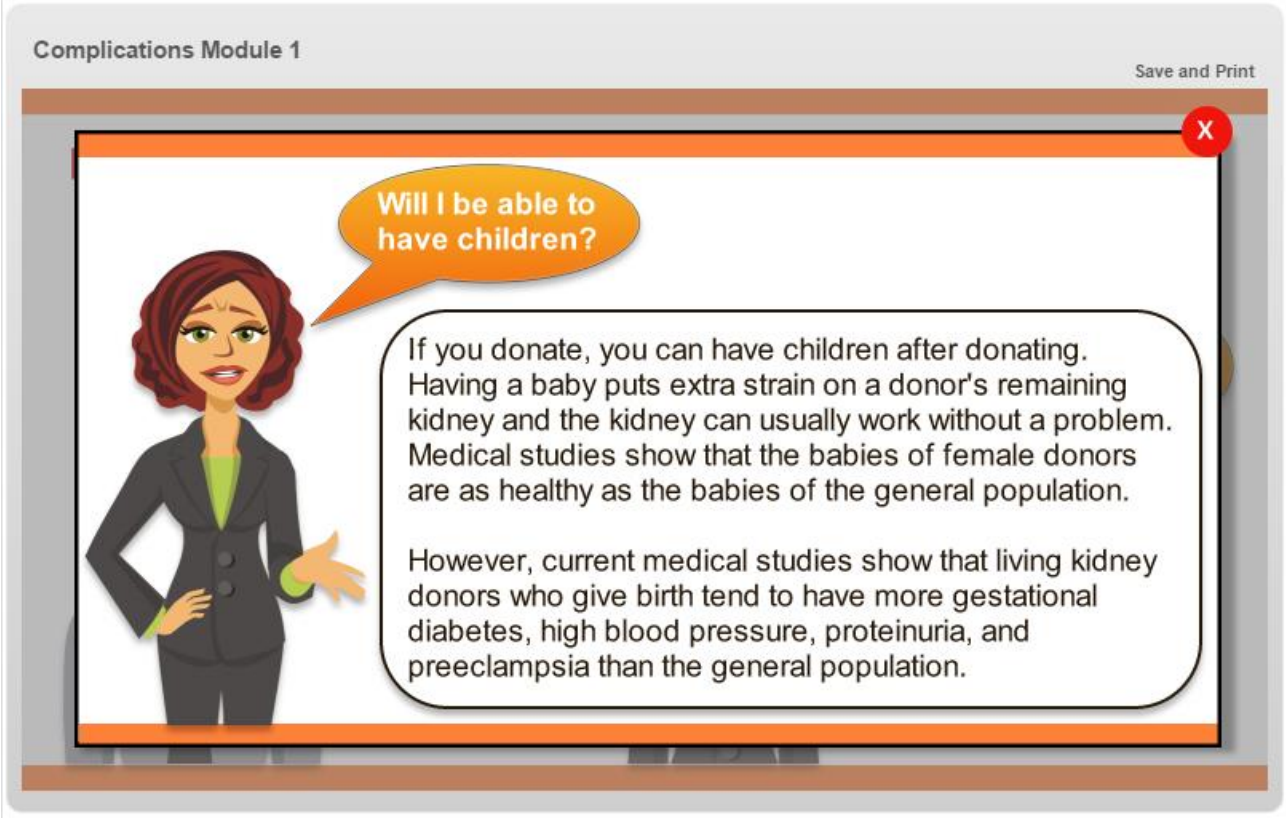

Figure 5. Screenshot from lifestyle changes discussion of the Benefits and Risks section, which addresses a concern about being able to play sports after donating. Screenshot also illustrates the interactive nature of this kidney-shaped module containing pictures that provide more information when selected.

Usability Testing

User Centric provided two reports summarizing their analyses and recommendations for website improvement after each phase of testing. Both waves of testing generated a “relatively good” SUS score compared to other websites (Table 1) [41]. The NPS scores fell into the “promoter” category representing loyal enthusiasts who will keep referring others to the site, fueling

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growth. Participants rated the ease of finding information highly, and participants rated their overall experience as extremely good.

Based on both reports, participants had a very positive overall impression of the *Infórmate* website. They described it as "easy to navigate and understand", "informative and helpful", and "very thorough". Participants reported that they would be interested in using this website for learning more about kidney disease and treatments. Participants reported that they felt *Infórmate* was easier to use and had more interactivity than other sites they had visited, and was better than visiting multiple websites when searching for the same information. Participants found the bilingual content and topics related to immigration and financial issues to be particularly useful and unique. Both usability testing reports supported the feasibility and cultural acceptability of *Infórmate*.

Based on usability feedback, changes included increasing the size of and making more prominent the En Espaňol link used to switch from English to Spanish, creating a large play button to initiate the interactive modules, increasing the font in tables and charts, converting a complex Articulate Storyline module into a drop-down format, converting full text presentation into a drop-down format, creating cross-links between sections to facilitate ease in finding content relevant to two sections, and including animated scrolling and section-expansion to orient navigation actions. As one participant commented about the living donor testimonials:

> *I like it [video], these are real people, not just participants. The person who is trying to get more information, they might get more comfort knowing that they are satisfied and that it was a success.* [Participant 7]

Table 1. Characteristics and aggregated satisfaction scores of usability testing participants.

	Total n=18	Wave 1 n=12	Wave 2 n=6
Male, n (%)	8 (44)	4 (33)	4 (67)
Female, n (%)	10 (56)	8 (67)	2 (33)
Spanish, n (%)	7 (39)	5 (42)	2 (33)
English, n (%)	11 (61)	7 (58)	4 (67)
Have access to the Internet, n (%)	18 (100)	12 (100)	6 (100)
Mean System Usability Scale (SUS)		84.09	84.58
Mean Net Promoter Score (NPS)		9.91 (range 9-10)	9.67 (range 9-10)
Information findability		Range 4.11-4.75	Range 3.67-4.83
Information satisfaction		Range 4.44-5.00	Range 4.20-4.83
Overall website experience		6.64 (range 6-7)	6.0 (range 5-7)

Health on the Net Certification (HONcode)

We also obtained Health on the Net (HONcode) certification, which is a non-governmental organization's ethical standard for ensuring that websites offer quality health information and support transparent information to foster objectivity [66]. Our HONcode seal of certification serves to provide assurance of the quality of the website, which is consistent with research documenting Hispanics' desire for websites to display company certifications or awards [52], and with Hofstede's concept of uncertainty avoidance [50].

Discussion

Principal Results

This manuscript outlines the development process and theoretical approaches undertaken to develop a bilingual, community-focused, interactive, multimedia website about living kidney donation and transplantation targeted to Hispanics. Internet-based educational interventions can be an effective, low-cost, and private way to reach and empower many individuals [67]. The Internet can also be an optimal venue to reach underserved, low-literate populations [19], and Hispanics are increasingly using the Internet to find health-related knowledge [26]. However, even though the digital divide is shrinking, the quality, depth, and readability of transplant-related websites is poor [37,68,69]. Culturally targeted websites can reduce Hispanic health disparities by increasing knowledge [70]. Our website, *Infórmate*, was designed to redress disparities in Hispanics' knowledge about LKD.

Given that 74% of Hispanics spoke Spanish at home in 2012 [71], our bilingual website is well suited to accommodate Hispanics of all levels of English proficiency [65]. Many of the design and formatting dimensions that we used were recommended by our Hispanic study participants and other studies' Hispanic focus group participants' perspectives on developing a website on cardiovascular disease prevention [40]. The sections *Financial Issues* and *Immigrant Issues* provided detailed content that addresses Hispanics' preferences for information on immigration and insurance coverage issues [52]. Research shows that US Hispanics prefer culturally adapted website design and marketing messages [65]. Further, other research found that Internet sites involving greater use of instructional design strategies that provide feedback and foster interactivity, such as video clips, interactive modules, and animations, can increase knowledge gains and satisfaction over sites without such features [72].

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Evaluation of *Infórmate* for increasing and retaining Hispanics' knowledge about LKD using concurrent control and pretest / posttest knowledge testing is nearly complete. Upon completion, we plan to disseminate the website to transplant and dialysis clinicians throughout Illinois and nationally using evidence-based approaches [73]. In our dissemination materials (eg, pamphlets and posters), we plan to use quotes from living donors provided in response to the question, "In your opinion, how would Hispanic potential donors, recipients, and family benefit from this website?" that was posed during our video-recording session at Northwestern:

> *They would have access to education that currently may not exist or they may not be aware of due to the language barrier.* [Female, English speaker]
>
> *The website would help them in answering any questions they have and having donors talking about their experiences would help them decide.* [Male, English speaker]
>
> *They will all learn more on transplantation. Unfortunately, not many people in the Hispanic community know about transplants and have many myths that need to be broken.* [Female, English speaker]

We will evaluate our dissemination efforts by tracking metadata and phone calls to the NKFI. Our intention is for *Infórmate* to be used to initiate inquiries into LKD and to supplement transplant center education. We expect *Infórmate* to be used multiple times and that patients will use the website together with their families; this is likely to be the case among older patients with less technological savvy. Studies of Hispanics' use of the Internet report that adult children often invite their parents to look at the website and interpret for them [32,52]. Involving family members in navigating *Infórmate* may coincide well with the integral role of Hispanic family members in decision making [74,75].

The website development process may have limitations. As the website development process was informed by Hispanics of diverse national heritages, albeit predominantly Mexican heritage, the cultural components may reflect predominantly Mexican perspectives. However, we intentionally sought to avoid using or excluding a single Hispanic/Latino cultural perspective by ensuring that our research team included Hispanics from diverse countries including Colombia, Puerto Rico, Panama, and Mexico.

Conclusion

Infórmate is a bilingual Web-based educational resource about living kidney donation culturally targeted to Hispanic patients and communities. Improving Hispanics' understanding about living kidney donation will promote autonomy and self-determination by helping to ensure that Hispanics are well informed of treatment options for ESKD.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Diagrams used to depict the concept of disparities.

[JPG File, 31KB - resprot_v4i2e42_app1.jpg]

Multimedia Appendix 2

Website banner that appears on all pages and showcases photos of Hispanic living donors and living donor recipients.

[JPG File, 28KB - resprot_v4i2e42_app2.jpg]

Multimedia Appendix 3

Screenshot from one of many videos of a Hispanic transplant surgeon (JCC).

[JPG File, 20KB - resprot_v4i2e42_app3.jpg]

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Multimedia Appendix 4

Screenshot illustrating various interactive “Did you know?” questions used to engage the view. Different questions appear in different website sections.

[JPG File, 34KB - resprot_v4i2e42_app4.jpg]

Multimedia Appendix 5

Screenshot illustrating one of the 12 questions in the Myth vs Fact game.

[JPG File, 45KB - resprot_v4i2e42_app5.jpg]

Multimedia Appendix 6

Screenshot of a diagram illustrating how we provided the interpretation of the diagram’s meaning in the title, which serves as a health literacy best practice to facilitate adult learning.

[JPG File, 47KB - resprot_v4i2e42_app6.jpg]

Multimedia Appendix 7

Screenshot illustrating a video of a living donor describing the financial aspects of preparing for donation.

[JPG File, 9KB - resprot_v4i2e42_app7.jpg]

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Abbreviations

CAB: Community Advisory Board
CKD: chronic kidney disease
CMS: Centers for Medicare and Medicaid Services
DDKT: deceased donor kidney transplantation
ESKD: end-stage kidney disease
HKTP: Hispanic Kidney Transplant Program (Northwestern University)
HONcode: Health on the Net certification
LDKT: living donor kidney transplantation
LKD: living kidney donation
NKFI: National Kidney Foundation of Illinois
NPS: Net Promoter Score
SCT: Social Cognitive Theory
SUS: System Usability Scale

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Original Paper

Internet-Based Cognitive Behavioral Therapy for Residual Symptoms in Bipolar Disorder Type II: A Single-Subject Design Pilot Study

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Abstract

Background: Bipolar disorder is a chronic condition with recurring episodes that often lead to suffering, decreased functioning, and sick leave. Pharmacotherapy in the form of mood stabilizers is widely available, but does not eliminate the risk of a new depressive or (hypo)manic episode. One way to reduce the risk of future episodes is to combine pharmacological treatment with individual or group psychological interventions. However, access to such interventions is often limited due to a shortage of trained therapists. In unipolar depression there is now robust evidence of the effectiveness of Internet-based psychological interventions, usually comprising psychoeducation and cognitive behavioral therapy (CBT). Internet-based interventions for persons suffering from bipolar disorder could increase access to psychological treatment.

Objective: The aim of this study was to investigate the feasibility of an Internet-based intervention, as well as its effect on residual depressive symptoms in persons diagnosed with bipolar disorder type II (BP-II). The most important outcomes were depressive symptoms, treatment adherence, and whether the patient perceived the intervention as helpful.

Methods: A total of 7 patients diagnosed with bipolar disorder type II at a Swedish psychiatric outpatient clinic were offered the opportunity to participate. Of the 7 patients, 3 (43%) dropped out before treatment began, and 4 (57%) were treated by means of an online, Internet-based intervention based on CBT (iCBT). The intervention was primarily aimed at psychoeducation, treatment of residual depressive symptoms, emotion regulation, and improved sleep. All patients had ongoing pharmacological treatment at recruitment and established contact with a psychiatrist. The duration of BP-II among the treated patients was between 6 and 31 years. A single-subject design was used and the results of the 4 participating patients were presented individually.

Results: Initiating treatment was perceived as too demanding under current life circumstances for 3 patients who consequently dropped out during baseline assessment. Self-ratings using the Montgomery-Åsberg Depression Rating Scale—Self-rated (MADRS-S) showed symptom reduction in 3 (75%) of the 4 treated cases during iCBT. In the evaluation of the treatment, 2 patients reported that they perceived that the treatment had reduced symptoms a little, 1 that it had reduced symptoms very much, and 1 not at all. Treatment adherence (ie, module completion) was fairly high in 3 cases. In general, the modules were perceived as fairly helpful or very helpful by the patients. In one case, there was a reliable change—according to the Reliable Change Index—in self-rated symptoms of depression and perseverative thinking.

Conclusions: The treatment seemed to have acceptable feasibility. The iCBT intervention could be an effective way to treat residual symptoms in some patients with bipolar disorder type II. This should be investigated in a larger study.

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Trial Registration: ClinicalTrials.gov NCT01742351; https://clinicaltrials.gov/ct2/show/NCT01742351 (Archived by WebCite at http://www.webcitation.org/6XnVpv4C3).

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KEYWORDS

bipolar disorder; Internet; cognitive therapy; behavioral therapy; pilot projects

Introduction

The lifetime prevalence of bipolar disorder type II (BP-II) was estimated at 0.4% in a large international study in 2011 [1]. Although the prevalence might be low, BP-II remains a challenge for society due to the low age of onset—estimated to be approximately 20 years of age [2]—the chronic course of the illness, and the patient's need of lifelong outpatient care, often in combination with recurring hospitalization [3]. Bipolar disorder does not only lead to high levels of sick leave [4], but also to large role impairments in other areas of life, and around 20% of patients will attempt suicide [1]. Furthermore, comorbidity is high, especially with anxiety and substance abuse [1].

Residual symptoms are very common between the hypomanic or depressed episodes. On average, sufferers of BP-II can expect to experience symptoms more than half of the time [5], with continuing role impairment as a consequence in many cases [6]. Prospective studies [7,8] have revealed that bipolar patients with residual symptoms relapse considerably faster compared to those in full remission. Interventions targeting residual symptoms are clearly needed and psychological interventions, for example, cognitive behavioral therapy (CBT), have been used for this purpose [9]. Recent evidence shows that combining CBT with medication is effective in bipolar patients as it reduces symptoms [10] and lowers the risk of relapse [11]. However, while pharmacotherapy for bipolar disorder is widely available, access to CBT is often limited.

In the treatment of unipolar depression, there is a similar situation with limited access to effective psychological treatment. This has resulted in the emergence of Internet-based interventions for major depression based on cognitive behavioral therapy (iCBT), which has been shown to be effective in several studies, as well as in two recent meta-analyses [12,13].

Internet-based psychoeducation for bipolar patients—type I, type II, and not otherwise specified (NOS)—in full remission has been tested in a pilot study with a small beneficial effect on psychological quality of life compared to a control group, but with no effect on depressive symptoms during follow-up [14]. In a randomized controlled trial (RCT), no difference was found between Internet-based psychoeducation for bipolar disorder—any subtype—and a control condition on the reduction of depressive symptoms, although it was also demonstrated that guidance increased adherence to the online program compared to a completely self-guided intervention [15]. More trials on Internet-based interventions for bipolar disorder are being conducted [16-18], but few results have been published.

The aim of this study was to investigate the feasibility of iCBT and its effect on residual symptoms in persons diagnosed with BP-II. As the application of iCBT for bipolar disorder is a largely unexplored area, we employed a replicated single-case experimental design. While this design provides the opportunity to draw valid inferences of treatment effectiveness, the requirement to collect data on large and homogeneous groups is circumvented. Thus, the design is well suited to testing initial feasibility and obtaining a preliminary indication of effectiveness.

Specifically, this pilot study aims to answer the following questions:

Is iCBT a feasible approach? Specifically, (1) to what extent do patients show interest and participate in the treatment? and (2) to what extent do patients experience the treatment as helpful?

Does iCBT affect residual symptoms? Specifically, (1) does the intervention lead to a reduction in depressive symptoms? and (2) does the intervention lead to a reduction in sleep problems?

Methods

Participants and Procedure

The inclusion criteria were as follows: a minimum age of 18 years, a diagnosis of BP-II, stable and adequate pharmacological treatment for BP-II (ie, no medication change in the previous 3 months, antidepressants only allowed in the presence of mood stabilizers), Internet access, ability to read and write Swedish, and mild-to-moderate residual depressive symptoms defined as a score on the Montgomery-Åsberg Depression Rating Scale—Self-rated (MADRS-S) [19] of no less than 7 and no higher than 34 [20]. Exclusion criteria were as follows: having been diagnosed with a psychotic disorder or hospitalized within psychiatric care during the previous 12 months, previous suicide attempts, documented parasuicidal behavior or a score above 3 on item 9 on the MADRS-S—which would indicate suicidality—a history of mania, or ongoing psychotherapy.

The trial protocol was approved by the Regional Ethical Review Board in Uppsala (No. 2012/341) and registered at ClinicalTrials.gov (NCT01742351).

A total of 548 patients were extracted from a psychiatry database held by Region Örebro County based on having been diagnosed, at least once, with other bipolar affective disorder (F31.8)—the formal categorization of bipolar II in the International Classification of Diseases, 10threvision (ICD-10) [21]—bipolar affective disorder, currently in remission (F31.7), or bipolar affective disorder, current episode hypomanic (F31.0). After review of the patient records, 477 out of 548 (87.0%) were excluded, most often due to having also been diagnosed with

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bipolar disorder type I (BP-I) at some point, a documented manic episode, or lack of a clear record entry where a psychiatrist had diagnosed the patient with BP-II. Letters were sent to the remaining 71 patients out of 548 (13.0%) with information about the study, and 18 out of 71 (25%) expressed an interest for further assessment. During a telephone interview, the patients were asked about Internet access and whether their language skills were sufficient for participation, at which time they had an opportunity to raise questions about the project. Those who provided consent received instructions about filling out the MADRS-S on the study website by logging on with a username and password. Their current medication was also assessed by a psychiatrist (MH) to ensure that it was stable and adequate for BP-II. Of the 18 patients, 5 (28%) were excluded due to recent changes of medication and 1 (6%) due to an inadequately high dosage of benzodiazepine. Of the 18 patients, 7 (39%) fulfilled the criteria and were given instructions to start a 3-week baseline assessment. During the baseline assessment, 3 patients of the 7 (43%) withdrew from further participation. The reasons given for dropping out were as follows: lack of time, lack of energy, and prioritizing the care for an ill family member. The remaining 4 patients out of 7 (57%) started the intervention and their data is presented in this article. After baseline, the 6-week intervention period began during which the patients worked with the treatment modules. Patients could communicate with a personal therapist throughout the treatment via secure emails. Therapist contact was typically used for support and for clarifying interventions, as well as for feedback on homework. The therapists also prompted patients who were inactive. Table 1 shows the characteristics of the patients at the baseline assessment.

Table 1. Patient characteristics at baseline.

Patient number	Age in years	Gender	Medication	MADRS-S[a]	Duration of BD-II[b] in years
1	66	Female	valproate, olanzapine[c], fluoxetine, zopiclone (prn[d])	19	14
2	31	Female	aripiprazole, duloxetine, propiomazine (prn), zolpidem (prn), levothyroxine	11	6
3	49	Female	lithium sulfate, melatonin, levothyroxine, orlistat	12	31
4	49	Male	valproate, lamotrigine, olanzapine[c], venlafaxine	8	8
5[e]	24	Female	lamotrigine, olanzapine[c], sertraline	18	2
6[e]	32	Female	lamotrigine, fluoxetine, pregabalin, oxazepam (prn), zopiclone (prn), acetaminophen, pramipexole	20	3
7[e]	56	Female	lithium sulfate, propiomazine	10	30

[a]score on the Montgomery-Åsberg Depression Rating Scale—Self-rated (MADRS-S) at baseline screening

[b]years since first diagnosed with bipolar disorder type II (BD-II)

[c]The Olanzapine dosage for patient 1 was 5 mg hs (at bedtime), and for patients 4 and 5 was only 2.5 mg hs, thus hardly interfering with daytime cognition

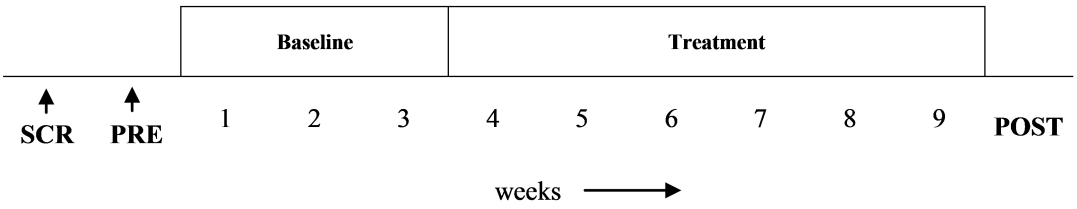
[d]prn: as needed

[e]patients 5, 6, and 7 dropped out during baseline

Design

A replicated single-case experimental design was used with a 3-week baseline period and a 6-week treatment period. The 4 participants functioned as their own control group in this design and the primary analysis was a visual comparison of the scores during baseline and treatment (see Figure 1).

Figure 1. An overview of the study design. SCR: initial screening (MADRS-S), PRE: pretest (BDI-II, PTQ, WSAS), Baseline: baseline assessment with weekly ratings (MADRS-S, ISI), Treatment: intervention phase comprising assessment with weekly ratings (MADRS-S, ISI), POST: posttest (BDI-II, PTQ, WSAS, patient evaluation).



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Measures

The primary outcome (ie, depressive symptoms) was measured by an Internet-based version of the Montgomery-Åsberg Depression Rating Scale—Self-rated [19] on a weekly basis during the baseline period and the treatment phase. The MADRS-S is a 9-item self-report measure that generates a total score from 0 to 54, with higher scores indicating more severe depressive symptoms. It has good internal consistency, for instance, a Cronbach alpha of .84 [22], and has been validated for online use [23]. Item 9 was employed to detect suicidality. When using this Internet-based version, the respondent sees 1 item per frame but can go back and change previous answers until the last question is answered. Only one alternative can be chosen per item and it is not possible to skip items.

The Beck Depression Inventory—Second Edition (BDI-II) [24] was employed to measure depressive symptoms before and after treatment. The BDI-II is a 21-item self-report measure that was used as a complement to the MADRS-S. The instrument's psychometric properties have been shown to be very good [25] and it has been validated for online use [23].

The Insomnia Severity Index (ISI) [26] was employed weekly to measure the severity and impact of sleeping problems. It is a 7-item self-report measure with excellent internal consistency and generates a score between 0 and 28 [27].

The Work and Social Adjustment Scale (WSAS) [28] was employed to measure the level of functioning of the participating patients. This 5-item self-report measure was administered before and after treatment.

The Perseverative Thinking Questionnaire (PTQ) [29] is a 15-item self-report instrument that was used to assess repetitive negative thinking before and after treatment. The internal consistency has been shown to be excellent [29].

The Affective Self-Rating Scale (AS-18) for manic, depressive, and mixed states is an 18-item self-report measure with very good internal consistency [30]. It is divided into two subscales—depressive and (hypo)manic—and in this study we used the subscale that measures mania by means of 9 items with a score ranging from 0 to 36 in order to detect any deterioration into manic episodes.

Patient satisfaction was measured by the question "How satisfied are you with the treatment?" Answers were given on a 5-point scale from "Very dissatisfied" (1) to "Very satisfied" (5). The perceived helpfulness of the modules in the treatment was rated by the patients on a 5-point scale from "Unhelpful" (1) to "Very helpful" (5). The patient also rated if, and how much, their problems had decreased during treatment using a 5-point scale from "Not at all" (1) to "Very much" (5).

Intervention and Therapist Contact

The iCBT material comprised six modules, one of which was to be completed every week for 6 weeks. The modules were (1) Psychoeducation, (2) Emotion regulation by behavioral activation and regularity in day-to-day life, (3) and (4) Improving sleep quality, (5) Cognitive restructuring, and (6) Long-term goals and relapse prevention. The modules contained theoretical information, treatment rationale, examples, work sheets, and homework assignments. At the end of each module there were questions about the theoretical content, as well as homework. The patients did not gain access to the next module until they had sent written responses to their therapist. The individual module should have been seen as a chance to learn about a topic relevant to BP-II, and a chance to try and evaluate new strategies. Patients were encouraged to spend time practicing the strategies they perceived as effective, and to incorporate them into daily life so that they could continue to benefit from them after the end of treatment. The total amount of text in the modules was slightly above 30,000 words. A secure system for asynchronous emails was used for the therapist contact. It was not restricted, for instance, the participants chose the frequency of the contact. The therapists were supervised by a clinical psychologist experienced in Internet treatment, and an effort was made to be clear about the framework early in the project, for example, what the patient could expect from the therapist. This and other features of the support were inspired by supportive accountability [31]. There was no face-to-face contact between patients and therapists.

Analyses

In order to judge feasibility, the degree of interest in the study exhibited by eligible patients, as well as dropout rate, is described. In addition, the evaluation of the 4 participants who completed the intervention is presented. In the evaluation, patients were asked to rate satisfaction, perceived decrease of problems, and helpfulness of each module on a 5-point scale. To investigate the effectiveness of the intervention on symptoms, analyses of pre-/posttest differences in depression (BDI-II), repetitive negative thinking (PTQ), and function (WSAS) were conducted. The Reliable Change Index (RCI)—defined by Jacobson and Truax in 1991 [32]—was calculated to investigate whether there was a reliable difference between depression, repetitive thinking, and function scores before and after the intervention period. For this calculation, the standard deviation and test/retest reliability of the BDI-II, the PTQ, and the WSAS were obtained from previous research [28,29,33]. The weekly scores measuring depressive symptoms (MADRS-S), sleep problems (ISI), and symptoms of (hypo)mania (AS-18) across baseline (3 weeks) and treatment (6 weeks) were graphically displayed, and visual analyses conducted, in order to detect differences in levels and trends between baseline and treatment [34]. For the primary outcome (MADRS-S) the mean of each phase—baseline and treatment—was calculated and marked on the graph as a dashed horizontal line.

Results

Treatment Feasibility

To What Extent Do Patients Show Interest and Participate in the Treatment?

As described under Participants and Procedure in the Methods section, 71 patients were invited to participate in the study based on initial screening of patient records. Of these, 18 (25%) responded and exhibited an interest in participating in the treatment. Of the 18 patients, 3 (17%) subsequently withdrew from the study and 8 (44%) were excluded with reference to

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the predefined exclusion criteria. Of the 18 patients, 7 (39%) were thus offered participation in the study, of whom 3 (43%) dropped out during baseline assessment or before the start of the intervention. Of the 7 patients, 4 (57%) started the treatment and all of them participated during the full intervention period of 6 weeks. Patients 1 and 3 completed all six modules. Patient 4 completed four of the modules and started the fifth. Patient 2 completed the first module and started the second.

To What Extent Did the Participants Experience the Treatment as Helpful?

The 4 patients who participated filled out a treatment satisfaction evaluation form at the end of the treatment period. Table 2 presents the results of their evaluations.

As can be seen in Table 2, patient 1 was very satisfied with the treatment, patient 4 was fairly satisfied, and patients 2 and 3 were neither satisfied nor dissatisfied. Patient 1 stated that her problem decreased very much as a result of the treatment. Patients 3 and 4 reported that their problems decreased a little, while patient 2 stated that her problems did not decrease at all. Patient 1 experienced all modules as very helpful. Patient 4 perceived modules 3 and 4—sleep modules—as very helpful and the other modules as fairly helpful. Patient 3 experienced modules 3 and 4 as fairly helpful and the other modules as neither helpful nor unhelpful, or fairly unhelpful. Patient 2 experienced modules 1 and 2 as fairly helpful—the only modules that patient 2 received.

In summary, 25% (18/71) of patients who were invited to participate in the study reported interest. The participants who completed more than four modules felt that their problems decreased a little, or largely, as a result of the treatment. All participants found that some or all of the modules were fairly, or very, helpful.

Treatment Effect

Can Any Symptom Change Be Observed in the Weekly Self-Reports?

The weekly ratings of depressive symptoms (MADRS-S), symptoms of (hypo)mania (AS-18), and insomnia (ISI) for the 4 patients are discussed in the following sections, and illustrated in the following Figures.

Patient 1

The weekly MADRS-S ratings showed that patient 1 had an average of 9.25 (SD 4.79) points during the 3-week baseline period and 4.7 (SD 3.7) points during treatment. During the baseline period, the scores were in a subclinical range on three of the four occasions and in the range of mild depression—value of 16—on one occasion. During treatment, all scores were at a subclinical level and the last two measurement occasions revealed a very low presence to complete absence of depressive symptoms. Both phase averages were within the range of subclinical depressive symptoms. Visually, a difference in level between the phases could be inferred. The change was gradual, indicating a long latency. For patient 1, the averages of the weekly sleep problem scores were the same—6.3 points—during the baseline period (SD 2.3) and the treatment phase (SD 4.0). The visual analysis showed a stable baseline with scores within the subclinical range. A slight increase in perceived sleep problems occurred in connection with the first week of treatment and then decreased continuously during subsequent weeks. Symptoms of hypomania were for the most part in the subclinical range, but on two occasions in the area a hypomanic episode might have been suspected for patient 1, but the symptoms soon returned to a subclinical level. Figure 2 shows the weekly estimates by patient 1 for all symptoms.

Patient 2

For patient 2, the average of the weekly scores of depressive symptoms (MADRS-S) was 7.75 (SD 4.20) points during the baseline period and 6.2 (SD 2.6) points during treatment. The baseline scores were in a subclinical range on three of the four occasions, and in the range of mild depression on one occasion—value of 14. During the treatment phase, all ratings of depressive symptoms were on a subclinical level. For patient 2, the averages of the weekly insomnia symptom scores were the same—13 points—during both the baseline period (SD 2.4) and the treatment phase (SD 3.0). During baseline, the scores were within the subclinical range, except for the first measurement where the value indicated clinically significant insomnia (ie, intermediate). During treatment, the scores varied between subclinical and clinically significant insomnia (ie, intermediate). The AS-18—symptoms of hypomania—scores were low during the whole study for patient 2, indicating no problems with hypomania or mania. Figure 3 shows the weekly estimates by patient 2 for all symptoms.

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Table 2. Results from the patient evaluation form distributed after completion of the intervention period.

Evaluation categories and responses		Patients
Treatment satisfaction		
	Very dissatisfied	
	Fairly dissatisfied	
	Neither satisfied nor dissatisfied	Patient 2, Patient 3
	Fairly satisfied	Patient 4
	Very satisfied	Patient 1
Perceived problem decrease		
	Not at all	Patient 2
	A little	Patient 3, Patient 4
	Some	
	A lot	
	Very much	Patient 1
Perceived helpfulness of module 1 [a,b]		
	Unhelpful	
	Fairly unhelpful	
	Neither helpful nor unhelpful	Patient 3
	Fairly helpful	Patient 2, Patient 4
	Very helpful	Patient 1
Perceived helpfulness of module 2		
	Unhelpful	
	Fairly unhelpful	
	Neither helpful nor unhelpful	Patient 3
	Fairly helpful	Patient 2, Patient 4
	Very helpful	Patient 1
Perceived helpfulness of module 3		
	Unhelpful	
	Fairly unhelpful	
	Neither helpful nor unhelpful	
	Fairly helpful	Patient 3
	Very helpful	Patient 1, Patient 4
Perceived helpfulness of module 4		
	Unhelpful	
	Fairly unhelpful	
	Neither helpful nor unhelpful	
	Fairly helpful	Patient 3
	Very helpful	Patient 1, Patient 4
Perceived helpfulness of module 5		
	Unhelpful	
	Fairly unhelpful	Patient 3
	Neither helpful nor unhelpful	
	Fairly helpful	Patient 4
	Very helpful	Patient 1

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Evaluation categories and responses		Patients
Perceived helpfulness of module 6		
	Unhelpful	
	Fairly unhelpful	
	Neither helpful nor unhelpful	Patient 3
	Fairly helpful	
	Very helpful	Patient 1

[a]Patient 2 only received modules 1 and 2.

[b]Patient 4 only received modules 1 to 5.

Figure 2. Weekly ratings of depressive symptoms (MADRS-S, maximum score is 54 points), symptoms of (hypo)mania (AS-18, maximum score for mania section is 36), and insomnia (ISI, maximum score is 28 points) for patient 1. The vertical line marks the start of the intervention period. Dashed blue lines indicate the mean level of depressive symptoms (MADRS-S) during the baseline period and the treatment phase.

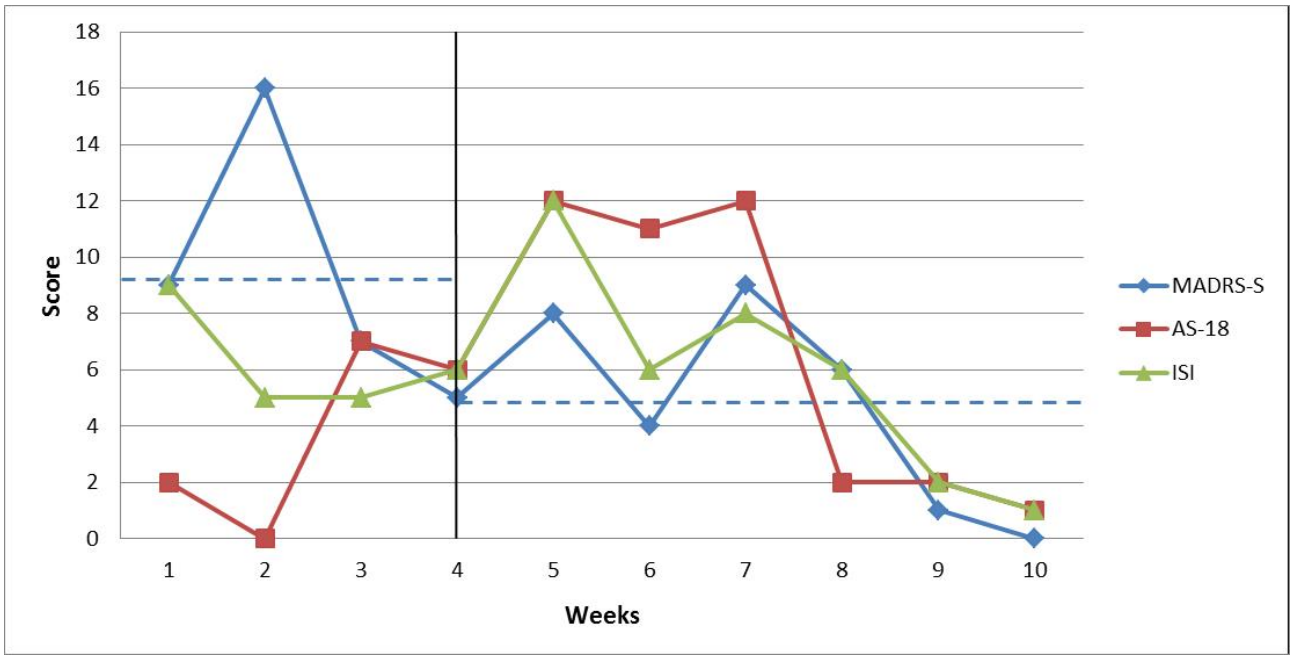

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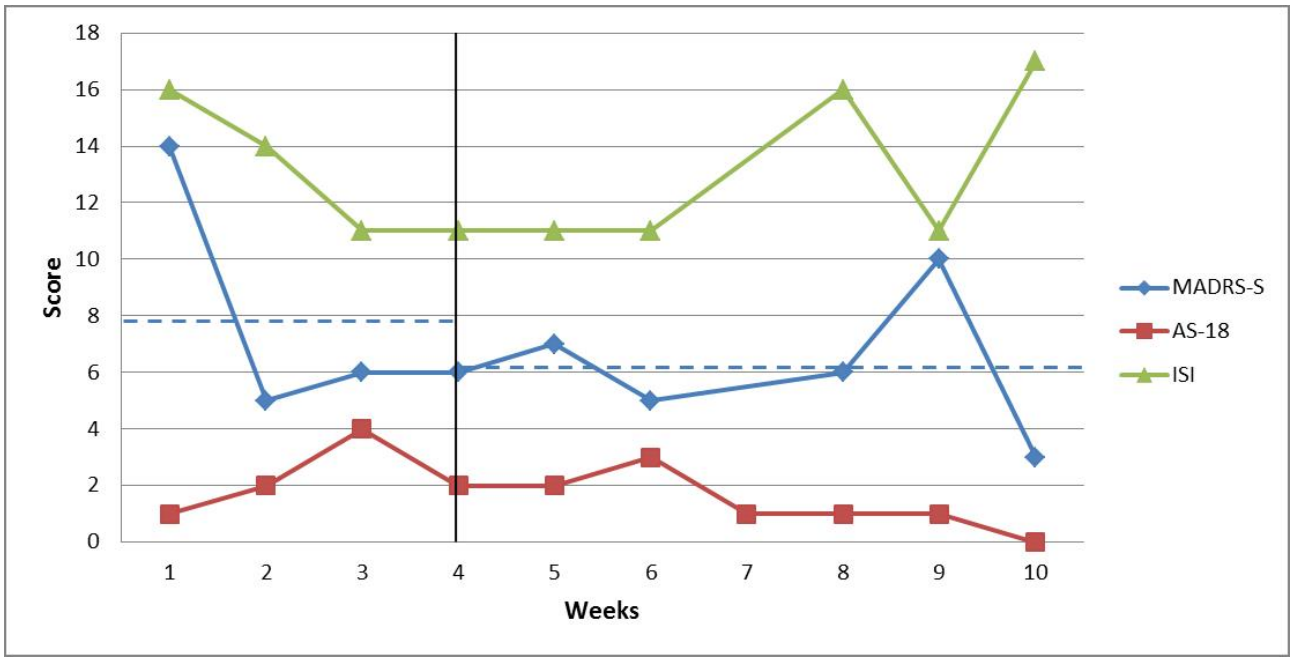
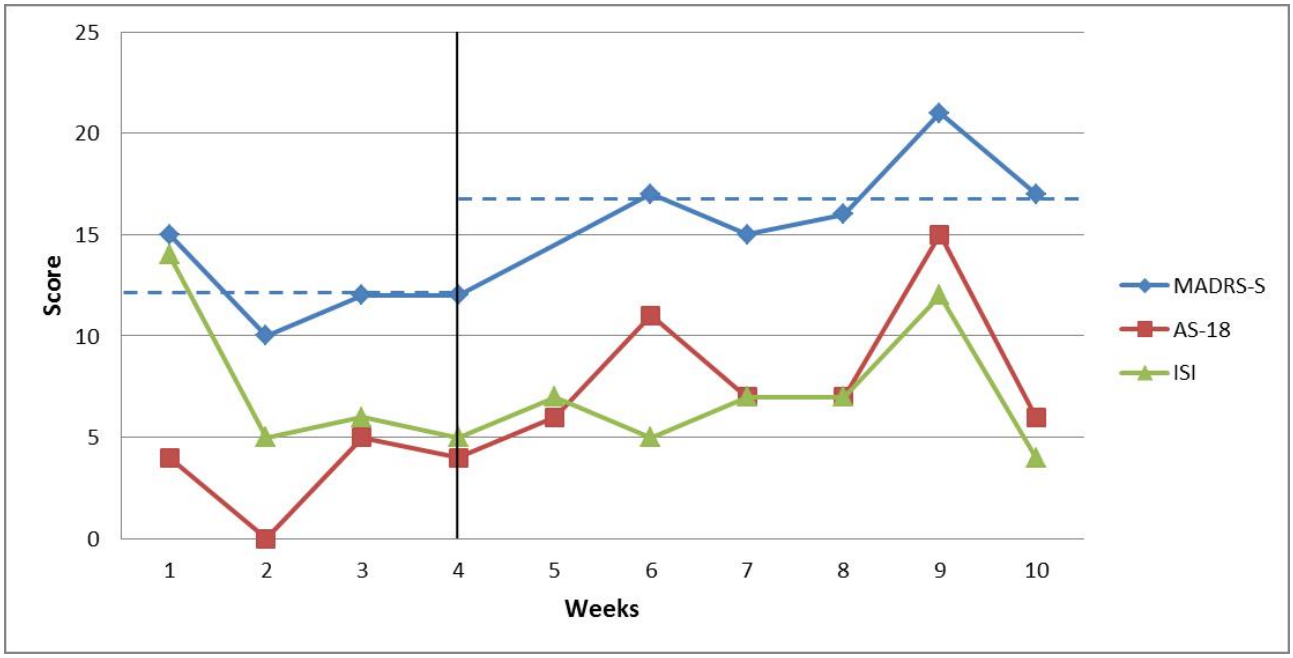
Figure 3. Weekly ratings of depressive symptoms (MADRS-S, maximum score is 54 points), symptoms of (hypo)mania (AS-18, maximum score for mania section is 36), and insomnia (ISI, maximum score is 28 points) for patient 2. The vertical line marks the start of the intervention period. Dashed blue lines indicate the mean level of depressive symptoms (MADRS-S) during the baseline period and the treatment phase.



Patient 3

For patient 3, the average of the weekly ratings of depressive symptoms was 12.25 (SD 2.10) points during the baseline period and 17.2 (SD 2.3) points during treatment. Visually, there was a change between phases, suggesting a higher level of depressive symptoms during treatment. During the baseline period, the scores were in the mild depression range on three of the four occasions and on a subclinical level on one occasion. During treatment, most values were within the mild depression range, but one value—value of 21—reached the limit of moderate depression. For patient 3, the averages of the weekly ratings of insomnia symptoms were almost identical—7.5 (SD 4.4) during the baseline period and 7.0 (SD 2.8) during treatment. These ratings were within the subclinical range during both the baseline and the treatment phase. The hypomania symptom ratings showed an increasing trend during the baseline period and the treatment phase, and at one point they were clinically significant, but returned quickly to a subclinical level. Figure 4 shows the weekly estimates by patient 3 for all symptoms.

Figure 4. Weekly ratings of depressive symptoms (MADRS-S, maximum score is 54 points), symptoms of (hypo)mania (AS-18, maximum score for mania section is 36), and insomnia (ISI, maximum score is 28 points) for patient 3. The vertical line marks the start of the intervention period. Dashed blue lines indicate the mean level of depressive symptoms (MADRS-S) during the baseline period and the treatment phase.



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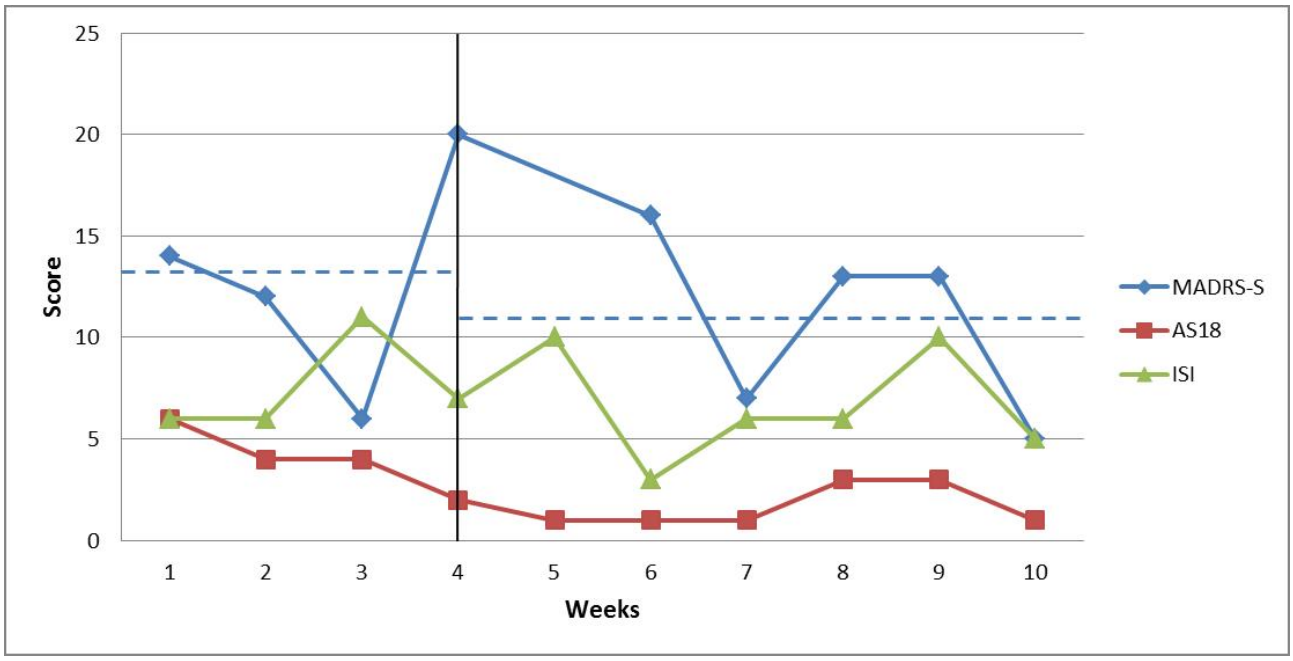
Patient 4

For patient 4, the average of the weekly ratings of depressive symptoms was 13.0 (SD 5.8) points during the baseline period and 10.8 (SD 4.6) points during treatment. The visual analysis showed a relatively high degree of fluctuation in both phases, making it difficult to draw conclusions regarding a change in level. During the baseline period, the ratings fluctuated between subclinical symptoms, mild depression, and moderate depression. During the treatment phase, the ratings varied between subclinical symptoms and mild depressive symptoms. For patient 4, the average of the weekly insomnia ratings (ISI) was 7.5 (SD 2.4) points during the baseline period and 6.7 (SD 2.8) during the treatment. The AS-18—symptoms of hypomania—ratings were low during the whole study for patient 4, indicating no problem with hypomania or mania. Figure 5 shows the weekly estimates by patient 4 for all symptoms.

Figure 5. Weekly ratings of depressive symptoms (MADRS-S, maximum score is 54 points), symptoms of (hypo)mania (AS-18, maximum score for mania section is 36), and insomnia (ISI, maximum score is 28 points) for patient 4. The vertical line marks the start of the intervention period. Dashed blue lines indicate the mean level of depressive symptoms (MADRS-S) during the baseline period and the treatment phase.



Pre-/Posttest Evaluations for All Patients

Table 3 presents the patients' pre-/posttest ratings of depressive symptoms (BDI-II), repetitive negative thinking (PTQ), and function (WSAS). Between the pre- and posttest ratings, patient 1 exhibited a reliable change on the BDI-II and the PTQ, while patients 2, 3, and 4 did not exhibit any significant changes between pre- and posttest ratings.

Table 3. Pre-/posttest evaluation on BDI-II, PTQ, and WSAS.

Patient number	Evaluation of symptoms											
	Depression (BDI-II)[a]				Repetitive thinking (PTQ)[b]				Function (WSAS)[c]			
	Pre[d]	Post[d]	RCI[e]	*P*	Pre	Post	RCI	*P*	Pre	Post	RCI	*P*
1	12	0	- 2.52	*.01*[f]	33	0	- 4.20	*<.001*	20	24	0.35	.73
2	10	1	- 1.89	.06	24	13	- 1.40	.16	14	14	0	1
3	20	25	1.05	.29	10	10	0	1	15	26	0.97	.33
4	9	6	- 0.63	.53	39	34	- .64	.52	11	6	- 0.44	.66

[a]As compared to bipolar patients (n=34) as reported in Beck et al [33], Beck Depression Inventory—Second Edition (BDI-II).

[b]As compared to depressed patients (n=45) as reported in Ehring et al [29], Perseverative Thinking Questionnaire (PTQ).

[c]As compared to mild to moderately depressed patients (n=382) as reported in Mundt et al [28], Work and Social Adjustment Scale (WSAS).

[d]Pretest value (Pre), posttest value (Post)

[e]Reliable Change Index (RCI)

[f]Significant values are shown in italics (*P*<.05).

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Discussion

Principal Findings

The results of this study indicate that for some individuals with BP-II, iCBT can lead to a decrease in depressive symptoms. Our results also revealed that there is an interest in Internet-based CBT on the part of such patients. Module completion was fairly high in 3 out of 4 cases, and the patients mostly rated the treatment modules as fairly or very helpful. On the whole, the patients who initiated iCBT were satisfied with, or neutral toward, the treatment. Of the patients, 1 reported that her problems did not decrease at all, but she only completed one module. Of the patients, 2 felt that their problems had decreased a little and 1 felt that the problems had decreased very much. Entering treatment was perceived as too demanding under current life circumstances by the 3 patients who dropped out during the baseline assessment. As there was interest in the treatment, and module completion was fairly high, we deem the feasibility of the treatment to be acceptable.

CBT has previously had a favorable outcome among bipolar patients when delivered face-to-face [35]. This study indicates that the intervention can also be effectively administered via the Internet. However, the results should be replicated in larger studies, and if found to be efficacious it could improve access to psychological treatment for many patients with a serious mental condition. We are not aware of any previous research on iCBT for BP-II, thus this study clearly adds to the knowledge about Internet-based CBT and future possibilities for treating the disorder. A study on Internet treatment of bipolar disorder type I and type II has been published recently with positive results [36]. Lauder et al found that 48% of their participants completed all the modules, which is similar to the adherence in this study.

There were some seemingly contradictory results in our study in that patients were fairly satisfied with the intervention and considered the modules helpful, but at the same time 3 out of 4 individuals perceived little or no reduction of their problems. One explanation could be that symptom reduction is not the only outcome desired by patients, which is in line with the findings from a qualitative study on an Internet-based intervention for bipolar disorder [37]. The researchers found that learning to live with bipolar disorder (ie, experience, knowledge, and skills) was just as important for some participants as reduced symptoms. The participants actually considered these two goals intertwined in creating a good quality of life.

Somewhat surprisingly, there was almost no effect on sleep problems during treatment in the 4 patients, which is in contrast to an earlier study demonstrating the effect of iCBT on insomnia [38]. However, the patients in this study suffered from BP-II and, thus, had a more severe psychopathology. In addition, their levels of sleep disturbance were rather low from the outset in most cases, and the treatment duration was only 6 weeks. Perhaps more comprehensive treatment material about sleep is necessary to improve the effect.

By communicating with the patients, we gained the impression that the treatment may need some alterations. First, we think that its duration should be longer to allow the patient more time to perform the exercises in the modules. This would also be more in line with other treatments for unipolar depression and anxiety, which often comprise 10 to 12 weeks [39,40]. There are also indications that it takes time to establish and maintain behavior change in patients with bipolar disorder [41]. A module about pharmacological treatment and side effects could have been included. Such a module was pilot-tested during development of an Internet-based psychoeducational intervention for bipolar disorder by Latalova et al and received a great deal of interest from patients [41]. Perhaps the modules about sleep would have had a greater impact if the therapists had monitored the ISI ratings more closely and used them actively in their feedback to the patients. A module could also be included that systematically aims to involve a next of kin in the treatment.

Limitations

A few limitations should be acknowledged. First, as there was no follow-up we were unable to obtain knowledge of symptom levels during the time period after the treatment. Second, we included few patients and some dropped out, therefore, our results cannot be generalized to all individuals who suffer from BP-II. Third, we relied on diagnoses from patient records instead of diagnosing the patients ourselves. This makes it likely that not all of them were diagnosed using the same (ie, standardized) procedure, although on the other hand the cases are likely to be representative in severity of patients with BP-II in a clinical setting. A strength of the study is, therefore, ecological validity as well as the fact that we used patient-rated outcome of depressive symptoms. The risk of an allegiance effect is reduced compared to clinician-rated outcome. Another strength is that the self-report measures of depressive symptoms have been validated for online use. However, complementary objective measures could have increased reliability.

More studies on this treatment are necessary. An experimental design could be used to assess the relative efficacy of the Internet-based intervention by comparing it with an established form of therapy (eg, group CBT). A study with a larger sample could possibly include patients with BP-I and BP-II. A longer follow-up time is needed and relapse, as well as hospitalization, should be included as variables in future studies.

Conclusions

This small pilot study showed that iCBT can have an effect on depressive symptoms in some patients with BP-II. This should be further investigated in larger studies.

Conflicts of Interest

None declared.

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Abbreviations

AS-18: Affective Self-Rating Scale
BDI-II: Beck Depression Inventory—Second Edition
BP-I: bipolar disorder type I
BP-II: bipolar disorder type II
CBT: cognitive behavioral therapy
hs: at bedtime

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iCBT: Internet-based cognitive behavioral therapy
ICD-10: International Classification of Diseases, 10threvision
ISI: Insomnia Severity Index
MADRS-S: Montgomery-Åsberg Depression Rating Scale—Self-rated
NOS: not otherwise specified
prn: as needed
PTQ: Perseverative Thinking Questionnaire
RCI: Reliable Change Index
RCT: randomized controlled trial
WSAS: Work and Social Adjustment Scale

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Original Paper

Bilingual Text Messaging Translation: Translating Text Messages From English Into Spanish for the Text4Walking Program

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Abstract

Background: Hispanic adults in the United States are at particular risk for diabetes and inadequate blood pressure control. Physical activity improves these health problems; however Hispanic adults also have a low rate of recommended aerobic physical activity. To address improving physical inactivity, one area of rapidly growing technology that can be utilized is text messaging (short message service, SMS). A physical activity research team, Text4Walking, had previously developed an initial database of motivational physical activity text messages in English that could be used for physical activity text messaging interventions. However, the team needed to translate these existing English physical activity text messages into Spanish in order to have culturally meaningful and useful text messages for those adults within the Hispanic population who would prefer to receive text messages in Spanish.

Objective: The aim of this study was to translate a database of English motivational physical activity messages into Spanish and review these text messages with a group of Spanish speaking adults to inform the use of these text messages in an intervention study.

Methods: The consent form and study documents, including the existing English physical activity text messages, were translated from English into Spanish, and received translation certification as well as Institutional Review Board approval. The translated text messages were placed into PowerPoint, accompanied by a set of culturally appropriate photos depicting barriers to walking, as well as walking scenarios. At the focus group, eligibility criteria for this study included being an adult between 30 to 65 years old who spoke Spanish as their primary language. After a general group introduction, participants were placed into smaller groups of two or three. Each small group was asked to review a segment of the translated text messages for accuracy and meaningfulness. After the break out, the group was brought back together to review the text messages.

Results: A translation confirmation group met at a church site in an urban community with a large population of Hispanics. Spanish speaking adults (N=8), with a mean age of 40 (SD 6.3), participated in the study. Participants were engaged in the group and viewed the text messages as culturally appropriate. They also thought that text messages could motivate them to walk more. Twenty-two new text messages were added to the original database of 246 translated text messages. While the text messages were generally understood, specific word preferences were seen related to personal preference, dialect, and level of formality which resulted in minor revisions to four text messages.

Conclusions: The English text messages were successfully translated into Spanish by a bilingual research staff and reviewed by Hispanic participants in order to inform the use of these text messages for future intervention studies. These Spanish text messages were recently used in a Text4Walking intervention study.

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KEYWORDS

text messaging; mobile phone; translating; language; focus groups; exercise

Introduction

In the United States, Hispanic adults are at increased risk for diabetes and inadequate blood pressure control as compared to white, non-Hispanic adults [1]. Obtaining regular physical activity improves diabetes and hypertension [2]. However, the Hispanic adult population has lower rates of aerobic physical activity (29.1%) compared with the non-Hispanic white population (43.1%) [3]. One area of rapidly growing technology that is being utilized to change health behaviors is SMS text messaging (short message service, SMS) [4]. Intervention studies have shown that text messages can be effectively used in improving physical activity [5,6]. Using text messaging as an intervention to promote physical activity is important to consider in the United States, as 90% of adults use mobile phones and 81% of Americans overall engage in texting. Text messaging is even higher for the Hispanic population (87%) [7], a growing population that has increased by 50% since 2000 in the United States and now represents 53 million Americans [8].

A research team, called Text4Walking has completed formative work in the development of motivational physical activity text messages to be used in physical activity intervention studies. In order to develop an initial database of physical activity text messages in English that could be used for intervention studies, the Text4Walking research team held three focus groups with adults (N=23). To promote group discussion, pictures were used that depicted walking barriers and scenarios. Participants were asked to develop text messages to encourage people to overcome barriers to walking and become more physically active [9]. Additional text messages were later added to this original database by the Text4Walking team.

The research team wanted to include the Hispanic population in their physical activity intervention work because of the low physical activity rates in Hispanics residing in the United States. The vast majority of Hispanic adults (95%) consider it important for future US Hispanic generations to be able to speak Spanish [10]. In addition, Spanish was shown to be the preferred contact language in a longitudinal research program conducted with Mexican Americans to improve diabetes self-management [11]. Therefore, in order for this population to be part of future Text4Walking intervention studies, the team needed to translate existing English text messages into Spanish, to provide participants with a choice of receiving either Spanish or English text messages. However, no study has been located that specifically addresses the process of translating motivational physical activity text messages from English into Spanish.

Translation is an activity that inevitably involves at least two languages and two cultural traditions. The cultural implications for translation may take several forms ranging from lexical content and syntax to ideologies and ways of life in a given culture [12]. Therefore, the translator/facilitator in a research group has to decide on the importance given to certain cultural aspects. Important components to consider with bilingual interventions are bilingual and bicultural facilitators and materials, inclusion of family-based activities, literacy appropriate materials, social support, and a clear understanding of Hispanic cultural values [13].

Federal regulations in the United States require that information about participation in research be presented in a language understandable to the potential subject or their representative [14-16]. The informed consent process is one of the most basic concepts of human subject research. In the *Belmont Report*, the ethical principle of Respect for Persons requires that all subjects be given the opportunity to choose what they will or will not participate in [17]. Consenting requires adequate information, comprehension, and voluntariness. Thus, to meet the requirements of informed consent, if a study's focus is a population whose principle language is not English, consent documents must be translated into that language. During the consent process an interpreter should be available as well. Each organization's Institutional Review Board will require verification that the translated consent documents are true translations. Most organizations require a certified translation. It is important for researchers to know how their local policies meet federal requirements [18]. The purpose of this study was to translate a database of English physical activity text messages into Spanish and review those text messages with a group of Spanish speaking adults to inform the use of these text messages in an intervention study.

Methods

Design, Sample, and Setting

A translation confirmation group was used for this study [19]. Eligibility criteria for this study included being an adult who spoke Spanish as their primary language, 30 to 65 years old, not engaging in regular physical activity, with no health problems that prohibited them from increasing physical activity, and familiar with texting. The group met at a church site in an urban city with a large population of Hispanics as more than one-fourth (28%) of the city self-identifies as Hispanic [20].

Procedures

The consent form and study documents, including the existing English physical activity text messages, were translated from English into Spanish initially by a native English speaker fluent in Spanish. These translated messages were then reviewed by a native Spanish speaker fluent in English. These bilingual research team members then gained consensus on the translated documents. The team members used Columbian Spanish for translation. After this, all study documents were reviewed, revised as needed, and approved by a certified translator. Rush University Institutional Review Board approved the study.

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The 1.5 hour session was co-moderated by a bilingual doctoral level researcher and a master's prepared researcher. An English speaking doctoral level experienced focus group researcher was also present. A research assistant recorded participant contributions on a flip chart. The translated text messages were placed into PowerPoint, accompanied by a set of 44 culturally appropriate photos depicting barriers to walking, as well as walking scenarios. Prior to group activity, participants completed a brief survey regarding questions about their text message usage. A general introduction was then provided after which participants were placed into smaller groups of two or three. Each small group was asked to review a segment of the 246 translated text messages for accuracy and meaningfulness. Participants were given handouts with specific translated text messages upon which they were asked to write their comments. After the break out, the group was brought back together to review the text messages.

Data Analysis

The bilingual group leaders along with an experienced qualitative researcher reviewed three sources of data. First, they reviewed the handwritten participant notes on the handouts. Second, they reviewed the audiotape transcripts that were first transcribed into Spanish and then translated into English. Third, they reviewed the flip chart notes containing group reflections. A consensus was reached by the three researchers who reviewed the data as to when and how to edit any of the translated text messages, as well as determining which text messages should be added as a result of participant suggestions.

Results

Of the 13 adults screened for the study, 5 were either unable to attend the group or were ineligible. As a result, 8 Spanish speaking adults participated in the study (Table 1).

Table 1. Demographics and text message use.

Demographics	
Age (years), mean (SD)	40 (6.3)
Gender (%) – women	63
Ethnicity (%) – Hispanic	100
Education	
Some high school or less (%)	37.5
Completed high school (%)	37.5
Some college or completed college (%)	25
Body mass index, mean (SD)	32.25 (5.78)
Text message use	
Mobile phone has text messaging capability (%)	100
Unlimited text messaging plan (%)	88
Sends > 4 SMS text messaging weekly (%)	75
Receives > 4 SMS text messaging weekly (%)	63
Ease of use of text messaging function (%)	
Very easy	50
Somewhat easy	38
Neither easy nor difficult	12
Somewhat difficult	0
Very difficult	0

Participants were engaged in the group. They thought that text messages could motivate them to walk more and suggested that receiving two text messages a day would be motivational for them. Twenty-two new text messages were added to the original database of 246 translated text messages, which resulted in a total of 268 text messages. While text messages were generally understood and seen as culturally appropriate, specific word preferences were seen related to personal preference, dialect, and level of formality which resulted in minor revisions to four text messages. Table 2 provides examples of 25 of the translated text messages from the approved database.

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Table 2. Examples of Spanish text messages translated from English.

English text message	Spanish text message
Get up. Today is a good day to walk.	Levántase. Hoy es un buen día para caminar.
Encourage family walking	Anime a la familia a caminar juntos
Activity begins with childhood and never ends	La actividad empieza con la niñez y nunca termina
Get up and start walking	Levántese y empiece a caminar
Walk for peace of mind	Camine para despejar la mente
Enjoy nature – walk	Disfrute de la naturaleza. Camine
Walking is exercise – you can do this!	Caminar es ejercicio - ¡usted puede!
Increase steps today – hike at a park	Aumente sus pasos hoy - tome una caminata en el parque
Get out to walk	Salga a caminar
Eat less. Walk more	Coma menos. Camine más.
Walk with the family	Camine con la familia
Get out and enjoy the day	Salga y disfrute del día
Take some me time – walk	Dedique tiempo para usted
Make leisure time a healthy time	Haga su tiempo libre un tiempo saludable
Schedule time to walk	Reserve tiempo para caminar
Walk around, look around and be safe	Camine, observe y manténgase seguro
Walk and think about life	Camine y piense sobre la vida
Challenge yourself and walk a little further	Póngase la meta de caminar un poco más lejos
Walking daily helps to maintain walking	Caminar diariamente ayuda a mantener el hábito de la caminata
Encourage others to walk with you by exploring as you walk	Anime a otros a que caminen con usted mediante explorar cuando camina
Walk with the kids	Camine con los niños
Relax by walking	Relájese caminando
Take a walk and clear your mind	Salga a caminar y despeje la mente
Get out and move about	Salga y manténgase active
Don't sit still, time doesn't	No se siente por mucho tiempo - el tiempo no espera

Discussion

This study demonstrated a method whereby English motivational physical activity text messages could be successfully translated into Spanish by a bilingual research team and then reviewed with Hispanic participants in order to inform the use of these text messages in a future intervention study. It is important to use culturally appropriate text messages translated into Spanish to promote healthy behavior changes in the Hispanic population. While intervention sustainability is still a challenge, there is now an opportunity for text messaging programs to be used in the Hispanic population to improve health [21-23]. When ready to be used in the public policy arena, text messages need to be reviewed for both cultural and linguistic appropriateness [24].

This study had some limitations. The sample size was small, from one geographic location, and participants self-selected to be in the study. However, qualitative research is not conducted so that findings can be generalized to other populations. The purpose of this study was to review a translated set of text messages for use in a future intervention study.

Developing culturally appropriate text messages necessitates the use of bilingual and bicultural facilitators and materials to facilitate the development of tailored text messaging [13]. By assuring cultural appropriateness, this study demonstrated an effective method to translate and review physical activity text messages. The research team recently successfully included these Spanish text messages in a Text4Walking intervention study.

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Authors' Contributions

Dr Buchholz was the lead writer on this manuscript. Dr Sandi and Dr Ingram advised and wrote on the cultural aspects of the study. Dr Welch advised and wrote on the IRB aspect of the study. Ms Ocampo advised and wrote on the Spanish text message aspect of the study.

Conflicts of Interest

None declared.

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Original Paper

Men's Responses to Online Smoking Cessation Resources for New Fathers: The Influence of Masculinities

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Abstract

Background: Smoking cessation is the single most important step to preventing cancer. Drawing on previous research, Web-based resources were developed to complement a program to support expectant and new fathers to quit smoking.

Objective: The objectives of this research were to: (1) describe the responses of expectant and new fathers who smoke or had recently quit smoking to the website resources, and (2) explore how masculinities shape men's responses to and experiences with online smoking cessation resources.

Methods: Using semi-structured, individual face-to-face interviews, the Dads in Gear Web-based resources were reviewed and evaluated by 20 new fathers who smoked or had recently quit smoking. The data were transcribed and analyzed using NVivo 8 qualitative data analysis software.

Results: We describe the fathers' reactions to various components of the website, making connections between masculinities and fathering within 5 themes: (1) Fathering counts: gender-specific parenting resources; (2) Measuring up: bolstering masculine identities as fathers; (3) Money matters: triggering masculine virtues related to family finances; (4) Masculine ideals: father role models as cessation aids; and (5) Manly moves: physical activity for the male body.

Conclusions: A focus on fathering was an effective draw for men to the smoking cessation resources. The findings provide direction for considering how best to do virtual cessation programs as well as other types of online cancer prevention programs for men.

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KEYWORDS

Cancer prevention; smoking cessation; gender; men's health promotion; fathers; oncology

Introduction

Tobacco use remains one of the leading causes of cancer death among men [1-3]. The links between smoking and cancer are irrefutable, and secondhand smoke is also a proven cause of lung cancer in nonsmoking adults [1-2]. Smoking cessation (SC) programs are the most cost-effective interventions to decrease cancer incidence, and there is growing evidence that gender-specific and gender-sensitive approaches can promote SC [4]. There is also a recognized need for men-friendly health promotion interventions that mobilize positive aspects of masculinities and gender relations to enhance men's well-being [5,6]. However, a systematic review of SC programs targeting men revealed that few men-specific SC interventions exist [7].

Men's smoking decreases their partners' success in quitting smoking and maintaining a quit during pregnancy and the

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postpartum period [8-11], negatively impacts the health of their children [12-14], and triples the chances of their children smoking [15]. Becoming a father is a significant life transition, which challenges men to reconcile their protector and provider roles with continued smoking [5,8,16-17]. To maximize SC when men's aspirations to be good fathers and role models for their children are at odds with smoking, we designed a targeted 8-week group program, Dads in Gear (DIG) [4]. The DIG program uses men-friendly approaches to integrate SC support, fathering skills, and healthy living (ie, physical activity and healthy eating) to increase the success of quitting. This novel approach drew on our research findings [16,18-20] and participants' suggestions that peer support was key to SC.

Although the focus of the DIG program facilitates peer support in a face-to-face group format, emergent literature suggests that integrating Web-based technologies can aid feasibility and increase accessibility and dissemination of men's health promotion programs [21-24]. Accordingly, a suite of online resources were developed to augment and supplement the DIG program in order to: (1) offer easily accessible resources, (2) provide content to support and sustain men's self-management, and (3) facilitate an online community of fathers who want to quit smoking (see Figure 1).

The three focus areas of the DIG website were smoking cessation (eg, Being a Smoke-free Dad), fathering (eg, Being a Dad), and healthy living (eg, Being a Healthy Dad). The resources affirmed fathering and included a variety of avenues toward SC, avoiding the stigma, guilt, and shame associated with parental smoking. Included among the resources were YouTube-style videos that incorporated fathers' testimonials about quitting smoking; interactive quizzes related to fathering, fitness, and smoking; infographics that translated information on a variety of topics, including managing cravings, healthy eating, and the benefits of exercise; and a webpage for fathers to share their own stories. The resources were initially reviewed by experts in men's health, smoking cessation, and Web-based technologies, and refined based on their feedback. The purpose of the current research and this article is to: (1) describe the responses of expectant and new fathers who smoke or had recently quit smoking to the online DIG resources and, (2) explore how masculinities shape men's responses and experiences to online SC resources.

Figure 1. Dads in Gear website [25].

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Methods

Recruitment

The DIG website resources were pilot-tested with 20 expectant and new fathers who were interested in quitting smoking or who had recently quit. The study took place in 2 urban centers in British Columbia, Canada. Following ethics approval, fathers were recruited using advertisements on social media (eg, Twitter, Facebook), online media outlets, and printed flyers in community settings. Participants' demographic characteristics are included in Table 1.

Semi-structured, 3-hour long, individual, face-to-face interviews were conducted by 2 researchers, 1 acting as a facilitator and 1 as note-taker. Following written consent, the fathers completed a short questionnaire to collect data on smoking patterns and demographics, and then engaged in 15 minutes of self-directed browsing of the DIG website. They were asked to "think aloud" as they looked through the website and completed online activities. Field notes were used to capture fathers' nonverbal behaviors and engagement with the website. The fathers then completed a set of directed tasks and responded to questions about the efficacy, appeal, and usability of the website resources. Finally, open-ended questions gathered men's perceptions of their overall experiences using the website. The men were provided with an honorarium of $150 CAD. The interviews were digitally recorded, transcribed, and reviewed for accuracy. The field notes were integrated into the transcriptions to contextualize the data.

Table 1. The participants' demographic characteristics and smoking history.

Demographic characteristics	No. of participants (N=20)
Age range, y (mean=33 y)	
20-29	8
30-39	5
40-49	4
50-59	1
Unknown	2
Ethnicity	
Euro-Canadian	16
First Nation	2
Other	2
Education	
Incomplete high school	5
High school	5
Postsecondary	9
Other	1
Employment	
Working	12
Not working	7
Student	1
Marital status	
Married	5
Common-law	11
Single	4
Parental status	
Have children	19
Expecting first child	1
Avg age of youngest child, years	4.54 y
Smoking history	
Mean age started smoking, years	16.5 y
Mean cigarettes/day when smoking	9.3

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Data Analysis

The analyses involved a close reading of the data by the research team to identify the prevailing meanings, experiences, and views of the fathers. Through an iterative process of discussion and in-depth review of the data, the team developed an analytical framework that delineated major categories and subcategories [26]. The coding schedule derived from this process was used by individual team members to code initial transcripts and, based on further discussion, consensus was reached on minor revisions to refine the framework. All the data were then coded using NVivo 8 qualitative data analysis software. Data segments that were coded to each category were then reviewed, compared, and examined using a gender lens to identify patterns, meanings, and themes. Critical reflection throughout the analyses generated rich and nuanced findings.

Results

Overview

Overall the participants responded positively to the DIG website and Web 2.0 resources. The men presented themselves as wanting to be good fathers and showed great interest in fathering and "being a dad," healthy living, and strategies and tools for reducing and quitting smoking. Connections between masculinities and fathering are reflected in 5 themes describing men's reactions to the various components of the website: (1) Fathering counts: gender-specific parenting resources; (2) Measuring up: bolstering masculine identities as fathers; (3) Money matters: triggering masculine virtues related to family finances; (4) Masculine ideals: father role models as cessation aids; and (5) Manly moves: physical activity for the male body.

Fathering Counts: Gender-Specific Parenting Resources

The DIG home page attracted men with the promise of information specific to their interests in being good fathers. Generally confident in their fathering ability, the participants also expressed uncertainty about their knowledge. A 25-year-old father of an infant wondered if he really was the great dad that he aspired to be, saying, "I'm always going, 'Am I a good dad?' I wanna be a good dad. How good of a dad am I?"

The participants gravitated toward learning content that provided new activities for involvement with their kids and for keeping their kids healthy and safe. Several men indicated that being able to access fathering information on their own was important so that they did not need to rely on their female partners. A 25-year-old father of 3 stated, "I don't really like having to go to my kids' mom to ask her things, 'cause then I kinda feel like I'm not as good of a parent as her." This father believed he was healthy despite smoking a pack of cigarettes a day, and though he skipped over the health-related content, he was enthusiastic about the variety of resources for fathers. He said, "It wouldn't really matter what kind of a person you were, or what your interests were . . . there's something [here] for any dad."

In contrast to gender norms promulgating the notion that men are unconcerned about nutrition [27], with few exceptions the men genuinely appreciated the cooking and nutrition segments. Participants actually lobbied for more nutrition information and quick healthy recipes. A 28-year-old father, who smoked a pack a day and was raising his 4 children alone, talked about his desire for better nutrition and how the DIG website had already provided him with new healthy food information:

> *I'm by myself, so I always need something new to cook, right? Cause the kids, you can't just keep feeding them the same thing all the time. And the different nutrition . . . like the different colors. . . . I didn't really know that.*

A 22-year-old father, one of the youngest and lightest smokers in the study, also responded enthusiastically after viewing the cooking and nutrition segments:

> *I wanna be a healthy father, and I know a lot of kids are picky on what to eat and it's really hard to get them to have certain nutrients and vitamins in their food. So blending up some soup with, like, peas and ginger, those are both really healthy. . . . I learned quite a bit, like the more colors, the more nutrition you get. That can make a healthier eating family.*

A 41-year-old lone parent of 3, who quit smoking a few years ago, endorsed the Healthy Dad section of the website, stating that he would go back to it to try out the recipes. He positioned himself as a "passionate" father, and redefined domestic work as a masculine project whereby competence was capital within the context of fathering:

> *I'm a stay-at-home dad, or a full-time dad, whatever you wanna call it. Perhaps a father that's passionate about being a father would come back for this resource again and again.*

Only 1 man—a 55-year-old father of 5 who had smoked for 35 years and had no intention of quitting—criticized the DIG website as more suitable for "moms." He separated himself from images of fatherhood amid feminizing domestic responsibilities that he perceived as counter to traditional masculine ideals—practices he espoused as being features of a "typical guy." Nevertheless, he responded positively to the Cooking Pea Soup video featuring a proficient male chef (and father), saying, "Now I could see this [making soup] 'cause I like cooking." Here cooking was aligned with expertise and choice, which draws on traditional male ideals of autonomy and control.

Measuring Up: Bolstering Masculine Identities As Fathers

The DIG website included interactive quizzes and polls related to smoking cessation, fathering, and healthy living. Most participants enjoyed completing the quizzes and comparing their knowledge with other fathers. Some men stated that the quizzes and polls were the best part of the website. A 33-year-old father of 3 suggested:

> *I have an interest in what other dads [are saying] and what the statistics are, basically how I relate in thoughts to others and what's the No. 1 reason for quitting smoking, 'cause I want to apply them in my own life.*

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Many men expressed pride and appreciation when their scores validated and/or directly complimented their parenting skills. A 41-year-old father of 2 showed delight in the "dad score" he received, exclaiming, "I must be a good dad. I got a 5! Woo-hoo! Best thing I've heard all night." This same father explained that the interactive polls and quizzes on the website were "reassuring that, hey, I'm a pretty normal guy. . . . I think some guys like to do the quizzes and sort of see how they match up or measure up, or to see how they're doing." Validation that they were capable fathers was viewed as important, as a 25-year-old father of an infant explained:

> *That was a good reinforcement to let you know that you're probably doing better than you thought you were. . . . Like, for me, I wanna be a good dad. But you don't really know [how you are doing], because there's no real, like, grade, or no real landmarks, or no real milestones that say you are a good dad or a bad dad.*

Another man, a lone parent more confident in his fathering skills than other participants, also stated that the quiz scores provided important affirmation, adding, "I'm 95% sure I'm doing the right thing, but there's still 5% of doubt."

Money Matters: Triggering Masculine Virtues Related to Family Finances

The DIG website component with the most impact was the interactive Smoking Calculator, an SC resource. The calculator prompted men to enter the number of daily cigarettes they smoked and the cost per carton. It then generated the monthly and annual dollar amount they spent on cigarettes. This number never failed to elicit shock at the amount of money they were spending on cigarettes. High expenditures on tobacco were particularly meaningful to men for whom financial success and related achievements (eg, providing for a family, buying a car) were important to fulfilling the breadwinner role.

One participant who smoked 15 cigarettes per day, a 23-year-old father of 2 young children, reacted strongly to estimates provided by the calculator by exclaiming loudly, "That is disgusting! Almost $6,000 [CAD] a year! On cigarettes! Holy crap! That makes me sick to my stomach! That's like double what I thought I spent!" Similarly, a 28-year-old father of 1 child expressed dismay, albeit in a more restrained way, saying, "[I spend] $3,100 [CAD] per year. Staggering. . . . Like, that's your money. That's a lot of money." This new information prompted many to reflect on the benefits of quitting smoking. A few participants found the calculator so persuasive they suggested that it should have a more prominent placement on the DIG website.

Masculine Ideals: Father Role Models As Cessation Aids

The Smoke Free Dads section of the website offered video testimonials from real-life fathers who had quit smoking. The most popular testimonial, David's Story, featured a contemporary, fit-looking father talking about his successful quit and how thinking about his family helped him deal with cravings. The video purposely positioned a focus on fathering and being a father as a successful quit strategy. Most participants watched the video with interest and remarked how David inspired them to think about their own quitting. For example, a 22-year-old father who had smoked for 10 years described how he connected to David as an authentic role model:

> *I just watched a video of Dave talking about quitting smoking . . . it's pretty heart-warming. And I think that's one of the videos that will help me, encourage me to quit smoking. Because I was raised by family that smoked while I was younger, too, and that might be 1 of the reasons why I smoke. So, I don't want my daughter to start smoking because she sees me smoking.*

A 33-year-old father who had smoked for 20 years confirmed that he found the notion of using fatherhood as a cessation aid a novel approach:

> *. . . [B]ecause the less time I spend smoking, the more time I'm gonna be spending with my kid, right? I think it's good, I've never seen it before, so I'm gonna try it . . . just supporting the idea of getting out and doing things with your children instead of smoking's pretty big.*

The few participants who dismissed or rejected David as credible espoused more traditional masculine ideals and presented themselves as committed smokers. These men made it clear that they could not identify with David or contemporary discourses of involved fathering. For example, the 55-year-old father of 5 children stated:

> *I think there's a big misconception about dads. And this stuff with them lying in the park, playing with the kids all the time. Going back a million years, dads go out, make the money, bring it home . . . the mammoth, or whatever they're cooking that night. Right. And the mums do all this [child care] stuff.*

A 37-year-old father of 2 who had smoked for 20 years dismissed the Tips on Fathering video by stating that he couldn't trust a man wearing an earring and "sounding like a hippie," thereby distancing himself from such masculine tropes. Other men who rejected David's Story or the underlying relational approach reflected in the website used the argument that the videos or website lacked "hard facts" or new, helpful strategies for quitting. Curiously, the medical facts about smoking and cancer did not appear to threaten their current smoking practices.

Manly Moves: Physical Activity for the Male Body

The exercise videos and fitness poll components evoked the widest range of responses from the men. These website components focused on the importance of regular physical activity to men's health and as an aid to cessation, and the components were intended to prompt men to consider how they could integrate physical activity with their responsibilities as fathers. For example, in one video a father pushes a stroller with his infant through the park and does step-up exercises on bleachers while his baby sleeps. Although most of the men presented themselves as sensitive and sensible fathers, when it came to exercise, stereotypical masculine gender norms that frame men as strong and tough trumped their responses. Several men mocked the video, which demonstrated how fathers could

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exercise with their baby in tow, and criticized the video for portraying exercise that was not vigorous enough. A 43-year-old father of 3 who had quit smoking scorned the video as "too easy" saying, "I dunno if I'd consider it a workout, 'cause this is just everyday exercise that you do with your children." The baby stroller in the video may have tested the degree to which men could relate to the content, suggesting that strollers and workouts in the same frame were not compatible with the types of physical exertion that provide opportunities for men to challenge themselves.

The suggestions men gave for enhancing the physical activity components of the website highlighted the desire for toughness, competition, and physical performance—all of which align to masculine ideals about what constitutes exercise. A 25-year-old father, while applauding the wide range of workout ideas on the website, stated that for him, exercise was synonymous with lifting weights or using weight machines. Overall, the men were less interested in aerobic workouts such as running or cycling, and instead focused on building muscular strength. A 34-year-old father said, "Yeah, I don't know if I'd do this. I'd rather just use weights."

Several men were uninterested in physical activity of any kind and distanced themselves from prescribed workouts with performance evaluations and outcomes. A 37-year-old father of 2, self-described as "lazy," said that listening to a fit man tell him how to work out just "pisses me off." This father refuted the legitimacy or motivating influences of such "coaching" or the need to perform physically to claim prowess. Although physical activity to promote cardiovascular fitness was the hardest sell of all the DIG components, it was relevant to a few smokers who were motivated to quit or had already engaged in quitting. For instance, a 33-year-old father of 3, one of the few men who said he wanted to quit for his health, expressed interest in cardio-based workouts. After taking the fitness poll, this father stated that it motivated him because he liked to know "what the going trend is" and "because cardio is something I would like to do, it would encourage me to do it more."

Discussion

Principal Findings

The potential of the Internet to engage men with their own health has been touted as an important antidote to men's reticence in taking up professional medical services [21]. Indeed, in the context of smoking, stigma exists, rendering many men more likely to deny or conceal their smoking rather than seek "in-person" help toward SC. In addition to providing anonymity, tone and content are lynchpins to engaging men with online SC programs. The current study findings confirmed 3 features as central to online resources for fathers who smoke: (1) a focus on fathering was an effective draw to an SC website for new fathers, (2) nestling masculine virtues of strength and compassion with fathering were conduits for SC among men invested in protecting and providing for their families, and (3) the Internet provided acceptable and accessible avenues for men to find and critique an array of health-promoting strategies that are tangential to and directly target SC. Each of the aforementioned features should also be understood as provisional; some content was taken up, some was dismissed. Indeed, the influence of content varies depending on: (1) the readiness of fathers to take on SC, (2) their buy-in to contemporary fathering discourse and alignments to manly ideals about physical activity, and (3) the believability of our representations of those ideals. In this study we have offered insights into what, as well as why, some content of the DIG website engaged fathers who smoke, but want to quit.

Beyond pretesting, from which the current study findings are drawn, formal, longitudinal evaluations are vital to adjust content and make empirical claims of effectual men's SC interventions. While Oliffe et al have suggested that Google and YouTube analytics are useful for monitoring the general traffic to men-centered health websites and specific online content [28], there is a need to provide greater empirical assurances about the tangible benefits derived by end-users. Based on the findings from the current study, we suggest 2 key considerations in designing evaluation strategies for men's Web-based SC interventions. First, many SC interventions are judged entirely on their ability to deliver successful quits. However, interventions are often focused on pre-contemplative and contemplative stages of change in the hope of driving men's preparation and actions toward the maintenance of behavior change—or in our specific context, sustained SC [29]. In this regard, the expectations and, therefore, the evaluation criteria should be adjusted to capture the stage of change as a means to more reasonably report the impact of specific content and Web pedagogies. Second, it is important to recognize the great diversity that exists within the category of fathers and how this influences the uptake of online SC resources. Expanding the resources to allow users to meet their specific needs/preferences and address a range of masculinities is therefore a key element. Rather than espousing a one-size-fits-all SC intervention, the current study findings demonstrate the usefulness of a multipronged approach to resonate with the diverse masculine ideals embodied by fathers.

Conclusions

The current study findings add to the nascent body of knowledge about how becoming and being a father represents an opportunity to engage men in SC. Moreover, offered here are some insights for how that might be achieved online. In accord with previous research distilling men's health promotion program principles [4], Web platforms can provide mechanisms for engaging fathers in SC. The challenge remains to better understand and account for end-user outcomes and thoughtfully consider how best to do virtual SC programs as well as other types of cancer prevention programs for men.

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Authors' Contributions

JB and JO conceived and designed the study. GS and AC collected data. GS, AC, and MK analyzed data. JB, JO, GS, MK, and AC drafted sections of the manuscript. All authors contributed in the review and revision of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DIG: Dads in Gear
SC: Smoking cessation

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Original Paper

Usage and Users of Online Self-Management Programs for Adult Patients With Atopic Dermatitis and Food Allergy: An Explorative Study

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Abstract

Background: Two online self-management programs for patients with atopic dermatitis (AD) or food allergy (FA) were developed with the aim of helping patients cope with their condition, follow the prescribed treatment regimen, and deal with the consequences of their illness in daily life. Both programs consist of several modules containing information, personal stories by fellow patients, videos, and exercises with feedback. Health care professionals can refer their patients to the programs. However, the use of the program in daily practice is unknown.

Objective: The aim of this study was to explore the use and characteristics of users of the online self-management programs "Living with eczema," and "Living with food allergy," and to investigate factors related to the use of the trainings.

Methods: A cross-sectional design was carried out in which the outcome parameters were the number of log-ins by patients, the number of hits on the system's core features, disease severity, quality of life, and domains of self-management. Descriptive statistics were used to summarize sample characteristics and to describe number of log-ins and hits per module and per functionality. Correlation and regression analyses were used to explore the relation between the number of log-ins and patient characteristics.

Results: Since the start, 299 adult patients have been referred to the online AD program; 173 logged in for at least one occasion. Data from 75 AD patients were available for analyses. Mean number of log-ins was 3.1 (range 1-11). Linear regression with the number of log-ins as dependent variable showed that age and quality of life contributed most to the model, with betas of .35 (P=.002) and .26 (P=.05), respectively, and an R^2 of .23. Two hundred fourteen adult FA patients were referred to the online FA training, 124 logged in for at least one occasion and data from 45 patients were available for analysis. Mean number of log-ins was 3.0 (range 1-11). Linear regression with the number of log-ins as dependent variable revealed that adding the self-management domain "social integration and support" to the model led to an R^2 of .13. The modules with information about the disease, diagnosis, and treatment were most visited. Most hits were on the information parts of the modules (55-58%), followed by exercises (30-32%).

Conclusions: The online self-management programs "Living with eczema" and "Living with food allergy" were used by patients in addition to the usual face-to-face care. Almost 60% of all referred patients logged in, with an average of three log-ins. All modules seemed to be relevant, but there is room for improvement in the use of the training. Age, quality of life, and lower social integration and support were related to the use of the training, but only part of the variance in use could be explained by these variables.

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KEYWORDS

self-management; Internet; food allergy; atopic dermatitis

Introduction

Atopy refers to the genetic tendency to develop allergic diseases such as atopic dermatitis (AD), allergic rhinitis, asthma or food allergy (FA). Allergic diseases are common in children in the age group up to twelve years; a study showed that at twelve years 58% of the children had AD, asthma, and/or rhinitis at some time [1]. The prevalence of doctor-diagnosed FA is estimated to be 3-8% in children and 1-3% in adults [2]. The prevalence of AD in the Netherlands in children under six years of age is 11.3%, while in adults the prevalence is 2.3% [3]. AD as well as FA has a negative impact on quality of life [4-7].

Technological self-management systems for patients with chronic diseases can help them to understand and monitor their condition, and support patients in achieving behavioral change [8]. Self-management is defined as the individual's ability to manage symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent to living with a chronic condition [9]. Previous studies have shown that interactive eHealth technologies contribute positively to health care for patients with a chronic illness, realizing increased patient-provider communication, positive impact on behavioral change, improved therapy adherence, increased empowerment, and cost reductions [10-12].

We previously developed two online self-management programs based on scientific guidelines and professional experience for patients with AD or FA. The programs were aimed at helping patients cope with their condition, follow the prescribed treatment and deal with the consequences of their illness in daily life. Both programs "Living with eczema" [13], and "Living with food allergy" [14] have a version for adult patients and a version for parents of young children with AD or FA. The modules of the FA program are: (1) What is FA; (2) How is it diagnosed; (3) What to do in case of an allergic reaction; (4) Diet & food allergy; (5) Cross-reactivity; and (6) Coping with FA in daily life. The AD program has the following modules: (1) What is AD; (2) Treatment of AD; (3) Communication; (4) Coping with itch; and (5) Coping with AD in daily life. The programs are in addition to the care of the general practitioner (GP) or medical specialist and were developed in collaboration with patient associations. Both programs are accessible for all Dutch patients after referral to the program by the treating physician, dietician or nurse. Both programs consist of several modules with information, patient experience stories, videos, and exercises with feedback.

In 2010, a feasibility study of the self-management programs for adults took place to explore the usefulness and ease of use of the training. This was based on the Technology Acceptance Model (TAM) developed by Davis [15]. According to this TAM the perceived usefulness and perceived ease of use predict the acceptance and use of technology. The feasibility evaluation showed that both patients and caregivers considered the online training useful and easy to use and they appreciated the content of the training [16]. However, the feasibility study was carried out in a small sample of patients and caregivers and the use of both programs in clinical practice is unknown.

Therefore, the primary objective of this study was to explore the use and characteristics of adult visitors to the online self-management program "Living with eczema" and "Living with food allergy" in order to increase and optimize the use of the program in daily practice. The secondary objective was to investigate the factors related to the use of the program.

Methods

Study Design

A cross-sectional research design was used to explore the use of two online self-management programs among patients with AD or FA. The measure of usage was the total number of log-ins in the study period. Data of usage was obtained during the patient's use of the program and was embedded into the program design. Patients had access to the program for a three month period. The number of log-ins was measured for all participants of both programs, and the number of hits on the system's core features was measured only among the participants who provided informed consent. To explore the patients' characteristics a questionnaire-based online survey was conducted on a convenience sample of patients attending the online self-management programs. All patients who provided informed consent were included, and the questionnaires were incorporated at the start of the program.

Study Participants and Recruitment

Study population consisted of adult patients with FA or with AD who received an account for one of the online programs. To investigate patient characteristics, all patients who provided informed consent since the start of the programs were included. The gender of each patient and the health care provider who enrolled them in the program were registered, and from the start of the program the number of visits to the site was counted. To examine the usage of the program, patients were recruited from the participants of both online self-management programs between October 2012 and November 2013, because since October 2012 it has been possible to measure the number of hits on the system's core features.

Eligible patients were at least 18 years old, Dutch speaking, and had a clinical diagnosis of AD or FA. Patients were referred to the online programs by GPs, specialists, dieticians or nurses. After referral, they received an account from which they were given access to the training. The account was valid for a period of three months in which patients could complete the program, but this period could be extended at the request of the participant. Informed consent was asked at the start of the online program through a specific letter and was incorporated as a link in the webpage of the program. Their reply was registered and

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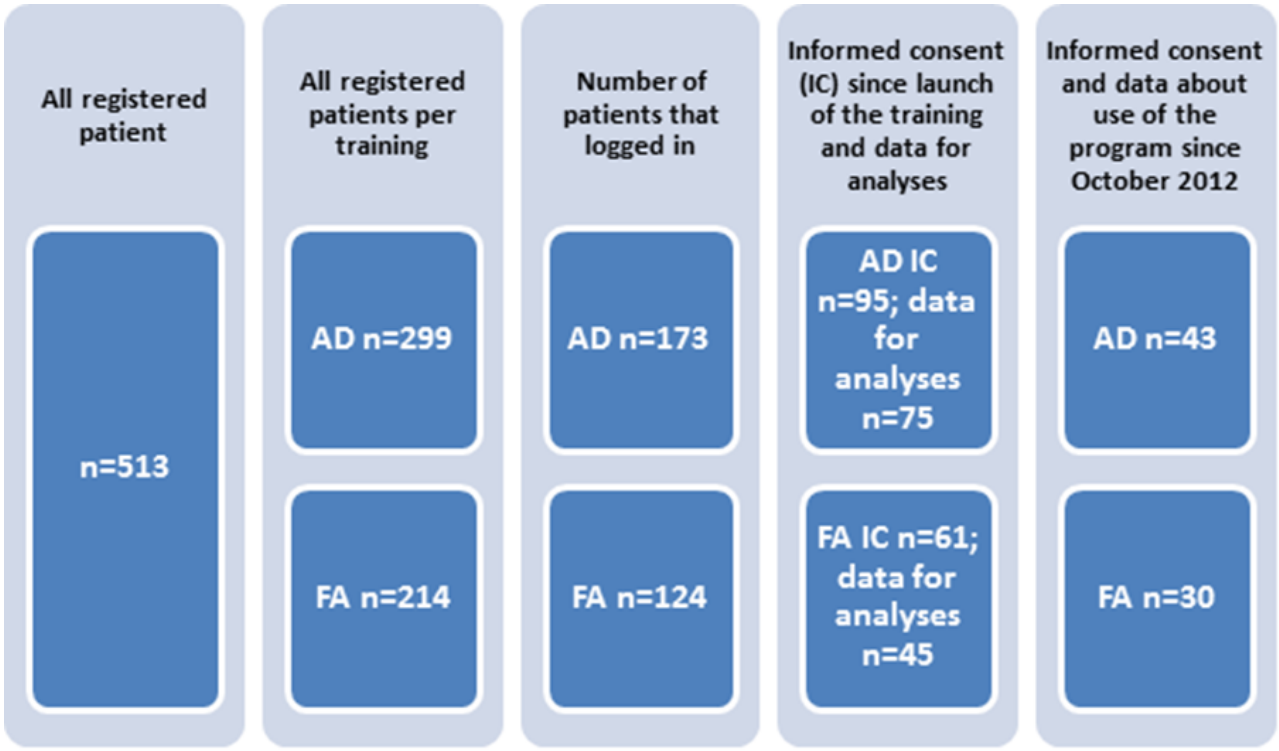
they received a copy via email. A flowchart of the study can be found in Figure 1.

The Medical Ethics Review Committee of UMC Utrecht confirmed that the Medical Research Involving Human Subjects Act did not apply to this study.

Figure 1. Accounts for the online programs.



Parameters and Research Instruments

Demographics

Measurement of the demographic variables (age and gender) was incorporated in the initial questionnaire.

Disease Severity

Disease severity of AD was measured using the extent+ severity part of the Impact of Chronic Skin Disease on Daily Life (ISDL) questionnaire [17]. Extent and severity of AD were measured for nine parts of the body: adding up the scores gives the total score of the affected area, ranging from 9 to 36. A Visual Analogue Scale (VAS) ranging from 0 to 100 was used to measure the intensity of itch.

Disease severity characteristics of FA were measured by two questions: (1) which food caused an allergic reaction; and (2) whether the patient had been prescribed an adrenaline auto injector.

Quality of Life

Quality of life (QoL) was measured using the Dermatology Life Quality Index (DLQI) for patients with AD. The DLQI is a self-administered general dermatology QoL instrument and consists of ten questions with a 4-point Likert scale ranging from 0 (not at all) to 3 (very much)[18]. The DLQI was translated into Dutch by means of forward-backward translation [19].

QoL of patients with FA was measured using the Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF). FAQLQ-AF contains 29 items and 4 domains about allergen avoidance & dietary restrictions, emotional impact, risk of accidental exposure, food allergy related health. The total FAQLQ score is the sum of all the items divided by the number of items and ranges from 1 (minimal impairment in health-related quality of life (HRQL)) to 7 (maximal impairment in HRQL) [20].

Self-Management

Self-management in patients with both conditions was measured using the health education impact Questionnaire (heiQ) version 3.0 [21]. The heiQ is a self-evaluation instrument that consists of 40 questions on eight different domains: positive and active engagement in life, health directed behavior, skill and technique acquisition, constructive attitudes and approaches, self-monitoring and insight, health service navigation, social integration and support, and emotional well-being. The heiQ items are scored on a Likert scale ranging from 1 (strongly disagree) to 4 (strongly agree). The scoring for the heiQ is a sum-score per subscale, with higher scores indicating higher self-management. The domain emotional well-being is a reverse scale, higher scores mean higher impact on well-being. The heiQ version 3.0 was officially translated into Dutch by means of repeated forward-backward translation and is used in the program.

Use of the Program

Number of log-ins and hits per module and per functionality (information, exercises, videos, and patient narratives) were automatically registered in the web system of the online

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program. This functionality has been available since October 2012.

Statistical Analyses

Statistical analyses were performed using SPSS Statistics 20.0 (IBM Corporation, Somers, NY, USA). Standard descriptive statistics were used to summarize sample characteristics and to describe numbers of log-ins and hits per module and per functionality.

The total score on the DLQI, FAQLQ-AF and the sum scores on the eight different domains of the heiQ are at interval/ratio level measurements, and correlations with the number of log-ins were calculated using Pearson's product-moment correlation. The correlation between the extent + severity part of the ISDL, and usage was also calculated using Pearson's product moment.

For the analysis of factors associated with number of log-ins into the online program, multiple linear regression was used. Variables related to the number of log-ins with a significance level of ≤ 0.1 were included in the model. Categorical variables were converted into dummy variables to perform the regression analysis. Prior to each regression analysis, data were checked for linearity and normality by performing a residual analysis, and checked for multicollinearity.

Results

Number of Referrals to the Program

Since the start of both programs, a total of 513 patients received an account for the online program by their physician, nurse or dietician: 299 patients for AD and 214 for FA (Figure 1). Of the AD patients, 62% were women; in the FA program 74% were women. Most patients were referred by the university hospital which developed and started the program (Table 1). The mean number of log-ins for the AD program was 1.4 (range 0-15). For the FA program the mean number of log-ins was 1.3 (range 0-16); 58% of patients of both programs logged in on at least one occasion.

Table 1. Referral to the online program.

Referral to the online program	Food allergy n(%)	Atopic dermatitis n(%)
University hospital	196 (92%)	178 (60%)
Dietician	3 (1%)	-
General hospital	12 (6%)	108 (36%)
General practitioner	3 (1%)	11 (4%)
Other		2 (1%)
Total	214	299

Users' Characteristics of the Online Program "Living With Eczema"

Of the 299 AD patients referred to the online program, 173 logged in on at least one occasion and 95 gave informed consent for the use of their data. Eighty-one patients filled in questionnaires, but 6 were excluded because they were under 18 years of age (n=4) or age was unknown (n=2). Reasons for not using the program or no informed consent were not given, because patients were asked to give their informed consent (yes or no) online when first visiting the program.

Data of 75 patients was available for analysis (Table 2). Of them 67 % were women and the mean age was 34 years (SD 15). Mean number of log-ins was 3.1 (range 1-11; SD 2.6). Patients had mild to moderate AD; mean ISDL 18.8 (range 10-34) and a mean VAS score of itching of 6.0 (range 1-10). AD had a moderate effect on patients' lives (mean score DLQI 9.6; range 0-27).

A low, but significant correlation was shown between the number of log-ins and age (Pearson correlation coefficient r=.38, *P*=.001), and between number of log-ins and quality of life (r=.32, *P* .01). Correlations between number of log-ins and domains of self-management, such as emotional well-being and skills and techniques were .2 (*P*=.09) and -.19 (*P*=.1), respectively. No correlation was shown between number of log-ins and sex or with other domains of self-management. Linear regression with number of log-ins as dependent variable and entering age, quality of life, and two domains of self-management, namely emotional well-being and skills and techniques, led to an $R^2$of .23. Age and quality of life contributed the most to the model, with betas of .35 (*P*=.002) and .26 (*P*=.05), respectively. Two of the self-management domains, emotional well-being, and skills and techniques did not significantly contribute to the model.

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Table 2. Characteristics of users of the online program "Living with eczema".

Characteristics	Mean (SD) (range)
Age in years	34.4 (14.8) (18-78)
Number of log-ins	3.1 (2.6) (1-11)
Severity of AD (ISDL score)	18.8 (4.9) (10-34)
Intensity of itching (VAS)	6.0 (2.7) (1-10)
Quality of life	9.6 (7.0) (0-27)
Domains of self-management	
Health directed behavior	11.4 (2.4) (4-16)
Positive and active engagement in life	15.0 (2.8) (5-20)
Emotional well-being	12.4 (3.7) (6-22)
Self-monitoring and insight	16.7 (2.2) (6-22)
Constructive attitude and appeal	15.5 (2.9) (5-20)
Skills and techniques	10.3 (2.1) (4-16)
Social integration and support	14.6 (2.9) (5-20)
Health service navigation	14.8 (2.4) (5-20)

Users' Characteristics of the Online Program "Living With Food Allergy"

Of the 214 FA patients referred to the online program, 124 logged in at least once and 61 gave informed consent for the use of their data. Forty-nine patients filled in questionnaires, but 4 were excluded because they were under 18 years of age. Reasons for not using the program or no informed consent were not given.

Data of 45 patients were available for analysis (Table 3). Of them 80 % were women and mean age was 35 years (SD 13). Mean number of log-ins was 3.0 (range 1-11; SD 2.3). The mean number of food allergies was 3.5 (range 1-8), with highest percentages of allergies for tree nuts, peanut, and fruit/vegetables. Of them, 73% had been prescribed an adrenalin pen.

A low, but significant negative correlation was shown between the number of log-ins and the domain of self-management "social integration and support" (r=-.36, *P*=.02). No correlation was shown between number of log-ins and sex, age, possession of adrenaline pen, aspects of quality of life, and other domains of self-management. Linear regression with number of log-ins as dependent variable and entering "social integration and support" led to an $R^2$of .13.

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Table 3. Characteristics of users of the online program "Living with food allergy".

Characteristics	Score
Gender (female), n (%)	36 (80%)
Age, mean in years (SD)(range)	34.6 (12.5) (18-64)
Type of food allergy, n (%)	
Peanut	27 (60%)
Tree nuts	36 (80%)
Vegetables + fruits	29 (64%)
Milk	11 (24%)
Egg	8 (18%)
Seafood	5 (11%)
Sesame	7 (16%)
Other	3 (7%)
Number of food allergies,'mean (SD) (range)	3.5 (1.9)(1-8)
In possession of EpiPen, n (%)	33 (73.3%)
Number of log-ins, mean (SD) (range)	3 (2.3)(1-11)
Domains of self-management mean (SD) (range)	
Health directed behavior	11.9 (2.6)(7-16)
Positive and active engagement in life	16.1 (2. 5)(10-20)
Emotional well-being	11.0 (3.7)(6-17)
Self-monitoring and insight	17.1 (2.2)(10-21)
Constructive attitude and appeal	16.6 (2.6)(10-20)
Skills and techniques	11.2 (1.9) (6-16)
Social integration and support	15.3 (2.4) (10-20)
Health service navigation	15.3 (2.2) (9-20)
Food allergy quality of life mean (SD) (range)	
Allergy avoidance & dietary restrictions	3.5 (1.2) (1.2-6.0)
Emotional impact	3.9 (1.4) (1.0-6.1)
Risk of accidental exposure	3.9 (1.2) (1.1-5.8)
Food allergy related health	3.8 (1.7) (1.3-7.0)
Food allergy quality of life total score	3.8 (1.1) (1.2-5.5)

Use of the Different Modules of the Program

The modules "What is AD" and "Treatment of AD" were the most visited modules of the AD program with 34% and 32% of all hits respectively. The module "How is it diagnosed" in the FA program was most visited with 24% of all hits (Table 4).

Most hits (excluding hits on introduction of a module) were on the informational parts of the modules (55-58%), followed by exercises (30-32%). Ten percent or less of all hits were on videos and patient narratives (Table 5).

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Table 4. Use of the different modules of the program.

Atopic dermatitis (n=43 patients ; total of 109 log-ins)		Food allergy (n=30 patients; total of 65 log-ins)	
Usage per module	Number of hits (%)	Usage per module	Number of hits (%)
What is AD	179 (34%)	What is FA	127 (18%)
Treatment of AD	171 (32%)	How is it diagnosed	172 (24%)
Communication	46 (9%)	What to do in case of allergic reaction	120 (17%)
Coping with itch	78 (15%)	Diet & food allergy	125 (17%)
Coping with AD in daily life	56 (11%)	Cross-reactivity	53 (7%)
		Coping with FA in daily life	128 (18%)
Total number of hits	530	Total number of hits	725

Table 5. Use of different functionalities per program.

Number of hits	Living with eczema (n=43 patients)	Living with food allergy[a] (n=30 patients)
Informational parts	307 (58%)	331(55%)
Exercises	157 (30%)	189 (32%)
Videos	33 (6%)	57 (10%)
Patient narratives	33 (6%)	21 (4%)

[a]Hits on the introduction of a module were not counted.

Discussion

Principal Findings

The online self-management programs “Living with eczema” and “Living with food allergy” were mostly used by patients of our university center. Of all referred patients, 58% logged in for at least one occasion. Patients who participated in the online program had an average of three log-ins and mostly visited the modules with information about the disease (AD or FA) and its treatment. Most hits were on the informational sections of the modules and on exercises. It seemed that higher age and lower quality of life influenced use of the AD program, while the lower scores on “social integration and support” influenced use of the FA program. However, explained variance of use was low.

The feasibility evaluations of both online programs, carried out previously, showed that usefulness and usability of the programs were well-appreciated. According to the TAM model [15], this could predict use of the program. However, the underlying study showed that about 40% of patients referred to the online program never logged in. Because no data are available about patients who received an account but chose not to use the program, we do not know if there were differences between users and non-users. It is known that high attrition rates in eHealth interventions are not uncommon [8,22,23]. We did not investigate reasons for the non-usage attrition, but some patients mentioned during face-to-face consultations at the outpatient department that they had already received enough information. So it could be that the “right” users, who could benefit the most from the program, were not enrolled in all cases, which might lead to increased non-use [22,24]. Moreover, the online program is not fully integrated in the usual clinical face-to-face care, but was offered as an addition to usual care, which could also lead to non-use [23]. During the program, there was little room for human interaction. Patients could only receive feedback from a nurse on one specific exercise in the AD program. In the FA program, patients received automatic feedback on most exercises and they received personal feedback from a dietician on only one exercise. It was earlier reported that involvement of interactive technologies with human interaction and support can reduce attrition rates [8,24,25].

Besides the factors related to the online program itself, patient characteristics may also influence the use of the program. We concluded that higher age and lower quality of life were associated with use of the “Living with AD” program, but the explained variance was 23%. The mean age of users of the AD program was 34 years. It is possible that relatively older patients more often took the opportunity to visit the program than young adults. Usage of eHealth interventions has also been studied in patients with other chronic diseases. For example, users of a health weight assistant [26] and a Web-based intervention for heart disease self-management [27] were also more often of older age. Besides age, it was pointed out that the need for information or the need for care influenced use of the eHealth intervention [24,27], which was confirmed by our finding that decreased quality of life increased use of the online AD program. The FA patients in this study had a moderately impaired quality of life (mean score 3.8, SD 1.1). However, quality of life was not correlated to the use of the online program as in the AD patients. One explanation might be that for both patient groups, disease specific quality of life questionnaires were used, which were not comparable due to different aspects of quality of life being measured. On the other hand, lower scores on “social integration and support”, a domain of self-management, influenced the number of log-ins by FA patients. It is known

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that the social consequences of having a food allergy, such as feeling isolated or embarrassed, also influence quality of life [6].

Because of the low explained variance in the use of both programs, other factors than demographics, disease severity, quality of life, and self-management may be of influence. We expect that eHealth literacy is such a factor. eHealth literacy is defined as "*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*" [28]. eHealth literacy is not a static skill but develops over time and can be influenced by the health status of a person, his educational background, motivation to look for information, and the technologies that are used [28]. The eHealth literacy of participants of this study are not known, but it is of interest to further explore these skills and investigate their relation to the use of these online programs.

There is no doubt about the importance of patient education and self-management support for patients with AD [29] or FA [30]. However, little is known about the most preferred method for these patients. In the studied online programs, the information parts were most frequently visited, while we expected that videos and patient narratives would be more appealing. It was shown in one earlier study that online videos providing patient education were effective and attractive to patients with AD [31]. Another Web-based program for AD patients also found lower use of videos than expected, despite careful development of that program and adaptation after initial feedback [32]. Parents of food allergic children reported that they preferred a variety of formats for patient education, because of the differences in learning styles: paper-based, Web-based, and video-based information. They also preferred that these materials were recommended by reliable organizations [33,34]. We expected that the high use of the informational parts of these programs might also be related to the low number of log-ins. The different modules of the AD and FA program always start with the information pages, and participants have to take further steps for the online exercises and videos. A change in the order in which the different functionalities are offered might give the users more freedom of choice in using the online program.

Limitations

A limitation of the study was that disease severity, quality of life, and self-management were only measured at the start of the program; as a result, effects of the program on these clinical outcomes are unknown and it is not possible to analyze which patients will benefit most from the program. Further research with a longitudinal design will give additional insight into the effects of the programs. Moreover, most patients were referred by a university center. In this center specialized nurses or dieticians already support patients with information and education The actual need for information in this university center may be lower in than in less specialized or general hospitals. Implementation of the program at regional hospitals or in community care would probably increase the use of the programs and extend it to a more diverse patient group. Knowledge about use and factors influencing use of specific self-management programs can contribute to optimal usage of these programs, which in turn will increase the intended effects on clinical outcomes. However, generalizability of the findings of this study is limited due to the small sample size and specific adult patient group.

Conclusion

Physicians, dieticians, and nurses, mostly from a university center, regularly referred their patients to the online programs "Living with food allergy" or "Living with eczema" for online self-management training, in addition to the usual face-to-face care. Nearly 60% of all referred patients logged in. All modules seemed to be relevant, but there is room for improvement in use of the program. Age, quality of life, and lower social integration and support were related to use of the program, but only a part of variance in use could be explained. Further research is needed into predictors of use related to the program and characteristics of users, as well as further research into the effects of the program on clinical outcomes.

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Conflicts of Interest

None declared.

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Abbreviations

AD: atopic dermatitis
DLQI: Dermatology Life Quality Index
FA: food allergy
FAQLQ-AF: food allergy quality of life questionnaire-adult Form
heiQ: health education impact questionnaire
HRQL: health-related quality of life
ISDL: Impact of Chronic Skin Disease on Daily Life
QoL: quality of life
VAS: Visual Analogue Scale

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Original Paper

Development of the OnTrack Diabetes Program

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Abstract

Background: Type 2 diabetes affects an estimated 347 million people worldwide and often leads to serious complications including blindness, kidney disease, and limb amputation. Comorbid dysphoria is common and is an independent risk factor for poor glycaemic control. Professional support for diabetes self-management and dysphoria has limited availability and involves high costs, especially after regular hours, and in rural and remote areas. Web-based cognitive behavior therapy offers highly accessible, acceptable, and cost-effective support for people with diabetes. This paper describes the development of OnTrack Diabetes, a self-guided, Web-based program to promote improved physical and emotional self-management in people with Type 2 diabetes.

Objective: The objective of the study is to describe the development of the OnTrack Diabetes program, which is a self-guided, Web-based program aimed to promote euthymia and improved disease self-management in people with Type 2 diabetes.

Methods: Semistructured interviews with 12 general practitioners and 13 patients with Type 2 diabetes identified enablers of and barriers to effective diabetes self-management, requirements for additional support, and potential program elements. Existing resources and research data informed the development of content, and consultants from relevant disciplines provided feedback on draft segments and reviewed the program before release. Using a self-guided delivery format contained costs, in addition to adapting program features and modules from an existing OnTrack program.

Results: A separate paper describes the protocol for a randomized controlled trial to provide this required evaluation.

Conclusions: Development of the OnTrack Diabetes program demonstrates strategies that help ensure that a program is acceptable to users. The next stages involve testing users' experiences and examining the program's effectiveness and cost-effectiveness in randomized controlled trials.

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Trial Registration: The Australian New Zealand Clinical Trials Registry (ACTRN): 12614001126606; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12614001126606 (Archived by WebCite at http://www.webcitation.org/6U0Fh3vOj).

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KEYWORDS

type 2 diabetes; depression; anxiety; self-management; Internet; online; intervention; randomized; protocol

Introduction

Type 2 Diabetes Self-Management

Type 2 diabetes is a burgeoning epidemic that affects an estimated 347 million people worldwide [1], and is becoming one of the leading causes of global disease burden [1]. Inadequate diabetes self-care is strongly associated with poor glycaemic control [2,3], which increases the risk of diabetes complications including peripheral limb amputation, blindness, and end-stage renal disease [1], as well as cardiovascular disease and stroke [4]. A 21% decrease in the incidence of diabetes complications occurs with each 1% improvement (reduction) in glycosylated haemoglobin A1c level [5], which indicates the utility of improving diabetes self-management. However, patients often struggle to meet recommended treatment targets and find it difficult to implement the behavioral changes required to achieve such improvements.

Diabetes patients are two to three times more likely than people without diabetes to experience depression, anxiety, stress, and reduced well-being [6-8]. Dysphoria appears to be both a consequence of Type 2 diabetes and to have a role in the condition's pathogenesis [9], impairing glycaemic control both directly via physiological mechanisms, and indirectly via reduced diabetes self-care [10,11]. As a result, dysphoric patients have an increased risk of diabetes complications [12,13] and premature mortality [14]. Optimal diabetes management therefore requires that both mood and behavioral disease self-management be targeted.

Controlled trials of diabetes self-management interventions have shown that effective components include diabetes education [15,16], promotion of adherence to blood glucose self-monitoring [17,18], physical activity [19,20], dietary [21], and medication regimes [22], and emotional support [23]. Interventions that incorporate only behavioral components have generally failed to produce robust and sustained improvements in psychological and emotional outcomes [23]. Similarly, interventions that specifically target depression or anxiety have typically failed to produce substantial improvements in diabetes self-management and physical outcomes [24]. Even for high-functioning individuals, the complexity of the Type 2 diabetes treatment regime exposes patients to a range of daily physical and emotional challenges [8]. A holistic intervention that incorporates both behavioral and psychological support may therefore offer optimum efficacy.

While some key components of effective support for Type 2 diabetes self-management have been identified, health system limitations prevent their reliable provision [25], especially after regular hours or in more remote locations, where greater population spread and reduced practitioner to population ratios conspire to reduce access. Diabetes self-management support services that offer wide outreach and cost-effectiveness are needed.

Web-Based Programs for Type 2 Diabetes

Over recent years, Web-based interventions, and in particular those based on cognitive-behavior therapy (CBT), have produced substantial improvements in emotional and behavioral outcomes in a range of problem areas [26], with effects similar in size to those of face-to-face treatments [27]. CBT-based Type 2 diabetes interventions similarly have produced significant improvements in diabetes self-care [28,29], and psychosocial outcomes. These programs have also shown high user uptake, acceptability, and usability, even in older users [30].

Globally, Web access is increasing rapidly; with the proliferation of cable and mobile networks increasingly bridging geographical and even socioeconomic divides [31]. Web-based delivery of intervention programs may assist with meeting the need for improved access to additional disease self-management support for people with Type 2 diabetes [25], conveying the advantages of 24-hour availability, broad access, privacy, and lack of stigma. Self-guided programs also show steeply falling unit costs as user numbers increase.

Web programs based on empirically well-established theories have shown superior efficacy in improving diabetes self-management outcomes compared with programs that do not have a strong theoretical and empirical basis [28]; in particular, chronic disease self-management programs that use social cognitive theory (SCT) [31] as their theoretical underpinning have demonstrated efficacy [32]. SCT is appropriate to chronic disease self-management intervention, as it specifies predictors of human motivation and behavior that can be targeted in self-management [33], including specific skills, self-efficacy [32,34], goals, and self-administered incentives [31]. SCT encourages patient empowerment, positing that humans actively make sense of the world and shape their own experiences, giving them the capacity to exercise choice and change their behavior. The theory holds that environmental, interpersonal, and intrapersonal variables are interlocked in processes of reciprocal determinism. Research that demonstrates that diabetes self-management [35-38] and mood [39,40] have strong associations with cognitive and psychosocial factors is consistent with this view, and lends support to diabetes interventions being based on SCT principles.

While Web-based CBT has shown efficacy in reducing depression and anxiety symptoms in people with diabetes [41], interventions primarily focused on targeting mood have yielded mixed results in terms of their effects on glycaemic control [42].

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Similarly, behaviorally focused Type 2 diabetes interventions have demonstrated improved glycaemic control and behavioral outcomes, but they do not typically produce substantial differential improvements in psychological well-being [28]. Programs that simultaneously address behavioral aspects of Type 2 diabetes self-care are needed [42]. Such interventions would be appropriate for implementation in the mainstream Type 2 diabetic population and may support those experiencing primarily psychosocial barriers to self-care, as well as those with co-occurring distress.

Most current Web-based CBT interventions are guided programs that incorporate support from a health professional [43,44]. However, studies that compare guided CBT-based programs with minimal support have similar impacts on clinical [44,45] and behavioral [46] outcomes, as well as user engagement [47]. Self-guided Web-based interventions have shown equal effectiveness to guided interventions [48] and offer the advantages of self-paced learning and skill acquisition, and higher perceived autonomy and privacy. Further, Web-based programs encourage users to adopt an independent role in their disease management, which may enhance patient empowerment. There remains a need for further research on self-guided, Web-based Type 2 diabetes self-management programs that incorporate mood support.

This paper describes the development of the OnTrack Diabetes program [49], which attempts to address the need for a Web-based program that targets both Type 2 diabetes self-management and dysphoria. SCT [31] and Elaborated Intrusion Theory [50-52] inform OnTrack Diabetes, which incorporates both CBT and motivational strategies. The program is designed to provide a holistic approach to improving Type 2 diabetes self-management and mood, and to endorse user empowerment by encouraging users with diabetes to take an autonomous role in managing their condition; it can also be used in either a self-guided or therapist-assisted mode. Practitioners can also use the program to guide sessions supporting patients' self-management; they are given a separate log-in.

Methods

Development of the OnTrack Diabetes Program

Step 1. Qualitative Research

Figure 1 shows the Steps in the development of the program. Semistructured interviews were conducted to explore enablers and barriers associated with effective Type 2 diabetes self-care, together with diabetes-related emotional challenges, requirements for additional disease management support, and suggestions for elements in an online support program. The sample comprised 13 people with Type 2 diabetes and 12 general practitioners (GPs). GPs were asked the circumstances in which they would refer patients to an online Type 2 diabetes self-management support program, and the factors that may inhibit patient referral. Results revealed that patients and GPs shared most perspectives on diabetes self-management. Both the patients with diabetes and GPs identified a need for additional informational, motivational, emotional, and social support. Suggestions for program content included self-monitoring tools, informational support, motivational assistance with improving and maintaining physical activity and diet, goal setting assistance, progress feedback, social support via a chat room and accessibility to health professionals. Detailed results are available in a separate paper [53].

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Figure 1. Steps involved in OnTrack Diabetes program development.

Step 2. Basic Structure and Functionality

The existing OnTrack Alcohol and Depression program [54] was proposed as a basis for the layout of OnTrack Diabetes, and the appropriateness of this was confirmed by a review of its structure. Motivational videos, mindfulness and relaxation audios, and information technology coding from some of the self-monitoring and program tools were adapted for use in OnTrack Diabetes.

Step 3. Assembly of Information Resources

Sources that informed the development of OnTrack Diabetes information resources and tools included the Diabetes Australia guidelines for Type 2 diabetes management [55]; National Health and Medical Research Council Physical Activity and Nutrition Guidelines for Australian Adults [56]; Optometrists Association Australia [57]; Australasian Podiatry Council [58]; Medicare Australia [59], and relevant peer-reviewed empirical

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literature. A nutritionist, ophthalmologist, and podiatrist were consulted to discuss proposed content.

Step 4. Content Development

MC compiled the obtained information and discussed proposed content inclusions with DK. The program content addressed the barriers to Type 2 diabetes self-care identified in qualitative research, and attempted to maximize enhancers. Information resources complement the program's interactive tools and provide the impetus for goal setting and planning, while providing material that can be integrated into primary care. For example, the "My Feet Check" resource contains a diagram of feet on which the date and any changes can be marked, and a checklist to tick off symptoms that can be taken to podiatry appointments.

Step 5. Programming

OnTrack Diabetes information technology programming logic is based on eXtensive Markup coding developed for OnTrack Alcohol and Depression by SE and JG. In collaboration with them, MC coded tools and guidebook pages for the site. Programming modifications and the development of new features exclusive to OnTrack Diabetes was then undertaken. The administration site was built to include functions specific to this trial, including data recording and storage, access to study measures, and a schedule of follow-up study measure reminders. A graphic designer designed the website interface, inserted relevant images, and formatted the program.

Step 6. Preliminary Testing

Both the information technology programmers and external observers tested OnTrack Diabetes several times for bugs, errors in functionality, and design issues.

Step 7. Test of the Live Program

OnTrack Diabetes then had a soft initial launch to enable further screening for bugs and tests for functionality by MC and programmers.

Step 8. Expert Review

An endocrinologist and diabetes educator were invited to provide feedback on OnTrack Diabetes' contents, and AH, AS, PS, and two people with Type 2 diabetes who participated in the qualitative interviews (Step 1) also reviewed the program and provided feedback.

Step 9. Program Revision

The program content was revised in response to the reviews that were undertaken in Stage 8. Specifically, some information fact sheets were added, including on providing ideas for safe physical activity for individuals with limited physical capacity. Further, modifications were made to the program's information technology functionality, as the reviewers had provided feedback regarding bugs that they had found while testing the site's tools and resources.

Step 10. Launch and Efficacy Trial

A randomized controlled trial was commenced with potential participants registering interest on the site's home page.

OnTrack Diabetes Program Content

Key Elements

Figure 2 shows the initial screen in the program, which includes the key elements.

Figure 2. Screenshot of the OnTrack Diabetes program layout.

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Self-Monitoring and Goal Attainment Scaling

The "My Diary" tab provides an electronic self-monitoring record of daily goal attainments in relation to physical activity, eating, and health routines (on a sliding scale from 0% to 100%); highest and lowest blood glucose levels; and mood (on a scale from best to worst). Figure 3 shows a diary page. Entries are represented in feedback graphs that are shown under the "How I'm Doing" tab. The graphs display averages per day over the previous month, and averages per week over the previous 3 months, for each self-monitoring area. Users are encouraged to recognize correlations between the different outcomes, in order to better understand their interrelationship and how they can improve their diabetic and dysphoria control. The monitoring and feedback functions emphasize the SCT focus on goals and on the motivational effects of feedback on goal attainment.

Figure 3. Diary for self-monitoring.

Resources

At the top right of each screen, a "Resources" tab provides access to over 40 fact sheets and quizzes on diabetes and its management, and also to 8 mindfulness audios to guide practice sessions, which can be accessed on the computer as audios or text, or downloaded onto mobile phones in the MP3 format.

Journey Map

Based on our previous research on user preferences concerning Web program formats [60], modules in OnTrack Diabetes are available in any order and at any time, using the tabs shown under the "Journey Map" at the right hand side of Figure 2. All of the tools within the program are also available at any time under the respective tabs at the top of the screen. However, users are advised to apply the strategies in a module for at least a couple of weeks before working on another, and the natural order of the program (by clicking "next") leads them through a logical sequence of resources and skills.

The overall program ("My Journey") contains five modules ("signposts"), which each includes a series of interactive tools. Tools are preceded by "guidebook" screens, which inform them about the tool and its relevance to diabetes. All tools produce a printable summary page, which can later be reviewed under the tab "What I've Done" at the top of the screen. In advertisement-length videos, actors illustrate key concepts such as reconceptualizing a problem. Users with low bandwidth Web connections can access the script of these videos. Throughout the program, written material is kept below a secondary school (Year 7) reading level, to maximize accessibility for users with limited education.

OnTrack Diabetes Signposts

As shown on the right side of Figure 2, the program has five signposts or modules: (1) "Keeping Active and Feeling Great", (2) "Eating Well and Feeling Healthy", (3) "Health Routines", (4) "Thinking Well and Feeling Fine", and (5) "Keeping OnTrack". All but the last two have two sections. The first section of signposts on activity, diet, and medical regimens, asks users to select potential behavioral strategies, to imagine undertaking one, consider and image advantages of that action (Figure 4 shows this), and consider strategies to address potential

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barriers. Self-efficacy is boosted by a consideration of past relevant successes, and a detailed stepwise plan is formulated, including the timing of those steps and a consideration of sources of potential social support (Figure 5 shows this).

The second section of each signpost (“More on...”) contains tools that assist with making behavioral changes routine. For example, users can plan to add incidental and short bursts of activity to their week, as well as longer physical activity sessions, and specify the times and days that they will do them. It also includes a problem-solving tool [61] to assist with overcoming challenges to reaching users’ personalized goals. This tool can also be used to solve other problems, including threats to emotional well-being.

Users are asked to focus on practicing the skills learned in each section for 1-2 weeks before moving forward in the program. In the meantime they are encouraged to log on to the site regularly to self-monitor, use resources, undertake, and revisit tools as needed. The signpost “Keeping OnTrack” provides support while aiming to support the maintenance of progress. It focuses on moving on from past maladaptive behaviors and maintaining positive, new beginnings in the broader context of the individual’s life. Users are asked to evaluate positive changes since starting the program without losing sight of other life goals (eg, education, travel).

Figure 4. Example screen from OnTrack Diabetes: Consideration of good things about a selected physical activity.

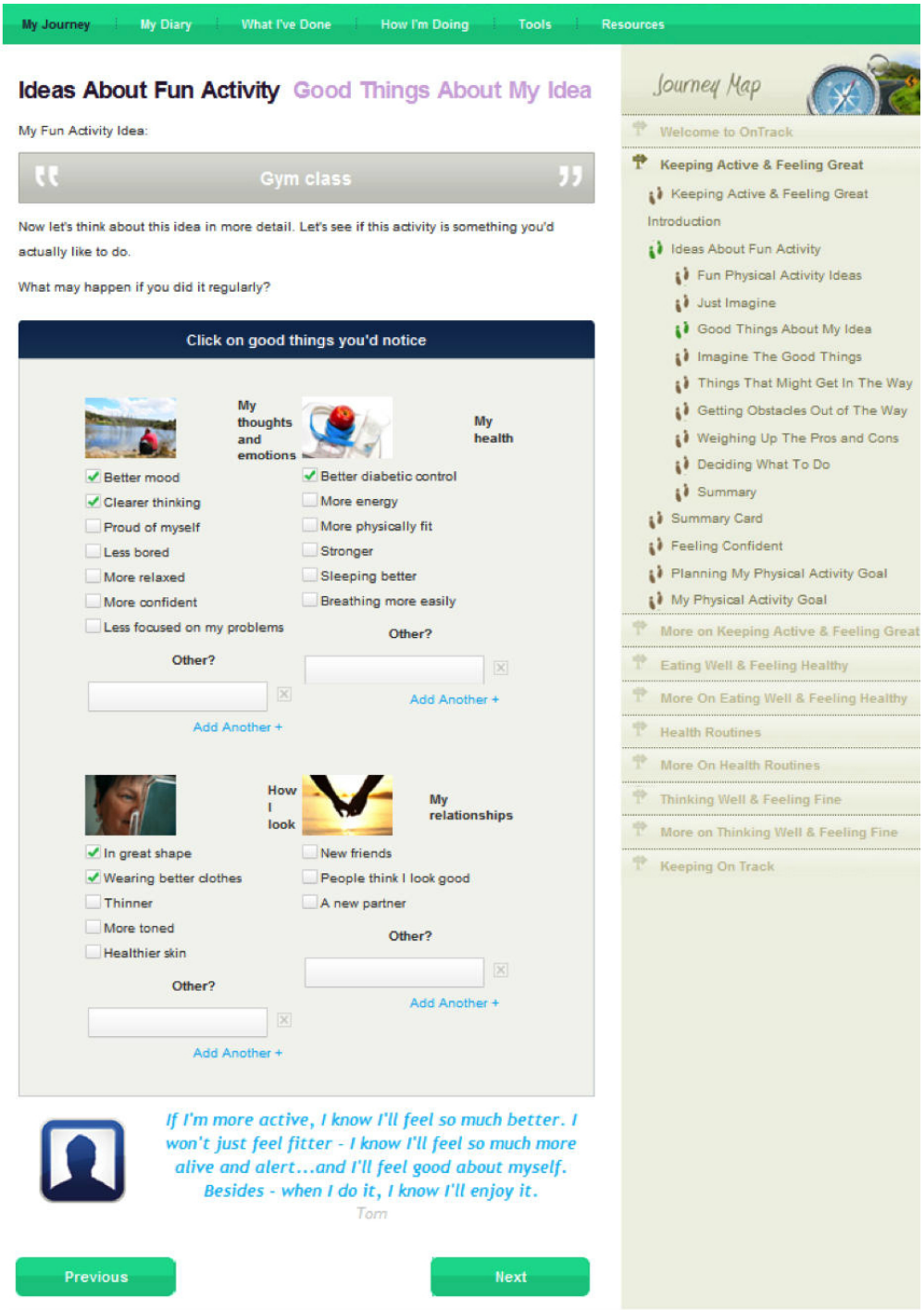

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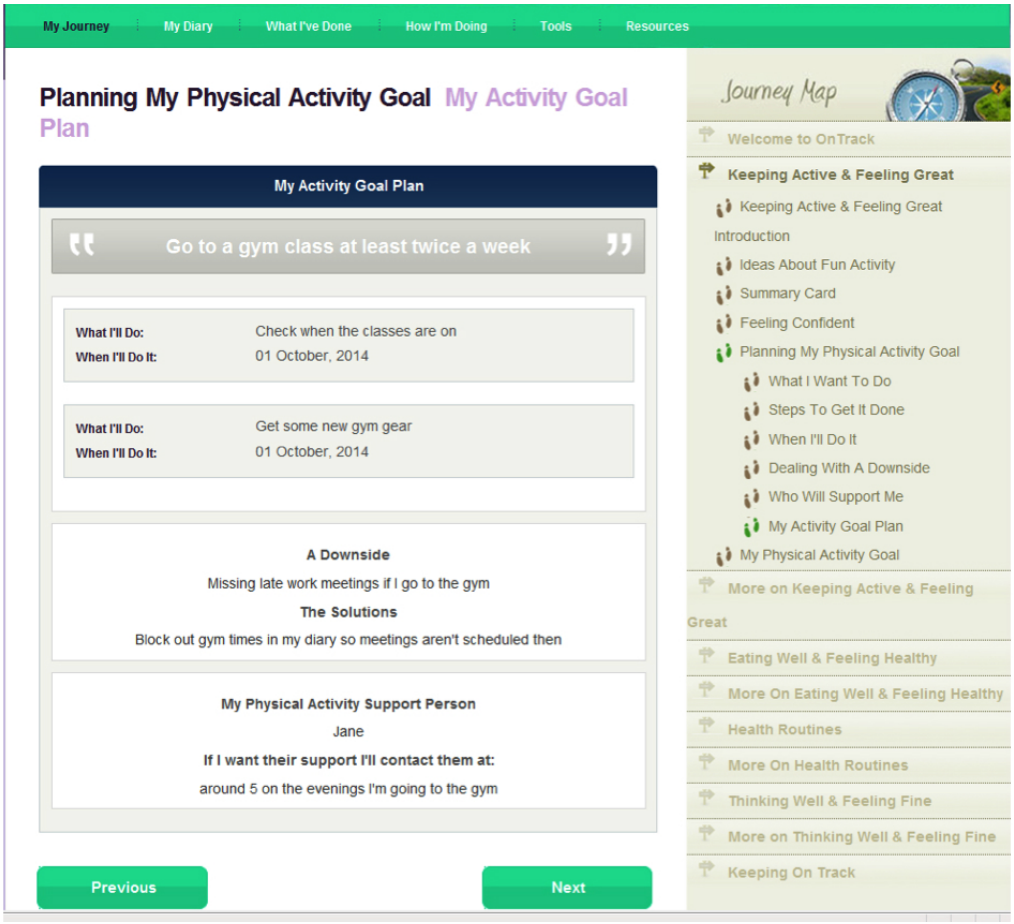
Figure 5. A sample summary sheet: Plan for increasing an activity.



Self-Screening by Quizzes

There are four self-administered quizzes that enable users to evaluate their participation in diabetes self-care activities [62], mood [63], physical activity participation [64], and fat and fiber intake [65]. Self-screening enhances early recognition of distress and depression [66,67], which are important foci for ongoing assessment in diabetes patients [6], and commonly remain undetected in primary care [68]. Participants receive instantaneous, automated feedback on their results via the program, which provides a brief description of what their score indicates about how they have doing in each of the above areas.

OnTrack Diabetes Program Information Resources

Information resources on a number of Type 2 diabetes-related areas are included as printable fact sheets within the program. Specifically, information and resources are provided in the areas of: (1) general Type 2 diabetes information; (2) hyper- and hypo-glycaemia; (3) weight management; (4) physical activity guidelines and steps to increasing physical activity; (5) nutritional guidance including reading nutrition labels, counting carbohydrates, sugars, the glycaemic index and glycaemic load, protein, fats, fiber, dairy, salt intake, and alcohol; (6) eye care; (7) foot care; and (8) erectile dysfunction. Information sheets detail the roles of each primary care professional to diabetes management and include Web addresses to relevant organizations that allow a search for primary care professionals within any area of Australia to be performed.

Additional Resources, Mindfulness Resources, and Videos

The “Resources” section also contains mindfulness audios that provide spoken instructions on performing various forms of mindfulness (eg, mindfulness meditation and mindfulness of pleasure). Users are encouraged to listen to the audios on their computer or download them to an MP3 player for use offline. Guidebook pages throughout the program refer users to the most relevant mindfulness resources to each area. Inclusion of these resources is based on evidence regarding the deleterious effects of stress on glycaemic control and its tendency to increase susceptibility to dysphoria and diabetes-specific distress. Users are trained to mitigate worrying thoughts by meditative practice.

Brief videos that feature role models on key health-related and behavior change areas (eg, alcohol modification, physical activity) are also included, and provide vicarious experience.

Results

A separate paper describes the protocol for a randomized controlled trial to provide this required evaluation [69].

Discussion

This paper provides information on the processes involved in developing a self-guided, Web, CBT-based intervention for Type 2 diabetes self-management and dysphoria. Providing details about Web program development has implications for

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researchers with an interest in developing or refining current Web interventions. The focus of the current project is to provide Web-based self-guided support. Once these foundations have been evaluated, there will be scope to consider additional features that may increase its efficacy, such as the addition of a chat room or blog site to increase access to social support.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive-behavior therapy
GPs: general practitioners
SCT: social cognitive theory

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Original Paper

Bit by Bit: Using Design-Based Research to Improve the Health Literacy of Adolescents

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Abstract

Background: Although a low health literacy level has been found to be among the most powerful predictors of poor health outcomes, there is very little research focused on assessing and improving the health literacy skills of adolescents, particularly those from socioeconomically disadvantaged backgrounds. The vast majority of existing research focuses solely on reading comprehension, despite the fact that health literacy is actually a multifaceted concept, which entails many different types of skills.

Objective: The aim of this paper is to first mine existing literature to identify the many different skills that have been posited to constitute health literacy, and then, using this collection of skills as an overarching structure, to highlight the challenges that disadvantaged youth participating in our HackHealth after-school program encounter as they identify and articulate their health-related information needs, search for health-related information online, assess the relevance and credibility of this information, and manage and make use of it.

Methods: We utilized the design-based research method to design, implement, and revise our HackHealth program. To collect data regarding HackHealth participants' health literacy skills and associated challenges, we used a variety of methods, including participant observation, surveys, interviews, focus groups, and logging of Web browser activities. We also collected data through specialized instructional activities and data collection forms that we developed for this purpose. Quantitative and qualitative techniques were used to analyze this data, as well as all of the artifacts that each student produced, including their final projects.

Results: We identified the various challenges that the 30 HackHealth participants faced in completing various health-related information activities during the course of the program. Based on these findings, we describe important implications for working with youth from socioeconomically disadvantaged backgrounds, how to assess and improve their health literacy skills, and offer specific recommendations for health literacy instruction aimed at this population.

Conclusions: With an increased societal focus on health and a shift from viewing patients as passive recipients of medical care to viewing them as active arbiters of their own health, today's youth need to possess an array of health literacy skills to ensure that they can live long and healthy lives. Working with adolescents to help them develop and practice these skills will also help to break the cycle between poor health literacy and poor health outcomes, thereby reducing health disparities and improving the long-term outlook for the health of our nation.

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KEYWORDS

health literacy; information literacy; computing literacy; consumer health; health informatics; K-12 education; adolescents; informal education; vulnerable populations; literacy programs

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Introduction

Background

A low level of health literacy has been found to be a stronger predictor of an individual's health than age, race, education level, employment status, and income [1]. According to the National Assessment of Adult Literacy (NAAL), 36% of adults in the United States have limited health literacy (characterized by NAAL as basic or below basic health literacy), with lower health literacy levels even more prominent among immigrants, minorities, older adults, and lower-income populations [1,2].

But what exactly is health literacy? Due to the dynamic nature of health information, including its format, sources, and potential and actual uses, the definition of health literacy is evolving. Berkman et al [3] provide a complete retrospective and prospective view of health literacy that demonstrates the changes from individual-static definitions to individual-dynamic definitions to system-social definitions. What it means to be health literate has shifted from a narrow focus on one's "ability to perform basic reading and numerical tasks required to function in the health care environment" [4] to a broader focus on possessing and applying a range of skills. According to NAAL, "Health literacy is not simply the ability to read. It requires a complex group of reading, listening, analytical, and decision-making skills, and the ability to apply these skills to health situations" [1]. Additionally, as the Internet becomes an increasingly integral part of the set of sources people regularly consult for information, we see novel challenges related to seeking, assessing, understanding, and using online health information.

According to Lenhart et al, 31% of teenage (aged 12 through 17) Internet users go online to find information about health, dieting, or physical fitness, and about 17% use the Internet to search for health topics that are difficult to discuss, such as drug use, depression, and sexual health. Further, teens from low-income households (< $30,000/year) are more likely than those from higher income households (> $75,000/year) to use the Internet to find health information (23% vs 11%, respectively) [5]. However, data regarding the health literacy levels of adolescents are not available [6], as this population has largely been ignored in health literacy research and intervention development [7,8,9,10]. Adolescence is a formative time when young people are in the process of developing health behaviors and habits that will influence their health in later years [6,9,11,12]. Thus, channeling energy and resources toward the development of health literacy and health information seeking skills among adolescents is vital.

In this study, we unpack the skills (which we term "health literacy bits") needed to articulate one's health-related information needs, search for health-related information online, assess the relevance and credibility of this information, and manage and make use of it. We draw from the various literatures that describe components of health literacy (ie, eHealth, information literacy, media literacy, computer literacy, digital literacy, etc). The primary objective of this study is to highlight the challenges that a group of disadvantaged adolescents participating in an after-school program (called HackHealth) face in acquiring these skills. We then provide recommendations for facilitating mastery of these skills among this population and share the changes we will make in the next iteration of the HackHealth program.

The HackHealth after-school program was designed to devise innovative ways to assist adolescents with health literacy development. HackHealth's overarching goals are to increase adolescents' interest in the health sciences, their health information literacy levels, their health-related self-efficacy, and their understanding of the crucial link between their daily health-related behaviors and their ability to maintain their health and prevent disease. Adolescents participating in the 8-week HackHealth program choose a health topic of personal interest, conduct research on this topic using both print and digital resources, create a final product incorporating what they have learned, and then present it to their peers and family members. Our curriculum (featured on the HackHealth website) focuses on topics such as keyword/query formulation, credibility assessment, topic refinement, and the use of online tools to create final products [13].

To date, the HackHealth program has been conducted in 3 Title I middle schools (ie, at least 40% of the school's students are from low-income families [14]) in the mid-Atlantic region of the United States. All 3 schools have very high free and reduced-price meals program participation rates, ranging between 81% and 89% [15]. These indicators suggest that our research participants are from families of lower socioeconomic status. Middle schools in this region include grades 6 through 8, with the age of students falling between 10 and 15 years old. Each after-school session lasts between 60 to 120 minutes. Each school is staffed with a full-time librarian, all of whom participated in co-designing program activities using methods of cooperative inquiry [16-18] that utilized a variety of "low-tech" materials to create prototypes and sketches of HackHealth sessions. The librarians then implemented the HackHealth program in their school library alongside the research team.

Prior Work

Adolescents and Their Information-Seeking Behavior

Health-related websites have become more prevalent and more diverse over the past 2 decades, growing to encompass newer types of content, such as user-generated content found in forums, blogs, and online communities. Adolescents are at an age where independent search becomes more enticing, particularly when their questions pertain to issues that are difficult to discuss [19-22]. Unfortunately, due to a relative lack of life experience and experience with searching [23], adolescents often have difficulty identifying relevant sources [24,25]. The various thoughts, feelings, and actions that typically occur during each stage of an individual's search are identified in Kuhlthau's [26] information search process model, clearly showing the challenges and resulting feelings youth experience.

A more tangible challenge to information seeking is the lack of basic access to computers. Without computer access, youth have limited opportunities to experience new open Web technologies, practice online searches, and gain experience with identifying

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the best search engines for their needs and the sources likely to contain the best information for their purposes [5,27]. Developing and refining questions is also difficult for youth, as they frequently lack domain knowledge [23,28,29] and may not understand the relevant terminology [30]. Their searching is frequently impeded by poor spelling ability [31], overreliance on website appearance when evaluating content [19,32-36], and a preference for search engines over library databases [37]. Even assuming that youth have access to computers and the ability to search for and evaluate health information, they may lack the motivation to do so. Youth may not conduct a search if they have no personal interest in a topic [38,39] or if they feel they already know the answer to a health-related question [40]. Similarly, they may not engage in a health-related information search due to a lack of self-efficacy in this area, as determined by associated factors such as optimism, persistence, and goal-orientedness [41,42].

Once youth locate health-related information, they need skills related to recall, numeracy, visual literacy, relevance assessment, and information integration in order to comprehend what they have found. Numeracy requires such basic knowledge as identifying numbers, but also requires computational, analytical, and statistical knowledge [43], much of which has yet to be taught to young adolescents. Youth often struggle with credibility assessment, automatically choosing search results that are listed first; believing websites in proportion to the amount of information they appear to contain; and/or using other novel, but often unreliable, methods [33,35,39,44]. Managing information requires skills in organization, such as storing information for future use. Individuals must analyze what information is needed and keep track of where they obtained it. However, this can be challenging, as adolescents are still "developing the cognitive ability to organize and logically process multiple information objects" [24].

Finally, once all of these steps have been completed, youth may then apply the information they have located by answering questions, solving problems, making decisions, advocating for others, and/or changing their behaviors based on what they learned during the search [1,4,45-52]. Youth may also communicate with others about what was found, which calls for an awareness of ethical issues, such as copyright infringement and privacy concerns. Such issues are incredibly complex and require abstract thinking, which is something adolescents are only starting to develop [24].

Health Literacy Skills

Due to constant changes in both the landscape of information and communication technology and in the personal, social, and environmental health needs of the individual, health literacy is not a static attribute of an individual, but rather a developmental process that unfolds over time [47,50,53]. Because health literacy is socially negotiated (ie, embedded within the social, cultural, and environmental context and norms of the individual and his/her community) [10,49,54-56]; contingent upon the resources an individual has access to at any given moment [54,56]; and variable dependent upon the complexity of the task at hand [56,57], we break down health literacy into individual skills, which we label here as "health literacy bits." We use the term "literacy bits" to reflect the nature of the development of any type of literacy (ie, traditional, new media, health, etc), which is incremental and cumulative. Breaking the multifaceted construct of health literacy into separate literacy bits will enable health literacy teachers to focus on subsets of health literacy skills for a particular intervention.

We closely examined health literacy definitions and enumerations of associated health literacy skills (and literacies) from articles/resources that offered unique definitions and skills. (See our resulting health literacy skills inventory in Table 1.) We unpacked the skills and definitions that we found into 8 phases, with general abilities and characteristics (ie, health-related knowledge; ability to listen/communicate; motivation, attitudes, and intentions; and self-efficacy) and information access serving as the foundational elements/phases that must be in place in order to engage in the subsequent phases. In other words, without the motivation and self-efficacy to engage in health-related information seeking and use, and without information access, the other phases are likely to remain unattainable. Further, the extent and nature of an individual's self-efficacy and information access will influence the fruitfulness of the other phases, which are information need identification and question formulation, information search, information comprehension, information assessment, information management, and information use. Although the use of a table structure and the term "phases" implies linearity, the health information seeking process is, in reality, a fluid and iterative process.

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Table 1. Health literacy skills inventory.

Phase	Literacy Bit(s)	Source(s)
Foundational element: general abilities/characteristics		
	Health-related knowledge	48, 49, 50, 52, 57, 58, 59, 60
	Ability to listen/communicate	1, 11, 44, 45, 49, 50, 51, 54, 58, 59, 60, 61
	Motivation/attitudes/intentions	11, 45, 48, 52, 59, 61
	Self-efficacy	11, 47, 53, 59, 60
Foundational element: information access		
	Able to adapt to new technologies	46, 50, 51, 53, 61
	Aware of primary health resources to begin search	46, 47, 50, 51, 58, 62, 63
	Access valid information, products, and services	45, 47, 48, 50, 51
	Have exposure to computers in everyday life	46, 50, 53
	Awareness of search engines and their capabilities	50
Information need identification and question formulation		
	Develop and refine a range of questions to frame search	46, 50, 58, 64
	Understand relevant health terms	46, 47, 49, 50, 51, 57, 60, 63
Information search		
	Develop appropriate search strategies	46, 49, 50, 62, 64
	Use correct keyword searching strategies	65
	Use correct spelling in search terms	30, 65
	Use the library's electronic resources, such as databases, etc	46, 64
	Maintain a critical stance, such as by using keywords that do not prematurely close off a search	11, 39, 64, 66
	Perform search informed by recommendations by health professionals and/or teachers (ie, reputed credibility)	68
	Understand how search engines work (ie, hits, order of search results, snippets, inclusion/placement of ads, etc).	46, 62
	Limit reliance on surface characteristics, such as the design of a website, the language used, etc (ie, surface credibility)	38
	Reduce search result selection based solely on word familiarity	38
	Use translation features on the search engine or Web page	38
Information comprehension		
	Able to read, comprehend, and recall information located	4, 11, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 57, 60, 61, 65
	Able to perform basic mathematical functions (ie, numeracy)	4, 11, 44, 46, 49, 50, 51, 52, 52, 53, 60, 61
	Able to comprehend simple charts (ie, visual literacy)	1, 46, 50, 61, 64
	Filter information found and extract only relevant information	46, 50, 58, 61, 62
Information assessment		
	Evaluate information based on its accuracy, validity, and appropriateness (ie, message credibility)	48, 50, 51, 53, 58, 61, 64, 69
	Evaluate source (eg, site sponsor or type of site (.com, .gov, .edu, .org)) to determine the believability of the person providing the information (ie, source credibility)	38, 53, 63, 68, 69, 70
	Evaluate the site based on when it was last updated (ie, currency)	64, 69
	Update generalized credibility perceptions, as applicable (ie, presumed and experienced credibility)	63
	Evaluate the credibility of the medium (ie, media credibility)	38, 45, 68

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Phase	Literacy Bit(s)	Source(s)
	Evaluate (not just accept without questioning) others' claims regarding the validity of a site or of specific information (ie, reputed credibility, conferred credibility, tabulated credibility, emergent credibility)	38, 45, 46, 68
	Make sense of information gathered from diverse sources by identifying misconceptions, main and supporting ideas, conflicting information, point of view, and bias	28, 39, 53, 63
	Conclude which sites/information are valid and accurate by using conscious strategies (rather than simply using intuitive and heuristic judgments)	39, 50, 66, 67
	Refine search, as necessary	
Information management		
	Organize gathered information to optimize future retrieval/use	61, 64
Information use (dependent on context/goal of health information seeking)		
	Synthesize information from multiple sources; draw conclusions	50, 61, 64
	Answer questions originally formulated to represent information need	46, 50, 66
	Able to use information to address/solve health problems	4, 46, 47, 48, 49, 50, 51
	Use information located to make health-related decisions	1, 44, 45, 47, 48, 49, 50, 51
	Practice health-enhancing behaviors and mitigate/avoid health risks	45, 47, 48, 49, 51, 58
	Articulate potential limitations of published research findings and the cumulative impact of scientific knowledge (ie, incremental process of discovery) and wrong information	46, 53
	Share, collaborate, communicate, and create information, adapting as needed for intended audience (eg, self, peer, family, etc)	49, 50, 64
	Practice appropriate information ethics (eg, copyright, security, privacy, etc)	50, 64
	Advocate for personal, family, and/or community health	45

Contribution of the Study

Through identification of the challenges encountered by HackHealth participants in the course of acquiring various health literacy skills, we will be able to ascertain the specific components of health literacy that we should emphasize in the next iteration of HackHealth. Additionally, we also examine our health literacy pedagogy (ie, our modules and our instructional strategies) in light of the challenges faced by HackHealth participants, and make targeted changes to the ways that we facilitate health literacy instruction. We also hope that our health literacy skills inventory and our revised HackHealth modules can serve as a guide to health educators who work with adolescents.

We will also use our health literacy skill inventory (Table 1) to develop a prototype digital health literacy assessment tool that will provide an objective measure of youths' baseline health literacy level and their subsequent development of various health literacy skills, enabling us to move beyond a sole reliance on researcher observation and the few existing tools for assessing adolescents' health literacy, which merely measure their perceptions of health information and of their own health literacy skills [6]. The inadequacy of existing health literacy assessment tools has been pointed out by many researchers [11,58-61]. In addition, there are few assessments of any type that focus specifically on the health literacy of adolescents [6,11,62,63]. Current instruments, such as the Rapid Estimate of Adult Literacy in Medicine-Teen (REALM-Teen), have primarily focused on reading ability and occasionally numeracy, rarely acknowledging the wider range of abilities and dispositions needed to achieve robust health literacy [58,64]. Considering the relative lack of knowledge about adolescent health literacy [9,10], the development of an appropriate tool to measure a comprehensive array of the skills involved in health literacy is critical.

Objective of the Study

The objective of this study is to identify the challenges that a group of disadvantaged adolescents participating in the HackHealth program encounter in mastering the health literacy bits that we have identified from existing literature (Table 1). Using these literacy bits as an organizational framework, we provide salient examples of the common challenges that our participants faced as they navigated the various phases of health information seeking and use. Based on this analysis, we provide pedagogical recommendations that we will implement during the next iteration of our HackHealth program and that can be used by other health literacy coaches and teachers in their health literacy instruction.

Methods

Recruitment

Adolescents are recruited for the HackHealth program by school librarians through school-wide announcements, consultations with health teachers, and referrals by homeroom teachers. A total of 30 students across 3 schools have participated in HackHealth, comprising 7 (23%) boys and 23 (77%) girls. Four (13%) of our participants were in sixth grade, 14 (47%) were in seventh grade, and 12 (40%) were in eighth grade. Of these

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30 participants, 20 completed the entire program. The range of ages of participants was 10 to 15 years old, averaging 12.8 (SD = 1.15). The vast majority were 13 (n=14; 47%) or 14 (n=7; 23%) years old. All 30 participants belong to minority groups in the United States: 15 (50%) are Hispanic/Latino, 10 (33.3%) are African American, 4 (13.3%) self-identify as "Other," and 1 (3.3%) is Asian. A majority (n=22; 73%) of our participants reported that they have a computer at home, and most (n=21; 70%) had accessed the Internet from home using at least 1 type of device, such as their own or a parent's computer, cell phone, and/or tablet.

Data collection

Our approach is informed by design-based research (DBR), which is often used in the learning sciences [65]. DBR entails researchers and educators actively collaborating in designing and implementing learning programs and relevant technologies. Using both qualitative and quantitative methods, the researchers seek to collect rich data that uncovers the pedagogical and technological factors that play a role in students' learning processes. This type of research is termed "design-based," as data collection and the insights gained are continuously used to inform the subsequent design of the learning program and technology. The DBR process is iterative, and our goal is to continuously refine and develop the HackHealth health literacy curriculum.

Prior to commencing the HackHealth study, we obtained approval to conduct this study from the University of Maryland's Institutional Review Board and the school district's Department of Research and Evaluation. We held an introductory meeting at each school to explain the program to interested adolescents and to distribute parental and student consent forms. At the meeting, we explained the goals of the project, walked the students through the content on the consent forms that they and their parents would need to sign before they could participate, and addressed any questions they had.

To obtain a complete description of the health literacy perceptions and practices of our participants, we employed several different data collection methods throughout the 8-week program. Table 2 lists the data collection methods we used, along with the approximate time we spent implementing each of these methods.

Our data collection efforts resulted in a total of 650 pages of materials, 176 pages of observation notes, and 80 hours of audio recordings of our interactions with participants (which includes recording of interviews, focus groups, and 1-to-1 sessions). Interviews and focus group sessions were transcribed in their entirety, and other audio-recorded materials were transcribed as needed.

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Table 2. Data collection methods.

Instrument	Session(s)	Approximate Time Spent	Description
Pre-/post-program survey	1 and 8	15 min	Collects participant demographics, preferred sources of health information, interest in science and health, and students' perceptions regarding their health literacy skills
Topic and goal selection form	2	20 min	Collects students' choice of topic, as well as their motivation for choosing this particular topic
Credibility screenshot activity	4	30-40 min	Using large poster-sized screenshots of 6 obesity-related websites—including a government site, a KidsHealth site, a blog, a Wikipedia site, a WebMD site, and a Dr. Oz site—we ask the students to place green sticky notes on the posters next to aspects of each site that they feel make the site credible and to put pink sticky notes next to aspects that they feel make the site not credible. Students write explanations on each sticky note. (For a more detailed description of this activity, see Subramaniam et al, 2015.)
Google search results activity	5	20-30 min	Using a printout of a Google Search results page for the keyword "obesity," we ask students to put a star next to the 3 links they would most likely click on. We then engage them in a group discussion on the reasons for their choices. (For a more detailed description of this activity, see Subramaniam et al, 2015.)
Search log	4-6	30 min per session	Students fill out a search log form as they search for information regarding their selected topic. The form elicits the keywords they used for each of their searches; the URLs of the sites they visited; and their perceptions regarding the usefulness, credibility, and ease-of-use of each of these sites.
Final project goal sheet	4-6	5 to 10 min per session	The students fill out (and update, as needed) a form indicating their selected topic, the mode they will use to deliver their final project, and a list of the information and skills that they still need to complete their final project.
Participant observation	All	Eight 60- to 120-min sessions per school	All researchers attending the sessions conducted participant observation for the full duration of every session at each school.
Browser history downloading and documentation	Most sessions	30 min per session	Following the sessions during which students conducted research on their health topics, we collected their browser histories for future analysis.
Artifacts	Most sessions	Varies	This includes the research organizers (in which students recorded notes regarding what they were learning and the sources they consulted) and their final projects.
Post-program interviews	8	30 min per student	Interviews were conducted using open-ended questions that elicited students' perceptions regarding the impacts of the program in terms of their interest in health, their learning, their health-related self-efficacy, etc.
Focus group	Final party/focus group	60 min	The questions focused on students' experiences during the program. Focus group size is between 3 to 8 students.

Data Analysis

Two members of the research team undertook the data analysis. They began by practicing open coding on a complete data set from 1 participant and all researcher observation notes from 1 week at 1 school. Each researcher developed a personal codebook based on the research goals articulated for the study and the health literacy skills inventory (Table 1). By comparing their personal codebooks, the researchers identified the central themes of interest, resulting in the development of a shared codebook. The final version of the codebook was entered into NVivo 10 qualitative data analysis software and then used to code the remaining data. Each data artifact was coded by 1 researcher, with another researcher checking the codes for agreement. As additional codes emerged during the coding process, the researchers discussed how to categorize and define them. Where there were disagreements, the excerpts were discussed. Extensive memos were kept of coding decisions to establish an audit trail.

Results

Overview

Based on analysis of the data we collected, we highlight the challenges that participants encountered in their health information-seeking, as these challenges reflect the deficits in their health information literacy. Our analysis is structured by the literacy bits outlined in Table 1, focusing on the literacy bits that are delineated in each of the information-seeking phases. As the 2 types of foundational elements—general

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abilities/characteristics and information access—delineated in the first 2 sections of the table are required for a student to be able to engage in information-seeking phases, we focus this paper only on the literacy bits that pertain to participants' actual information need identification/articulation, information seeking, information comprehension, information assessment, information management, and information use processes. For each bit, we share relevant quotes, observations, and/or narrative that exemplify the nature of these challenges. In this paper, we utilize the pseudonyms personally selected by participants. Our analysis is based on data collected throughout the program, but we only highlight the literacy bits that participants had trouble with, excluding those that adolescents appeared to have mastered or that we did not have a chance to observe.

Information Need Identification and Question Formulation

Difficulty Understanding Relevant Health Terms

Although our participants were quite accomplished at formulating research questions, they sometimes lacked familiarity with relevant health terminology, which affected their ability to frame and/or refine their questions and to understand and make use of the information they located. Many participants conducted 1 or more definition searches embedded within their information searching processes. For example, 1 researcher described the following regarding her observations of Betty Boop's information searching processes: "She selected a link to a MedlinePlus article called 'Infant of diabetic mother.' She found this article extremely useful; however, it contained several vocabulary words that she was not familiar with, such as 'bilirubin' and 'neonatal polycythemia.' . . . When she came to words that she didn't know . . . she would open another tab in the browser and type in the URL bar 'definition of [fill in the blank].' For example, she looked up 'bilirubin' this way, but said that the definition provided wasn't useful because it used the word 'hemoglobin,' which she also didn't know. At 1 point, she ended up with multiple tabs open, looking up unfamiliar words contained in the definition of the words she had originally looked up." [Observation 01/29/2014] This often-multitiered chase after the meanings of unfamiliar health terms frustrated our participants and sometimes caused them to lose focus of their original questions.

Difficulty Framing Relevant Search Queries

Another challenge they faced was a lack of familiarity with health terms to use in their initial search queries in order to retrieve accurate, relevant information. For example, Emily was searching for information on "cancer in blood" and was unfamiliar with the term "leukemia," until a researcher shared it with her. A researcher observed, "It is fascinating how the framing of a search [for] 'cancer in blood' versus 'leukemia' makes a difference [in the search results]." [Observation 08/10/2013]

Information Search

Use of Less Effective Keyword-Searching Strategies

Many HackHealth participants used 1-word queries to search for information. We observed some of them typing 1-word queries, such as Captain searching for "concussions" and Jerry looking up "coma," which returned so many results that participants spent a lot of time just sifting through them. As 1-word searches are typed into search box, participants frequently use Google's "autocomplete" feature that offers suggestions as a searcher is typing his/her query. Our observations revealed that participants typically use the autocomplete feature for 1 of the following reasons: (1) they know the broader topic that they are interested in, but don't know the specific subtopic, questions, or proper search terms that should be used; (2) they know the search terms that they would like to use, but don't know the exact spelling for the terms; or (3) they do not know the actual terminology for the illness or health topic that they are interested in and rely on autocomplete for suggestions. For example, Jerry knew he was interested in researching comas, but he relied on autocomplete to select his particular subtopic of interest. We found that our participants frequently clicked on 1 of the search suggestions brought up by the autocomplete function, even if it was not what they had intended to type in the search box in the first place.

Lack of Understanding Regarding How Search Engines Work

Our participants had little understanding of the organization of the search results page. They did not always distinguish between ads and other search results. For example, they paid little attention to the presence of links to advertisements that appeared among their search results, and at times, believed that the advertisements, which were listed at the top of the search results page, were actually credible sites to obtain health information. For example, 1 researcher observed, "Ariana then went to Google and typed the query 'how to cure heart disease.' She clicked on the first ad, which took her to the Mikey Network... " [Observation 01/14/2014] Participants did not understand the order of the search results page, believing the list to be alphabetical or based on popularity. Andy Sixx, for example, believed that search results were returned alphabetically. Jerry believed that the top search results (starting with the ads) are the most popular. Some participants relied solely on the snippets, rather than clicking through to the website, as 1 researcher reported, "When [Ariana] got the search results for each of these searches, she just used the snippets to get the information needed and . . . did not actually click any of the links." [Observation 02/26/2014]

Tendency to Select Search Results Based on Word Familiarity

We observed an overreliance on word familiarity among many of the participants who come from non-English speaking homes. During 1 of the activities designed to capture how they decide which search results to click on, we discovered that they were relying on recognizing words that were familiar to them. For example, 1 student chose a link entitled "Obesity Information" just because she recognized the term "information," even though the listing was an advertisement on the search result page. Once arriving on a page, another student deemed it trustworthy because it had the option to translate the page to Spanish. More

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information on this phenomenon can be found in Subramaniam et al, 2015.

Information Comprehension

Difficulty Reading, Comprehending, and Recalling Information

The primary obstacles that hinder these adolescents from comprehending the health information they find on the open Web are a lack of mastery of the English language and an inability to understand the health terms/phrases that are embedded within the information they find. In addition to unfamiliarity with scientific or health-related terms, participants typically do not recognize common health terms such as "symptoms" and "diagnosis." For example, a researcher noted, "Nicole's vocabulary seems to be a barrier . . . I had to explain what the terms 'symptoms' and 'diagnose' meant." [Observation 11/12/2013]

Trouble With Filtering Information Found and Extracting Only Relevant Information

While we did have participants who actually read through paragraphs of texts from their selected information sources with tremendous patience and attempted to capture only the relevant information, the majority of participants skimmed through Web pages rather quickly and sometimes missed relevant information and/or ended up with the wrong information. For example, 1 researcher wrote, "[Mr. Science Guy] was skimming too quickly to retrieve good information. In point, he ended up with completely incorrect information, though the site has it spelled out correctly. . . . [Similarly, Star Wars] read off the article's main points, though like Mr. Science Guy she ended up with misinformation because she perused much too quickly." [Observation 05/01/2014]

Information Assessment

Difficulty With Evaluating a Source to Determine Its Credibility

One common reason participants trusted information was because the author had professional expertise, such as in the case of a doctor, but they also extended their perceptions of credibility to news reporters and celebrity doctors. Jaysa explained her belief in reporters: "They are reliable, the news reporters, 'cause, you know, I don't think they would lie." Nunu identified Kathleen Doheny as the author of a WebMD article that she had found, and learned that she's a journalist who specializes in health, fitness, and behavior topics. Nunu explained why she trusts her: "She's a journalist, but . . . she still knows about health topics and fitness and stuff. Even though you're not a doctor, you might still know a little about the health-related topic." Betty Boop said that she trusts the Dr. Oz website because her mother watches his show and has used some of the information he provided and found that it worked.

At times, our participants faced challenges in correctly identifying the true source of information on the Internet. Sometimes they could not find an author name. Other times, they incorrectly inferred who the author was. For example, several students believed that WebMD is written by doctors from Maryland. Captain said, "The first website I would go to is WebMD because . . . it's doctors from Maryland." Another student, Phenomenal, incorrectly identified the webmaster of a site as the author of the content on the site.

Participants also encountered problems as they evaluated the credibility of a website based on its domain. They tended to feel that .org websites were more trustworthy than .com sites. Chocolate Rain, for example, explained, "It's a .org website, so you know they're not getting too much money from it, I guess. . . . Most .com websites, even though some of them have good information, some of them . . . get money from it." However, participants sometimes found it confusing to try to judge a site based on its domain. As Chocolate Rain put it: "I'm still confused because it's like, how do we trust the sites, because . . . most of us trust .org and then some of us don't trust .com because most of .com's are being paid by . . . they're like money sites. And then we don't trust .gov because it's the government, but then there's Wikipedia.org. I'm just like, . . . it's a .org site, why don't you trust it?"

Difficulty Evaluating the Credibility of the Medium

Sometimes participants felt that information on the Internet was only credible if it retained features from generally trusted media, such as books. Cherry Marshmallow stated, "I found out from my friends, if it [the website] has, you know, those copyright things in a book, if it has that, it's credible . . . that's what they say." Some participants also felt that online information was credible if they already knew the source from another context. Little Man said he trusted the Let's Move website because he had seen Mrs. Obama talking about this website in a television ad. Star Wars agreed that this website is credible, explaining "because Mrs. Obama said so." However, there is also danger of completely trusting everything on the open Web, as Ariana explained, "It has to be true because you can't put fake stuff on the Internet!"

For some participants, the presence of special types of content or functionality—such as pictures, videos, or the ability to listen to the content read aloud, to read the content in Spanish, or to perform a search on the site—signaled credibility. Chocolate Rain, for example, explained that a particular website was credible because she had used it previously and found that "it has extra things, like you can listen to it . . . so if you have trouble reading, it reads to you, and then it has it in Spanish and . . . different things." However, other types of functionality, such as the ability to log in (which is intended for users to save searches within WebMD, among others), signaled a lack of credibility to some participants. Jaysa, for example, felt that WebMD is not credible "because you can see right here, sign up . . . or sign in, and then it's like a blog, so no."

Difficulty Evaluating Others' Claims Regarding the Validity of a Site or of Specific Information

Some participants described trusting (or distrusting) a site because a relative or teacher trusts (or distrusts) it. Cherry Marshmallow, for example, said she trusts WebMD because her mom trusts it. Mr. Science Guy stated, "I know I went there (teenshealth.org) 'cause my teacher said it was a reliable website."

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A few participants used social measures, such as number of followers or number of viewers, as indicators of credibility. Jerry, for example, explained that he chose the link DonorsChoose.org because he noticed that it had 2,609 followers on Google+. Sometimes, however, they misread these cues. For example, Phenomenal said that a diabetes-related video he watched was credible because the person who posted the video had posted many other videos on this topic. However, the figure he was referring to actually reflected the number of Internet users who had viewed this particular video.

Use of Inaccurate Strategies for Cross-Checking Information From Multiple Sources

Out of the 30 HackHealth participants, only 5 deliberately compared (or mentioned that they will compare) the information found across multiple sources/websites to verify or triangulate information. For example, Chocolate Rain mentioned in her post-program interview that she will "check and see . . . other sites have the same information" before actually deciding to use the information that she found. However, even these 5 participants do not exercise credibility assessment strategies in parallel with the synthesis of information from multiple sources. For example, as 1 researcher reflected on JMoney's strategy, " . . . [S]he compared the information she found at several sites and if a lot said the same thing she knew it was right. She didn't really mention the 5Ws," which is the credibility assessment checklist that we provided to the participants. [Observation 05/01/2014] Another example is Jerry, who always clicks on the Wikipedia link first, and said to just "search another website to just double-check if it's right . . . ," which indicates his eagerness to validate the information in Wikipedia by comparing it with other sites. Some participants (Jerry and Jaysa) say that they will check "another" site and some (Kaylee, Chocolate Rain, and JMoney) mentioned that they will compare the information found with "several" and "other" sites, referring to more than 1 other source.

Information Management: Difficulty Organizing Gathered Information to Optimize Future Retrieval/use

Participants do not generally organize the information they find so as to make it easy to return to for use in their presentations. A researcher observed that Nuya "skimmed [websites] hastily and took notes haphazardly . . . currently, her results and notes are mixed for all types of cancer." [Observation 01/15/2014] Some participants made no (or very few) notes after identifying information that could be used for their presentations. For example, Nunu had no notes at the point when she wanted to create her presentation and primarily worked from her memory of the information that she read.

Information Use: Unawareness of Appropriate Information Ethics

We did not have many opportunities to observe participants' information ethics practices in using the information they found, with the exception of their citation/referencing practices and note-taking strategies. Participants generally did 1 of the following: (1) used information without citing because they are ignorant about the need to do so; (2) forgot to cite the resources that they used but know that they should have; and (3) did not know how to cite the sources that they used. Regarding (1), 1 researcher wrote, "Arianna had heard about the word plagiarism but she didn't know what it meant." [Observation 02/19/2014] Regarding (2), the HackHealth team noticed many instances where participants failed to cite the sources that they used in their presentations. When this point was brought up with them, participants often readily agreed that they should have done so. Regarding (3), participants were frequently unsure of when to cite and how to go about including references in their slides. For example, when Andy Sixx noticed that some of her peers had references in their presentations, she checked with a researcher to find out how to include the references she had used in preparing her slides.

Participants often lacked ethical note-taking strategies. A common observation among researchers is the tendency for participants to copy word-for-word the information they found. For example, as a researcher observed, Betty Boop "took extensive notes, pretty much copying word-for-word what was on the Web. . . ." [Observation 01/29/2014] The same researcher observed another student, "Arianna really wanted to just copy-paste text from the Internet directly into her presentation. She explained that she didn't like having to switch windows back and forth in order to be able to type things in her own words." [Observation 02/19/2014]

Discussion

Principal Findings

Through our experiences working with adolescents in the HackHealth program, we have identified several challenges that they encounter when moving through the phases involved in identifying an information need, formulating one (or more) specific questions, looking for information, and processing, assessing, managing, and using online health information. In this section, we identify some of the implications of our findings, describing the types of learning activities that we have specifically designed in order to try to address these particular areas of difficulty. Next, we outline the limitations of our work and the novel contributions that we are making to both practice and research related to health literacy instruction for this population. In conclusion, we discuss the importance of increasing young people's motivation, self-efficacy, and health literacy to enable them to live long and healthy lives, as well as the role of HackHealth in carrying out this important mission, thereby helping to reduce health disparities and improve the long-term health outlooks for participating youth.

Implications

Findings from our work with HackHealth participants raise a number of important implications for working with youth from socioeconomically disadvantaged backgrounds to assess and improve their health literacy skills. First, we need to ensure that they have the basic necessities, as laid out in the foundational elements sections of Table 1. That is, they need to have a basic level of health-related knowledge and an ability to effectively listen and communicate, as well as the motivation and self-efficacy needed to engage in health-related information need identification and information seeking and use. They also

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need to have access to information and information technologies, an awareness of some trustworthy sources of health information, and a basic understanding of how search engines work.

Moving beyond the foundational elements, today's youth need to have a toolkit of search strategies to use if their preferred method proves unsuccessful. They could use help with converting an information need into a question and then converting a question into a search query. They also need to understand how Google (their preferred search engine) works—for example, how the order of search results is determined—and that Google's autocomplete feature can be, but isn't always, helpful. Importantly, they need to have lots of opportunities to practice searching, as well as adequate instruction in this area. Ideally, this will help to make them more comfortable with online searching, thereby reducing their anxiety and frustration. Based on these needs, we have revised our original HackHealth modules (we call them "pods") to include more streamlined instruction on research question and query formulation in addition to activities that focus specifically on how the Google search engine selects returns based on a user's search terms/query. For example, one of our activities details the various aspects of a search engine results page and how to make educated choices about which websites to visit to research a topic. This helps reinforce optimal information seeking and use strategies, such as the need to read the content of Web pages carefully and critically.

Additionally, youth would benefit from instruction on bookmarking pages (so they don't have to rely solely on their memories) and on distinguishing ads from true search results on search engine result pages. In acknowledgment of the former, we emphasize the need to record sources used in our pods on note-taking (discussed below). We also include instruction on how to use online bookmarking and organization services, such as Evernote.

Along with increasing their familiarity with health terminology, we need to ensure that they are aware of the limitations of relying solely on word familiarity when selecting search results. Youth would benefit from instruction on the difference between the words "useful" and "credible," with special attention paid to pointing out that the presence of particular types of content (eg, pictures, videos) and/or particular types of functionality (eg, translation, read-aloud) is not, in and of itself, an indicator of credibility. Our pods now include examples of incorrect information that gets spread rapidly around the Internet, even being reposted or tweeted from otherwise reputable sources.

Regarding information assessment, we can help students by increasing their pre-existing knowledge and by pointing out that relying on one's pre-existing knowledge when selecting a search result and when assessing the credibility of a site may prove unsuccessful if they have an insufficient or incorrect understanding of the topic they're searching. Helping youth know where to look when trying to identify the author and the date of a site (or information on a site) is also extremely important, as is emphasizing the need to not only identify the name of the author, but also his or her qualifications. Nuanced instruction regarding the definitions of the different domain types and the general strengths and weaknesses of each of these types of sites is also called for. Helping students to develop better heuristics and engage in more conscious and effortful strategies in assessing the credibility of online information is also important. Included in our pods is an activity where students work in groups to develop their own heuristics. Increasingly important is imparting an understanding of the more social types of credibility measures, such as number of followers, number of viewers, and user ratings. Additionally, students need to understand the importance of consulting multiple sites to gather, cross-verify, and synthesize information, as well as the need to assess the credibility of each individual site even when in the process of conducting cross-verification, as this will help to improve their likelihood of ending up with truly credible information.

Moving to the latter phases of information management and use, instruction on note-taking is vitally important. Students need to know how to identify the relevant portions of information on a Web page and how to take good notes on this content, using their own words. Further, they need to understand what plagiarism is and why it is important to avoid. To address this need, we included activities focused on note-taking skills, plagiarism, and on the ethical use of information in our pods.

Limitations

Our work blends research with practice—our research informs our practice, just as our practice informs our research. While this arrangement affords us with some important strengths, such as increased relevance and suitability of our instruction and research methods for our particular population, it also means that our findings may not be generalizable beyond the 30 youth who have participated in HackHealth so far. However, as we work with more and more youth across time, we will be able to ascertain whether there are particular patterns that tend to recur across both individuals and schools, which could suggest broader applicability of some of our methods and findings.

Another limitation of our work pertains to our use of the school library setting and of imposed tasks throughout the program. Although the use of a non-home setting for the program and the assignment of set tasks could lead to nonnatural behaviors, we attempted to limit the potential impacts of these decisions in three ways. First, we elected to use each group's own school library setting, as it was already a part of the participants' daily lives. We felt that this would increase their comfort level as they participated in the program and help to elicit more natural behaviors than an outside space might have done. Second, although we use set, imposed tasks, we nearly always do so in the context of health topics that the participants selected. In this way, we aimed to ensure each participant's interest in his/her topic and the personal relevance of that topic for him/her. Third, we decided to use multiple data collection methods, so that we could analyze participants' behavior from a variety of perspectives.

Conclusions

Today's youth have an unprecedented opportunity to live long and healthy lives; however, they need to have self-efficacy, information access, and a wide array of health literacy skills to do so. Our HackHealth after-school program for middle school

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students from socioeconomically disadvantaged backgrounds aims to capitalize on this population's interest in science and health, simultaneously increasing their health-related motivation and self-efficacy, their digital and health literacy skills, and their understanding of the crucial link between their daily health-related behaviors and their ability to maintain their health and prevent disease. With an increased societal focus on health and a shift from viewing patients as passive recipients of medical care to viewing them as active arbiters of their own health, it will only become more imperative that youth possess these many different types of health literacy skills.

Although the vast majority of existing literature on health literacy assessment has focused on adults and has generally sought to measure reading comprehension, shifting our focus to this younger, more vulnerable (in terms of both age and socioeconomic class) population and widening our focus to encompass the much broader range of skills that actually constitute health literacy provides us with an opportunity to intervene at an early point in the pernicious cycle between poor health literacy and poor health outcomes. We can thereby contribute toward improving the long-term health outlook for this population and reducing health disparities. Furthermore, our intervention takes place at a critical stage in these individuals' development, as adolescence is often the time when people begin to develop health-related habits and to enact (or not) particular health behaviors of their own accord. Moreover, this age range is very often the time when parents of children with chronic health conditions pass along self-care responsibilities, resulting in poorer health outcomes for those adolescents who fail to successfully adapt to this transition and undertake the necessary self-care activities on their own. By assessing and improving the health literacy skills of this population, we can increase their motivation and their belief in their ability to exert control over their own health, as well as their ability to find, understand, manage, and make use of credible health-related information.

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Conflicts of Interest

None declared.

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Abbreviations

DBR: design-based research
NAAL: National Assessment of Adult Literacy
REALM-Teen: Rapid Estimate of Adult Literacy in Medicine-Teen

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Original Paper

Development of a Culturally Appropriate Bilingual Electronic App About Hepatitis B for Indigenous Australians: Towards Shared Understandings

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Abstract

Background: Hepatitis B is endemic in Indigenous communities in Northern Australia; however, there is a lack of culturally appropriate educational tools. Health care workers and educators in this setting have voiced a desire for visual, interactive tools in local languages. Mobile phones are increasingly used and available in remote Indigenous communities. In this context, we identified the need for a tablet-based health education app about hepatitis B, developed in partnership with an Australian remote Indigenous community.

Objective: To develop a culturally appropriate bilingual app about hepatitis B for Indigenous Australians in Arnhem Land using a participatory action research (PAR) framework.

Methods: This project was a partnership between the Menzies School of Health Research, Miwatj Aboriginal Health Corporation, Royal Darwin Hospital Liver Clinic, and Dreamedia Darwin. We have previously published a qualitative study that identified major knowledge gaps about hepatitis B in this community, and suggested that a tablet-based app would be an appropriate and popular tool to improve this knowledge. The process of developing the app was based on PAR principles, particularly ongoing consultation, evaluation, and discussion with the community throughout each iterative cycle. Stages included development of the storyboard, the translation process (forward translation and backtranslation), prelaunch community review, launch and initial community evaluation, and finally, wider launch and evaluation at a viral hepatitis conference.

Results: We produced an app called “Hep B Story” for use with iPad, iPhone, Android tablets, and mobile phones or personal computers. The app is culturally appropriate, audiovisual, interactive, and users can choose either English or Yolŋu Matha (the most common language in East Arnhem Land) as their preferred language. The initial evaluation demonstrated a statistically significant improvement in Hep B-related knowledge for 2 of 3 questions (P=.01 and .02, respectively) and overwhelmingly positive opinion regarding acceptability and ease of use (median rating of 5, on a 5-point Likert-type scale when users were asked if they would recommend the app to others).

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Conclusions: We describe the process of development of a bilingual hepatitis B-specific app for Indigenous Australians, using a PAR framework. The approach was found to be successful with positive evaluations.

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KEYWORDS

culture; development; health literacy; hepatitis B; indigenous population; language; portable electronic apps

Introduction

Overview

Chronic hepatitis B (CHB) is endemic in the Indigenous communities of the Northern Territory (NT) of Australia with prevalence rates estimated to be between 3% and 14.2% [1-7], compared with 1% in Australia as a whole [8]. Despite the availability of effective, government subsidized treatments, only 25% of all individuals living with CHB in Australia are estimated to be receiving guideline-based care, with only 5% receiving antiviral therapy [9]. This disparity in rates of hepatitis B and low uptake of treatment is also seen in other Indigenous populations across the world [10,11].

The barriers to Indigenous Australians accessing care for CHB are multifactorial but mainly include the following: gaps in knowledge, low health literacy, ineffective cross-cultural communication, and logistical challenges in accessing the appropriate care. The challenges of effective cross-cultural communication in the context of remote Indigenous communities of the NT have been documented extensively [12-15] with miscommunication said to be pervasive and language translation felt to be only part of the problem. Although many health promotion or information resources exist for hepatitis B [16], the Australian National Hepatitis B strategy [17] and a number of other studies [18-22] specifically highlight the lack of culturally appropriate resources available to facilitate shared understandings of hepatitis B for Indigenous Australians.

We have previously described the results of a qualitative study exploring the knowledge, perceptions, and experiences of remote dwelling Indigenous adults and their health care providers relating to hepatitis B infection [23]. User preferences from this study included the preference for an electronic format with a predominance of pictures; sufficient medical details; human-like figures, not animal analogies; to be in *Yolŋu Matha* (local Indigenous language) as well as in English; to be interactive; and to use a culturally appropriate world view, building on existing knowledge to facilitate shared understandings. An unrelated scoping study [21] that examined ways to improve and support health education and language interpreting in Aboriginal communities in East Arnhem Land (NT) concluded that user-friendly, interactive, tactile, and aesthetically appropriate resources were most successful at facilitating communication. Involvement of the community in the development of resources in a "bottom-up fashion" was also highlighted as crucial to their eventual success. Multimedia resources were felt to be the most useful with a "touch pad body electronic device" being proposed as a tool to facilitate communication around health issues [24].

In Australia, 64.6% of the population owns a mobile phone [25] with the ability to download electronic apps. There has been an explosion in the development and use of apps with 46 billion downloads worldwide in 2012. This figure is estimated to exceed 200 billion/year by 2017 [26], at which time it is predicted that 50% of mobile phone users will have downloaded a health-related app. The potential to harness this technology as a means to improve health literacy, communication, and treatment uptake is yet to be fully realized. Only recently have published articles started to emerge with respect to the evidence base used to develop health-related apps and any subsequent evaluation of their utility and impact [27,28]. Further, only limited literature exists in this field and it raises concerns regarding the accuracy of information [29,30], alignment of advice with evidence-based guidelines [31], and lack of input from users/patients into product design and evaluation of effectiveness [32]. The data with regard to apps specifically targeted at Indigenous or culturally and linguistically diverse groups are even sparser. We are aware of the development of a number of mental health apps and a rheumatic heart disease app (Menzies School of Health Research, Darwin, Australia) specifically for Indigenous Australians but not of any published literature with respect to the development process of health apps for Indigenous populations.

Participatory Action Research Methodology

Participatory action research (PAR), a cyclical process of reflection, evaluation, and action, where respect for and involvement of the community in all aspects of the research process is an integral part of the methodology, is increasingly recognized as valuable in Indigenous health research [33-35]. There are a number of studies reporting successful outcomes of PAR projects in the context of developing health resources in Indigenous communities [36,37]. This paper aims to describe the process of the development and report the results of the initial evaluation of a culturally appropriate bilingual app about hepatitis B as part of a PAR project.

Methods

Overview

This project was undertaken in northern Australia between September 2012 and October 2014. It was based at the health clinic of a remote community in Arnhem Land, 521 km northeast of Darwin (the capital city of Australia's NT). This community has a population of 2124 with an average age of 24 years, of which 88.98% (1890) are Indigenous Australians and only 9.5% (202) of the population speak English as their first language. On average, there are 4.2 people for each available bedroom and 83.19% (1767) of people live in households considered to

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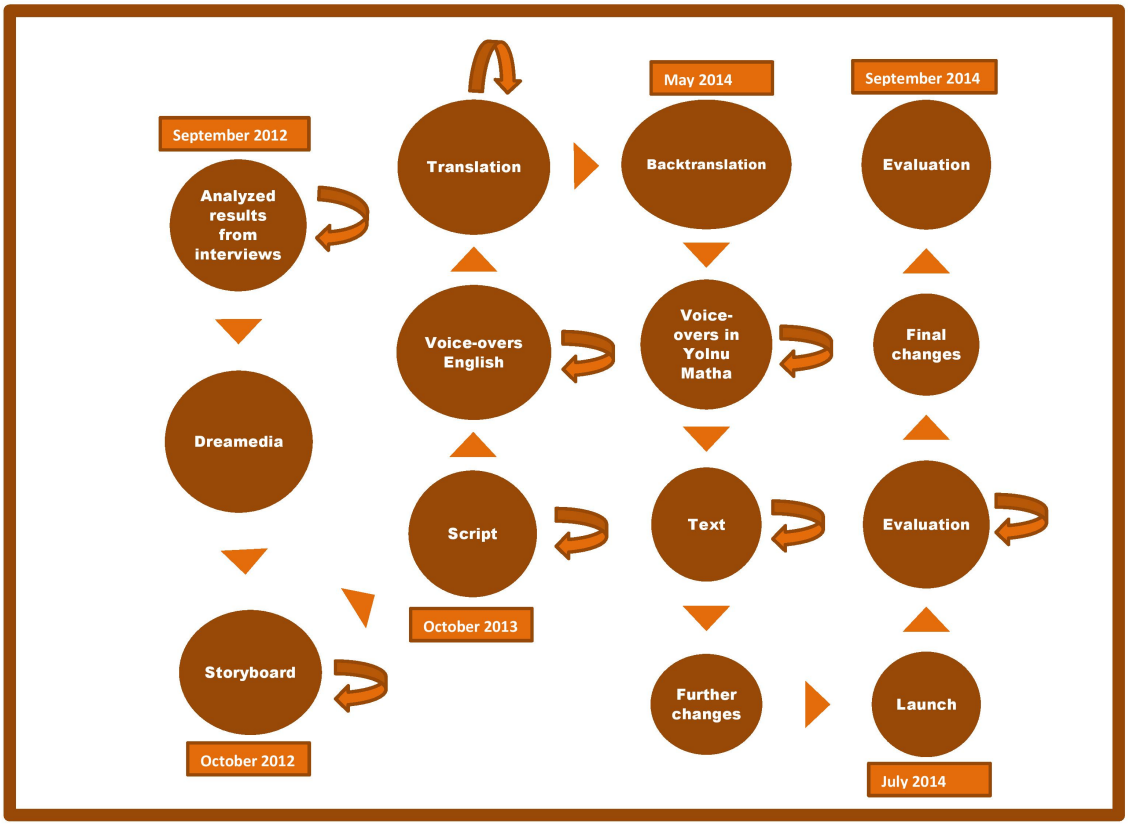
be overcrowded. The community has 3 general stores, a school, a library, a police station, and a community church.

Herein we report the results of the second phase of this PAR project. Phase 1 (previously reported in detail [23]) was a qualitative study consisting of semistructured interviews carried out with 3 groups of people, namely, key informants (health clinic staff, community health educators, and liver clinic staff from both urban and remote areas, including doctors and nurses from both Indigenous and nonindigenous groups), Indigenous people living with CHB, and Indigenous community members. Interviews explored the following: background of the individuals, their hepatitis B knowledge, their experience of health communication/education about hepatitis B, available resources, and their perspectives about potentially useful educational tools. The results of phase 1 of the study then formed the evidence base for the development of the bilingual app (phase 2). The original impetus for the project came from the staff of the community clinic. Their enthusiasm for the project led to the development of a collaborative research partnership between the Miwatj Health Aboriginal Corporation Community Clinic (an Aboriginal-controlled health service representing communities across East Arnhem Land), the Royal Darwin Hospital Liver Clinic, and the Menzies School of Health Research.

Ethical approval for the study was obtained from the Human Research Ethics Committee of the NT Department of Health and Menzies School of Health Research as well as Miwatj Health Aboriginal Corporation. Figure 1 details the timelines for the development process.

Figure 1. Major stages and timelines for the development of the Hep B Story electronic app. Curved arrows represent time points where episodes of community consultation occurred.



Development of the Storyboard

Using the specifications and concepts derived from phase 1 of the PAR process (Figure 2), the project team, which included JD, SB, JSD, LC, SS, and VJ, developed an initial storyboard detailing important ideas, images, and themes to be included in the education tool (Figure 3).

This was then developed by Dreamedia, a Darwin-based graphic design and software company, into an initial screen-by-screen storyboard. Subsequently detailed screen-by-screen scripts were developed by the project team, initially in simple English. These preliminary versions of the app were presented back to the community to facilitate and enable evaluation by clinic staff and liver clinic patients. Appropriate modifications were made according to community input. There were in excess of 20 iterations of the storyboard over the period from February 2013 to July 2014.

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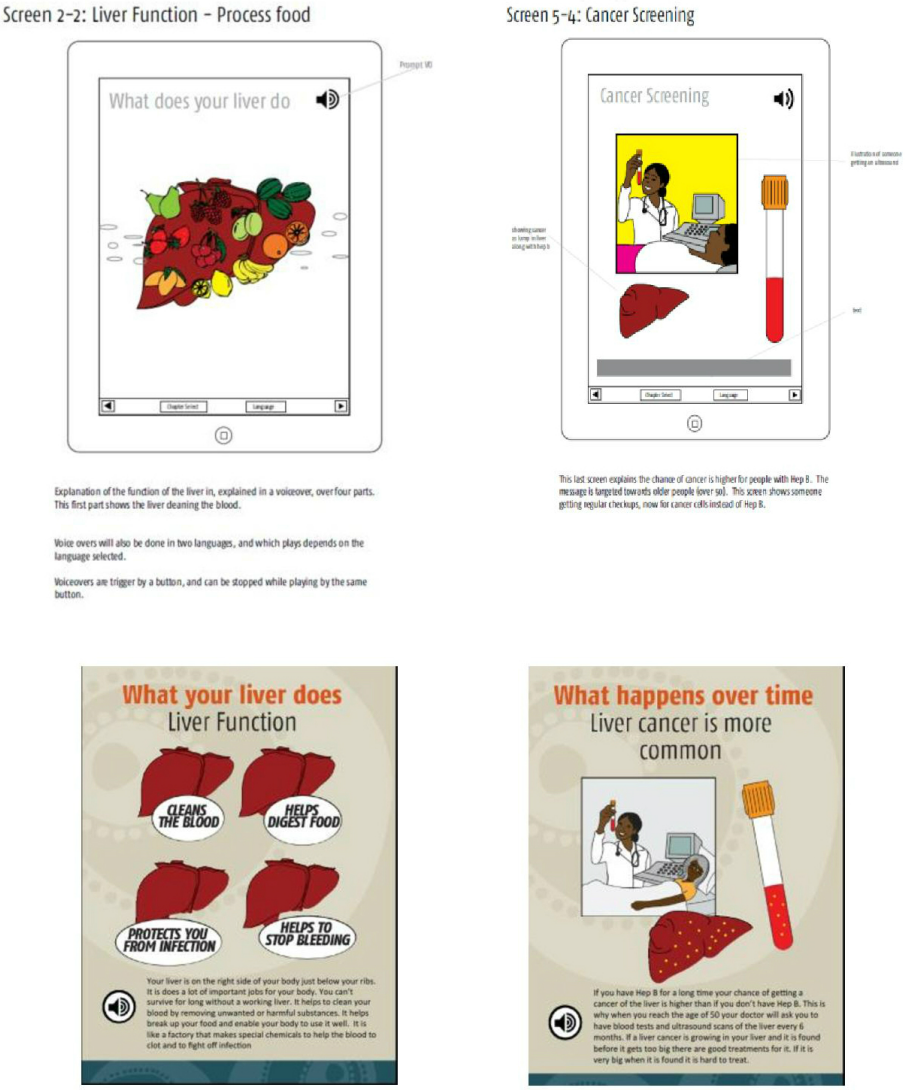
Figure 2. Main concepts and ideas taken from phase 1 [23] of the participatory action research (PAR) process to provide the initial evidence base for the culturally appropriate hepatitis B electronic app. The PAR cycle shows the principle stages involved in a PAR project.

Figure 3. Screen-by-screen examples of the development process showing first and last versions.



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Translation Process

The specific language that the app is translated into is "Djambarrpuyngu," a member of the "Yolŋu Matha" group of Australian Indigenous languages used by Yolŋu people in Northeast Arnhem Land. The term "Yolŋu Matha" will be used in this paper to refer to the language from this point forward as this is the term used in the app in line with community wishes. Two experienced interpreters from the local community were identified, one allocated to do the forward translation (ie, English to Yolŋu Matha) and one to undertake the backtranslation (ie, Yolŋu Matha back to English, so as to check the accuracy of the translation) according to the World Health Organization guidelines [38]. Both interpreters had previously translated health education materials and participated in a pretranslation hepatitis B education session to enable familiarization with the material. Conceptual equivalence (aiming for shared understanding of a word or phrase rather than a word-for-word literal translation) was discussed and encouraged wherever appropriate. Backtranslation was undertaken independently by the second of the interpreters, then the English checked, and clarified by JD (English-speaking doctor with experience in a cross-cultural environment) and SB (bilingual Aboriginal Health Worker), again with emphasis on conceptual and cultural equivalence rather than linguistic equivalence. The final Yolŋu Matha translation was reviewed again by SB. Voice-overs were recorded at Dreamedia studios in both English and Yolŋu Matha.

Prelaunch Community Review

Functional prototype versions of the electronic app were produced on 4 occasions by Dreamedia and presented to the community for review. Discussion and input from clinic staff (both Indigenous and nonindigenous) and Indigenous liver clinic patients were sought on each occasion. Changes were then incorporated into the next version of the app and the process was repeated until unanimous approval was achieved.

Launch and Initial Community Evaluation

In July 2014, a launch event was organized in the community, which involved presentation of the app by JD and SB, and an invitation to take part in the initial evaluation process. The evaluation questionnaires had sections to be completed before and after exploring the app. People were guided through the questionnaire process in real time by a bilingual research assistant who translated the questions and answers into Yolŋu Matha where needed or requested.

Viral Hepatitis Conference Launch and Initial Evaluation

The inaugural Indigenous Peoples' Conference on Viral Hepatitis in Alice Springs, NT (September 2014) was chosen as an appropriate place to launch the app to the wider sector. The app was presented as part of an exhibit where individuals could explore the app in their own time. We invited all conference delegates to help evaluate the app using the aforementioned questionnaire.

Evaluation Questionnaire Analysis

Data were entered into Microsoft Excel 2010 (Microsoft, Redmond, WA, USA) and analyzed using Stata version 13 (StataCorp, College Station, TX, USA). Overall preapp and postapp knowledge scores were created by calculating a total score out of 6 (based on the number of correct responses to Q1 and Q4) and presented as percentages. Quantitative continuous variables were presented as mean ± standard deviation for normally distributed parameters and median ± interquartile range (IQR) for non-normally distributed parameters. Bivariate analyses were performed using Student *t* test, paired Student *t* test for preapp and postapp knowledge comparisons, Fisher exact test for comparisons with any cell value less than 5, and Mann-Whitney test for nonparametric data.

Likert-type items (Q2 and Q3) were treated as ordinal data, presented as median values with frequencies, and associations between groups were calculated using Kendall Tau-b [39]. For each Likert type, item 1 equates to "strongly agree, 2 "agree," 3 "neutral," 4 "disagree," and 5 "strongly disagree." For positive statements, allocated scores were the inverse of the assigned number to enable higher scores to reflect more positive responses.

Results

Main Findings

The app we produced is called "Hep B Story" and is available as a free download for Apple devices through the Apple App Store, for Android devices through the Google Play Store, and as a Web-based app through the Menzies School of Health Research website. The app's title screen allows the user to choose the language as either English or Yolŋu Matha and they can navigate from the beginning to the end through the entire app (except for the "women's business" section), or choose to go to the "chapter select" screen to skip to a specific section or to enter the women's business section. There are 7 "chapters" as detailed in Figure 4, some of which contain animations. The treatment section includes a game, which involves dragging tablets into a man's mouth each day. If you do not get him to take the medicine consistently enough, his hepatitis B virus becomes resistant to the tablets and his liver becomes diseased. Each screen has an audio button, which will play the voice-over in English or Yolŋu Matha and the text is also displayed on the screen in the preferred language.

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Figure 4. The contents of the Hep B Story app.

Chapter	App subheadings	Information included
The Story	Introduction Common in NT Fishing Other ways to get Hep B	What is Hep B, where in the body does it live, animation included Epidemiology How you can catch Hep B from blood to blood contact, animation included Details transmission through Mother to child, day to day blood contact, needle contact, razors, sexual
What your Liver Does	Liver Function	Basic liver functions; cleans the blood, helps digest food, protects you from infection, helps to stop bleeding
Only your blood can tell the story	Bloods Test Regular Checks Sleeping Disease	Asymptomatic nature, need for a blood test to know if you are infected Need for regular ongoing follow up even if you feel well Asymptomatic nature, potential to change and "wake up" over time hence need for recurrent assessment
You can be protected	Immunisation	It is a vaccine preventable disease, if you are not sure if you or your family members are protected, check and they can be vaccinated if needed.
What happens over time	School Adults Alcohol Liver Cancer is more common	Natural history in childhood Natural history in adults The synergistic effects of alcohol and kava on the liver The need to check for liver cancer
Treatment	Not everyone needs treatment Damaged Liver How to take your tablets Important messages	Treatment is available but not everyone needs it, this can change over time Long term liver damage, animation included Tablet game, levels easy, medium and hard Summary of key messages re regular check-ups, treatment and healthy lifestyle
Women's Business	Pregnant Women Treatment Paths Treatment for baby	Pregnancy another important time to know if you have Hep B or not If you do, need to know viral load to decide best treatment path Aim of treatment is for baby to not get infected, baby needs immunisation as well

Development of the Storyboard

As with the text, the images for each screen were discussed in detail over several iterations. Particular emphasis was placed on getting an appropriate balance of gender representation throughout the app, as well as a desire for the individual on the front screen to be gender neutral. Initially, the title screen figure had brown skin, but after community review it was felt that this may imply that all people with hepatitis B have brown skin, and therefore, the color was changed to blue to be ethnically neutral.

The cultural appropriateness of an image to represent sexual transmission was the subject of much discussion. This mode of transmission was, however, downplayed at the community's request for reasons of stigma and also as the main route of transmission in this population is thought to be mother-to-child transmission during parturition.

The screen representing liver function initially had visual representations of various liver functions (eg, fruit to represent its role in helping to process food). On consultation with the community, this was felt to be a culturally inappropriate use of lateral thinking and was described as a decoy and confusing. People preferred to remove all the pictures and just have the words over the liver images as in the final version (Figure 3).

A separate women's business section was a recurrent request. It was important to community members that this was not something that you would "stumble upon" while looking through the app and it had to be separate, warranting an active decision to visit this section. "Women's business" is the commonly used local term for health and other matters specific to women, such as pregnancy.

Translation Process

The script was translated taking into account context and cultural appropriateness. The Yolŋu Matha version was much longer than the English version (10 pages of text as opposed to 5). There were a number of reasons for this: Yolŋu Matha is a more verbose storytelling language; there is not a direct translation for many terms, for example, "Hep B" in the backtranslation was "those invisible germs that are the sickness in your blood called Hep B." For clarity, this phrase was then used on each occasion Hep B was mentioned, and therefore increased the number of words. The text was translated meticulously by a senior male Yolŋu elderly person with great attention to detail, contextualization of the text, and cultural appropriateness. For example, the sentence talking about how one of the liver's functions is to produce clotting factors in the translated version says "it is like a factory that makes good oil, it will help the blood to clot and fight sickness." A senior female elderly person backtranslated this again with the same attention to detail. Issues raised following the backtranslation were literal interpretation of concepts, the difficulty when there are many words for one thing, and the importance of choosing the most appropriate one for the specific context needed.

Prelaunch Community Review

One of the key requests from phase 1 of this study was for a visual tool; however, an app prototype without the full text appearing alongside the audio was not well received. The community consensus was to have the full text there so that people could either listen or read depending on their preference.

A request was made to add *kava* drinking (a drink made from the extract of the root *Piper methysticum* with sedative and anesthetic properties, which is commonly used as a recreational drug in parts of Arnhem Land) to the screen about the dangers of the combination of alcohol and hepatitis B for the liver. An image of a family with several members infected was also suggested to be included on the screen talking about epidemiology.

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Launch and Initial Community Evaluation

The launch in the community was met with excitement and pride at seeing an electronic app in Yolŋu Matha. The evaluation questionnaire was completed by 16 people, median age 34 years (IQR 30-59), with 12 (75%) being women. Results are presented in Tables 1 and 2.

Viral Hepatitis Conference Launch and Initial Evaluation

The launch and 3-day exhibit at the Viral Hepatitis Conference in Alice Springs, NT (September 2014) were also met with a positive response. The questionnaire was completed by 56 people, median age 45 years (IQR 36-54), with 50 (89%) being women. Results are presented in Tables 1 and 2.

Table 1. Demographics of participants and results of the opinion-based component of the evaluation questionnaire.

		Community launch group (N=16)	Conference delegate group (N=56)	*P* value[a]
Demographics of groups				
	Age in years median (interquartile range)	34 (30-59)	45 (36-54)	.34
	Indigenous status (%)	94 (15/16)	21 (12/56)	<.001
	Female gender (%)	75 (12/16)	89 (50/56)	.20
Self-rated hepatitis B knowledge (% who strongly agree or agree) [a]				
	Never heard of hepatitis B	50 (8/16)	4 (2/56)	<.001
	I knew a lot about hepatitis B	31 (5/16)	66 (37/56)	.02
Postapp opinion using the 5-point Likert scale Median score, % giving that answer (n/N) [b]				
	I found the app easy to use (for Q3a)	5, 67 (10/15)	5, 80 (44/55)	.29
	Easy to understand (for Q3b)	5, 67 (10/15)	5, 75 (41/55)	.43
	Contained enough information for my needs (for Q3c)	5, 47 (7/15)	5, 67(37/55)	.42
	Contained too much information for my needs (for Q3d)	2, 50 (6/12)	4, 17 (9/54)	.005
	I would recommend the app to my family and friends (for Q3f)	5, 69 (9/13)	5, 67 (36/54)	.72
	Use the app again myself (for Q3g)	5, 64 (9/14)	5, 55 (29/53)	.56

[a]*P* values are comparisons between the community launch group and the conference delegate group.

[b]"Self-rated hepatitis B knowledge" and "Postapp opinion" constituted the results of opinion-based questions.

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Table 2. Results of the knowledge-based component of the evaluation questionnaire.

Knowledge-based questions	Community launch group (n=16)[a]			Conference delegate group (n=56)[a]		
	Preapp	Postapp	*P* value[b]	Preapp	Postapp	*P* value[b]
Can you name 3 ways by which hepatitis B can be passed from one person to another?	33 (16-50)	58 (39-77)	.01	100 (100-100)	97 (96-100)	.32
If you have hepatitis B what is the best way to tell if the virus is causing damage to your liver?	25 (1-49)	38 (11-64)	.16	92 (85-99)	89 (83-99)	.56
If you have hepatitis B what can you do to help your liver to stay healthy (name 2 things)?	47 (29-65)	50 (28-72)	.58	84 (76-93)	94 (88-99)	.02

[a]Values are presented as mean score % (95% CI).

[b]*P* value for paired *t* test comparing preapp versus postapp knowledge scores.

Evaluation Questionnaire Results

Overall, 72 individuals completed the evaluation questionnaire of whom 62 (86%) were women and 27 (38%) were Indigenous Australians, with a median age of 44 years (IQR 34-54). There was a good representation of individuals from most parts of Australia with only Tasmania and Australian Capital Territory not being represented. With regard to preapp and postapp knowledge assessment, there was a statistically significant increase in the first knowledge-based question in the community launch group (*P*=.01) and in the final one in the conference delegate group (*P*=.02, Table 2).

Participants' opinions of the app after use were generally positive, with 5 of the 6 questions on this achieving a median rating of 5 on the 5-point Likert-type scale. The free text comments were overwhelmingly positive with multiple references to ease of use, culturally appropriate graphics, and the importance of being able to both read and listen in Yolŋu Matha. Multiple requests were made for the app to be translated into other languages. A recurrent criticism was made referencing the lack of inclusivity with regard to gender and sexually diverse communities by the wider key informant group.

Discussion

Principal Findings

We describe in detail the process of development of the "Hep B Story" app, a culturally appropriate educational resource about CHB, through a community partnership using a PAR framework. "Hep B Story" is the first app to be produced in Djambarrpuyngu, a member of the Yolŋu Matha group of Australian Indigenous languages spoken widely in the North East Arnhem Land in Australia's NT. The continuous iterative cycle of consultation, evaluation, and adaptation has led to the production of a tool that the community was proud of and excited about. Initial evaluations from both the community and a wider group of key stakeholders have been overwhelmingly positive.

The production of apps and literature concerning their development are rapidly increasing; however, for the vast majority of health-related apps, there is currently no standardized development or regulatory process for assessment of their quality or effectiveness [27]. There are few published descriptions of the process of health app development and it is often difficult to ascertain, when considering using or recommending an app, who exactly has produced the content and if end users have been involved in the process. Recent reviews of apps for specific disease areas have highlighted concerns regarding factual accuracy, lack of end user involvement, and the effectiveness of apps to add value to standard health care practice [28]. A Cochrane review [31] looking specifically at apps facilitating the self-management of asthma (>100 apps available) concluded that the current evidence base (only 2 studies included) is not sufficient to advise clinical practitioners, policy makers, or the general public regarding app effectiveness. A number of reviews on dermatology apps directed toward skin cancer screening have reported wide ranges of sensitivity and specificity for the diagnosis of melanoma [30,40], with one reporting that 88.2% of biopsy-proven melanoma was classified by the app as "medium risk" and individuals were thus advised to "monitor only" [41]. A trial protocol has been published for an evaluation of the effectiveness of a suicide-prevention app in Indigenous Australian youth (currently recruiting); however, no details are currently available as to how the app was developed [42]. Recently, regulations have been introduced by both the United States Food and Drug Administration and the European Union for "medical device" apps (those intended as an accessory to a regulated medical device or those that transform a mobile platform into a regulated medical device, such as an app intended to diagnose cardiac arrhythmias). These regulations do not currently apply to health information or education apps [43]. A number of app clearinghouse websites are now available

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with varying levels of review and accreditation of health-related apps [27].

In the context of Indigenous health, community partnerships and the use of PAR methodologies have been shown to help break down barriers to communication [34,36], and understandably people respond to information in their own language more positively than that in a second language. Our experience highlights the importance of meticulous translation, backtranslation, and the attention to detail needed to ensure that the messages you are giving are both linguistically and contextually correct and will be understood in the way intended. There is great potential for harm if this process is not robust. This was highlighted in phase 1 of the PAR process when during the process of the interviews it became apparent that there was a lack of shared understanding of the word "silent" between nonindigenous health workers and Indigenous patients in the context of hepatitis B. The health workers used this to describe the asymptomatic nature of hepatitis B noted at times, whereas the patients understood this to mean that the sickness is brought about by sorcery [23].

We also highlight the great value that can be gained from repeated reviews of and conversations about a product throughout the development process, particularly having a real prototype version of the app to comment on. This allowed multiple changes and additions to the visual appearance and aesthetics of the app such as the color of the person and the images on the liver function screen, which would have been difficult to tease out from verbal-only communication. It also provides multiple opportunities to open up communication facilitating collective agreement making and allowing "bottom-up" changes to occur, which have been highlighted as crucial to change in the context of remote Indigenous communities [24].

Initial evaluations of the Hep B Story app were overwhelmingly positive, with all but 1 question (question 3d) assessing user's opinions achieving a median rating of 5 on a 5-point Likert-type scale. Question 3d was a negative statement compared with all the others, which were positive and it may be that this was confusing or difficult to translate as the lowest score for this question came from the community evaluation. This needs further clarification and exploration before the design of any subsequent evaluation. It will also be important to consider why the numbers of people completing the questionnaire in the community launch group were much lower than the conference delegate group. It may be that due to different cultural and communication protocols, as a questionnaire-based evaluation is not the optimal methodology to use in this setting.

There was a significant increase in knowledge after use of the app for questions 1a in the community launch group (P=.01) and 1c in the conference delegate group (P=.02). Although the mean score increased from 25% to 38% in the community launch group for knowledge question 1b, this was not statistically significant (P=.16), and it is possible that this would reach significance with a larger sample size. It is also important to acknowledge the persistence of low levels of knowledge in the community launch group even after exploring the app and pertinent to critically examine whether this is likely to be a problem with the app itself or the way the questions were asked and the methodology used in this initial evaluation. Culturally appropriate measurement of the impact of interventions aimed at improving health knowledge is problematic, with a tendency to attempt to quantify "knowledge" without having any validated tools to achieve this in an Indigenous setting. There are a number of studies in progress in an Australian Indigenous setting using adapted versions of validated health literacy measurement tools such as the Health Literacy Management Scale and Health Literacy Questionnaire, which will hopefully provide much needed information in this area [44-46]. Christie and Verran [24] have suggested that, in the context of East Arnhem Land, low health literacy is not so much a knowledge problem but a need for allowing shared understandings to develop, and our work from the first phase of this PAR project would generally concur with this [23]. It is, therefore, worthwhile considering the cultural appropriateness of any kind of "knowledge measurement" within our further evaluation. It is important that a larger more formal evaluation of this app does take place to confirm and add more detail regarding the impact on knowledge and ultimately behavior change; however, it may be that an interview-based evaluation methodology is more appropriate. Because of the nature of the PAR process, it would be difficult to objectively evaluate this app's effectiveness and acceptability in a community that has already been so involved in its development. We are therefore planning a separate evaluation in a different location where Yolŋu Matha is spoken and hepatitis B is common.

Even in a community where there has been significant engagement, involvement, and interest in the hepatitis B project, levels of knowledge around CHB were low with 50% (8/16) of people having never heard of it. This is consistent with the work done in the Torres Strait region of Australia [19,22], which reported a lack of awareness and/or knowledge of CHB and the measures to reduce its health impact both at the patient and at the health care provider level. The free text comments from the conference delegate group with respect to gender and sexually diverse communities highlighted the conflicts that can arise in PAR projects. Obtaining the right balance between cultural appropriateness and community wishes versus inclusivity of potentially underrepresented groups in this context can be challenging.

Limitations to extensive engagement and involvement of end users in the process of app development include the length of time needed to undertake this process robustly, particularly in communities where English is not the first language, and worldviews of health are very different. This is especially relevant to digital technologies where the pace of change is so fast. As an intended consequence of the methods used to produce the app, it is very specifically tailored to the culture and needs of Yolŋu people; therefore, its translatability to other groups is always going to require further consultation and adaptation. Although this process can be streamlined when the framework and technical coding for the app are available, it is still a significant undertaking. Another obvious issue is that not everyone has access to a mobile phone or tablet device. As such, we felt it crucial to also have the app available through an

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Internet site that can be accessed from nonportable computers such as those in health care facilities.

The potential for adaptation to other languages is important in the context of hepatitis B, which disproportionately affects Indigenous people both in Australia and across the world. There is also great potential to personalize and incorporate clinical tools into the app such as tracking of blood test results, triggers for follow-up, medication reminders, and even self-assessment tools. One example would be adapting the "number connection test," which is a widely used method for detecting the reduced spatial awareness and coordination present in hepatic encephalopathy. This currently consists of a timed test connecting numbered dots on a sheet of paper, which could be adapted into a game-style version and included in the app. The section about alcohol and kava could incorporate harm-reduction strategies, monitoring of consumption, and abstinence encouragement tools.

Conclusions

Health-related apps have a huge potential to contribute and impact positively on health care; however, there is also substantial risk of harm in the absence of an evidence base to guide standards, regulation, and development. This is particularly true for populations where health beliefs and worldview are different and English is not the first language. These are the very populations that are most affected by CHB. We described using a PAR framework with both end users and key informants providing their inputs into the content and development of a hepatitis B-specific app. Although this process was time consuming, the approach was very successful, with a majority of participants providing positive responses. The long-term effectiveness with respect to improving patient's health literacy leading to behavior change and increased treatment uptake will be evaluated over time.

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Conflicts of Interest

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Abbreviations

CHB: chronic hepatitis B
IQR: interquartile range
NT: Northern Territory
PAR: participatory action research

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Original Paper

QuickSilver: A Phase II Study Using Magnetic Resonance Imaging Criteria to Identify "Good Prognosis" Rectal Cancer Patients Eligible for Primary Surgery

Rectal Cancer Alliance Of Canada (RCAC)[1]

see Acknowledgements

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Abstract

Background: Recently, two nonrandomized, prospective cohort studies used magnetic resonance imaging (MRI) to assess the circumferential resection margin to identify "good prognosis" rectal tumors eligible for primary surgery and have reported favorable outcomes.

Objective: The objective of this project was to conduct a Phase II trial to assess the safety and feasibility of MRI criteria to identify "good prognosis" rectal tumors eligible for primary surgery in the North American setting.

Methods: Patients with newly diagnosed primary rectal cancer attending surgical clinics at participating centers will be invited to participate in the study. The inclusion criteria for the study are: (1) diagnosis of rectal cancer (0-15 cm) from the anal verge on endoscopy and proximal extent of tumor at or below the sacral promontory on computed tomography (CT) or MRI; (2) meets all MRI criteria for "good prognosis" rectal tumor as defined by the study protocol; (3) 18 years or older; and (4) able to provide written consent. The initial assessment will include: (1) clinical and endoscopic examination of the primary tumor; (2) CT chest, abdomen, and pelvis; and (3) pelvic MRI. All potentially eligible cases will be presented at a multidisciplinary cancer conference to assess for eligibility based on the MRI criteria for "good prognosis" tumor which include: (1) predicted circumferential resection margin (CRM) > 1 mm; (2) definite T2, T2/early T3, or definite T3 tumor with < 5 mm of extramural depth of invasion (EMD); (3) any N0, N1, or N2; and (4) absence of extramural venous invasion (EMVI). All patients fulfilling the MRI criteria for "good prognosis" rectal cancer and the inclusion and exclusion criteria will be invited to participate in the study and proceed to primary surgery. The safety of the MRI criteria will be evaluated by assessing the positive CRM rate and is the primary outcome for the study.

Results: We expect to have a minimum of 300 potentially eligible patients, and based on a 30% eligibility rate and 80% participation rate, it is expected that 75 patients will be recruited over the two year study period. A Data Safety Monitoring Committee has been organized, and the study will be stopped if a positive CRM of >10% is reported at any interim assessment, which will occur after every 25 patients accrued in the study.

Conclusions: It is expected that the results of this study will show that use of MRI criteria to identify "good prognosis" rectal cancers eligible for primary surgery will be safe (ie, positive margin less than 10%). Therefore, these results will have significant potential to change the current management of rectal cancer in North America and result in improved quality of life for rectal cancer patients and survivors, while reducing overall health care costs.

Trial Registration: ISRCTN05107772; http://www.controlled-trials.com/ISRCTN05107772/ (Archived by WebCite at http://www.webcitation/6WhhUhXkA).

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KEYWORDS

MRI; Stage II and Stage III rectal cancer; primary surgery

Introduction

Preoperative Chemoradiotherapy for Stage II and III Rectal Cancer

Preoperative chemoradiotherapy (preCRT) is recommended for Stage II and III rectal cancer based on several, well designed randomized controlled trials (RCTs) that have shown preCRT significantly reduces the risk of local recurrence (LR) from 15% to 7.5% at 2 years [1-6]. Unfortunately, while preCRT reduces the risk of LR, it does not improve survival, leads to significantly poorer bowel and sexual function, and increases the risk of developing second malignancies compared to surgery alone [7-11]. Therefore, new approaches to improve selection and limit preCRT to Stage II and Stage III rectal cancer patients who are most likely to benefit from preCRT are important to improve the long term functional results and overall quality of life for rectal cancer patients, provided optimal oncologic outcomes can be obtained.

There are two recent, nonrandomized, prospective cohort studies (United Kingdom, MERCURY, and Germany) that have used magnetic resonance imaging (MRI) to assess the predicted circumferential resection margin (CRM) to identify "good prognosis" rectal tumors eligible for primary surgery [12,13]. The MRI criteria used for each of these studies are shown in Table 1. In these studies, patients with a MRI predicted "good prognosis" tumor underwent primary surgery, and the results showed favorable clinical outcomes with low rates of positive CRMs (3.3%, 4/122; 6.0%, 11/181) and 2 year LR (3.3%, 4/122), respectively.

Objective of the Study

Therefore, the objective of this study is to conduct a Phase II trial to assess the safety of MRI criteria to identify "good prognosis" Stage II and Stage III tumors eligible for primary surgery in the North American setting.

Table 1. MRI criteria for "good prognosis" rectal cancer tumors eligible for primary surgery.

	United Kingdom (Mercury)	German
Predicted CRM	CRM > 1 mm	CRM > 1 mm
T[a]-category and EMD[b]	T1, T2, or T3 with ≤ 5 mm EMD[b]	T1, T2, or any T3
N[c]-category	N0, N1, N2	N0, N1, N2
EMVI[d]	EMVI[d] negative	Not assessed
Tumor height	Tumors 5 to 15 cm from the anal verge Tumors < 5 cm from anal verge with no invasion of the intersphincteric plane	Tumors 6 to 12 cm from the anal verge

[a] T=primary tumor

[b] EMD = extramural depth of invasion

[c] N=regional lymph nodes

[d] EMVI = extramural venous invasion

Study Overview

This is a 2 year Phase II study to evaluate the safety of MRI criteria to identify "good prognosis" Stage II and Stage III rectal cancer eligible for primary surgery. The safety of the MRI criteria will be evaluated by assessing the positive CRM rate in this "good prognosis" subset of the Stage II and Stage III rectal cancer patients. The MRI criteria will be considered safe if a positive CRM rate of less than 10% is achieved.

Methods

Start-Up Period, 0-3 Months

Research Ethics Board approval and data sharing agreements have been obtained at the lead and participating sites for the study. The project will be launched via radiology, surgery, and pathology webinars with all participating physicians (at all sites) to review the study protocol and data collection processes and complete relevant training sets.

Patient Sample and Recruitment, 3-21 Months

Newly diagnosed rectal cancer patients attending surgical clinics at participating centers will be invited to participate in the study.

The *inclusion criteria* for the study are: (1) diagnosis of rectal cancer (0-15 cm) from the anal verge on endoscopy and proximal extent of tumor at or below the sacral promontory on computed tomography (CT) or MRI; (2) meets all MRI criteria for "good prognosis" rectal tumor as defined by study protocol (see Table 2); (3) 18 years or older; and (4) able to provide written consent.

The *exclusion criteria* for the study are: (1) planned abdomino-perineal resection (APR) based on pretreatment assessment; (2) planned local excision based on pretreatment assessment; (3) T1/early (primary) T2 tumor on preoperative imaging (MRI and/or transrectal ultrasound); (4) suspicious extramesorectal lymph nodes on MRI; (5) unable to undergo MRI due to contraindications (ie, claustrophobia, metal fragments, implanted metal devices); (6) metastatic disease

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(including extramesorectal lymph nodes, carcinomatosis, liver, lung); (7) pregnancy; (8) inflammatory bowel disease; (9) previous pelvic radiation; and (10) more than one primary tumor.

Clinical Assessment

A participating surgeon at each center will perform the initial clinical assessment. The surgeon will be responsible for facilitating the standard preoperative assessment that includes: (1) clinical and endoscopic examination of the primary tumor; (2) CT scan of chest, abdomen, and pelvis; and (3) pelvic MRI. The participating surgeon will be responsible for presenting all potentially eligible rectal cancer cases at a multidisciplinary cancer conference (MCC), which must be attended by the surgeon and at least one radiologist and radiation oncologist affiliated with the participating center. Alternatively, if a MCC is not available, the surgeon will be responsible for organizing a multidisciplinary meeting with Radiology and Radiation Oncology Site Leads. At MCC (or multidisciplinary meeting), all patients fulfilling the MRI criteria for "good prognosis" rectal cancer (Table 2) and the inclusion and exclusion criteria will be invited to participate in the study. Figure 1 shows an example of a MRI with a good prognosis tumor. After obtaining consent, this group of patients will proceed to primary surgery.

Table 2. MRI criteria for "good prognosis" and "poor prognosis" rectal tumors.

MRI criteria	Good prognosis	Poor prognosis
Predicted CRM	>1 mm (nonthreatened)	≤ 1 mm (threatened)
T-category[a] and EMD[b]	Definite T2, T2/early T3, or definite T3 with EMD[b]< 5 mm	Definite T3 with EMD[b] > 5 mm or T4
N[c]-category	Any N0, N1, or N2	Any N0, N1, or N2
EMVI[d]	Absent or equivocal	Present

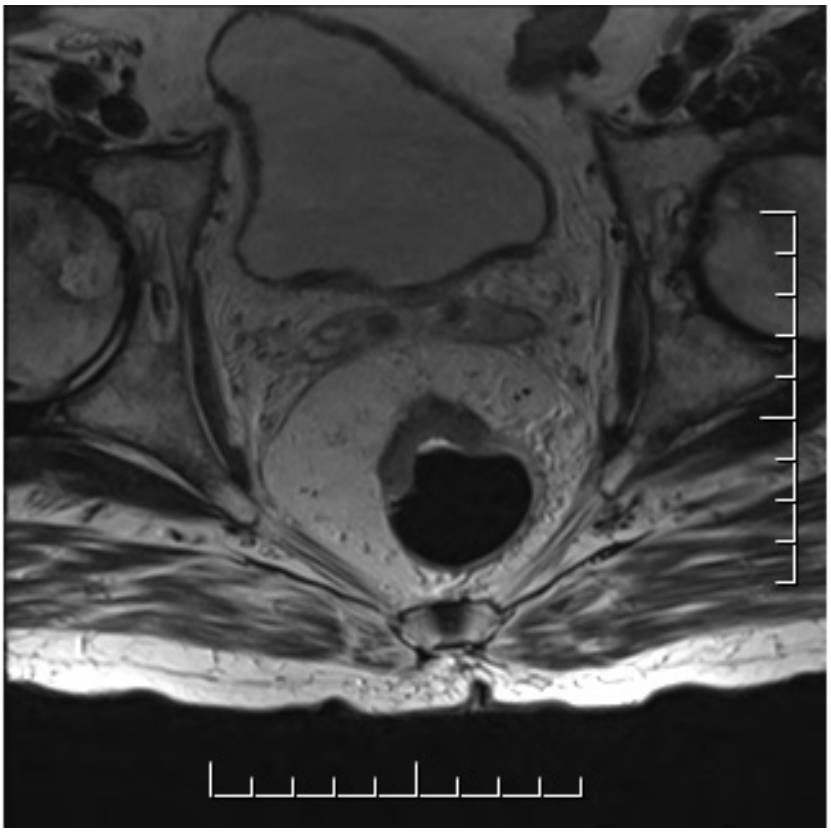
[a] Includes, primary tumor, discontinuous tumor nodes, suspicious lymph nodes, and extramural venous invasion; definite T1 and T1/early T2 tumors will be excluded from study protocol

[b] EMD = extramural depth of invasion

[c] N=regional lymph nodes

[d] EMVI = extramural venous invasion

Figure 1. Mid rectal T3 tumor < 5 mm EMD and predicted CRM > 1mm. No suspicious lymph nodes and no EMVI. T: primary tumor; EMD: extramural depth of invasion; CRM: circumferential resection margin; and EMVI: extramural venous invasion.



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Radiologic Assessment

Each MRI will be reported according to the standard protocol for the study [14]. At minimum, the MRI protocol must include high resolution, axial oblique T2 weighted sequences. The MRI report must include: (1) distance to the mesorectal fascia (predicted CRM), (2) T-category (includes, primary tumor, discontinuous tumor nodes, suspicious lymph nodes, and extramural venous invasion; definite T1 and T1/early T2 tumors will be excluded from study protocol) including extramural depth of invasion into the mesorectum (EMD) for all tumors T3 or greater, (3) absence or presence of suspicious lymph nodes, and (4) absence or presence of extramural venous invasion (EMVI). Although presence of suspicious lymph nodes is not a MRI criterion for "good prognosis" tumors, this information will be recorded so that we will be able to assess the accuracy of lymph node assessment on MRI compared to the final pathology since all patients are undergoing primary surgery. If there is any uncertainty regarding these MRI criteria, the reporting radiologist will be instructed to review the MRI with the Site Lead Radiologist to achieve consensus. If consensus is not achieved and/or uncertainty still exists after review by the Site Lead, the reporting radiologist will be asked to contact the Lead Radiologists (LM, MF) for the study for central review. The central study office (SS, EK) will review the MRI reports to ensure that all of these MRI criteria are reported. In the case of missing data, the Radiology Site Lead will be contacted to obtain this data. Participating centers and radiologists will be encouraged to use a synoptic MRI template for the study; however, this is not mandatory for participation in the study [15]. Prior to the start of the study, a Radiology Webinar will be organized to review MRI protocol, definitions, and interpretation of MRI criteria, and educational materials will be provided. In addition, Radiology training sets will be developed and will be required to be successfully completed by participating radiologists.

Surgical Assessment

The surgical procedure will be left to the discretion of the surgeon and will involve a partial mesorectal excision for upper rectal cancers (above the anterior peritoneal reflection) and total mesorectal excision (TME) for mid and low rectal cancers (below the anterior peritoneal reflection) [16]. To be eligible for the study, surgeons must have completed colorectal or surgical oncology fellowship training in Canada or the United States. Surgeons will also be encouraged to use a synoptic Operative Report template that has been pilot tested and is currently being used in British Columbia; however, this is not mandatory for participation in this study [17]. The central study office (SS, EK) will review the surgical reports to ensure that all of the surgical information required is reported. In the event that there is missing data, the treating surgeon and Site Lead will be contacted.

Surgery should occur as soon as possible from the time of decision for surgery. Prior to the start of the study, participating surgeons will be required to attend the Pathology Webinar in which the protocol for gross evaluation of the TME specimen will be reviewed and discussed. Participating surgeons will be provided with educational materials and will be encouraged to present cases with positive CRM or incomplete TME at MCC for feedback and audit from the site group.

Pathologic Assessment

Each surgical specimen will be processed and reported according to the standard protocol by Quirke et al and must include both macroscopic (quality of the TME) and microscopic assessment (including T-category; EMD; EMVI; and N-category, regional lymph nodes) [18]. Photographs of the gross specimen and serial section are required. If there is any uncertainty about any of these criteria, the reporting pathologist will be instructed to have this reviewed by the Site Lead to achieve consensus. However, if consensus is not achieved or uncertainty still exists after review by the Site Lead, the Site Lead will be asked to contact the Lead Pathologists (RK, DD) for central review. The central study office (SS, EK) will review the pathology reports to ensure that all of the required criteria have been reported. In the case of missing data, the Pathology Site Lead will be contacted to obtain the missing data. Prior to the start of the study, a Pathology Webinar to review the Quirke method will be organized. At the webinar, there will be a review of the Quirke protocol and definitions and interpretation of the reported criteria. Educational materials will be provided and a Pathology training set will be developed and will be required to be successfully completed by participating pathologists. Participating pathologists will be encouraged to use the College of American Pathologists checklist, however, this is not mandatory for participation in the study [19].

Recommended Follow-Up

Figure 2 shows the recommended follow-up for the study. For patients with a negative CRM and no lymph node involvement, no further treatment will be recommended and these patients will be placed in a surveillance program as per the institutional protocol. However, chemotherapy may be considered in these patients if there are other high risk features such as EMVI present. Patients with a negative CRM and positive lymph nodes will be recommended to undergo adjuvant chemotherapy as per institutional protocols. It is preferred that these patients do not receive postoperative radiation, as the main objective of the study is to avoid radiotherapy, however, the final decision about postoperative radiation will be left to the discretion of the treating physicians. Patients with a positive CRM irrespective of lymph node status (ie, positive or negative lymph nodes) will be recommended to have postoperative chemoradiotherapy as per the institutional protocols. The follow-up for each study patient will be recorded.

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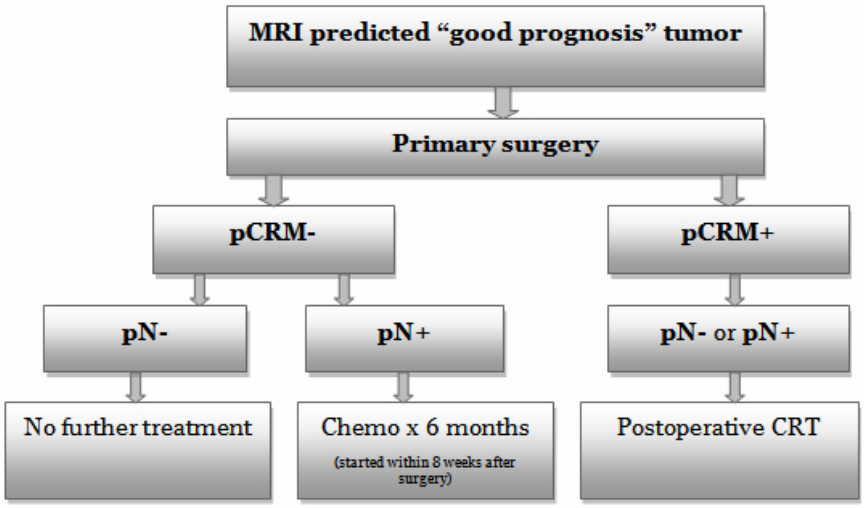
Figure 2. Recommended follow-up for trail participants. MRI: magnetic resonance imaging; pCRM-: negative circumferential resection margin; pCRM+: positive circumferential resection margin; pN-: lymph node negative; pN+: lymph node positive; CRT: chemoradiotherapy; and Chemo: chemotherapy. *No further treatment (bottom, left box): Chemotherapy may be considered at the discretion of the treating oncologist for CRM- and LN- patients for high-risk features such as extramural venous invasion (EMVI).



Data Collection

Participating surgeons will be required to send the MRI report, operative report, and pathology report to the central study office via facsimile (FAX). All patient documents will be assigned a unique identification number by the study coordinator and will be deidentified by the participating center. The study coordinator at the central office will send regular reminders and updates to all participating physicians and will ensure data collection is complete for each patient. A stand alone FAX machine will be kept in the study coordinator's locked office and will be used only for the purposes of this study.

Results

The primary outcome for the study is the positive CRM rate. A positive margin will be defined as any macroscopic or microscopic tumor, discontinuous tumor nodule, or a positive lymph node located within 1 mm of the CRM on final pathologic assessment. We have 30 high volume surgeons at 16 centers participating in this study who see a minimum of 10 new rectal cancer patients over the 18 month time period. Therefore, a minimum of 300 potentially eligible patients will be assessed, and based on the United Kingdom and German studies, it is estimated that 30% (n=90) will be eligible to participate in the study. Assuming an 80% participation rate, it is expected that 75 patients will be recruited over the two year study period.

If seventy-five patients participate, this will provide a 95% confidence interval half-width precision of 6.7% around a point estimate of 10% for the positive CRM rate. If the point estimate for the positive CRM rate is smaller than 10%, the precision around the point estimate will increase.

A Data Safety Monitoring Committee has been organized and will consist of the study statistician, one surgeon, one radiation oncologist, and one pathologist (who are not participating in the study). The study will be stopped if a positive CRM of >10% is reported at any interim assessment, which will occur after every 25 patients accrued in the study.

The secondary outcomes for the study include 2 year LR and disease free survival rates. Descriptive statistics will be used to report: (1) tumor characteristics, (2) positive CRM rate, (3) MRI findings (T-category, N-category, predicted CRM, EMVI), and (4) final pathology (quality of the TME, CRM, T-category, N-category, EMVI). Regression analysis will be performed to assess if any clinical variables are predictive of positive CRM. In addition, comparing the MRI and pathology findings and assessing interobserver agreement for each of the MRI criteria used to identify "good prognosis" tumors will evaluate the accuracy of the MRI interpretation.

This trial is currently recruiting patients.

Discussion

One Day Investigator's Meeting

Our team organized a one day investigator's meeting on June 28, 2013 in Toronto, Ontario, Canada. Colorectal surgeons (n=22), radiation oncologists (n=8), radiologists (n=4), and pathologists (n=1) from high volume rectal cancer centers across Canada attended the meeting. In addition, Dr Gina Brown, the principal investigator of the MERCURY trial attended the meeting. The overall objective of the meeting was to: (1) select MRI criteria to identify "good prognosis" rectal tumors (ie, tumors at low risk for LR) eligible for primary surgery, and (2) finalize a protocol to evaluate the safety of using these MRI criteria to select "good prognosis" tumors eligible for primary surgery. Prior to the meeting, the MERCURY and German trial papers, as well as a draft study protocol, were circulated to the participants.

At the meeting, Dr Brown gave a formal presentation of the MERCURY trial results, and the investigative team presented the German trial results. After each presentation, there was a

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moderated discussion in which the following "good prognosis" MRI criteria were discussed: (1) definition of a threatened CRM in millimeters, (2) T-category and EMD, (3) lymph node assessment, (4) height of tumor, and (5) EMVI.

For the meeting, the following definitions of terms were used. CRM refers to the MRI predicted distance to the mesorectal fascia (MRF). EMD is the extension of the tumor into the perirectal fat beyond the muscularis propria and applies to all T3 and T4 tumors. EMVI is a pathologic, microscopic feature that refers to invasion of large vessels deep to the muscularis propria and is an independent, negative prognostic factor of survival and can be accurately detected on MRI. The highlights of the group discussion for each MRI criteria are detailed below.

Definition of a Threatened Circumferential Resection Margin

Both the MERCURY and German trial defined a threatened CRM on MRI as < 1 mm, since a CRM < 1 mm has been shown to significantly increase the risk of LR [20,21]. While the German trial defined a threatened CRM as < 1 mm to the primary tumor, discontinuous tumor deposit, EMVI, or suspicious lymph nodes, MERCURY did not include suspicious lymph nodes in their definition of threatened CRM. However, for both studies a positive pathologic margin was considered < 1 mm to the primary tumor, discontinuous tumor deposit, EMVI, or positive lymph nodes. In the MERCURY trial, the majority of the positive pathologic margins were due to the primary tumor. There is also some evidence from the Dutch trial that the LR rate from a positive margin due to a lymph node is significantly lower than a positive margin due to a primary tumor [20]. Overall, our group was concerned about the definition of a threatened margin as < 1 mm, as this was considered very little room for error, especially in a low, anterior tumor in a male pelvis. While an alternative definition of < 5 mm was proposed, the main concern with the use of this definition was that it would result in many more patients being ineligible for the study due to a threatened CRM, and significantly affect recruitment. Furthermore, since a large proportion of these patients would have a negative margin with primary surgery, our group felt that this definition would limit the generalizability of the study. At the end of the discussion, while all of the group members indicated they would not use the < 1 mm definition in their current clinical practice, the majority agreed that they would be willing to evaluate the safety of the < 1 mm definition within the context of the study protocol. The group also felt that use of the < 1 mm definition was important to validate the results of the MERCURY and German trials and the generalizability of this approach.

Primary Tumor-Category and Extramural Depth of Invasion

The MERCURY trial considered T3 tumors with < 5 mm EMD as "good prognosis" tumors, while the German trial considered any T3 tumor as a "good prognosis" tumor. The rationale for the MERCURY trial definition was based on a population-based study in which T3 tumors were classified based on EMD [22]. This study reported similar LR and disease free survival rates between T2 tumors and T3 tumors with < 5 mm EMD. Based on these data, the MERCURY group conducted a prospective cohort study to assess the accuracy of EMD measured on MRI using the pathologic specimen as the gold standard in 295 rectal cancer specimens. The MERCURY investigators found a mean difference of only -0.05 mm (95% CI -0.49 mm to 0.40 mm) between MRI and pathologic measurements for EMD [14]. Based on this evidence and expert opinion, our group achieved consensus to consider patients with T3 rectal tumors with < 5 mm EMD as having "good prognosis" tumors [23].

While the MERCURY study included T1 tumors as "good prognosis", the German trial excluded T1 tumors. Since all of the participating centers across Canada currently were not offering preCRT to T1 or T2 tumors, our group decided to exclude definite T1 and T1/early T2 tumors from the study protocol. However, due to the difficulty discriminating T2/early T3 tumors on MRI, our group decided to include T2/early T3 tumors, as we felt there was relatively high potential for these tumors to be understaged on MRI.

Lymph Node Assessment

Both the MERCURY and German trials considered any N-category (N0, N1, N2) as "good prognosis" tumors. The rationale for this was that lymph node evaluation on MRI (as well as other imaging modalities) is relatively poor. Furthermore, the results of the MERCURY trial showed that lymph node involvement was not an independent predictor of LR or survival. This finding is particularly controversial since the small proportion of node positive cases (18.0%, 22/122) in the study does not provide enough power to strongly support this conclusion and all previous rectal cancer RCTs have shown lymph node involvement is a positive and independent predictor of LR. However, it is important to note that the preoperative staging in previous rectal cancer RCTs was primarily based on clinical examination, which has shown to be highly inaccurate and overstaging was reported in 20% of patients in the German trial undergoing preoperative staging with transrectal ultrasound [3,24]. Therefore, it may be that with more appropriate staging (with MRI) that lymph node involvement may not be as important a predictor of LR as previous RCTs have shown. While our group was very concerned about considering N1 and N2 disease as "good prognosis" tumors due to the limited and contradictory evidence, the group also agreed that this was one of the most critical issues to address in the study protocol. Therefore, while all of the group members indicated that they would not be willing to consider N1 and N2 disease as "good prognosis" tumors in their own practice, the majority agreed they would be willing to evaluate the safety of considering N1 and N2 disease as "good prognosis" within the context of a study protocol. The group also felt that considering N1 and N2 disease as "good prognosis" tumors would be important to validate the results of the MERCURY and German trials and the generalizability of this approach.

Height of Tumor

The MERCURY trial included patients with tumors 0-15 cm from the anal verge and included low rectal cancers requiring APR, while the German trial included tumors > 6 cm and < 12 cm from the anal verge.

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For our study, our group decided to include tumors 0-15 cm from the anal verge on endoscopy. However, in order to ensure that rectosigmoid tumors were not included in the study, we added an additional criterion that the proximal extent of the tumor had to be either at or below the sacral promontory on the sagittal sequence of the MRI.

Furthermore, the majority of participating centers indicated that their institutional protocol was to recommend preCRT to all patients with T2/early T3 tumors undergoing a planned APR. The rationale for this was the difficulty completing postoperative chemoradiation following APR, when a T2N0 MRI staged tumor is found to be T3 or node positive on final pathology. Therefore, our group decided to exclude patients with low rectal cancers requiring APR and include only patients for whom a restorative procedure was planned. In addition, patients undergoing a planned local excision were also excluded from the study.

Extramural Venous Invasion

EMVI is a pathologic, microscopic feature that refers to invasion of large vessels deep to the muscularis propria and is a known independent prognostic indicator of distant recurrence and survival in rectal cancer [25]. In previous work, the MERCURY group developed a MRI-based classification for EMVI. Using this classification, the MERCURY group reported a 62% sensitivity and 88% specificity for MRI to detect EMVI using the pathologic specimen as the gold standard and reported fair interrater reliability for accurate detection of EMVI on MRI (kappa=.41, 95% CI 0.31-0.49) [26]. While univariate regression analysis showed that MRI detected EMVI was a negative predictor of recurrence free survival, this was not significant on multivariable regression analysis. While the group had some concern that EMVI was a relatively new MRI criterion for many radiologists, the group acknowledged that EMVI is most often found in the presence of other "poor prognosis" features and seldom the sole MRI criteria used to classify "good" and "poor" prognosis tumors. Therefore, similar to the other MRI criteria, the majority agreed to include MRI predicted EMVI within the context of the study protocol to validate the results of the MERCURY trial and assess the accuracy of MRI detected EMVI by comparing this result to final pathology. The group also agreed that an educational component and training session for participating radiologists be developed as part of the study protocol.

Summary

Based on these discussions, the following MRI criteria were proposed by the group for "good prognosis" tumors: (1) rectal cancers 0-15 cm from anal verge with proximal extent at or below the sacral promontory on MRI and anterior resection (ie, restorative procedure) is planned; (2) distance to the MRF or predicted CRM > 1 mm (margin not threatened); (3) T2 and T3 tumors with < 5 mm EMD; (4) any N (N0, N1, or N2); and (5) EMVI absent.

A consensus vote on the proposed MRI criteria was conducted. The group voted anonymously using ballots, and the results of the vote were presented to the group. The group discussed the results of the vote, and revisions of the MRI criteria and subsequent rounds of voting were planned as necessary. The investigative team agreed a priori that consensus would be reached if 80% of the group voted "yes" to the proposed MRI criteria and had planned for 2 to 5 rounds of voting. However, after the first round of voting, 91% (31/34) of the participants voted "yes" to the proposed MRI criteria. The results were presented, and the three individuals who voted "no" identified themselves and explained the reasons for their vote. There were two of these individuals that were concerned about the definition of a threatened margin < 1 mm and would have preferred this to be < 5 mm, and the third individual was concerned about including N1 and N2 disease as "good prognosis" tumors. Since consensus had been achieved on the first round of voting, no subsequent rounds of voting were conducted.

This study is highly relevant, as it is expected that the results of this study will show that use of MRI criteria to identify "good prognosis" rectal cancers eligible for primary surgery will be safe (ie, positive margin rate less than 10%). Therefore, these results will have significant potential to change the current management of rectal cancer in Canada and result in improved quality of life for rectal cancer patients and survivors, while reducing overall health care costs. Furthermore, these results would provide the necessary data to determine if an international RCT to address this question would be feasible based on sample size, recruitment, and cost. Last, standardization of preoperative MRI imaging, surgical, and pathological assessment across centers of excellence in Canada will be important for reporting long term outcomes for this study (ie, 2 year survival and LR rates, quality of life), improving the quality of patient care across Canada, and facilitating participation in future clinical trials on both a national and international level.

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Authors' Contributions

EK and NB drafted and prepared the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

APR: abdomino-perineal resection
CRM: circumferential resection margin
CT: computed tomography
EMD: extramural depth of invasion
EMVI: extramural venous invasion
FAX: facsimile
LR: local recurrence
MCC: multidisciplinary cancer conference
MRF: mesorectal fascia
MRI: magnetic resonance imaging
preCRT: preoperative chemoradiotherapy
RCTs: randomized controlled trials
TME: total mesorectal excision

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Protocol

Rural Versus Urban Health Service Utilization and Outcomes for Renal Patients in New South Wales: Protocol for a Data Linkage Study

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Abstract

Background: Kidney disease is a significant burden on health systems globally, with the rising prevalence of end stage kidney disease in Australia mirrored in many other countries. Approximately 25% of the Australian population lives in regional and rural areas and accessing complex tertiary services is challenging.

Objective: We aim to compare the burden and outcomes of chronic kidney disease and end stage kidney disease in rural and urban regions of New South Wales (Australia's most populous state) using linked health data.

Methods: This is a retrospective cohort study and we have defined two cohorts: one with end stage kidney disease and one with chronic kidney disease. The end stage kidney disease cohort was defined using the Australia and New Zealand Dialysis and Transplant Registry, identifying all patients living in NSW receiving renal replacement therapy at any time between 01/07/2000 and 31/07/2010. The chronic kidney disease cohort used the NSW Admitted Patient Data Collection (APDC) to identify patients with a diagnostic code relating to chronic renal failure during any admission between 01/07/2000 and 31/07/2010. Both cohorts were linked to the NSW APDC, the Registry of Births, Deaths and Marriages, and the Central Cancer Registry allowing derivation of outcomes by categories of geographical remoteness.

Results: To date, we have identified 10,505 patients with 2,384,218 records in the end stage kidney disease cohort and 159,033 patients with 1,599,770 records in the chronic kidney disease cohort.

Conclusions: This study will define the geographical distribution of end stage and chronic kidney disease and compare the health service utilization between rural and urban renal populations.

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KEYWORDS

end stage kidney disease; chronic kidney disease; kidney transplant; data linkage; dialysis; rural health care; cohort study

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Introduction

Kidney disease is a significant burden upon health systems globally. The rate of new end stage kidney disease (ESKD) cases in 2012 was 357 per million in the United States, 108 in the United Kingdom and 110 in Australia [1-3]. The overall incidence of treated ESKD in Australia has increased by 19%, between 2000 and 2007 [4]. This increasing burden of disease is largely borne by older Australians, with prevalence rates much higher in those aged 65-84 years [3]. As the population ages, it is likely to drive further increases in the prevalence of ESKD.

The cost of renal service provision in the United States in 2010 was US$47.5 billion [1] and is expected to rise to $1.5 to 1.8 billion by 2019 in Australia [5]. Dialysis is the most common reason for hospitalization in Australia, and chronic kidney disease (CKD) contributed to 15% (1.2 million) of hospitalizations in Australia in 2007 and 2008. [5].

New South Wales (NSW) is Australia's most populous state and includes 32.3% of Australia's population, with approximately 25% living in rural and remote areas. There is currently inadequate data regarding differences in growth in demand for renal replacement therapy (RRT) in rural versus urban areas in Australia [6]. Although it has been documented that increasing remoteness corresponds to increasing incidence of ESKD amongst indigenous Australians, such geographic patterns have not been well defined for non Indigenous Australians [7]. This is despite the fact that nationally non Indigenous Australians constitute the majority of ESKD patients in all regions except remote areas. A United States Renal Data Service (USRDS) analysis published in 2006 found a geographic difference in access to types of RRT, with rural facilities less likely to offer home based therapies, but did not explore many other important elements of nephrology service access (eg, dialysis access creation, distance to nephrology services) [8]. Poorer outcomes for patients with increasing distance from nephrology services [9,10] have been documented internationally, but this has not been examined in an Australian context. American, Canadian and Australian studies show that there is a reduced access to kidney transplantation in remote and rural areas, but differences in access to other forms of renal replacement therapy are poorly delineated [11-15].

The Australian Diabetes, Obesity and Lifestyle Survey (AUSDiab) estimated that approximately 16% of the Australian adult population has a marker indicating the presence of kidney damage [16]. This study was conducted in a community-based cohort. There is limited information regarding the health service use and burden of disease of those with CKD especially for those that live in rural and remote areas. A further challenge in nephrology care is that 21% of all patients in Australia starting ESKD treatment programs are referred 'late' to nephrological care (ie less than 3 months before first RRT [3]. There is currently a paucity of data on the geographical distribution of late referral and given that the majority of tertiary nephrology services are provided in large urban areas, areas with fewer nephrologists would appear especially vulnerable to this problem.

Validation of administrative datasets with renal disease specific registries has been conducted in Australia and a high level of agreement between the two collections was found [17-20]. This suggests that the use of an administrative dataset combined with a disease specific registry will allow us to estimate the geographical distribution of kidney disease and derive data on outcomes and burden of both CKD and ESKD. This study will use data linkage of clinical and administrative datasets to study the difference in health service utilization and outcomes between rural and urban CKD and ESKD patients in NSW.

Methods

Overview

Our study hypotheses are that rural patients with ESKD and CKD have higher mortality, higher hospitalization rates, and longer lengths of stay, require more inter-hospital transfers and have higher rates of late referral for RRT compared to similar urban patients. We expect that in an Australian setting, rural patients with ESKD use home-based therapies more often than urban patients, despite evidence to the contrary in a North American setting. We also expect that rural patients with CKD or ESKD and at least one other comorbid condition (cardiovascular disease, diabetes or cancer) have a greater burden of disease defined as a higher mortality, higher hospitalization rates, longer lengths of stay and more requirements for inter-hospital transfer compared to similar urban CKD and ESKD patients.

Study Population

This is a retrospective cohort study consisting of two cohorts (see Figure 1); the first an ESKD cohort and the second a CKD cohort.

The ESKD cohort will be identified using the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). This registry was established in 1963 and maintains records of all patients with ESKD receiving chronic renal replacement therapy (dialysis or transplantation) in Australia and New Zealand. All patients residing in NSW at initiation of ESKD treatment between 1/7/2000 and 31/07/2010 will be included in the ESKD cohort.

The CKD cohort will be identified from within NSW Admitted Patient Data Collection (NSW APDC) by the Centre for Health Record Linkage (CHeReL) [21], and will be defined as any patient admitted to a NSW hospital between 1/07/2000 to 31/07/2010, with a recorded admission using International Classification of Diseases 10 - Australian Modification (ICD-10AM) primary or secondary codes for chronic renal failure or chronic renal impairment including transplantation (Table 1). Patients with ESKD that are in receipt of RRT will also be identified within the CKD cohort. If these patients are also part of the ESKD cohort, in other words identified via ANZDATA, then they will be tagged during record linkage as belonging to the ESKD cohort. Those patients with ESKD that are not in receipt of renal replacement therapy will only be identified as part of the CKD cohort because ANZDATA only records patients that are in receipt of renal replacement therapy.

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Both cohorts will be linked to NSW Admitted Patients Data Collection (NSW APDC), the NSW Registry of Births, Deaths and Marriages (NSW RBDM), and the NSW Central Cancer Registry (NSW CCR). The NSW APDC records all admissions to all NSW health care facilities, the NSW RBDM records all births, deaths and marriages within NSW and the NSW CCR records all new cancers in NSW residents.

Those that are under the age of 18 at the commencement of RRT or at the time of their first admission with a code for CKD will be excluded as well as those that do not normally reside in NSW. Residence will be assessed on the basis of postal code at the commencement of RRT or at the first admission with a code for CKD.

Table 1. ICD-10AM[a] codes used to identify CKD cohort.

ICD 10 code	Description
N18.1	Chronic kidney disease stage 1
N18.2	Chronic kidney disease stage 2
N18.3	Chronic kidney disease stage 3
N18.4	Chronic kidney disease stage 4
N18.5	Chronic kidney disease stage 5
N18.8	Other Chronic renal failure
N18.9, N18.90, N18.91	Chronic kidney disease unspecified
N19	Unspecified renal failure
N 16.0-N16.8	Renal tubulo-interstitial disorders in diseases classified elsewhere
I12.0, I13.1, I13.2	Hypertensive kidney disease with kidney failure
E10.2, E11.2, E12.2, E13.2, E14.2	Diabetes with kidney complication
N00-N07	Chronic nephritic syndrome, Nephrotic syndrome
N11.0, N11.1, N11.8, N11.9, N12	Chronic tubulo-interstitial nephritis
N14.0-N14.4	Drug and other tubular conditions such as analgesic nephropathy
N25.0, N25.1, N25.8, N25.9, N26	Impaired tubular function and unspecified contracted kidney
N27.0, N27.1, N27.9	Small contracted kidney
N28.0, N28.1, N28.8, N28.9	Other disorders of kidney not elsewhere specified
N39.1	Persistent proteinuria
N39.2	Orthostatic proteinuria
B52.0	Plasmodium with nephropathy
D59.3	Hemolytic uremic syndrome
E85.3	Secondary systemic amyloidosis
Q60.0-Q60.6	Renal agenesis
Q61.3	Polycystic kidney disease unspecified
T 82.4	Mechanical complication of vascular dialysis catheter
T86.1	Kidney transplant failure and rejection
Z94.0	Renal transplant

[a]International classification for diseases 10 – Australian Modification

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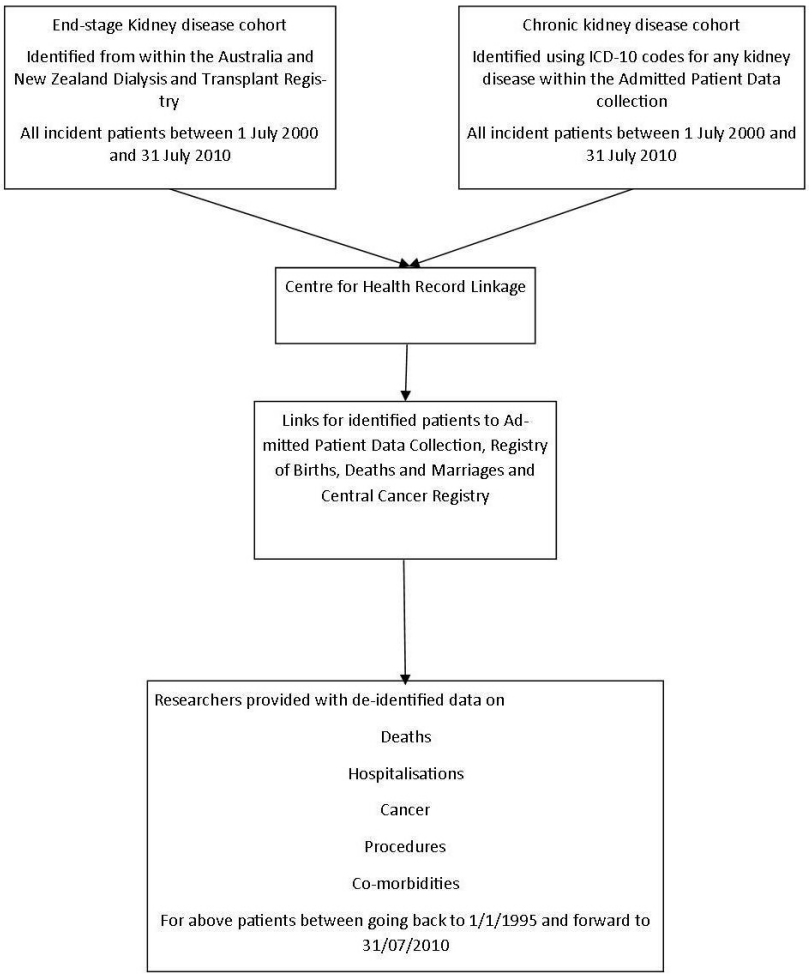
Figure 1. Data linkage process chart.



Exposures and Outcomes

The exposure is rural residence defined using the Accessibility/Remoteness Index of Australia (ARIA) [22]. ARIA provides a measure of remoteness (from service centers) for all places and points in Australia using Geographic Information System (GIS) technology and was developed by the Commonwealth Department of Ageing and Health Care. Categories of remoteness are defined based on road distance to service centers and are: highly accessible (relatively unrestricted accessibility to goods and services), accessible (some restrictions to accessibility of some goods and services), moderately accessible (significant restriction to accessibility to goods and services), remote (very restricted accessibility to goods and services) and very remote (very little accessibility of goods and services). We will use residential postal codes to classify people into categories of remoteness. It is expected that the majority of postcodes will be located within the highly accessible (urban) areas and thus we will define this group as the index group [23]. All other postcodes will be considered as rural. There is no data currently on the geographical distribution of the burden of disease and thus we may need to either combine or separate categories depending on their size.

For the ESKD and the CKD cohorts, the following outcomes will be compared amongst the categories of remoteness: mortality (derived from fact and date of death via the NSW RBDM); hospitalizations (number of hospitalizations and location of hospitalization derived from NSW APDC); length of stay (using the hospitalization data provided by NSW APDC); inter-hospital transfers (calculated using the admission and discharge data gained from the NSW APDC). For the ESKD cohort, an additional outcome of rate of late referral to specialist care (identified via ANZDATA using the late referral flag, which measures those referred to nephrology care who subsequently start RRT within 3 months) and patterns of use of RRT (identified and compared using data on modalities of RRT used by patients from within ANZDATA) will also be compared between the categories of remoteness.

For both cohorts (ESKD and CKD), we will identify those with an additional diagnosis of cardiovascular disease (ICD10-AM Codes: I00-I52.8, I170 to I99), diabetes (ICD10-AM Codes: E10-14), or cancer (ICD10-AM Codes: C00-D48) and compare the outcomes of mortality, hospitalizations, lengths of stay and inter-hospital transfers as defined above.

Data Linkage Methods

Data linkage is probabilistic using demographic markers such as name, date of birth, gender, country of birth, medical record number (MRN), date of first RRT, postcode at first RRT, treating hospital and date of death to link patients identified by

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ANZDATA to the NSW APDC, NSW RBDM and the NSW CCR [24]. All admissions from NSW hospitals going forward to 31/07/2010 and backwards to 1/1/1995 for patients in the two cohorts will be identified using NSW APDC and any diagnosis of cancer will be identified using NSW CCR. Fact of death and date of death will be ascertained using NSW RBDM.

Data linkage will be performed using the services and processes of the CHeReL. CHeReL was established in 2006 with the aim of linking multiple sources of data and maintaining a record linkage system that protects data privacy and is jointly managed by the Cancer Institute NSW and the NSW Ministry of Health. Each data custodian provides information relating to individual persons to the CHeReL. This information consists solely of personally identifying information, plus an encrypted source record number (which is the link to the health dataset records). CHeReL uses the personally identifying information to link records for the same person across different datasets, and assigns a 'person number' to each of these groups of linked records (note that this 'person number' never leaves the CHeReL). CHeReL then develops a set of 'project person numbers' (PPN), which identifies all the records that correspond to a single person. CHeReL uses the *Choicemaker* software package to link records. Clerical review is also conducted for records with doubtful matches, resulting in a false positive rate of <0.5% [25].

Once the required linkage has been completed with the groups of linked records identified and PPNs allocated, the CHeReL removes all identifiable information from the linked data sets and sends the data back to the respective data custodians. The data sent to the custodians contains their own encrypted source record numbers plus corresponding PPNs. The PPNs indicate which records correspond to a single individual so that the researchers can combine data from the different data custodians. Each data custodian then removes the source record numbers, and provides the researchers with the PPNs and the associated requested health data. This process ensures that the researchers are provided with deidentified data in which re-identification is effectively impossible.

Statistical Analysis

We will separate the ESKD and CKD cohorts into categories of remoteness using the ARIA index as explained above [22]. We expect approximately 10,000 patients in the ESKD cohort and approximately 100,000 patients in the CKD cohort, however the CKD cohort is difficult to estimate accurately as there is scant data available on the prevalence of CKD in an admitted patient cohort in Australia. We expect approximately 25% of both cohorts to live outside of urban areas. Baseline characteristics for patients within both cohorts will be compared using *t* test, chi-square and ANOVA. The association between remoteness and mortality will be explored deriving hazard ratios and 95% CIs using Cox proportional hazards models. Hospitalizations and inter-hospital transfers will be compared using logistic regression and Poisson regression. The length of stay outcome, being a continuous variable, will be analyzed using linear models. All models will be multivariable to adjust for demographic variables, comorbid conditions, and geographical access to services. We estimate that our study is powered to detect at least a 5% mortality difference between the urban and rural cohort with at least 90% power and a 0.05 level of significance with 10,000 ESKD and 100,000 CKD patients of which 75% are urban and 25% are rural. Stata 12.1 will be used for analysis and a two - tailed *P* value of <0.5 is set as the level of significance.

Ethical Considerations

This study has been granted ethical approval in January 2012 by the NSW Population & Health Services Research Ethics Committee along with approval from all data custodians. As no identifiable data will be provided to the investigators the risk to privacy of participants from the misuse of personal information used in the record linkage process is extremely small. This risk is further minimized by separating the processes of record linkage and data analysis. All data will be reported in aggregated form and no reports or presentations will identify any individual or organization.

The linkage keys, which allow linking of the relevant datasets, are destroyed 12 months following the supply of the data. After this time there will be no potential to reidentify the data. The data will be stored on secure servers for five years to enable the researchers to answer any queries arising from the publications as per ethical approval.

Results

Overall Population

11,036 patients were identified by ANZDATA, of whom 10,827 patients also had records within NSW APDC. A further 322 patients either had missing postcodes or a non-NSW postcode leaving a total of 10,505 patients with 2,403,455 records in the ESKD cohort. Based on the ARIA categories, 85.46% of patients (8978/10,505) live in highly accessible areas; 11.77% (1236/10,505) in accessible areas; 1.84% (193/10,505) in moderately accessible areas; 0.66% (69/10,505) in remote areas and 0.28% (29/10,505) in very remote areas. For the purposes of analysis, patients living in accessible, moderately accessible, remote and very remote areas were combined as the rural cohort – 14.54% (1527/10,505).

The CKD cohort comprised of 164,236 patients. Exclusion of patients with missing or non-NSW postcodes resulted in 159,033 patients with 1,599,770,776 records in this cohort. Based on ARIA categories, 84.05% (133,667/159,033) live in highly accessible areas; 13.14% (20,904/159,033) in accessible areas; 2.05% (3260/159,033) in moderately accessible areas; 0.65% (1027/159,033) in remote areas and 0.11% (175/159,033) in very remote areas. For the purposes of analysis, patients living in accessible, moderately accessible, remote and very remote areas were combined as the rural cohort – 15.95% (25,366/159,033). The baseline characteristics of both cohorts are detailed in Table 2.

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Table 2. Baseline characteristics of ESKD and CKD patients in New South Wales between 01/07/2000 and 31/07/2010.

	ESKD (Urban) n=8978 (85%)	ESKD (Rural) n=1527 (15%)	*P* value for difference	CKD (Urban) n=133,667 (84.1%)	CKD (Rural) n=25,366 (15.95%)	*P* value for difference
Age (median & IQR)	61 (48-72)	61 (48-71)	.43	75.0 (62-83)	74.0 (62-81.8)	<.001
Male (%)	5246 (58.43%)	888 (58.15%)	.84	69,142 (51.73%)	13,392 (52.80%)	.002
Indigenous Australians (%)	157 (1.75%)	166 (10.87%)	<.001	1161 (0.87%)[a]	1143 (4.55%)[a]	<.001
Comorbidities (%)						
Diabetes (From ANZDATA)	2745 (30.57%)[b]	454 (29.73%) [b]	.51	NA	NA	NA
(From NSW APDC)	1536 (17.11%) [c]	310 (20.30%)[c]	.002	43,072 (32.22%)	8,019 (31.61%)	.06
Cardiovascular disease (From ANZDATA)	3164 (35.24%)[b]	592 (38.77%) [b]	.008	NA	NA	NA
(From NSW APDC)	1237 (13.78%)[c]	220 (14.41%)[c]	.51	46,137 (34.52%)	8,355 (32.94%)	<.001
Peripheral vascular disease (From ANZDATA)	2060 (22.94%)[b]	440 (28.81%) [b]	<.001	NA	NA	NA
(From NSW APDC)	3 (0%)[c]	1 (0%)[c]	.55	107 (0.08%)	9 (0%)	.02
Chronic lung disease (From ANZDATA)	1273 (14%) [b]	291 (19%) [b]	<.001	NA	NA	NA
(From NSW APDC)	198 (2.2%)[c]	41 (3%)[c]	.25	11,545 (8.6%)	2,256 (8.9%)	.18

[a]Recorded for 157,792 (99.21%) patients.

[b]For the ESKD cohort, these were derived from ANZDATA.

[c]Derived using ICD – 10 codes from the NSW Admitted Patient Data Collection. For the CKD cohort these were derived using ICD-10 codes for the index admission and in any admission prior to the index admission from within the NSW Admitted Patient Data Collection. The ICD – 10 codes were as per AIHW: *Australian Institute of Health and Welfare 2011. Cardiovascular disease: Australian facts 2011. Cardiovascular disease series. Cat. no. CVD 53. Canberra: AIHW.*

Results of Data Linkage

The mortality linkage identified a total of 96,313 records (88,020 patients) comprising 5463 records (5028 patients) in the ESKD cohort and 90,850 records (82,992 patients) in the CKD cohort. The linkage with the NSW CCR identified a total of 40,668 cancer records (36,110 patients) comprised of 1905 records (1693 patients) in the ESKD cohort and 38,763 records (34,417 patients) in the CKD cohort.

Discussion

Anticipated Outcomes

This research which has identified 11,036 ESKD patients and 164,236 patients in the CKD cohort will define the geographical distribution of CKD and ESKD as well as the demand for RRT in the NSW population. It will compare and contrast health service utilization between rural and urban populations with a view to informing the design and implementation of strategies to provide appropriate rural health care in the future. We will be able to delineate areas of higher incidence and prevalence and aid prediction of the need for future renal services. Given that 32.3% of the Australian population resides in NSW, this research has relevance for renal policy nationally.

The ANZDATA registry has made significant contributions to our understanding of kidney disease. This study expands the scope of ANZDATA and therefore will increase our insight into the drivers of mortality and poor outcomes in the kidney disease population. The ANZDATA registry however only records patients with ESKD that commence RRT and there has been no avenue previously for obtaining data on those with CKD/ESKD who are not receiving RRT except in the context of clinical trials. Our study allows us to comment on longitudinal outcomes in treated and untreated ESKD patients in a geographical context.

A notable limitation of our study however, is that the ascertainment of CKD relies purely on coding practices and coding intensity. Whilst there is no Australian data estimating prevalence of CKD in an admitted patient cohort, making it difficult to comment on the accuracy of coding for the CKD cohort, this dataset will be an important baseline for future research. Linkage with the ANZDATA registry for the ESKD cohort provides us the opportunity to report on validation of coding for the ESKD cohort as well as their comorbidities. Administrative health data, such as that used in this study, may represent a cheaper and effective alternative to performing large de novo longitudinal studies or maintaining large datasets. If so, it may also be a sustainable long-term option for measurement of disease burden and informing service delivery. A further strength is that because Australia has universal health coverage, our study includes all patients with kidney disease over a 10 year period that have had contact with private or public health care facilities in NSW.

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Conclusions

This is a large retrospective Australian cohort study of patients with ESKD and CKD that uses the linkage of an existing renal registry and administrative datasets to compare the burden and outcomes of kidney disease in rural compared to urban settings. The results will enhance our understanding of the capability of administrative data in measuring kidney disease in Australia, compare the burden and outcomes in patients with kidney disease between rural and urban settings, and contribute to the design and development of renal health service provision in future years.

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Conflicts of Interest

None declared.

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Abbreviations

ANZDATA: Australia and New Zealand Dialysis and Transplant Registry
ARIA: Accessibility/Remoteness Index of Australia
AUSDiab: Australian Diabetes, Obesity and Lifestyle Survey
CHeReL: Centre for Health Record Linkage
CKD: chronic kidney disease
DOB: date of birth
ESKD: end stage kidney disease
GIS: Geographic Information System
HREC: Human Resources Ethics Committee
ICD-10AM: International Classification of Diseases 10 – Australian Modification
MRN: Medical Record Number
NSW: New South Wales
NSW APDC: New South Wales Admitted Patient Data Collection
NSW CCR: New South Wales Central Cancer Registry
NSW RBDM: New South Wales Registry of Births Marriages and Deaths
PPN: project person numbers
RRT: Renal Replacement Therapy
USRDS: United States Renal Data Service

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Original Paper

Household Transmission of Zoonotic Influenza Viruses in a Cohort of Egyptian Poultry Growers

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Abstract

Background: The highly pathogenic avian influenza H5N1 viruses and the low pathogenic H9N2 viruses are enzootic in Egyptian poultry. Several cases of human infection with H5N1 were reported in Egypt. We previously determined that the seroprevalence of H5N1 antibodies in Egyptians exposed to poultry is 2.1% (15/708), suggesting that mild or subclinical infections with this virus occur. We aim to measure the incidence of avian influenza infection in Egyptians exposed to poultry, study risk factors of infection, study the resulting immune response, study household transmission rates, and characterize the viruses causing infections.

Objective: The objective of the study is to design a 7-year, prospective, household-based cohort investigation to determine incidence and household transmission of avian influenza viruses in humans exposed to poultry.

Methods: At baseline, we will collect sera to measure antibodies against influenza A. Field nurses will visit enrolled subjects at least weekly to check for influenza-like illness symptoms and verify influenza infection by a point of care rapid test. From subjects with influenza infection and their household contacts, we will collect nasal swabs, throat swabs, and nasal washes to characterize the antigenic and genetic makeup of influenza viruses infecting humans. The nurse will also obtain 2x 3-ml blood samples, one for serology, and another for isolating peripheral blood mononuclear cells.

Results: Results from this cohort will enhance our understanding of the transmission of avian influenza viruses to humans in a country where such viruses are enzootic.

Conclusions: This may enhance public health efforts aimed at reducing this burden.

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KEYWORDS

influenza; avian; epidemiology; cohort

Introduction

Epidemiology of Avian influenza

Several subtypes of influenza A virus adapted to poultry hosts from wild birds and some were able to cause infections in humans exposed to infected poultry [1,2]. Only two subtypes of influenza A, H3N2 and H1N1, currently circulate in humans. However, avian influenza viruses (AIV) of the H5, H7, and H9 subtypes are known to infect humans. H5N1 has caused more than 660 human infections since 2003, of whom, around 60% died [3]. Recently, an H7N9 virus emerged in China, where it continues to cause severe infections among humans [4]. H9N2 viruses are also capable of causing human infection, but cases

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are sporadic and the infection is not fatal [5,6]. In Egypt, H5N1 viruses are enzootic in poultry, and human cases have been reported continuously since 2006. The total number of cases reported so far in Egypt is 177, of whom, 63 died [3].

Our surveillance for AIV in Egyptian poultry since 2009 revealed that the threat of H5N1 viruses is widespread, as the virus was detected in all poultry production sectors (commercial farms, backyard poultry, live bird markets, abattoirs), in most poultry species, and throughout the year [7]. In early 2011, H9N2 viruses were detected in Egyptian poultry and were found to cocirculate with H5N1 viruses and frequently infect the same avian host [8-10]. H5N1 and H9N2 viruses in Egypt were found to be continuously evolving and contain several markers of adaptation to the human host [11-13].

Alongside our poultry surveillance, we designed and conducted a 3-year, prospective, controlled, seroepidemiological study that enrolled 750 poultry-exposed and 250 unexposed individuals in Egypt [14]. We found that, at baseline, the seroprevalence of anti-H5N1 antibodies (titers ≥ 80) among exposed individuals was (2.1%) 15/708, significantly higher than that among the controls (0%) 0/224. Having chronic lung disease was a significant risk factor for infection. In follow-up, seroprevalence was low (< 0.62%) < 4/649, and not statistically different between the two study groups. Antibodies against H9N2 were not detected at baseline when H9N2 was not circulating in poultry. At follow-up, H9N2 was detected in poultry, and consequently, the seroprevalence among exposed humans was between 5.9% (38/648) and 7.5% (51/682), statistically higher than that among the unexposed subjects. Vaccination of poultry, older age, and exposure to ducks were risk factors for H9N2 [15].

However, by design, seroepidemiological studies do not accurately measure incidence of infection or transmission rates, and do not allow us to characterize the AIV causing infections and the associated immune response. Hence, we plan to conduct a large prospective household study among Egyptian backyard poultry growers designed to study, in real time, AIV infections in this population.

Study Objectives

This study has four primary objectives: (1) to estimate infection incidence of avian influenza (AI) in poultry-exposed human populations; (2) to estimate seroprevalence of AI in poultry-exposed human populations; (3) to investigate potential risk factors associated with AI infections in poultry-exposed individuals; and (4) to investigate secondary infection risk for household contacts.

The secondary objectives of this study are: (1) to characterize the antigenic and genetic makeup of AIV infecting humans; (2) to monitor the pathogenicity and disease severity of AIV causing human infections and the associated immune response; and (3) to investigate the serologic response following confirmed influenza virus infection.

The study design's main feature is close monitoring (up to twice weekly) of the study subjects by trained medical personnel. This will allow us to detect influenza infections in real time, thus enabling timely collection of biological samples and disease prognosis data.

Methods

Study Population and Setting

We will enroll 240 households from the rural areas of Egypt at which backyard poultry is raised. We expect that the 240 households will yield a sample size of 2400 poultry exposed individuals. The majority of the reported human cases of H5N1 in Egypt were located in the Nile Delta region north to the capital Cairo. Our cohort of poultry-exposed subjects will be assembled from villages from 4 governorates in this area, as well as one governorate south of Cairo, where human cases of AIV were also reported (Figure 1 shows this). A village, in which we already conduct poultry surveillance for AIV, will be selected per governorate.

From each study site, we will enroll 48 households (480 individuals) exposed to poultry. We expect that our study population will include adults, children, males, females, and ethnic minorities, reflecting the distribution of these groups in the general Egyptian population.

Enrolling households that raise poultry will fulfill the sampling quota. Within the village, households will be randomly selected using the geospatial sampling capability of the R statistical software. All members of a selected household older than 2 years of age, and where poultry is raised, will be invited to participate and enrolled. Current data show that almost all H5N1 cases were in individuals older than 2 years, thus we decided to exclude infants younger than 2 years. We will also exclude any person who is terminally ill or any person with any known immunosuppressive condition, immune deficiency disease (including human immunodeficiency virus infection), or ongoing receipt of immunosuppressive therapy because of their increased risk of acquiring infections.

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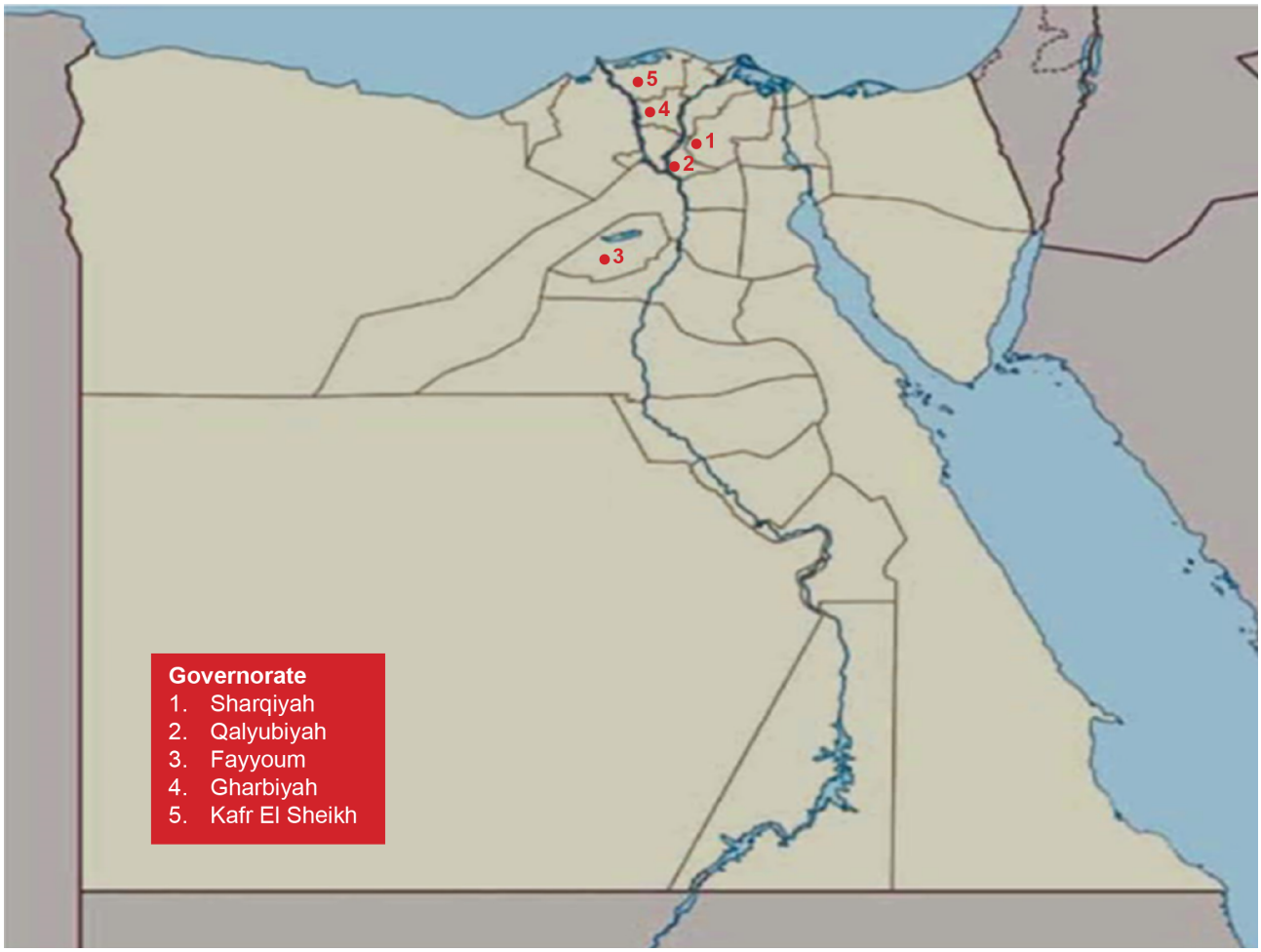
Figure 1. Map showing locations of the study sites.



Study Design and Procedures

Figure 2 shows a schematic of the study design. We designed a 7-year prospective, household-based, cohort study to determine incidence and household transmission of AIV in humans exposed to poultry. At the start of the study, study staff will obtain informed consent, determine eligibility, and collect a serum sample to establish baseline levels of antibodies against AIV. Questionnaires specifically tailored for this study will be used (see Multimedia Appendix 1). Data on the demographics, health status, use of seasonal influenza vaccines, poultry exposure, and use of poultry influenza vaccines will be collected.

After enrollment, field nurses will visit each household twice weekly in the winter season (October through March) or weekly during the summer (April through September) to check if any subject has influenza-like illness symptoms (ILI). This schedule matches the increase in seasonal and AI activity in Egypt. Subjects (index cases) with confirmed ILI (ie, measured body temperature of > 38^{o}C as well as cough and/or sore throat) will provide two nasal swabs for a point of care rapid influenza test and polymerase chain reaction (PCR). The nurse or physician will obtain nasal washes and throat swabs from subjects (index cases) testing positive for influenza A by rapid test or PCR on the nasal swab. The day on which a positive rapid test or PCR is obtained, will be day 1 of sampling. The nurse will also obtain 2x 3-milliliters (ml) blood samples, one for serology to test for antibodies against AIV, and another for isolating peripheral blood mononuclear cells (PBMC) on days 1 and 14. Furthermore, the nurse or physician will obtain nasal washes, throat swabs, and blood samples from all household contacts of the index case on days 1, 3, 6, 9, and 14. A symptoms diary will be started on day 1 and will continue to day 14. Field assistants trained to obtain swabs from poultry will collect cloacal swabs from the poultry in the household on day 1. Any household contact who reports ILI symptoms during the follow-up visits to the index case will then be followed up as per the same follow-up regime of the index case. Study subjects may get infected several times during the same season or over the course of the study.

Annually, all the study subjects will be interviewed again to note any changes in exposure variables. At this time, another blood sample will be obtained and tested for any changes in influenza-specific antibody level.

Human subjects' approval will be sought from the Institutional Review Board of St Jude's Children's Research Hospital, Memphis, Tennessee (FWA0004775) and the Ethics Committee of the National Research Centre, Giza, Egypt (FWA00014747). The Institutional Animal Care and Use Committee of St Jude Children's Research Hospital approved animal work.

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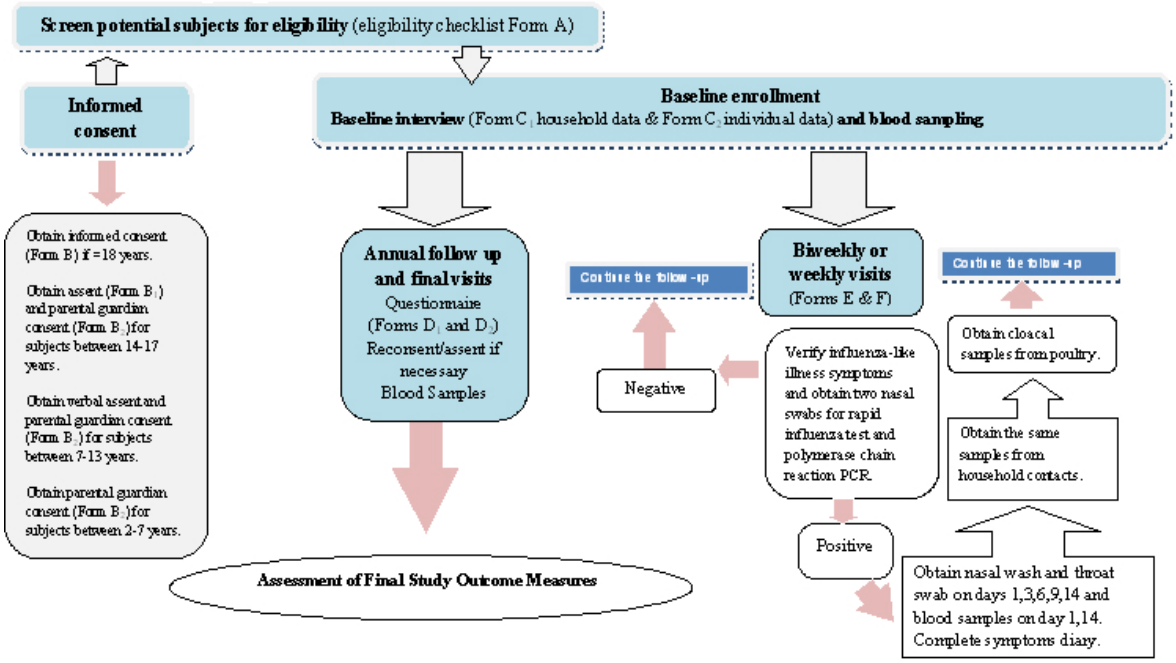
Figure 2. Schematic of the study design.



Sample Size Calculation

Our current data indicate that the seroprevalence of H5N1 among Egyptians exposed to poultry is around 2.1% (15/708); however, other experts estimate incidence rates to be around 0.5% [16]. Assuming that the infection rate in people exposed to H5N1 infected chickens is 0.5%, and that outcome in the unexposed population is 0.01%, and that the ratio of unexposed to exposed is equal to 9 (10% incidence in chickens), we estimate that 2134 people will be needed in our study to achieve 95% confidence and 80% power, to capture a difference (East 6). We plan to enroll 2400 poultry-exposed individuals, considering an approximate 10% lost to follow-up. If the sample seroprevalence of H5N1 is 1% or 2%, with about 10% of the participants lost to follow-up, the margin of error will be 0.4% or 0.6%, respectively. If the sample incidence rate is 0.5% or 0.25%, the margin of error will be 0.3% or 0.2%, respectively.

Specimen Collection and Handling

The field nurse will collect a tube of blood (3 ml) in serum separator tubes. The blood will be allowed to clot at room temperature, and then kept on ice until it arrives at the laboratory on the same day as collection, where the specimens will be then centrifuged. Serum specimens will be aliquoted into multiple cryo-vials, labeled, and preserved at -20°C until ready for laboratory study. Swabs and nasal washes will be kept in tubes and sterile cups, respectively, containing viral transport medium and kept on ice until received in the laboratory, where they will be stored at -80°C until ready for laboratory study. Blood collected for PBMC isolation will be collected in tubes specific for this purpose, then kept on ice until it arrives at the laboratory on the same day as collection, where the specimens will be then processed, collected PBMCs will be preserved in liquid nitrogen until ready for laboratory analysis.

Laboratory Analysis

Sera will be screened for human antibodies (IgG) against AIV H5N1 and H9N2 using a microneutralization assay at a dilution of 1:10 [17]. Viruses used in this assay will be matched to the viruses circulating in the poultry at the time of serum collection. Sera that screen positive will be further studied through a microneutralization assay procedure to determine full titer. Antibodies titer 1:80 and more will be considered positive; such high threshold of antibody titers met the criteria of The World Health Organization, and avoids cross reactivity that can result from anti-H3 and anti-H1 human influenza viruses. Due to the potential cross reactivity of antibodies against human influenza viruses, we will also evaluate the sera against recently circulating human influenza virus subtypes H1N1 and H3N2 using a hemagglutination inhibition assay [18].

Nasal swabs, oropharyngeal swabs, and nasal washes obtained from subjects reporting ILI symptoms and their household contacts will be screened for the presence of influenza A viruses by reverse transcriptase (RT) PCR amplifying the M gene. Further subtyping, culture, and sequencing will be conducted. PBMCs will be tested for innate and adaptive cell phenotyping by flow cytometry and functional assays that will be readout by flow cytometry and enzyme-linked immunofluorescence spot.

Cloacal swabs from poultry owned by subjects reporting ILI will be screened for the presence of influenza A viruses by RT PCR for the M gene. Further subtyping, culture, and sequencing will be conducted for identifying genetic and antigenic characteristics of AIV.

Results

We will estimate new cases (including both index cases and infected household contacts) in poultry-exposed individuals by

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detecting influenza viruses in throat and nasal swabs and nasal washes, obtained from subjects, using rapid tests and molecular techniques. As defined earlier, the overall incidence will be estimated as the proportion of all new cases identified among all study subjects per influenza season or per year. A 95% confidence interval will be provided.

We will measure antibodies against AI viruses in sera collected from all poultry-exposed individuals no matter whether they have confirmed influenza or not. The overall seroprevalence will be estimated as the proportion of sero-positive subjects among all study subjects per influenza season or per year. A 95% confidence interval will be provided.

We will use a questionnaire that collects specific occupational, environmental, and behavioral risk factors. Because we expect both the overall incidence and seroprevalence to be very low, descriptive statistics (frequencies, proportions, etc) stratified by potential risk factors will be summarized to briefly describe the potential trend.

For determining the human-to-human transmission rate, only secondary infections will be considered and analyzed. We will obtain throat and nasal swabs, blood, and nasal washes from the household contacts of poultry-exposed individuals with a confirmed influenza A infection and test them for the presence of influenza A viruses or antibodies against influenza A viruses. We assume that if an illness developed in a household contact of an index patient, the household contact is infected with the virus from the index patient. As defined earlier, the secondary infection rate will be estimated as the proportion of susceptible household contacts of identified index cases with confirmed influenza infection among all susceptible household contacts of identified index cases per influenza season or per year. A 95% confidence interval will be provided.

Discussion

Household Transmission Study

Our previous study about the seroprevalence of H5N1 infection in Egyptians exposed to poultry showed that the number of reported cases is greatly underestimated and that the case-fatality rate is consequently greatly overestimated. However, even the most accurate measurement of seroprevalence cannot indicate the true extent of human infection with H5N1 viruses, as we know too little about the factors that influence the timing and likelihood of seroconversion after exposure. By conducting a large-scale prospective household-based study, we will be able to study the immune response that pursues after infection, and we will be able to characterize the AIV causing infection and compare them to those circulating among the poultry.

This study may have several limitations. Because we will use convenience sampling, selection bias may affect our results. However, poultry backyard-raising practices in rural Egypt are generally homogenous, thus limiting the effects of selection bias on conclusions drawn from this study. Misclassification bias can occur in case of underestimated poultry exposure.

Conclusions

Data from this study may yield a better understanding of incidence and potential risk factors for infection with AIV in poultry-exposed individuals and secondary infection risk for household contacts. The data may well also assist in developing an understanding of the relationship of virus strains to disease severity. The data can estimate AI burden in exposed humans and help decision makers prioritize resources and plan public health interventions. Coupled with results from active AIV surveillance among Egyptian poultry, our findings would provide a better image of the current AIV situation in the country.

Acknowledgments

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Authors' Contributions

ASE, MAE, DAZ, and MRG participated in study design, drafted the manuscript, and will participate in coordination and data acquisition. LT participated in the study statistical design. PPM and RJW participated in study design. MAA participated in study design, will supervise laboratory procedures, and will participate in coordination, data acquisition, and analysis. GK conceived of the study, is the study's lead epidemiologist, will participate in coordination, data acquisition and analysis, and drafted the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Household questionnaire.

[PDF File (Adobe PDF File), 160KB - resprot_v4i2e74_app1.pdf]

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Abbreviations

AI: avian influenza
AIV: avian influenza viruses
ILI: influenza-like illness symptoms
ml: milliliters
PBMC: peripheral blood mononuclear cells
PCR: polymerase chain reaction

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Original Paper

Feasibility of Using a Multilingual Web Survey in Studying the Health of Ethnic Minority Youth

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Abstract

Background: Monolingual Web survey is a common tool for studying adolescent health. However, national languages may cause difficulties for some immigrant-origin youths, which lower their participation rate. In national surveys, the number of ethnic minority groups is often too small to assess their well-being.

Objective: We studied the feasibility of a multilingual Web survey targeted at immigrant-origin youths by selection of response language, and compared participation in different language groups with a monolingual survey.

Methods: The Adolescent Health and Lifestyle Survey (AHLS), Finland, with national languages (Finnish/Swedish) was modified into a multilingual Web survey targeted at a representative sample of 14- and 16-year olds (N=639) whose registry-based mother tongue was other than the national languages. The survey was conducted in 2010 (16-year olds) and 2011 (14-year olds). The response rate of the multilingual survey in 2011 is compared with the AHLS of 2011. We also describe the translation process and the e-form modification.

Results: Of the respondents, 57.6% answered in Finnish, whereas the remaining 42.4% used their mother tongue (P=.002). A majority of youth speaking Somali, Middle Eastern, Albanian, and Southeast Asian languages chose Finnish. The overall response rate was 48.7% with some nonsignificant variation between the language groups. The response rate in the multilingual Web survey was higher (51.6%, 163/316) than the survey with national languages (46.5%, 40/86) in the same age group; however, the difference was not significant (P=.47). The adolescents who had lived in Finland for 5 years or less (58.0%, 102/176) had a higher response rate than those having lived in Finland for more than 5 years (45.1%, 209/463; P=.005). Respondents and nonrespondents did not differ according to place of birth (Finland/other) or residential area (capital city area/other). The difference in the response rates of girls and boys was nearly significant (P=.06). Girls of the Somali and Middle Eastern language groups were underrepresented among the respondents.

Conclusions: A multilingual Web survey is a feasible method for gathering data from ethnic youth, although it does not necessarily yield a higher response rate than a monolingual survey. The respondents answered more often in the official language of the host country than their mother tongue. The varying response rates by time of residence, ethnicity, and gender pose challenges for developing tempting surveys for youth.

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KEYWORDS

feasibility; Web survey; ethnic minority; adolescents; response rate; representativeness; multilingual

Introduction

Population-based youth surveys to monitor young people's health and health behaviors were established in the 1980s in many Western countries, such as the cross-national survey of Health Behaviour in School-Aged Children and the European School Survey Project on Alcohol and Drugs. In these national surveys, the immigrant-origin population often is too small to assess their well-being. Only recently, it has been realized that for developing health-promotion policies and programs, the general surveys do not necessarily give a reliable picture of the ethnically diversified youth population in Western countries [1-4]. There is a need for new tools to gather population data on health and health behaviors of ethnic minority youth.

It has been suggested that multilingualism in survey design is a basic precondition for improving participation and representativeness of different ethnic populations among adults [5,6]. Although the reliability and the quality of standardized interview data are shown to be better than those of postal or telephone surveys [7,8], it is not always a realistic method to be used nowadays due to its high cost and time-consuming nature. Many Western-born ethnic minority youths can respond to the surveys in their host country's language. However, among those born outside their present host country, settlement age varies and their host country language skills might not be good enough to respond to a survey conducted in the host country's language. Cultural values or anxiety about the use of the survey results might be further reasons for not taking part in surveys.

Few tailor-made surveys for ethnic minority youth have been conducted [1-3]. In a German cross-sectional study, 51% (1,479/2,900) of the sample aged 0-17 years having immigration background participated, compared with 68% (16,162/23,768) of the ethnic German population. Computer-assisted personal interview with a translated questionnaire and health examinations were performed on the participants in that study [1]. The participation rate in the Norwegian Youth, Culture and Competence study on ethnic minority minors' health varied between substudies from 43.5% to 65% [2,4]. In the Danish Longitudinal Survey of Children study, 47.5% of the 12-year-old ethnic youths participated in standardized interpreted interviews and completed questionnaires [3]. In Finland, only one tailor-made interview study for immigrant-origin youth has been conducted so far, and the study included Somali- and Kurdish-speaking adolescents living in the capital city area [9].

In Finland, the largest immigrant groups come from Russia, Estonia, Somalia, Iraq, former Yugoslavia, and China [10]. Finland has undergone a rapid ethnic diversification during the last 20 years. However, even today, most immigrant-origin adults and their children are born abroad, and thus, belong to the first generation of immigrants [10]. In Finland, the age structure of people of foreign origin is different from those of Finnish origin: in 2011, the average age was younger among foreign-origin people (37.7 years) compared with Finnish-origin people (42.0 years), and the second-generation Finns with foreign origin are especially young (87% are under 18 years of age) [10]. In Finland, approximately half of the immigrants live in the Southern part of the country in the capital city area where approximately every 1 in 10 persons speaks a non-national language [11].

Little is known about the feasibility and use of multilingual Web surveys in studying health and health behaviors of ethnic minority youth in nationally representative samples. When adolescents are offered an option to use their mother tongue, we expect that their participation is not related to time lived in Finland, country of birth, or ethnicity and that mother tongue is a primary language when answering the survey. Further, we hypothesize that immigrant adolescents' response rate is higher in multilingual surveys targeted specifically to them than in corresponding monolingual surveys targeted to all youths. In this study, we assess the feasibility of the multilingual Web survey targeted to ethnic minority adolescents in Finland using their officially registered mother tongue as a proxy for their ethnicity. First, we analyze the variation in response rates between ethnic groups according to gender, place of birth, time lived in Finland, residential area, and selection of survey language among 16- and 14-year-old adolescents. Second, we compare the response rate in this multilingual Web survey with the response rate in a corresponding survey carried out in the same year and same age group using only national languages.

Methods

Sample and Participants

The representative samples of 14- and 16-year olds whose registry-based mother tongue was other than one of the two official languages in Finland were drawn from the Population Register Centre, Finland, in 2010 (16-year olds) and 2011 (14-year olds). We combined these two data sets giving the total sample size of 800. Because of economic reasons and the small size of certain language groups, the original questionnaire was translated into the 12 most common foreign languages in Finland (Table 1), reducing the sample size from 800 to 639.

This study was built to correspond with the Adolescent Health and Lifestyle Survey (AHLS) database, a national monitoring system of adolescent health and health behaviors in Finland, in which self-administered questionnaires have only been available in the two official languages, Finnish and Swedish. The AHLS was established in 1977 and has been conducted once in every 2 years among nationally representative samples of 12-, 14-, 16-, and 18-year olds living in Finland. Samples have been obtained from the Population Register Center based on the particular dates of birth, so that all adolescents living in Finland and born on certain sample days in June, July, and August have been included in the surveys. From 2009 onward, respondents could have answered via either the Internet or a mailed questionnaire. The AHLS has been approved by the Ethical Committee of the Pirkanmaa Hospital District and by the Ethics Committee of the Tampere region. Details on the methodology

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of data collection using AHLS have been described elsewhere [12].

In the AHLS 2011, the number of 12-18-year-old ethnic minority youths was 383 (3.9% of the sample) and their response rate was 39.2% (150/383) compared with 47.1% (4,416/9,380) among those whose mother tongue was Finnish or Swedish (P=.002). For the comparison of the response rates, we used the data on 14-year olds in the AHLS 2011 of the same 12 language groups as the multilingual survey. The number of 14-year olds in the 12 language groups was 86. No data were available for 2010 as only the 16-year olds were surveyed.

We modified the AHLS into a multilingual Web survey, and the study participants were requested to answer in their preferred language. The self-administered questionnaire included 49 questions related to health behaviors (eg, smoking, use of alcohol, physical exercise, sleep, hobbies), health (eg, perceived health, stress symptoms), school, family, and religion. The vast majority of the questions were structured as *close-ended questions*, where respondents were given a list of answering options. Filling the questionnaire took approximately 30 minutes.

We classified adolescents into seven ethnic groups according to each person's registered mother tongue. We used the language as a proxy of participants' ethnicity. The groups were as follows: (1) Russian; (2) Estonian; (3) Somali; (4) Middle Eastern languages (Kurdish, Arabic, Persian, and Turkish); (5) Albanian; (6) Southeast Asian languages (Vietnamese, Chinese, and Thai); and (7) English. English-speaking youths could have come from different countries of origin, because in many past colonies of the Great Britain, English is still the official language. All participants in the Somali group and 9 of 10 in the Middle Eastern language group reported that they were Muslim.

Translation Process

The AHLS gathers data on health and health behaviors using both online and paper questionnaires in Finnish. The questionnaire includes questions about sociodemographics, self-reported health, and health-related behaviors. Unfortunately, we were not able to follow the key recommendations and guidelines regarding a valid and rigorous translation process (ie, backtranslation) fully in our study [13,14]. Translations were based on the English version of the questionnaire, which was first given to public health university students who were native speakers of the selected languages. They were informed about the objectives and target age groups of the study. The translated questionnaires were then revised by professional reviewers in the Finnish official translation center. Kurdish, Albanian, and Thai questionnaires were translated only in the translation center because there were no native speakers of these languages among the students. Professional translators checked that the texts were linguistically correct and understandable. Both professional translators and native-speaker students were consulted on whether or not different dialects of Persian, Kurdish, Chinese, or Arabian needed to be considered in the translation process. Because they both answered "No," only some minor revisions were made. Finally, professional translators translated the invitation letters and reminder notifications.

E-form Modification

We used a common Web-based e-form platform, which is designed for conducting Web-based surveys. The system allows users to choose the preferred language when answering the questionnaire. From the e-form, the collected information was easily transferrable into spreadsheets and statistics software. Because of software limitations, the original questionnaire was slightly modified concerning the layout of questions and how the answers were to be chosen (ie, drop-down scale). Owing to the technical difficulties in using non-Latin alphabets in the e-form platform, translated paper questionnaires were also created for Russian, Kurdish, Arabic, Persian, Vietnamese, Thai, and Chinese language groups. In 2010, these paper questionnaires were sent along with the first reminder so that the respondents could read the questionnaire in their mother tongue when they had problems typing with the non-Latin alphabet in the e-form. The respondents were informed to return the paper questionnaire by mail in prestamped envelopes. This possibility was not available in 2011 because very few respondents used paper questionnaires in 2010.

Data Collection and Processing

We mailed an invitation letter to the sample of 16-year-old youths in June-August 2010 and to the 14-year-old youths in March-June 2011. Participants received a letter both in their mother tongue and in Finnish. The introductory letter pointed out the confidentiality and the voluntary nature of the survey participation. Along with the invitation letter, a website address and a unique user ID and password were distributed. The minimum requirement for participation was access to the Internet. Nonrespondents were reminded two times via mailed letters. In 2010, the second reminder included a questionnaire asking for a reason for the refusal.

Results were exported from the e-form software to an Excel spreadsheet (Microsoft, Richmond, VA, USA). All personal identifiers were removed from the research file. After the Excel modifications, the data were analyzed using IBM SPSS Statistics, version 20 (IBM Corp, Armonk, NY, USA). All variables used in this study were categorical. The following categories were used in the analyses: gender (boy vs girl), place of birth (abroad vs Finland), time lived in Finland (≤5 years vs >5 years), and residential area (capital city area vs other). Statistical differences between groups were tested using Fisher exact test (two tailed).

Results

The overall response rate of the multilingual Web survey (N=639) was 48.7% (311/639). There was some variation in the response rates between the language groups but the differences were not significant (P=.58; Table 1). A total of 15 adolescents who actively refused to participate in the study gave reasons for doing so. The most common reasons were "I don't want to"/"I don't feel like answering," "Lack of time," and "I am Finnish"/"I don't feel like belonging to the target group."

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Table 1. Sample size, number of respondents, response rate, and the distribution of language groups among sample and respondents.

Language group	Sample size N	Number of respondents	Response rate (%)	Sample (%)	Respondents (%)
Russian	175	84	48.0	27.4	27.0
Estonian	87	49	56.3	13.6	15.8
Somali	86	37	43.0	13.5	11.9
Middle Eastern languages[a]	145	65	44.8	22.7	20.9
Albanian	46	24	52.2	7.2	7.7
Southeast Asian languages[b]	73	38	52.1	11.4	12.2
English	27	14	51.9	4.2	4.5
Total	639	311	48.7	100.0	100.0

[a]Kurdish, Arabic, Persian, and Turkish.

[b]Vietnamese, Chinese, and Thai.

The response rate of the 14-year olds in the 2011 multilingual survey was compared with the corresponding age group in the monolingual AHLS carried out in the same year. The response rate in the multilingual survey was higher (51.6%, 163/316) than in the monolingual survey (46.5%, 40/86) but the difference was not statistically significant (*P*=.47).

With regard to gender, girls participated more actively in the survey than boys: the response rate for girls was 52.5% (167/318) and that for boys was 44.9% (144/321). The difference was nearly statistically significant (*P*=.06). When only one language group was studied at a time, the response rate of girls was significantly higher only among the Southeast Asian language group (66.7%, 26/39 vs 35.3%, 12/34; *P*=.01) and English-speaking youth (80.0%, 8/10 vs 35.3%, 6/17; *P*=.046).

The response rate for those living in the capital city area was lower (45.1%, 119/264) than for those living in other areas of Finland (51.2%, 192/375) but the difference was not statistically significant (*P*=.15). When only one language group was studied at a time, only Russian-speaking youth had a significantly lower response rate among those living in the capital city area (36.7%, 22/60) than in the other areas (53.9%, 62/115; *P*=.04).

The response rate for adolescents born abroad was higher (50.1%, 212/423) compared with the response rate for those born in Finland (45.8%, 99/216) but the difference was not statistically significant (*P*=.32). When only one language group was studied at a time, only the Middle Eastern language group had a significantly higher response rate among those born abroad (50.0%, 54/108 vs 29.7%, 11/37; *P*=.04).

The response rate for those settled in Finland during the previous 5 years was 58.0% (102/176), whereas it was 45.1% (209/463) for those who had lived in Finland for more than 5 years. The difference was statistically significant (*P*=.005). When only one language group was studied at a time, only the Middle Eastern language group had a higher response rate among those having lived in Finland for 5 years or less (74.2%, 23/31 vs 36.8%, 42/114; *P*=.001).

As many as 57.6% (179/311) of the youths responded in Finnish and 42.4% (132/311) responded in their registered mother tongue (Figure 1). There was variation in the selection of the survey language according to ethnicity (*P*=.002). Most English- and Estonian-speaking adolescents answered in their mother tongue, whereas a majority of the youth speaking Somali, Middle Eastern, Albanian, and Southeast Asian languages chose Finnish.

Tables 2 and 3 present the language group distribution between respondents and nonrespondents, that is, whether some groups are overrepresented or underrepresented among the respondents when compared with the nonrespondents. The respondents and nonrespondents are compared by gender, residential area, country of birth, and time lived in Finland.

Estonian, Southeast Asian languages, and English-speaking girls were overrepresented among the respondents, whereas girls speaking Somali and Middle Eastern languages were underrepresented (Table 2). The difference between the respondents and nonrespondents was statistically significant (*P*=.01). Among boys, difference in the distribution of language groups between the respondents and nonrespondents was not statistically significant (*P*=.69). Differences in distribution of language groups between the respondents and nonrespondents also were not statistically significant among those living in the capital city area (*P*=.36), or elsewhere in Finland (*P*=.65), among those born abroad (*P*=.82) or born in Finland (*P*=.10), nor among those who had settled in Finland during the last 5 years (*P*=.43) or before (*P*=.12; Tables 2 and 3).

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Table 2. Distribution of language groups among respondents and nonrespondents according to gender and residential area, % (n), and *P* value for differences between respondents and nonrespondents.

Language group	Gender				Residential area			
	Boys (n=321)		Girls (n=318)		Capital city area (n=264)		Other (n=375)	
	Responded		Responded		Responded		Responded	
	Yes % (n)	No % (n)	Yes % (n)	No % (n)	Yes % (n)	No % (n)	Yes % (n)	No % (n)
Russian	25.0 (36)	27.7 (49)	28.7 (48)	27.8 (42)	18.5 (22)	26.2 (38)	32.3 (62)	29.0 (53)
Estonian	14.6 (21)	13.0 (23)	16.8 (28)	9.9 (15)	18.5 (22)	14.5 (21)	14.1 (27)	9.3 (17)
Somali	15.3 (22)	13.0 (23)	9.0 (15)	17.2 (26)	18.5 (22)	24.8 (36)	7.8 (15)	7.1 (13)
Middle Eastern languages[a]	25.7 (37)	23.7 (42)	16.8 (28)	25.2 (38)	16.0 (19)	15.9 (23)	24.0 (46)	31.1 (57)
Albanian	6.9 (10)	4.0 (7)	8.4 (14)	9.9 (15)	10.9 (13)	8.3 (12)	5.7 (11)	5.5 (10)
Southeast Asian languages[b]	8.3 (12)	12.4 (22)	15.6 (26)	8.6 (13)	12.6 (15)	7.6 (11)	12.0 (23)	13.1 (24)
English	4.2 (6)	6.2 (11)	4.8 (8)	1.3 (2)	5.0 (6)	2.8 (4)	4.2 (8)	4.9 (9)
Total	100 (144)	100 (177)	100 (167)	100 (151)	100 (119)	100 (145)	100 (192)	100 (183)
P value	.69		.01		.36		.65	

[a]Kurdish, Arabic, Persian, and Turkish.

[b]Vietnamese, Chinese, and Thai.

Table 3. Distribution of language groups among respondents and nonrespondents according to place of birth and time lived in Finland, % (n), and *P* value for differences between respondents and nonrespondents.

Language group	Place of birth				Time lived in Finland			
	Abroad (n=423)		Finland (n=216)		≤5 years (n=176)		>5 years (n=463)	
	Responded		Responded		Responded		Responded	
	Yes % (n)	No % (n)	Yes % (n)	No % (n)	Yes % (n)	No % (n)	Yes % (n)	No % (n)
Russian	31.6 (67)	35.1 (74)	17.2 (17)	14.5 (17)	30.4 (31)	35.1 (26)	25.4 (53)	25.6 (65)
Estonian	16.0 (34)	11.4 (24)	15.2 (15)	12.0 (14)	18.6 (19)	20.3 (15)	14.4 (30)	9.1 (23)
Somali	9.9 (21)	9.0 (19)	16.2 (16)	25.6 (30)	14.7 (15)	16.2 (12)	10.5 (22)	14.6 (37)
Middle Eastern languages[a]	25.5 (54)	25.6 (54)	11.1 (11)	22.2 (26)	22.5 (23)	10.8 (8)	20.1 (42)	28.3 (72)
Albanian	4.7 (10)	5.2 (11)	14.1 (14)	9.4 (11)	0.0 (0)	1.4 (1)	11.5 (24)	8.3 (21)
Southeast Asian languages[b]	9.9 (21)	10.0 (21)	17.2 (17)	12.0 (14)	9.8 (10)	9.5 (7)	13.4 (28)	11.0 (28)
English	2.4 (5)	3.8 (8)	9.1 (9)	4.3 (5)	3.9 (4)	6.8 (5)	4.8 (10)	3.1 (8)
Total	100 (212)	100 (211)	100 (99)	100 (117)	100 (102)	100 (74)	100 (209)	100 (254)
P value	.82		.10		.43		.12	

[a]Kurdish, Arabic, Persian, and Turkish.

[b]Vietnamese, Chinese, and Thai.

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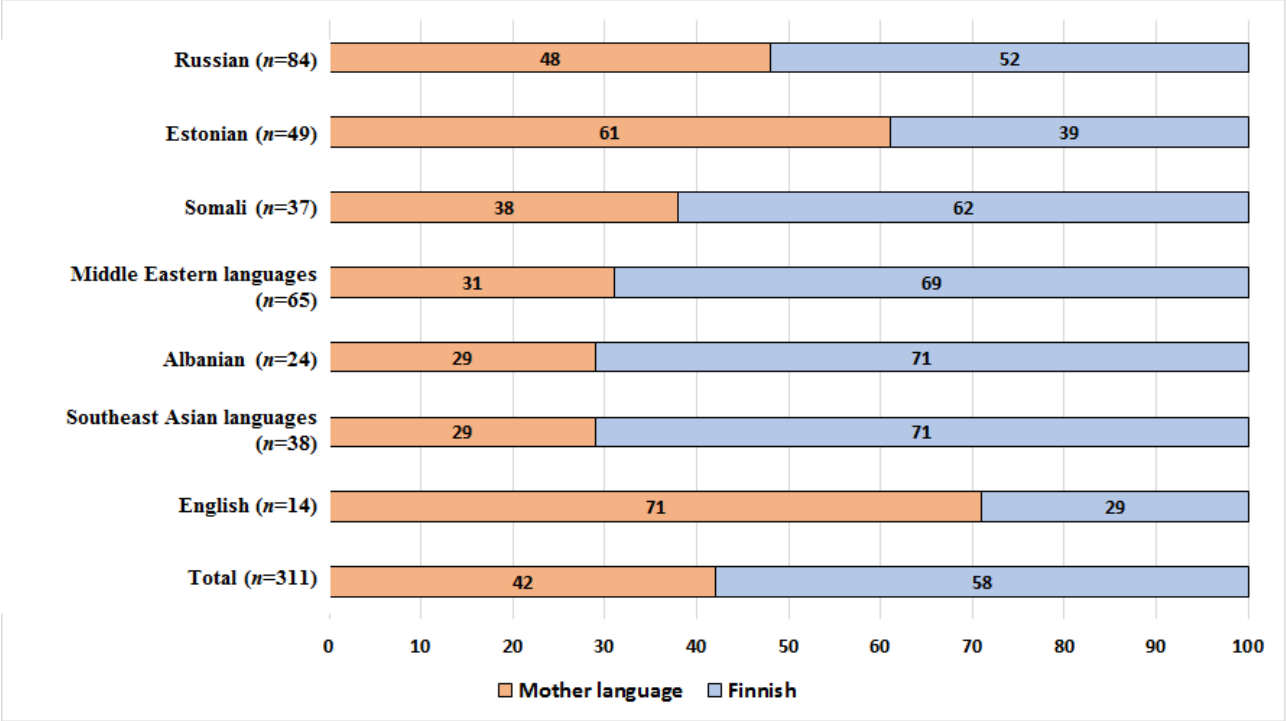
Figure 1. Response language (%) in multilingual Web survey by language group.



Discussion

Nearly half of the respondents used their own mother tongue in filling out the questionnaire. The overall response rate was 48.7% with some nonsignificant variation between the language groups. The overall response rate did not vary statistically significantly by place of residence or country of birth but youth who had lived in Finland for 5 years or less participated more actively than those settled in Finland over 5 years ago; the higher response rate of girls was statistically nearly significant (P=.06) when compared with boys. Some significant differences were observed when studying each language group separately. Among the girls, youths speaking Somali and Middle Eastern languages were underrepresented among the participants.

The multilingual survey made a difference among ethnic minority youth, because as many as 42.4% of the respondents filled in the questionnaire in their mother tongue. There was variation among respondents in terms of their ethnic background. Most Estonian- and English-speaking youths and nearly half of the Russian respondents answered in their mother language, whereas most youths in other language groups selected the Finnish language questionnaire. One explanation for filling the survey in Finnish could be the technical problems with the non-Latin alphabets of Persian, Kurdish, Chinese, Thai, and Vietnamese languages in Western-based software [15]. It could be that these youths were reading the paper questionnaire in their mother tongue while filling out the Web survey in Finnish.

Another explanation for filling out the survey in Finnish could be that some of these youth's language skills in Finnish are better than in their mother tongue. Most first- and second-generation ethnic minority adolescents can speak their mother language well but some of them may not be able to read and write well enough to answer a survey [16]. At home, adolescents may communicate in their mother tongue with their parents and siblings, whereas the selection of language at school with peers may depend on the context.

Some adolescents could have identified themselves more as Finnish-speaking youths or Finnish youths in this study context, rather than according to their ethnic family background, which was indicated in the invitation letter as a reason for sampling in the study. This might explain why they answered in Finnish and not in their mother language and also explain the higher response rate among those who had settled in Finland during the last 5 years compared with those who had lived in Finland for over 5 years.

Women usually participate more actively than men in surveys [17]. The same was observed in our survey although the difference was only nearly statistically significant (P=.06). Girls having their roots in Muslim countries were underrepresented among the respondents. Religion was asked in the questionnaire, and all Somalis and 9/10 in the Middle Eastern language group were Muslim. Somalis are the largest African-origin and Muslim-immigrant group in Finland [10], and health-related studies concerning the Finnish Somali population had been conducted recently, which might have negatively affected their willingness to participate in this survey. In addition, increased hate talk against Somalis and other African-origin immigrant groups on the Internet may have decreased their willingness to participate [18]. Further, culturally determined and gendered survey behavior could have affected Muslim girls' unwillingness to participate. In a Finnish national school survey, the number of participating girls with Somali and Iraqi background was remarkably lower than that of boys even though their numbers in the school population are approximately the same [19]. The actual response rates could not be calculated in that survey.

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Our study was the first population-based study for ethnic minority adolescents in Finland that used a multilingual Web survey. However, the response rate of ethnic minority youth was rather low. This is a common problem in surveys today regardless of the ethnicity of the respondents and it seems that, like our survey, non-school-based surveys also achieve approximately only 50% response rates among ethnic minority youths [1,3,4].

We hypothesized that immigrant adolescents' response rate would be higher in a multilingual survey than in a monolingual survey. We could compare only 14-year olds whose response rate was higher (51.6%) compared with participants in the same age and language groups in the monolingual survey (46.5%); however, the difference was not statistically significant (P=.47). Larger sample numbers are needed to diminish the possibility of chance variation.

For the sampling of ethnic minority youth, we used registered mother language information from the national population registry. The mother language is reported by parents when the child is born or when moving to Finland. Registry-based mother language as a proxy for ethnicity is the least problematic of the proxies normally used; nationality excludes immigrants who have Finnish nationality, and country of birth includes Finns who were born abroad but moved back to Finland. However, it does not necessarily correspond to ethnicity defined by an adolescent himself/herself. Self-defined ethnicity could not be used as a basis for sampling as such a kind of information does not exist in the registry, and this information was not asked in the questionnaire either. Lack of a cross-cultural validity of the translated questionnaires is a significant limitation in studies like this. We cannot exclude validity problems in our study. By contrast, in this study, we used only registry-based data on gender, place of residence, country of birth, and time lived in Finland as well as the language of the questionnaire for analysis. A further limitation of our study was that for economic reasons we could not translate questionnaires to all minority languages. This may have had effects, for example, on the overall response rates.

Internet-based surveys are increasingly used and considered to be a supplement or an alternative to traditional postal surveys. Our results show that a Web survey can be considered a relevant and valid survey method for studying ethnic youth. The advantages of the Web survey are that it is cheaper, eliminates mailing procedure, is faster in transmission of data, and is environmentally friendlier [15,20,21]. In terms of reliability, electronic surveys may reduce social desirability bias and eliminate interviewer effect [22]. In the United States, 13-17-year-old students evaluated an Internet-based health questionnaire positively and it resulted in equal scores of health status or health behavior compared with the paper-and-pencil model [23]. Especially among youth, the Internet is the most promising tool as a data-collection vehicle, because they have been the early adopters of the rapidly growing Internet in most countries [22,24-26]. In Finland, nearly every adolescent has access to the Internet and most have a mobile phone enabling direct access to the Internet [27]. Adolescents have grown up with this technology and it appears to be an integral part of their daily lives. Beside many positive aspects, Internet-based health surveys also pose challenges [22,28] in an age when survey participation rates have declined significantly everywhere. All things considered, a multilingual Web survey with specific ethnicity-related questions can be recommended for collecting data on health and well-being of ethnic minority youth. Such a survey can be linked with national youth surveys by oversampling of immigrant-origin youth and creating optional Internet-based questionnaires in all relevant languages.

To conclude, multilingual Web survey is a feasible method for gathering data from ethnic youth, although several questions need to be scrutinized when developing tempting surveys for youth. First, the multilingual survey is not a self-evident guarantee for a higher response rate than in monolingual national surveys. Response rate seems to vary according to ethnic background, gender and the time of residence in the host country. The longer the youths have lived in the host country, the less likely they are to answer the multilingual survey, and thus, the self-defined ethnicity might play a role in terms of participation. Second, the youths do not automatically respond in their mother tongue, but may prefer to answer in the official language of the host country.

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Authors' Contributions

AHR and SUR planned the survey. LAP and JMK transformed the multilingual survey into Web context, and LAP delivered the data. MM, JMK, and LAP did the analyses. All authors participated in planning and writing of the article.

Conflicts of Interest

None declared.

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Abbreviations

AHLS: Adolescent Health and Lifestyle Survey

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Original Paper

Feasibility of a Dynamic Web Guidance Approach for Personalized Physical Activity Prescription Based on Daily Information From Wearable Technology

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Abstract

Background: Computer tailored, Web-based interventions have emerged as an effective approach to promote physical activity. Existing programs, however, do not adjust activities according to the participant's compliance or physiologic adaptations, which may increase risk of injury and program attrition in sedentary adults. To address this limitation, objective activity monitor (AM) and heart rate data could be used to guide personalization of physical activity, but improved Web-based frameworks are needed to test such interventions.

Objective: The objective of this study is to (1) develop a personalized physical activity prescription (PPAP) app that combines dynamic Web-based guidance with multi-sensor AM data to promote physical activity and (2) to assess the feasibility of using this system in the field.

Methods: The PPAP app was constructed using an open-source software platform and a custom, multi-sensor AM capable of accurately measuring heart rate and physical activity. A novel algorithm was written to use a participant's compliance and physiologic response to aerobic training (ie, changes in daily resting heart rate) recorded by the AM to create daily, personalized physical activity prescriptions. In addition, the PPAP app was designed to (1) manage the transfer of files from the AM to data processing software and a relational database, (2) provide interactive visualization features such as calendars and training tables to encourage physical activity, and (3) enable remote administrative monitoring of data quality and participant compliance. A 12-week feasibility study was performed to assess the utility and limitations of the PPAP app used by sedentary adults in the field. Changes in physical activity level and resting heart rate were monitored throughout the intervention.

Results: The PPAP app successfully created daily, personalized physical activity prescriptions and an interactive Web environment to guide and promote physical activity by the participants. The varied compliance of the participants enabled evaluation of administrative features of the app including the generation of automated email reminders, participation surveys, and daily AM file upload logs.

Conclusions: This study describes the development of the PPAP app, a closed-loop technology framework that enables personalized physical activity prescription and remote monitoring of an individual's compliance and health response to the intervention. Data obtained during a 12-week feasibility study demonstrated the ability of the PPAP app to use objective AM data to create daily, personalized physical activity guidance, provide interactive feedback to users, and enable remote administrative monitoring of data quality and subject compliance. Using this approach, public health professionals, clinicians, and researchers can adapt the PPAP app to facilitate a range of personalized physical activity interventions to improve health outcomes, assess injury risk, and achieve fitness performance goals in diverse populations.

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KEYWORDS

exercise; Web-based interventions; activity monitoring; physical fitness; algorithms

Introduction

Despite an extensive history of evidence-based recommendations about the amount of physical activity needed to improve or maintain health [1-7], physical inactivity has emerged as a global health concern [8] and identification of an ideal, personalized physical activity dose remains elusive. Current physical activity guidelines [5] specify a minimum dose of physical activity to achieve health benefits, encourage increasing this dose to yield greater benefits, and warn that beyond an undefined threshold, risk of musculoskeletal injury [9] or adverse cardiac event [10] outweigh positive health gains. Characterization of the appropriate progression to complete the minimum dose to achieve specific health benefits and identification of a maximum dose that will not cause adverse effects, however, has been limited by a paucity of data [11]. Additionally, effective application of these guidelines is complicated by considerable heterogeneity in individual fitness and physiological responses to physical activity [12-14]. Given the complexity and ambiguity of the individual dose-response relationship between physical activity and fitness, it is not surprising that many physicians have undervalued the prescription of physical activity as part of routine clinical care [15,16], and many individuals do not achieve the minimum recommended physical activity level [17,18].

Web-based interventions offer an increasingly popular approach to dispense physical activity and health behavior guidance [19-24]. Internet access enables programs to reach large numbers of adults at reduced cost compared to face-to-face meetings, provides convenient access to health information, and allows greater management of the intervention process [23,25]. Advances in computing technologies have also permitted the generation of tailored guidance, the personalization of health messages based on variables related to models of behavior change [26]. Tailored physical activity programs have been shown to produce positive improvements in physical activity levels. These increases, however, are typically modest, short-term, and vary greatly based on intervention features [27-30].

Objective assessment of physical activity and health outcomes may improve the efficacy of tailored, Web-based physical activity interventions [21]. Many programs have relied on surveys to assess physical activity habits [19,27], but underestimation or biased responses [31,32] have contributed to inconsistent physical activity outcomes [21]. Use of pedometers and activity monitors (AMs) to track and provide physical activity feedback has demonstrated positive effects on physical activity habits [33], but to date, few studies have used these devices to guide, tailor or evaluate physical activity interventions [34-39]. Further, monitors used in previous studies used technology that was unable to accurately quantify both the intensity and duration of walking and running [40] and physiologic responses such as heart rate. Many individuals have a difficult time identifying physical activity intensity [18]. For these individuals, objective assessment of physical activity intensity using heart rate may allow for more refined and adaptive feedback to help them achieve an effective and safe physical activity dose [1].

The development of an integrated technology platform that combines the accessibility of the Internet with objective data from the growing number of wearable devices may provide new opportunities for public health professionals and clinicians to promote physical activity and understand its relationship to health. Public health groups, for example, could partner with wearable device companies to track compliance to workplace wellness programs and award incentives. Similarly, physicians could create physical activity interventions tailored to specific patient populations, monitor adherence and physiological response, and make adjustments to the plan to more effectively achieve diverse health outcomes. As a first step towards realizing these opportunities, the objectives of this study were to (1) develop a personalized physical activity prescription (PPAP) app that combines dynamic Web-based guidance with multi-sensor AM data to guide and promote physical activity and (2) to assess the feasibility of using this system in the field.

Methods

PPAP App Development

A series of steps were completed to develop the PPAP app. Initial processes included selection of a target population and creation of a physical activity intervention framework. An algorithm was then written to personalize the physical activity framework for each participant and create daily physical activity prescriptions. This algorithm was encoded into a combined AM and dynamic Web app that created physical activity prescription files, managed AM data, and provided feedback to participants regarding their progress in the physical activity intervention. Administrative features were added to the app to improve monitoring of data quality and participant compliance. Descriptions of these development processes are presented in the following sections.

Target Population

Adults with a low-risk for acute cardiovascular events during physical activity (asymptomatic men and women with ≤ 1 cardiovascular disease risk factor) and a sedentary lifestyle were the target population for the initial PPAP app. These individuals were selected because they (1) are likely to experience greater improvements in cardiorespiratory fitness (CRF) compared to individuals with moderate or high baseline CRF levels [41], (2) can safely pursue physical activity without medical examination or supervision [2], and (3) represent a large population that could potentially benefit from the PPAP app and improve various health outcomes. Prior to utilization of this PPAP app, potential participants would be screened via an in-person or telephone survey to assess their cardiovascular risk [42] and

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physical activity level [43]. Individuals with a moderate or high level of physical activity and those respondents categorized as moderate (≥ 2 or more cardiovascular disease risk factors) or high (have symptoms or diagnosed metabolic, pulmonary, or cardiovascular disease) risk for acute cardiovascular events during physical activity would not be considered part of the target population and would not be appropriate candidates for using this version of the PPAP app.

Standard Physical Activity Intervention Framework

A twelve-week physical activity intervention plan based on American College of Sports Medicine (ACSM) training progression guidelines for sedentary, low-risk adults was adapted as a standard intervention framework [1]. In this intervention, different combinations of the components of a physical activity dose (ie, activity type, intensity, duration, and frequency) are incremented until the individual achieves the minimum weekly physical activity volume recommended by current Federal physical activity guidelines [5]. Activity type is restricted to walking and running due to the measurement capabilities of the multi-sensor AM used in combination with the app. Specific guidelines for weekly physical activity frequency, duration, and intensity are outlined (Table 1). Recommended frequency is set to a minimum of three sessions per week with an optional fourth day of activity. Each activity session includes three phases: warm-up (5 minutes), endurance (variable duration), and cool-down (5 minutes). Physical activity intensity is prescribed with target heart rate zones defined with the heart rate reserve method, the most accurate method of establishing target heart rate [44], with the Target HR Zone = ([HRmax - HRrest] · percent intensity) + HRrest, and where HR = heart rate (beats per minute [bpm]), HRmax = maximum heart rate (bpm), and HRrest = resting heart rate (bpm).

Progressive increases in physical activity duration and intensity are created to gradually increase the physical activity stimulus each week to allow positive physiological adaptations and improve health [1]. Because the target population has low baseline levels of physical activity and CRF, initial physical activity doses have a short duration and low physical activity intensity (ie, low target heart rate zone). This approach reduces the risk of aggressive overload of the body's structures and may improve exercise adherence [1,46]. After the first week, increases in physical activity duration or intensity occur in an alternating biweekly manner by increments of approximately 20% and 5% of HRRe, respectively [1].

A 12-minute run/walk exercise field test (EFT) is included as the first activity session of the 12th week. The purpose of this EFT is to explore the feasibility of estimating CRF and measuring post-exercise heart rate recovery (HRR) in unsupervised conditions outside of clinical environments. This information is needed to advance the utility of EFTs to screen and monitor coronary heart disease risk in large asymptomatic populations [45].

Table 1. The standard physical activity intervention framework created for the PPAP app.

Week	Frequency (Sessions/Week)	Intensity (%HRRe[c])	Duration[a] (min)
1	3	40-50	20
2	3-4	40-50	25
3	3-4	45-55	25
4	3-4	45-55	30
5	3-4	50-60	30
6	3-4	50-60	35
7	3-4	55-65	35
8	3-4	55-65	40
9	3-4	60-70	40
10	3-4	60-70	45
11	3-4	65-75	45
12[b]	3-4	65-75	50

[a]Duration values do not include warm-up (5 min) and cool-down (5 min) periods.

[b]A 12-min walk/run exercise field test [45] is prescribed for the first activity session of the 12th week.

[c]%HRRe: percent of Heart Rate Reserve

PPAP Algorithm

An algorithm was developed to create daily, personalized physical activity prescriptions from the standard physical activity framework for each participant. Daily and weekly physical activity doses completed by a participant are monitored and used to create the next dose prescription according to the rule-sets written for the PPAP algorithm (Figure 1). The algorithm begins at day one of an intervention and advances by day number, incrementing a counter each week. Within each week, physical activity frequency is queried to determine if a physical activity or rest session should be prescribed. The

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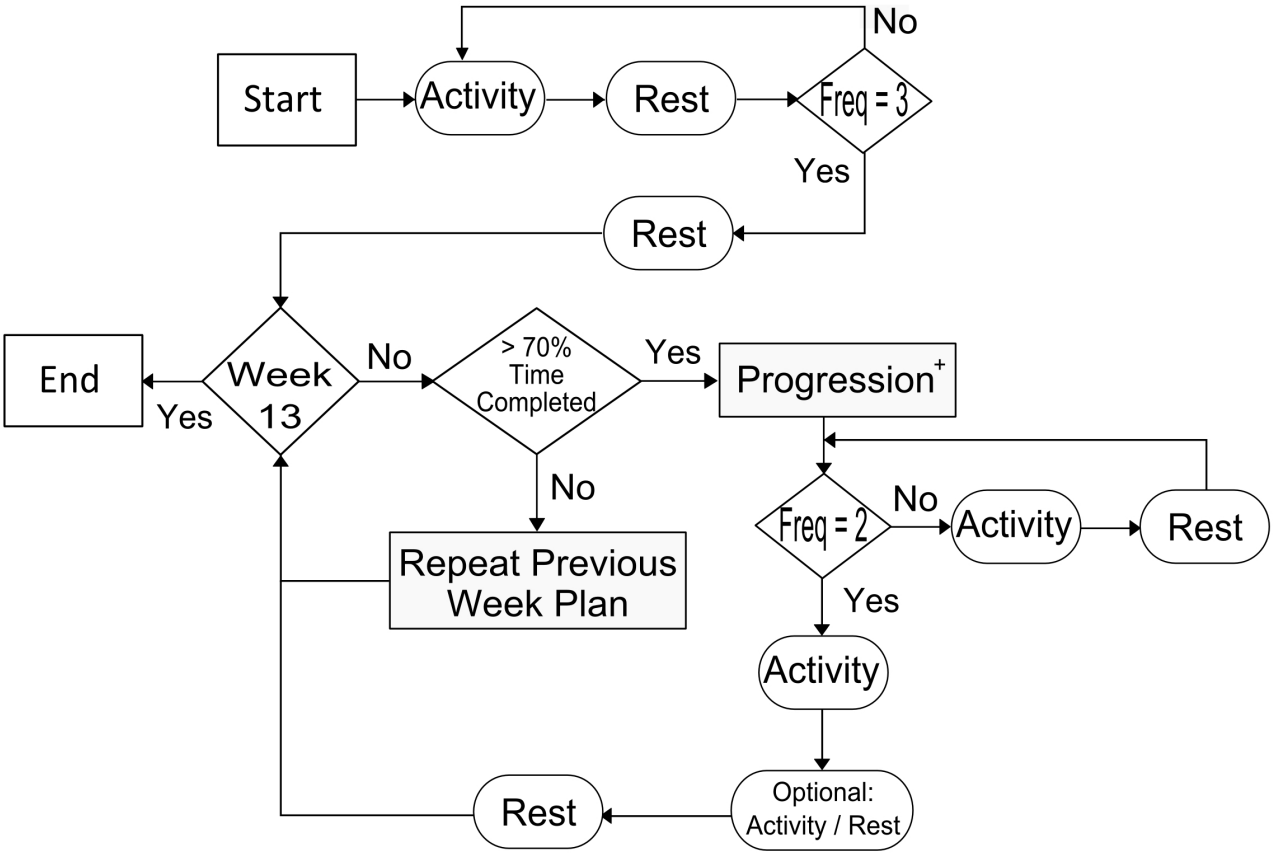
participant is presented an optional activity session on the sixth day of the week. If the optional session is selected, then its physical activity duration is added to the recommended total.

The algorithm includes two key personalization features: (1) the rate of progression and (2) adaptation of target heart rate zones. The rate of progression in the intervention is based on the individual's compliance with the recommended physical activity sessions. Starting at the end of week two, the user's weekly physical activity duration is calculated. If the user's total duration is less than 70% of the recommended amount, the intervention does not advance to the next week's prescription plan. Target heart rate zones are adjusted according to changes in each participant's weekly average HRrest. This step enables the recommended physical activity intensity to be adapted to possible changes in the participant's cardiovascular health that could occur in response to aerobic training over the time course of the intervention [47].

Figure 1. Illustration of the PPAP Algorithm used to decide the sequence of activity and rest sessions and the progression of exercise duration or intensity.



Combined AM and Dynamic Web-Based Guidance

Overview

A guidance program that combines AM data with a dynamic Web-based app was developed to generate personalized physical activity prescriptions, manage and store physical activity data, and provide interactive feedback to the participant. Data extracted from the participant's AM directly influences the operation of the PPAP app (Figure 2). An overview of the multi-sensor AM, software components, and website features is presented in the following sections.

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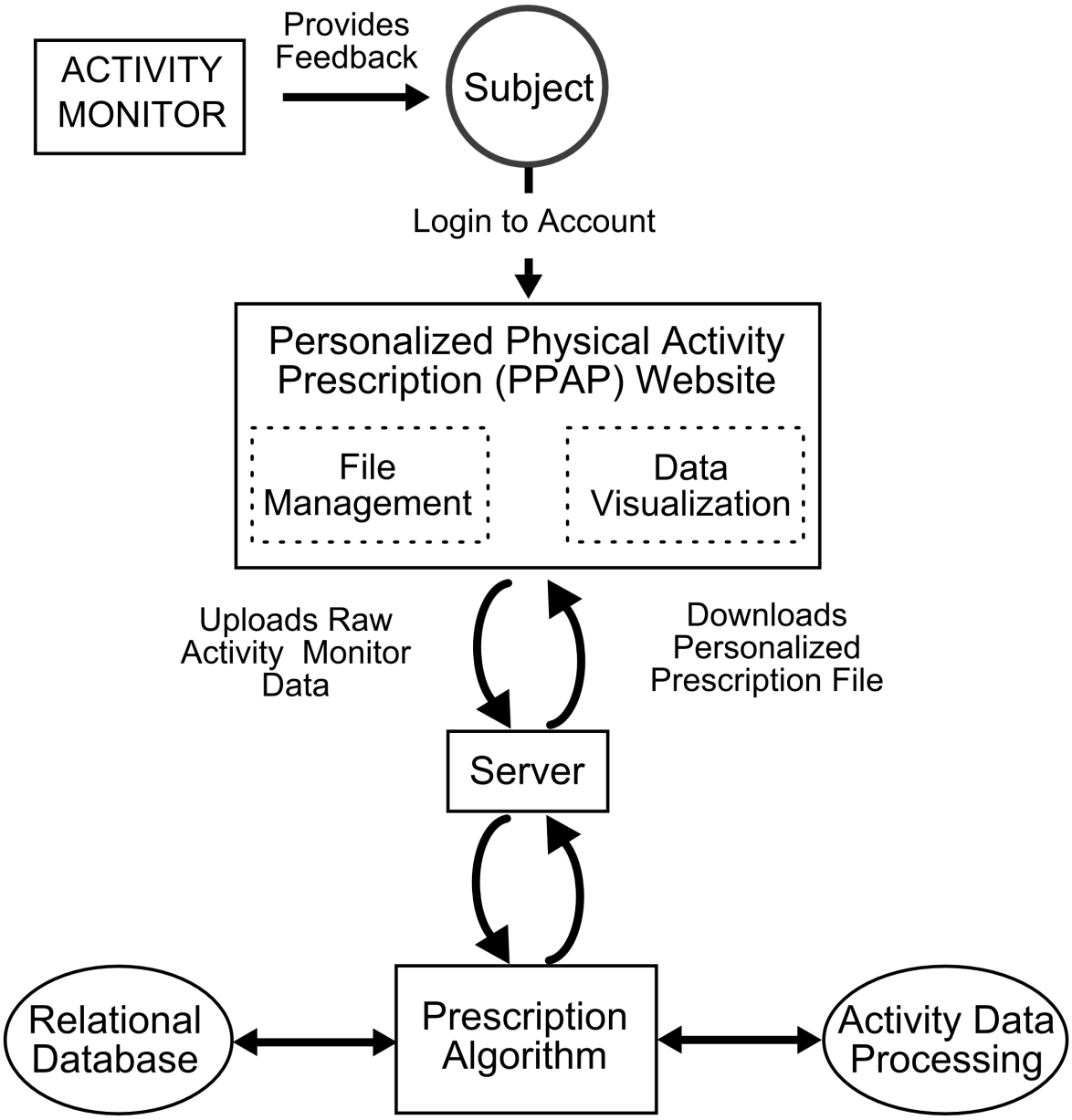
Figure 2. Diagram of the data-flow within the PPAP app.



Multi-Sensor Activity Monitor

A custom, multi-sensor AM (Figure 3) was developed to obtain objective measures of physical activity and resting heart rate for the PPAP app. The custom AM contains a triaxial accelerometer (ADXL345 ± 8g amplitude range, Analog Devices, Norwood, MA) and a commercially available heart rate monitor (Polar Wearlink Coded 31 Transmitter and OEM module, Polar Electro Oy, Kempele, Finland). Acceleration [48] and heart rate data [49] using these sensors have been previously shown to be accurate and reliable. The AM operates for up to 70 hours on single battery charge and can record approximately 728 hours of binary acceleration and heart rate data to a 1 GB micro-SD card, a sufficient data storage capacity for field-based physical activity surveillance studies.

The AM has two modes of operation: a default mode and a resting heart rate mode. During default mode, the AM records continuous triaxial acceleration and heart rate data to an "activity" file. These data are used to determine physical activity frequency, duration and intensity. When resting heart rate mode is initiated, ten minutes of instantaneous heart rate data are recorded to a "heart rate" file, and data from the middle five-minute interval are averaged to determine a daily HRrest value. Quantification of these AM data enables physical activity prescriptions to be personalized for each participant.

The AM also provides the participant with a tool to monitor his or her progress and compliance during an activity session. Daily physical activity prescriptions are written to a binary data file that is downloaded to the AM memory card. When the AM is turned on, the file contents (specific physical activity duration and target heart rate zone limits) are read and used to trigger visual feedback in the form of small lights. Two blinking lights on the top of the AM are illuminated for five seconds to inform the participant of the end of warm-up, endurance, and cool-down

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phases of the activity session. During the endurance portion, the AM computes a five beat moving average of instantaneous heart rate, and a sequence of lights are turned on if the average heart rate is above or below the target heart rate zone. This feedback is designed to encourage participants to avoid under- or over-estimation of moderate and vigorous intensity levels.

Figure 3. Illustration of the multi-sensor AM used to provide objective measures of resting heart rate and physical activity duration, frequency, and intensity to the PPAP app.

PPAP App Software Components

Free, open-source software components were chosen to implement the PPAP algorithm and create a dynamic website [50] that would vary according to user parameters. Open-source software was selected to capitalize on continuous performance and security developments, and to allow experienced contractors or software engineers to manage system administration. The selected LAMP (an acronym derived from the first letter of each software component) solution stack included: a Linux operating system (Ubuntu LTS version 12.04 (Precise Pangolin), Canonical Ltd, London, United Kingdom), Apache Web server (version 2.2, Apache Software Foundation, Forest Hill, MD), MySQL database management system (version 5.1.37 | Ubuntu, Oracle, Redwood City, CA, USA), and PHP scripting language (version 5.2.10, The PHP Group). In addition to these core software, format and layout of the website was completed using HTML, cascading style sheets (CSS), and JpGraph, an object-oriented graph library for PHP (version 3.0.7, Asial, Tokyo, Japan). Processing of AM files is performed using custom scripts written in MATLAB (version r2010a, The Mathworks, Natick, MA).

PPAP App Dataflow

Server-side scripting is used to control dataflow, manage user-specific Web content, and create physical activity prescription files (Figure 2). The server was designed to return responses to three specific participant requests: (1) account creation/login, (2) AM file management, and (3) data visualization. The server contains 2 TB of storage, and load testing was performed to ensure it could quickly manage simultaneous requests from a minimum of 50 participants without loss of data. PHP functions (“Prescription Algorithm”) process requests and coordinate actions via “Activity Data Processing” or “Relational Database” software. Interpretation of PHP functions by the server generates the resulting Web page for the participant.

The system administrator coordinates account creation and login. Following eligibility screening and baseline fitness testing, an account is created for each participant and populated with physiologic information (ie, HRrest and HRmax values) to customize target heart rate zones. This action triggers an automated email to the participant with instructions to select unique login and password information. Account information is encrypted to protect the participants’ anonymity from both external attacks and administrative oversight.

AM file management comprises the upload of new AM files and download of personalized physical activity prescription files. PHP functions eliminate empty or repeated files, identify file type (“activity” or “heart rate”), and initiate appropriate data processing scripts for each file uploaded to the server. Custom MATLAB functions complete a series of steps to process raw data into computable structures for the PPAP algorithm. First, binary files are converted to integer and character variable arrays. Data quality is then evaluated to assess AM functionality and subject compliance. Activity data are excluded from the PPAP algorithm if no heart rate data are recorded or the average heart rate during the physical activity session is < 80 bpm. Resting heart rate data are filtered with a 10 beat moving average to remove aberrant beats or noise. Heart rate data are not used for the calculation of weekly average resting heart rate if > 20% are filtered or if the file is less than 7.5 minutes in length. Finally, relevant processed data features

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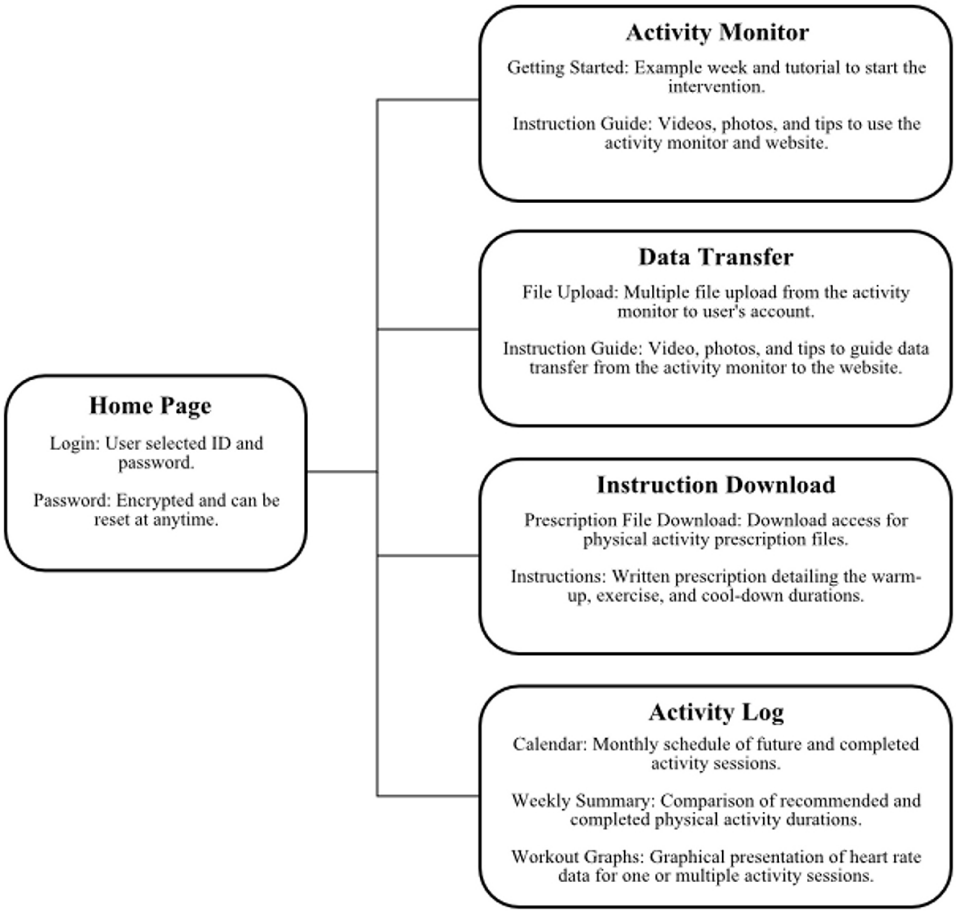
such as physical activity duration, calibrated triaxial accelerations, heart rate, and resting heart rate are exported to text files labeled with unique user and file identification keys for storage in the relational database. The relational database management system coordinated the storage and retrieval of data in response to PPAP algorithm and user driven queries. The database also contains physical activity duration and intensity limits based on the standard physical activity intervention framework (Table 1). PHP functions based on the PPAP algorithm (Figure 1) retrieve user-specific physiologic data (target heart rate zone), intervention date, and standard plan constraints to create personalized physical activity prescription files for the participant to download to the AM.

Lastly, an interactive Web environment was developed to provide resources and data visualization to guide users during the physical activity intervention (Figure 4). Instruction manuals, tutorial videos, and frequently asked questions and answers were created to provide guidance regarding the operation and maintenance of the AM. Data transfer and instruction download menus provided users with easily accessible tools to upload and download AM and physical activity prescription files, respectively. Participants could also compare completed and recommended physical activity data in multiple interactive formats. A calendar displayed both a monthly schedule of future physical activity recommendations to assist with weekly planning and a reference to track completed physical activity sessions. Daily and weekly physical activity duration totals were also summarized in a tabular format. Participants could use this feature to track improvements in weekly physical activity duration and monitor their progress in the intervention. Further, participants could graph up to three completed individual physical activity sessions to compare changes in heart rate response during activity.

Figure 4. Description of the content and interactive features of the PPAP website.



Administrative Monitoring Features

A series of quality assurance and administrative monitoring features were created to manage errors resulting from the complex interactions between the subject, AM, and PPAP app (Table 2). Ideally, participants uploaded AM files to the PPAP app on a daily basis. Perfect compliance with this schedule, however, was not expected due to possible Internet/computer access and time constraints. Management of delayed upload or missing data, therefore, was a primary concern for accurate personalization of physical activity prescriptions. Missing resting heart rate and activity data resulted in the insertion of a 'null' value or zeros in the database, respectively. If the subject uploaded the file on a different date, the filename and timestamp were used to determine allocation of the data to the correct intervention date in the database. If multiple resting heart rate files were uploaded on a single day, then the first file that passed quality assurance checks was saved. Multiple activity files, however, were concatenated so that the user received credit for all activity sessions completed on a given day. Generation of an optional physical activity session (Figure 2) required the subject to complete no more than two consecutive days of

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physical activity. If the optional file was not downloaded, its duration was not added to the weekly total. Calculation of completed weekly physical activity duration occurred at the end of the intervention week. Consequently, any activity files uploaded after the start of a new week were not included in the adherence check (Figure 2).

Additionally, the pattern of file management provided a method for study administrators to communicate and track participant compliance with the PPAP app. Automated emails were sent to both the participant and study administrator following account creation, at the start of the physical activity intervention, one day prior to the EFT, and at the conclusion of the intervention. These emails contained instructions, helpful links, and contact information for the study administrator. In addition, missing resting heart rate data for three consecutive days or the lack of file uploads for seven consecutive days triggered an automated email reminder and survey (Table 2), respectively. The survey was constructed to identify any possible problem with the participant's compliance with the intervention (e.g. injury, illness, travel, technical difficulties). The system administrator also received daily logs of file upload and quality assurance checks for each participant. These logs enabled the administrator to identify errors with file transfers and AM malfunctions such as a faulty heart rate monitor battery.

Table 2. Remote administrative data monitoring features in the PPAP app.

	Frequency	Error type	Corrective action
Heart rate			
	Single day	No data	Insert null into database.
		Late upload	Extract database location from filename.
		Multiple files	Use the first file that passes quality checks.
	Three days	No data	Insert null into database and email reminder.
		Late upload	Extract database location from filename.
Activity			
	Single day	No data	None.
		Late upload	Extract database location from filename and create prescription using these data.
		Multiple files	Concatenate physical activity duration data.
	Two days	Optional day	Recommend rest for optional day.
Prescription			
	Single day	Optional day	Add prescription to total if file is downloaded.
	Multiple days	No download	Email notification to study administrator.
All files			
	Missed 7 days	No data	Email user to identify problem source.

PPAP Feasibility Study

A feasibility study was completed to ensure that the PPAP app could administer a 12-week physical activity intervention and that website features were intuitive, easy to navigate, and motivational. Potential subjects were screened via a telephone survey to assess their physical activity level and risk for acute cardiovascular events during physical activity. Two apparently healthy, sedentary men who passed the screening and satisfied the target population characteristics were recruited from the Sacramento, CA area, and enrolled in the study. The University of California, Davis Institutional Review Board approved the protocol, and both subjects gave written informed consent.

Protocol

Overview

Each subject completed a preliminary session, baseline resting heart rate measurements, and 12 weeks of physical activity training.

Preliminary Session & Baseline Resting Heart Rate Measurements

During the preliminary session, subjects were given a multi-sensor AM, an account on the PPAP app, and an orientation to AM and website functions. Baseline resting heart rate measurements were completed for at least five days at the subject's home to establish a HRrest value for the PPAP algorithm. To complete a resting heart rate session, the subject would don the AM, initiate the resting heart rate mode, and lay supine for 10 minutes immediately after waking. If the resting heart rate data were not uploaded to the server, HRrest was set to 65 bpm to avoid algorithm errors.

Physical Activity Intervention

Subjects were provided with 12 weeks of personalized physical activity guidance via the PPAP app. Subjects were instructed to complete daily resting heart rate and prescribed physical activity sessions while wearing the AM and to regularly upload AM files from these sessions to the PPAP app. In addition,

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subjects received instructions to perform a 12-minute run/walk EFT at the start of the 12th week.

Data Analysis

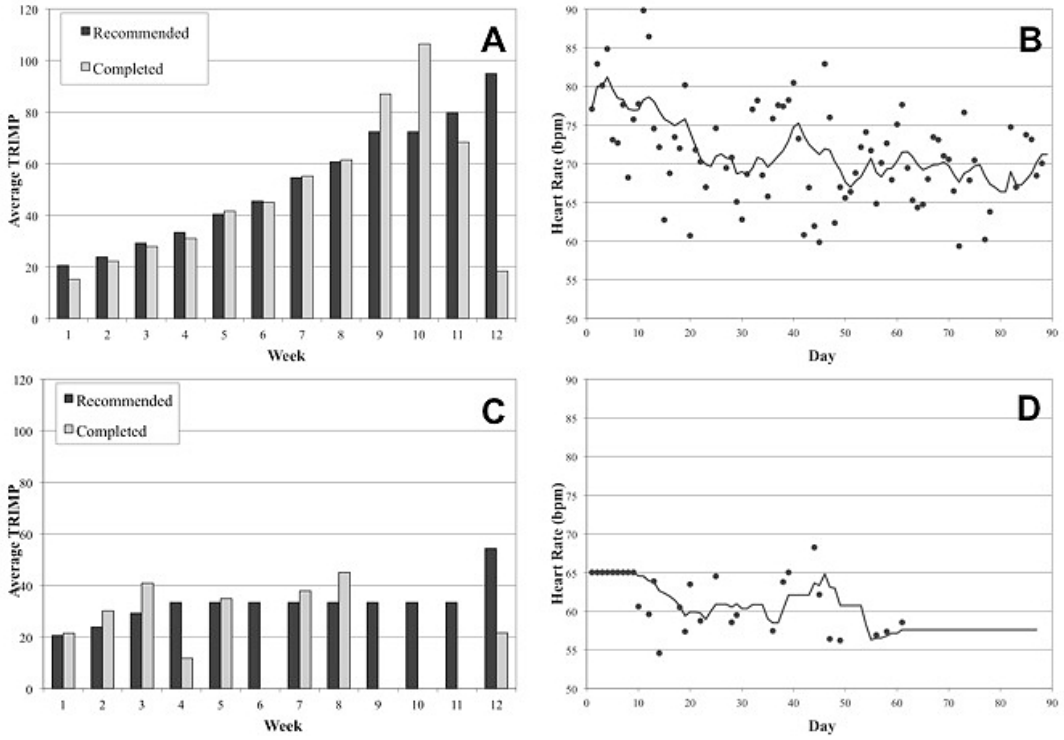
Weekly recommended and completed physical activity volume was calculated as mean training impulse (TRIMP). TRIMP captures both the duration and heart rate of a walking or running session with TRIMP = exercise time (min)· HRr · e $^{(1.92 \cdot HRr)}$, where HRr = heart rate reserve ratio, "e" is an exponential function, and 1.92 is the appropriate scaling coefficient for men (it would be 1.67 for women) [51]. The recommended TRIMP was calculated using the average of the target heart rate zone end points. For example, if the recommended % HRRe was 40-50%, then the heart rate reserve ratio (HRr) was 0.45. For completed physical activity sessions, HRr was calculated as the average heart rate during the endurance portion divided by average HRrest for that day.

Results

The two subjects (S1 and S2) demonstrated divergent adherence patterns to the PPAP intervention. S1 demonstrated excellent adherence to recommended physical activities progressing into week 10 of the standard physical activity training plan. Due to a late file upload after the end of week 9, S1 did not pass the compliance checkpoint (< 70% duration) resulting in the repeated prescription of week 9. He also did not pass the compliance check for week 11; however, the intervention was advanced to week 12 to initiate the prescription of the 12-minute run/walk EFT. S1 completed the 12-minute run/walk EFT achieving a distance of 2253m or an estimated peak oxygen consumption rate ($V^{\cdot}O_{2peak}$) of 48.5 ml·kg^{-1}·min^{-1}[45]. Comparison of recommended and completed TRIMP values (Figure 5A) indicated that S1 was able to achieve the recommended duration and intensity until weeks 9 and 10. At this point, S1 completed the appropriate physical activity duration, but his average heart rate during the endurance portion of the activity session was greater than the recommended target heart rate zone. Average resting heart rate data (Figure 5B) demonstrated a downward trend over the 12 weeks.

S2 completed recommended physical activity prescriptions during the first three weeks of the intervention, but his inconsistent participation prevented his progression past week four of the standard physical activity training plan (Figure 5C). S2 received email reminders during weeks five and eight of the intervention. Despite not completing physical activity during week six, S2 did upload resting heart rate data (Figure 5D), which prevented the generation of additional reminders. S2 did achieve the recommended TRIMP for week seven; however, he did not surpass the compliance checkpoint (< 70% duration) to trigger progression in the intervention. Response to a participation survey sent to S2 at week 9 indicated S2 had a lack of computer access for weeks 9-12; however, S2 did complete the 12-minute run/walk EFT at the start of week 12 achieving a distance of 2414m or an estimated $V^{\cdot}O_{2peak}$ of 51.4 ml·kg^{-1}·min^{-1}[45].

Figure 5. Comparison of physical activity and resting heart rate data recorded for two subjects during the 12-week PPAP application feasibility study. Completed TRIMP values for S1 demonstrated strong adherence to the recommended physical activity prescription (A). Observed (filled circles) and 10-day moving average (solid line) HRrest for S1 demonstrated a downward trend during the 12-week intervention (B). S2 progressed into week 4 of the intervention, but he did not achieve 70% of the recommended weekly physical activity duration for the subsequent weeks (C). Despite poor adherence to the program, the intervention progressed in week 12 to initiate an EFT. Email reminders were sent at the start of week 5 and 8, and S2 had limited computer access for weeks 9-12. A reminder was not sent for week 6 because S2 uploaded heart rate files to the server (D).



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Discussion

Principal Findings

Advances in technology have resulted in an unintended, systematic removal of physical activity from daily life [52], yet these same technologies offer new opportunities to encourage people to lead active lifestyles. Improved activity monitors enable objective assessment of an individual's health response to physical activity and have been primarily used to provide open-loop feedback to individuals regarding their heart rate and activity completed. These devices provide the potential to create closed-loop systems that acquire physiological signals which can be used to monitor an individual's activity and the physiological response to this activity. This information can then be used to tailor future physical activity recommendations. Therefore, we developed a Web-based app that combines a dynamic interface with quantitative multi-sensor AM data to personalize physical activity prescriptions. Although limited in sample size, the dichotomy of participation of two sedentary adult men in a feasibility study enabled thorough testing of key program features in the field including: adaptation of a standard physical activity framework to create personalized physical activity guidance, creation of interactive physical activity feedback and website features, and remote administrative monitoring of data quality and subject compliance. Further, the trial demonstrated that an EFT could be completed without supervision, a potentially important advance for using a technology-based approach to assess cardiovascular disease risk in asymptomatic populations.

PPAP App Development

A main contribution of the PPAP app is the tailoring of physical activity guidance according to principles of physical activity training (ie, overload, progression, and specificity) [46,53]. Contrary to this approach, many Web-based physical activity programs use tailoring strategies based on theories of behavioral change to determine the amount of physical activity recommended to the participant [19-23]. Increasing physical activity without consideration of the participant's physical activity history, however, could increase fatigue or risk for musculoskeletal injury [46], complications that can result in temporary or permanent stoppage of a physical activity program [54]. Individual response to exercise training is also highly heterogeneous [12-14], thus many individuals may be discouraged from physical activity participation due to a lack of observable improvements in fitness or health. The PPAP app can serve as an initial framework for clinicians, researchers, and public health professionals to remotely investigate and precisely characterize these barriers to regular physical activity participation. Physical therapists, for example, could use the survey tools in the PPAP app to identify individuals who experience a musculoskeletal injury, follow-up with the participant in clinic to make a formal diagnosis, and characterize precisely the amount of physical activity training that resulted in injury. Similarly, simple alterations to the PPAP algorithm could enable the creation of customized physical activity interventions to be used in conjunction with health coaching programs to better investigate behavioral components of physical activity programs [55].

The multi-sensor AM used in combination with the PPAP app enabled accurate assessment of subject compliance with recommended physical activity doses during the intervention. Previous Internet-based interventions have used step counts from pedometers [34,38] or "activity counts" and "PAM scores" from uniaxial AMs [35-37,56] to guide tailoring and provide feedback to participants. Pedometers, however, are unable to capture physical activity intensity, frequency, or duration [57], and uniaxial AMs lack accuracy to measure running or other activity types [58]. These device limitations may have affected the accuracy of physical activity recommendations and evaluation of the efficacy of these interventions to increase physical activity [35-37]. The multi-sensor AM used in this study was designed to accurately measure various speeds of walking and running [48]. While the lack of activity type diversity prescribed by the PPAP app could negatively impact program adherence [1], gait activities were advantageous as they required little skill or equipment, involved large muscle groups, and triggered positive cardiovascular adaptations [46].

PPAP Feasibility Study

Objective measures of physical activity recorded by the multi-sensor AM were also beneficial in educating subjects about their physical activity intensity. Current physical activity guidelines use relative terms (e.g. light, moderate, or vigorous) to describe the recommended physical activity intensity to achieve health benefits [5], yet many adults have difficulty interpreting this language resulting in an underestimation of intensity levels [18]. To overcome this limitation, we programmed the AM to use instantaneous heart rate and personalized target heart rate zones to provide visual feedback to the user during the activity session. In addition, workout charts comparing heart rate data obtained from different physical activity sessions allowed subjects to link periods of high intensity with changes in their physiological response, giving them the ability to self-monitor their physical activity intensity in subsequent activity bouts. S1 reported favorably about these features, which supports the agreement between his completed and recommended TRIMP values. As suggested by Hurling [35], charts and calendars comparing recommended and completed physical activity may have motivated this subject to increase his physical activity levels and set goals. Future quantitative studies, however, are necessary to monitor metrics such as how often and how long these interactive features are used to evaluate the potential effect of this material on physical activity [29].

Administrative features incorporated into the PPAP app were effective in monitoring data quality, subject adherence, and AM functionality. The study administrator independently verified rejection of activity or heart rate files due to data quality errors. The most common cause for rejection of heart rate data was filtering > 20% of the recorded data, which could occur if the heart rate monitor did not have adequate contact with the subject's chest. Email reminders, an effective tool to encourage exposure and reduce attrition in Internet-based interventions [59,60], sent to S2 also resulted in temporary increases in physical activity and website interaction. The subject's response to the seven-day survey at the start of week 9 also allowed the study administrator to identify limited computer access as the

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source of program attrition. Unlike other intervention programs [29], the email reminders and surveys in the PPAP app were based on user interaction with the website rather than a set schedule and did not require administrative action, which improves the feasibility of using this approach for large-scale population based interventions.

While the feasibility study demonstrated the functionality of the PPAP app in the field, the generalizability of these findings to a larger population are unclear. Both subjects in the study were adept at using technology and had daily access to the Internet at the start of the intervention (S2 did not have computer access for the end of the intervention). While data from the Pew Research Center indicate that 87% of American adults used the Internet in 2014 [61], offline adults, who are typically older (> 65 years), in the lowest socio-economic bracket, or have less than a high school education [62], would not benefit from using the PPAP app. Web-based interventions may also be ineffective for promoting physical activity in global communities where Internet access is limited [63]. Further, participants may be hesitant to use the PPAP app due to concerns with electronic data privacy [64]. While it may not be possible to address these general technical limitations, the PPAP app does include: (1) various instructional guides to help bridge technology education gaps, (2) a prescription algorithm and technology framework that can be implemented on smartphones or as a phone messaging service to reach global communities where cell phone access is more universal [63], and (3) a complex data encryption routine to provide safe data storage.

Next Steps

The PPAP app provides a foundation to use a technology-based approach to physical activity promotion; however, there are several challenges that must be addressed to make the program applicable to a range of populations. First, an efficacy trial needs to be performed with sufficient sample size to establish the generalizability of the PPAP app in a diverse population. A randomized control trial comparing the PPAP app to the ACSM physical activity intervention can then be conducted to assess the effect of the program on CRF and HRR in sedentary adults. Second, screening for sedentary physical activity behaviors via telephone survey does not provide objective measures of baseline fitness. It is possible that a spectrum of CRF levels exist within this classification. As a consequence, the low duration and intensity of the physical activity doses at the beginning of the standardized program may not be of sufficient magnitude to stimulate physiological adaptations in some individuals, and this population would experience smaller improvements in CRF compared to individuals with lower baseline fitness. One approach to mitigate this difference could include a baseline physical activity assessment period with the AM to establish an initial dose for each individual prior to entering a progression period in the intervention. Third, health outcomes could be influenced by performance of physical activities at work, home, or transportation that were not included in the intervention. As the multi-sensor AM is not currently capable of detecting multiple activity types, interactive physical activity surveys could be incorporated into the website to provide additional feedback to supplement AM data. Fourth, the PPAP app is limited in its generalizability to other subject populations. Incorporation of additional physiological measures such as heart rate variability or blood glucose readings may allow for customization of the PPAP intervention for a more aggressive physical activity intervention that could maximize CRF in recreational runners [65] or that could maintain glucose homeostasis in diabetic individuals, respectively. Lastly, integration of behavioral modification theories into website features and physical activity messages should be considered as a possible approach to improve intervention adherence [66].

Conclusions

This study describes the development and testing of a PPAP app that integrates objective AM data with dynamic Web-based guidance to provide a closed-loop approach to promote physical activity in sedentary adults. Results from a 12-week feasibility study demonstrated the ability of the PPAP app to create daily, personalized physical activity sessions, generate interactive Web-based feedback, and remotely monitor participant compliance and AM functionality with minimal investment of time and staff resources. The selection of ubiquitous software components as the foundation of the PPAP app allows healthcare professionals and researchers to replicate this technology framework, adapt the physical activity prescription algorithm, and personalize physical activity interventions to achieve health outcomes in a variety of subject populations. As advances in physiologic monitoring improve, patterns and thresholds for musculoskeletal injury risk and coronary heart disease risk reduction therapies can be incorporated into new interventions in the PPAP app, thus enabling the development of personalized physical activity prescriptions that minimize injury risk, maximize CRF, and reduce risk factors for coronary heart disease.

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Authors' Contributions

CC, SR, and DH were involved in the design and development of the PPAP app. SR made significant contributions to assemble, program, and perform utility testing for the PPAP app. CC had primary responsibility for coordinating pilot testing, analyzing data, interpreting results, and writing the manuscript. CC, SR, and DH participated in drafting and revising the article.

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Conflicts of Interest

None declared.

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Abbreviations

ACSM: American College of Sports Medicine
AM: activity monitor
bpm: beats per minute

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CRF: cardiorespiratory fitness
EFT: exercise field test
HR: heart rate
HRr: heart rate ratio
HRR: heart rate recovery
HRRe: heart rate reserve
HRmax: maximum heart rate
HRrest: resting heart rate
PPAP: personalized physical activity prescription
TRIMP: training impulse
S1: subject 1
S2: subject 2
$\dot{V}O_{2peak}$: peak oxygen uptake

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Original Paper

Using Ecological Momentary Assessment to Study Tobacco Behavior in Urban India: There's an App for That

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Abstract

Background: Ecological momentary assessment (EMA) uses real-time data collection to assess participants' behaviors and environments. This paper explores the strengths and limitations of using EMA to examine social and environmental exposure to tobacco in urban India among older adolescents and adults.

Objective: Objectives of this study were (1) to describe the methods used in an EMA study of tobacco use in urban India using a mobile phone app for data collection, (2) to determine the feasibility of using EMA in the chosen setting by drawing on participant completion and compliance rates with the study protocol, and (3) to provide recommendations on implementing mobile phone EMA research in India and other low- and middle-income countries.

Methods: Via mobile phones and the Internet, this study used two EMA surveys: (1) a momentary survey, sent multiple times per day at random to participants, which asked about their real-time tobacco use (smoked and smokeless) and exposure to pro- and antitobacco messaging in their location, and 2) an end-of-day survey sent at the end of each study day. Trained participants, from Hyderabad and Kolkata, India, reported on their social and environmental exposure to tobacco over 10 consecutive days. This feasibility study examined participant compliance, exploring factors related to the successful completion of surveys and the validity of EMA data.

Results: The sample included 205 participants, the majority of whom were male (135/205, 65.9%). Almost half smoked less than daily (56/205, 27.3%) or daily (43/205, 21.0%), and 4.4% (9/205) used smokeless tobacco products. Participants completed and returned 46.87% and 73.02% of momentary and end-of-day surveys, respectively. Significant predictors of momentary survey completion included employment and completion of end-of-day surveys. End-of-day survey completion was only significantly predicted by momentary survey completion.

Conclusions: This first study of EMA in India offers promising results, although more research is needed on how to increase compliance. End-of-day survey completion, which has a lower research burden, may be the more appropriate approach to understanding behaviors such as tobacco use within vulnerable populations in challenging locations. Compliance may also be improved by increasing the number of study visits, compliance checks, or opportunities for retraining participants before and during data collection.

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KEYWORDS

ecological momentary assessment; tobacco control; cell phones; mobile phones; mHealth; telemedicine; smoking

Introduction

Overview

This study describes the ecological momentary assessment (EMA) of tobacco use in urban India, using a mobile phone app for data collection. This exploration was the first step of a larger study examining overall use of, and exposure to, tobacco. In this paper, we focus on the feasibility of using EMA in the Indian cities of Hyderabad and Kolkata. To better understand tobacco use, particularly in low- and middle-income countries (LMIC) where usage is high [1,2], it is critical to use valid and reliable methods. Innovation and new technology may advance such work, but researchers must know the strengths and limitations of using such methods.

This paper begins by offering background information from the current EMA literature, which focuses mainly on work done in the United States and other developed countries. Next, we describe our design and protocols, done with a sample of 205 participants across India. Then, we review the EMA approach, drawing on participant completion and compliance rates. We conclude with general recommendations on implementing mobile phone EMA research in India and other LMIC.

Background

Current and past surveillance of global tobacco use relies primarily on retrospective recall—in the last two decades, EMA methods have been proposed as a viable counterpart to traditional recall methods in health behavior research. EMA is broadly defined as a repeated real-time collection of data on subjects' behavior and experience in their natural environments [3]. The use of multiple and brief—usually less than five minutes—assessments over a given period of time captures a representative experience of the participants' environments. EMA data may "shed light on relationships that are missed when relying on retrospective self-reports" [3]. EMA can be applied to a wide range of behavioral and clinical psychology research, and these methods are particularly advantageous in studying discrete and episodic behaviors, such as drug or substance use [4].

There is extensive EMA research in the United States on cues to smoke cigarettes among participants enrolled in cessation programs [5-8], as well as several studies of youth exposure to protobacco media [9,10]. In focusing primarily on regular smokers and cessation behaviors, EMA studies tend to offer implications for clinical and intervention advancements in substance abuse [4]. Studies by Martino, Shadel, and colleagues that consider adolescent and young adult social exposure to tobacco use and media often lead to discussions around advocacy and regulations [9,10].

In Japan, two EMA research studies using handheld computers have examined patient symptoms and clinical care. One study assessed aggravators of tension headaches and the other assessed symptoms experienced by home care hospice patients [11,12]. Both studies used compact computers as the EMA device and considered health behaviors among a disease-specific patient population.

Mobile technology health initiatives, also known as telehealth or mHealth, have occurred in LMIC and share some characteristics with EMA with respect to the use of technology. The difference, however, concerns research aims. The term mHealth refers to the "delivery of, and access to, health services and information" via mobile technologies [13]. While EMA employs mobile technology and can certainly fit under this definition, there are distinctions. A 2013 review of mHealth projects among the US clinical federal trial registry, conducted by Labrique and colleagues, identified over 90% of the work as "interventional" rather than "observational" [14]. Indeed, the primary focus of domestic and international mhealth research usually pertains to clinical or behavioral interventions, such as increasing treatment adherence via text message reminders, tracking and monitoring vitals, or facilitating communication between providers and patients [13]. EMA, in contrast, takes a more observational approach, assessing momentary events of a particular phenomenon as it is experienced by participants in the natural environment.

India and Ecological Momentary Assessment

To date, we are unaware of any EMA studies of tobacco cues in India, or for that matter, in any LMIC. India is a country with rates of high tobacco use as well as high mobile phone penetration, making it a strong fit for an EMA tobacco study. According to the World Health Organization (WHO) Global Adult Tobacco Survey (GATS) data from 2009, overall tobacco use in any form was nearly 50% for males and 20.3% for females in India [1]. Adolescent tobacco use is prevalent, and becoming more equally distributed between genders [15,16]. Surrogate advertising, or tobacco brand extension through nontobacco products, such as clothing or food, is a common method of increasing tobacco sales in India, even though it violates local and national legislation [17-19]. Point-of-sale tobacco advertising is largely unrestricted, and there is reportedly low success in preventing product sales to minors [18].

Amid a sharp worldwide increase of mobile phone penetration over the past decade, mobile phones are a practical way to collect real-time public health data. India had more mobile phone subscriptions in 2011 than Africa, the Middle East, and Europe—72 out of every 100 inhabitants in India have a mobile/cellular subscription [20]. Although advanced feature mobile phone users only make up 9% of all mobile users in India, the penetration is twice as high in urban areas [20]. Adults aged 18 to 24 years also make up a higher-than-average proportion of mobile phone users at 13% [20].

Methods

Surveys and Data Administration

A team of researchers beta tested early versions of the study protocol and EMA app in February 2013 in Hyderabad, India.

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Data collection was completed from February to May 2014 in staggered time periods, in Hyderabad and Kolkata, India. Ethics approval was obtained from the Johns Hopkins University Institutional Review Board (IRB), University of Maryland College Park IRB, and the BioMedical Ethics Committee in India. The project was supported by an award from the Institute for Global Tobacco Control at the Johns Hopkins Bloomberg School of Public Health with funding from the Bloomberg Initiative to Reduce Tobacco Use.

Prior to instrument and protocol development, the team conducted in-depth interviews with EMA field experts, as well as a series of focus groups to gain insight into the feasibility of conducting EMA research in a foreign setting using mobile phones. We contracted a local public health research company based in Hyderabad, India, to act as an in-country partner to assist with survey translation, field staff training, participant recruitment, and in hiring a local developer to create the EMA data collection app.

For this type of study, the EMA literature supported a time-based sampling approach, in which the researcher determines the intervals and moments at which participants are prompted for data collection. This approach, as opposed to event-based monitoring, in which participants can manually initiate a survey on their own, was a better fit because "time-based sampling typically aims to characterize experience more broadly and inclusively...without a predefined focus on discrete events" [3]. The developed EMA app consisted of two surveys. The first EMA survey was a momentary survey, consisting of multiple-choice questions adapted from EMA questionnaires typically done on personal digital assistants (PDAs). Questions came from the EMA literature [5] and adapted portions of the GATS India [21]. Momentary prompts asked participants to give their general location (eg, at home, in a restaurant), social setting (eg, alone, with friends), and tobacco environment (eg, do they see smokers or tobacco advertisements?). Figure 1 presents a screenshot of the first question of the momentary survey. We excluded fill-in responses in the momentary survey to maximize efficiency for survey completion time as well as data analysis, as per recommendations from an EMA field consultant (personal communication, S Shiffman, August 2012).

The second EMA survey was an end-of-day (EOD) survey that recorded the participants' tobacco use and observations from the previous 24-hour period. Although these types of questions required a brief period of recall, such daily diaries are considered a lower-burden form of EMA, and can be compared with momentary EMA data to determine whether it is a suitable proxy [3,22]. The end-of-day survey included a fill-in response to capture qualitative data in case the participant had a memorable or unique observation of the day's events. We did not set a limit on word count because we expected answers to be relatively brief. The complete momentary and end-of-day questions and response options are located in Multimedia Appendix 1 (sections A and B).

We also developed and employed a traditional paper-and-pencil baseline survey to be administered prior to app installment and training. This survey asked participants about demographic information, tobacco use, and perceptions. All surveys were written below an 8th-grade reading level to increase accessibility to lower-literacy participants.

No personal identifiers appeared in the data returned from the EMA surveys. We retained participant names and phone numbers during data collection for the purposes of compliance checks and follow-up, but these data were not linked to their responses. The app automatically forwarded and stored data from completed momentary and end-of-day surveys to a private secure server owned and operated by the in-country team. The app did not require Internet connection for survey completion. This was an important feature since intermittent power outages are common in the study area. Internet access, however, was required to eventually forward EMA data to the server. The app recorded incomplete or timed-out surveys as "expired" in the dataset and did not record partial responses. If participants turned off their mobile phones or if phones were in a poor reception area, the app would mark data as missing or display blank cells in the dataset.

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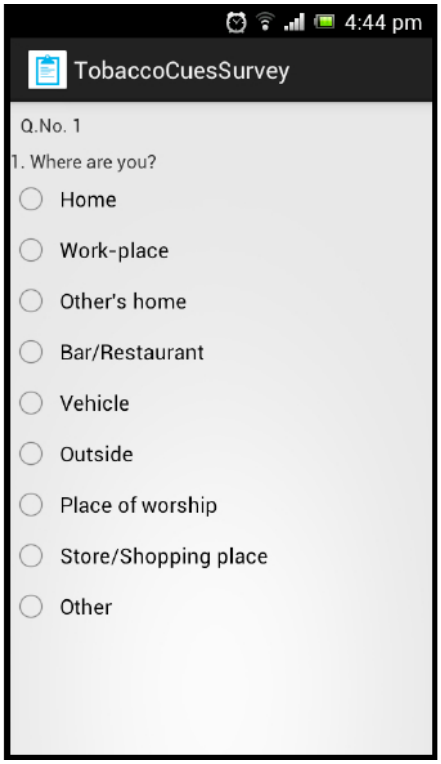
Figure 1. Screenshot of the ecological momentary assessment (EMA) mobile app.



Participant Recruitment and Training

Inclusion criteria for the study included possession of an Android-series mobile phone, or one with similar functions and app capabilities—several off-brand versions of the Android phone existed in the study site. Participants needed to be literate so that consent could be given, and so that one could read and complete surveys. The eligible age for participation was 16 to 40 years. The study did not require technological expertise with a mobile phone, as the research team provided extensive training on the app. Participants received a month of unlimited data for their phone upon enrollment in the study, as well as a flash drive when they completed the study.

Our in-country partner recruited participants from Hyderabad and Kolkata, India, through local schools and colleges, work offices, and popular neighborhood places, such as cafes, restaurants, and bars. Schools primarily consisted of local colleges and universities, but we included some high schools in the recruitment in order to enroll older adolescent participants. Participants 18 years of age and older provided written consent to join the study, while participants younger than 18 years were additionally required to provide parental consent as well as assent. After enrollment, participants completed the baseline survey and then research staff familiarized each participant with the study procedures. During this initial session, staff installed the EMA app onto the participants' mobile phones, and instructed participants on using the EMA app. They also discussed if and how various tobacco cues might be in the participant's environment. Participants practiced using the EMA app, and staff answered questions or alleviated difficulties.

Procedure

For 10 consecutive days in February 2014, the EMA app randomly signaled participants on their mobile phone five to eight times per day during waking hours—defined as 8am to 10pm—and prompted them to complete the momentary survey. Unless directed otherwise, the end-of-day survey prompt occurred at 10pm on each day of data collection. This sampling scheme resembled that of similar studies in the EMA tobacco literature [3,6,9]. Momentary and end-of-day prompts were designed to take 3 to 5 minutes and less than 5 minutes, respectively. Identical questions in the two surveys were used, though the order of momentary survey questions changed to prevent response fatigue. Participants had 30 minutes to complete a survey once they opened the app and started a survey—if they did not finish in time, the dataset would show the prompt as expired. If participants were unable to use their phone when signaled, for example, during a meeting or while driving, they could put the EMA app on hold or "snooze" for up to 20 minutes. During this "snooze" time, the app would signal every 5 minutes to remind them to take the survey. After 20 minutes, the participant could no longer take that particular survey and it would be recorded as expired. This feature was modeled from Shiffman's work [6]. The app signaled users automatically—participants could not manually initiate or self-initiate a survey.

Study Variables

The following section describes variables used in the baseline, momentary, and end-of-day surveys, although a separate paper considers the participants' tobacco use and exposure to tobacco use and messaging (personal communication, DG Borzekowski and JC Chen, February 2015).

Baseline Survey

Demographic variables included age, gender, employment, education level, and car ownership in the household. Participants' current tobacco use status consisted of separate

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variables for the use of smoked and smokeless forms, respectively—not at all, smoke less than daily, and smoke daily; not at all, use less than daily, and use daily. We did not exclude tobacco users in the study because we wanted to be able to compare differences in tobacco exposure and messaging as experienced in the natural environment by tobacco use status. These data are examined in a separate paper by Borzekowski and Chen (personal communication, February 2015). The baseline measured exposure to pro- and antitobacco messages, respectively—ever saw information promoting tobacco use, ever saw information discouraging tobacco use—for various locations that participants may have visited over the past 30 days (eg, government building, hospital, school, workplace, public transportation).

Momentary Survey

The momentary survey asked about participants' current use of tobacco as well as their social and environmental exposure to tobacco. First, the survey considered the participants' physical and social setting. Variables included location—home, workplace, other's home, bar/restaurant, vehicle, outside, place of worship, store/shopping place, other—and social setting—alone or with others. Next, the survey considered participants' momentary tobacco environment, with variables on personal use of tobacco—none, smoked, or smokeless—and tobacco use by other people nearby—none, in participant's social group, or in view. If the participant reported using or seeing others use tobacco, the survey generated additional variables for product type—brand name cigarette, rolled cigarette, bidi, cigar, cigarillo—and brand. Other environmental variables in the survey included observation—yes or no—of paraphernalia related to tobacco use, such as used ashtrays, butts, spit from oral tobacco, or smelling secondhand smoke. Lastly, variables related to tobacco media exposure included observation—yes or no—of pro- and antitobacco messages in their location appearing in various places—newspapers or magazines, television, radio, billboards or posters, or on cigarette or smokeless tobacco packs. Protobacco messages were defined as those promoting tobacco products and antitobacco messages were defined as those warning about the dangers of using tobacco or encouraging quitting.

End-of-Day Survey

The end-of-day survey considered participants' tobacco use that day—yes or no—with variables for product type—smoked or smokeless—and brand, if answered positively. Variables included observation—yes or no—of other people using tobacco that day and, if yes, who—friends, family/relatives, spouse, coworkers, or people they did not know. Variables on paraphernalia related to tobacco use—seeing ashtrays, butts, spit, or smelling secondhand smoke—were similar to those used in the momentary survey. Variables on exposure to pro- and antitobacco messages seen over the past day resembled those in the momentary survey, though the survey questions were structured slightly differently. A final measure asked participants to compare that day to others, indicating if they had witnessed higher, lower, or similar amounts of tobacco cues.

Data Analysis

This study examined participant compliance data to assess and demonstrate the feasibility of using an EMA approach. To analyze the data, the researchers considered the following: (1) what variables, such as participants' baseline characteristics, real-time tobacco use, and social and environmental cues, predicted the momentary and end-of-day compliance throughout the study period, and (2) the convergent validity of the daily end-of-day survey alongside the momentary surveys.

Ecological Momentary Assessment Compliance Measurements

The measurable outcomes for examining participant compliance involved identifying the total number of momentary and end-of-day surveys received by participants, and identifying the total number of momentary and end-of-day surveys completed by participants. With this information, we then calculated the proportion of momentary and end-of-day surveys received and completed, which we refer to as the completion rates. We also considered the number of days in the 10-day study period within which the participants completed the momentary or end-of-day surveys, and the amount of time involved for participants to complete momentary and end-of-day entries.

Statistical Analyses

We employed simple analyses to examine this dataset. To predict the factors influencing momentary and end-of-day compliance, we estimated two linear regressions. We used momentary completion rate as a dependent variable, and used the end-of-day completion rate, baseline characteristics, and other real-time tobacco-related measurements as independent variables. Similarly, in order to predict the factors that influence end-of-day compliance, we used the end-of-day compliance rate a dependent variable, and the same variables listed previously as independent variables. We also conducted zero-order correlation tests to analyze the relationship between momentary and end-of-day surveys, using outcome data from the first 5 and all 10 days of data collection.

Results

Sample Characteristics

The sample included 205 participants, of which 135 (65.9%) were male and 70 (34.1%) were female. The median age was 23 years (interquartile range [IQR] 9). Sample size for other baseline variables varied based on participant response—133 out of 202 respondents (65.8%) had attained less than a college degree, 147 out of 205 (71.7%) were unemployed, and 122 out of 200 (61.0%) owned a car. Most participants did not regularly use tobacco—out of 205, 106 (51.7%) smoked "not at all," 56 (27.3%) smoked "less than daily," and 43 (21.0%) smoked "daily." Smokeless tobacco use was extremely rare in the sample. Only 9 out of 205 participants (4.4%) reported any use of smokeless tobacco—7 (3.4%) used it "less than daily," and 2 (1.0%) used it "daily." All of the 9 smokeless tobacco users were dual users of smoked and smokeless products.

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Ecological Momentary Assessment Compliance Measurements

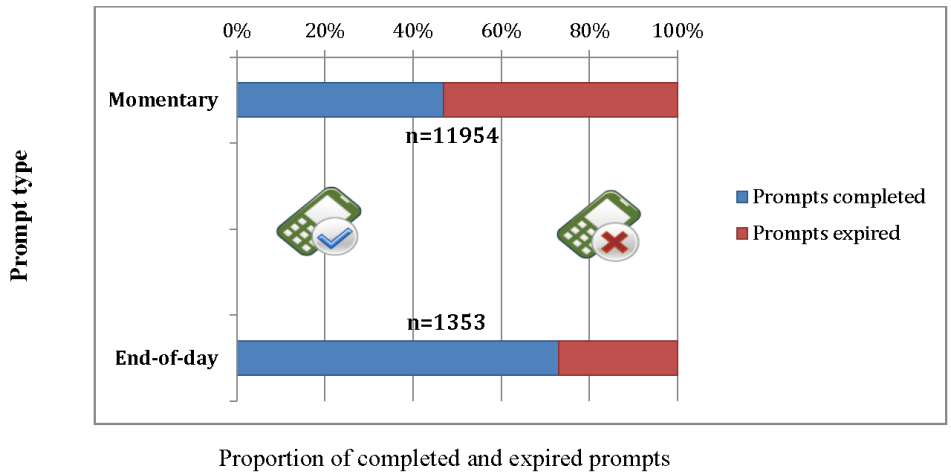
Momentary Survey

Participants received a total of 11,954 momentary surveys from the EMA app. Participants completed and returned a total of 5603 surveys—6351 surveys expired due to incomplete response or nonresponse.

The completion rate was .47 (SD .21), or 46.87% (5603/11,954). Figure 2 gives a visual comparison between the completion rates of momentary and end-of-day assessments.

On average, participants completed surveys for 7.29 (SD 2.56) days out of the 10-day period, and spent 3.84 (SD 2.21) minutes to complete a single survey. A total of 39 out of 205 (19.0%) of the participants completed at least one momentary survey every day during the 10-day study period.

Figure 2. Comparison of completed and expired ecological momentary assessment (EMA) survey prompts, by type.



End-of-Day Survey

Participants received a total of 1353 end-of-day surveys from the EMA app. Participants completed and sent back a total of 988 end-of-day surveys—365 surveys expired due to incomplete response or nonresponse. The completion rate for the end-of-day surveys was .73 (SD .27), or 73.02% (988/1353). On average, participants completed surveys for 6.98 (SD 2.62) days out of the 10-day period, and spent 3.62 (SD 2.82) minutes to complete a single survey. A total of 54 participants out of 205 (26.3%) completed all of the end-of-day surveys over the 10-day study period.

Ecological Momentary Assessment Compliance Predictors

Overview

Table 1 presents models predicting EMA and EOD completion rates. In the first model, a higher end-of-day completion rate (beta=0.11, 95% CI 0.05-0.15, P=.001), being employed (beta=0.10, 95% CI 0.02-0.17, P=.01), seeing other people using tobacco (beta=-0.17, 95% CI -0.27 to -0.05, P=.02), and not being exposed to messages discouraging tobacco use (beta=-0.15, 95% CI -0.29 to -0.02, P=.01) predicted a higher momentary completion rate. The overall model fit was R^2=.14 ($F_{14,173}$= 3.1, n=188). This model explained about 14% of the overall outcome variance. In the second model, the momentary completion rate (beta=0.64, 95% CI 0.16-1.13, P=.01) strongly predicted the end-of-day completion rate. The overall model fit was R^2=.03 ($F_{14,167}$=1.4, n=182). This model explained only 3% of the overall outcome variance. The relatively low R^2 of both models indicated that other unexplored factors might be associated with momentary and end-of-day compliance outcomes.

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Table 1. Predictors of momentary and end-of-day study compliance.

Variable item	Momentary compliance[a]				End-of-day compliance[b]			
	beta	SE	*P*	95% CI	beta	SE	*P*	95% CI
Momentary compliance	N/A[c]	N/A	N/A	N/A	0.64	0.25	.01[d]	0.16 to 1.13
End-of-day compliance	0.12	0.03	.004	0.07 to 0.18	N/A	N/A	N/A	N/A
Gender								
Male	Reference				Reference			
Female	0.02	0.04	.61	-0.05 to 0.09	-0.20	0.12	.14	0.16 to 1.13
Age	0	0	.70	-0.01 to 0	0	0.01	.86	-0.002 to 0.12
Education	0.01	0.16	.54	-0.02 to 0.04	0.07	0.05	.23	-0.04 to 0.17
Employment								
Unemployed	Reference				Reference			
Employed	0.10	0.04	.01	0.03 to 0.17	0.09	0.12	.48	-0.15 to 0.32
Household car ownership								
Did not own car(s)	Reference				Reference			
Owned car(s)	-0.03	0.03	.32	-0.09 to 0.03	0.13	0.10	.22	-0.08 to 0.33
Tobacco use status								
Not at all	Reference				Reference			
Less than daily	0.01	0.03	.85	-0.06 to 0.73	-0.10	0.11	.37	-0.32 to 0.12
Daily	-0.01	0.04	.78	-0.08 to 0.06	0.19	0.13	.14	-0.06 to 0.44
Location	-0.03	0.05	.60	-0.12 to 0.07	N/A	N/A	N/A	N/A
Companionship	-0.02	0.04	.66	-0.10 to 0.06	N/A	N/A	N/A	N/A
Self-reported tobacco use	0.04	0.09	.65	-0.14 to 0.23	-0.24	0.19	.20	-0.62 to 0.13
Saw other people using tobacco	0.23	0.10	.02	0.03 to 0.43	-0.20	0.23	.40	-0.65 to 0.26
Saw evidence of using tobacco	0	0.08	.99	-0.17 to 0.17	0.09	0.23	.69	-0.36 to 0.55
Smelled tobacco use	-0.11	0.06	.07	-0.23 to 0.01	0.10	0.22	.65	-0.34 to 0.54
Saw protobacco messages	0.01	0.08	.88	-0.15 to 0.18	0.07	0.19	.77	-0.44 to 0.32
Saw antitobacco messages	-0.17	0.07	.01	-0.31 to -0.04	-0.06	0.32	.77	-0.44 to 0.32

[a]R^2 of this model is .24, adjusted R^2 is .17 ($F_{16,171}$=3.4, n=188).

[b]R^2 of this model is .11, adjusted R^2 is .03 ($F_{14,167}$=1.4, n=182).

[c]Not applicable (N/A).

[d]*P* values in italics are significant.

Validity of Ecological Momentary Assessment Data

Tables 2 and 3 offer pairwise correlations for 5-day and 10-day assessments, respectively. For each pair of compliance outcomes, the correlations between momentary assessment and end-of-day assessment were significant. The correlation coefficient remains the highest for self-reported tobacco use (*r*=.54 and .55, *P*<.001), followed by seeing protobacco messages (*r*=.49, *P*<.001; *r*=.50, *P*<.001), and seeing antitobacco messages (*r*=.49, *P*<.001; *r*=.39, *P*<.001). The correlation coefficients varied slightly for compliance measurements when compared to the 5-day and 10-day assessments, indicating that momentary and end-of-day compliance level was steady during the 10-day study period.

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Table 2. The zero-order correlation of tobacco-related variables between momentary and end-of-day surveys, with assessment at study day 5.

Variable item	Momentary assessment, mean (SD)	End-of-day assessment, mean (SD)	Correlation, *r*	*P*
Used tobacco product(s)	.08 (.20)	.17 (.31)	.54	<.001
Saw other people smoking	.13 (.31)	.45 (.39)	.23	<.001
Saw evidence of smoking	.17 (.35)	.39 (.38)	.36	<.001
Smelled tobacco	.26 (.40)	.41 (.38)	.21	<.001
Saw protobacco messages	.15 (.25)	.08 (.21)	.49	<.001
Saw antitobacco messages	.25 (.30)	.28 (.35)	.40	<.001

Table 3. The zero-order correlation of tobacco-related variables between momentary and end-of-day surveys, with assessment at study day 10.

Variable item	Momentary assessment, mean (SD)	End-of-day assessment, mean (SD)	Correlation, *r*	*P*
Used tobacco product(s)	.08 (.20)	.17 (.30)	.55	<.001
Saw other people smoking	.13 (.32)	.44 (.37)	.23	<.001
Saw evidence of smoking	.17 (.36)	.38 (.37)	.34	.002
Smelled tobacco	.27 (.43)	.39 (.36)	.17	.02
Saw protobacco messages	.15 (.25)	.08 (.18)	.50	<.001
Saw antitobacco messages	.25 (.30)	.27 (.33)	.39	<.001

Discussion

Principal Findings

This project successfully used the EMA approach to collect data in the Indian cities of Kolkata and Hyderabad. Like EMA research done in the United States and other middle- to high-income countries, the approach was used among people of different demographics and smoking statuses [22]. While alterations can improve the quality of the data, this work shows that EMA is feasible in a low- and middle-income country.

In this study, only employment status predicted different EMA compliance rates and time to complete end-of-day surveys. Much of the sample's unemployed group included students. Possibly, these participants were more frequently in locations where it was less appropriate to use a mobile phone and were, therefore, less likely to comply. Future studies may benefit from identifying key time periods during the day when participants are most willing and able to use their phones, such as during lunch or break time, or on weekends. Additional formative research, such as focus groups, may also increase compliance by helping researchers better understand reasons why a person may or may not respond to EMA survey prompts.

We observed lower completion rates for momentary surveys than end-of-day surveys. This finding may be due to lower burden and randomness of survey prompting—participants expected end-of-day surveys daily at 10pm, while they received momentary surveys multiple times at random during active work and school hours. Yet, momentary and end-of-day completion rates were highly related. End-of-day compliance appeared to be the most significant predictor for momentary compliance. Likewise, momentary compliance appeared to be the only significant predictor for end-of-day compliance. This suggests that if one complies with momentary prompts, then he or she will also comply with end-of-day prompts. Another explanation for the disparity between momentary and end-of-day survey compliance is that the end-of-day surveys required less training and were, therefore, inherently easier to complete and were a lower burden. Future EMA studies could raise compliance with momentary prompts by increasing the number of study visits, compliance checks, or opportunities for retraining with participants before and during the data collection period.

Limitations

This study had several limitations. First, we did not examine the trend of momentary and end-of-day compliance across the study period. It would be valuable to analyze whether participant compliance changes over time, and future studies may benefit from using longitudinal data analysis methods, such as the generalized estimating equation (GEE) model, to explore trends. Additionally, the predictors used in the EMA and EOD compliance models only explained 14% and 3% of variance in compliance outcomes, respectively. Although previous EMA studies found low prediction power [22,23], future studies need to test a wider range of predictors (eg, time of day, and day of the week) or other psychologically relevant factors (eg, positive and negative affects), which could explain more of the variation in EMA compliance. Further, the EMA app did not retain data from partial or expired responses to momentary or end-of-day survey prompts, or display whether participants employed the snooze function, which would provide valuable information on individual behavior and factors that explain completion. The snooze feature allowed participants to delay starting a survey—the intention was to increase the chance that a participant could complete a survey and thereby increase compliance. It is possible that participants could have turned off their phones at any point if they did not want to be disturbed, and there was no way of knowing from the data if or when that

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occurred. In future studies, researchers could set up time blocks with participants as part of the study training to establish when to keep the phone turned on, for example, by programming the app to only prompt them during the times they prefer.

The self-reported end-of-day survey data was used to confirm the validity of EMA assessment, instead of a biomedical measure for testing tobacco exposure. Future studies could combine momentary assessments with biochemically verified assessments, such as carbon monoxide (CO) monitors, and hair, saliva, or urine samples collected through additional study visits. This approach has been used in several US-based studies, including one of Southern California high school students' physical activity, which paired mobile EMA data with heart rate and accelerometer data [24]. Another study of cocaine-addicted adults' cravings and use paired mobile EMA with urine samples [25].

We sampled only in urban areas and did not randomly sample within these areas. In this vein, the enrollment criterion of owning an Android-capable mobile phone was a limitation, since it effectively excluded lower-tech phones and, consequently, a lower socioeconomic (SES) demographic. It is worth noting, however, that inexpensive "bootleg" versions of mobile phones and Android phones were widespread in our sample and study sites. Thus, this limitation may be relatively minor. Regardless, as mobile phones are increasingly used in EMA research, it is important to consider optimizing EMA software or apps for older mobile phone platforms. Alternately, issuing participants a mobile device for EMA studies may yield a more generalizable sample, particularly as older models of mobile phones become less expensive and easier to employ in research. However, it is important to consider that this research was part of a pilot study exploring relationships between demographics, tobacco exposure, and tobacco use in real time and natural settings using mobile phone EMA. In this paper, we specifically examined relationships of EMA compliance with various participant characteristics and behaviors. Thus, we did not intend to have a sample of participants that was nationally representative. Nonetheless, future studies could explore EMA compliance with a more generalizable sample of the population.

Practice Implications

Overall, the participant completion rate of 46% in this study was lower than what has been observed in tobacco EMA studies performed in the United States and other developed countries, where rates ranged from 65% to 92% [9,26,27]. Researchers Stone and Shiffman suggest an 80% completion rate as a good measure of validity and generalizability of EMA data [28]. Our 72% end-of-day completion rate finding is promising. The end-of-day surveys were easier to employ in the app, and the higher completion rate than that of the momentary surveys suggests that the participants also experienced an easier time with these surveys. The literature supports brief recollection, such as a 24-hour recall period, as a legitimate EMA approach [3]. While end-of day assessment may risk capturing less of the momentary environment and experience [3], a lower-burden protocol may be better suited for more challenging populations and settings. Indeed, other mobile phone EMA research studies used a range of monitoring schemes that yielded high compliance, such as collecting data for one week or less [24,29,30], prompting participants to take a survey less than five times per day [30-32], or setting time blocks during the day in which participants will or will not be prompted [31]. Similar tobacco media exposure studies, such as that of Shadel and colleagues [9], used combined event- and time-based sampling. Adding in a component of user-initiated entry of tobacco exposure could increase completion rates of surveys and enrich the data.

It would be valuable to better understand expired or incomplete prompts. This study did not collect information on which of the prompts involved the snooze function before expiring. A possible extension of snooze time might result in more completed prompts. Additionally, the EMA app could be improved by allowing partial data from incomplete prompts to be visible because (1) data from those completed questions could still be extracted and analyzed, and (2) researchers could see whether participants tried to at least answer one question before letting the prompt expire, or if they simply did not respond. If most partially completed prompts had a certain number of the questions answered before expiring, it may indicate that the survey was too long.

We recommend repeated testing and fine tuning of an EMA protocol and technology to ensure protocol accuracy in future EMA studies, particularly when researchers build their own data collection app or software as was done in this study. The EMA field consultants interviewed during the planning phase reported using existing software services to collect and manage a dataset in their projects (personal communications by S Shiffman and M Rich, August 2012), but building a system from the ground up allowed more opportunity for customization and improvements. Additionally, we worked with local Indian developers to create the apps, endorsing the community-based research approach. Teaming up with local partners proved valuable for executing the EMA protocol and app development, as there were significant language and cultural barriers.

Conclusions

This study employed EMA methodology in India, a low- and middle-income country with high tobacco use prevalence, and provided rich and instrumental evidence around the feasibility of using EMA measurements to capture real-time tobacco-related behaviors and participant compliance with a rigorous monitoring schedule. To our knowledge, this was the first study to examine compliance of an EMA study of tobacco use and tobacco-related cues in India or any LMIC. It is also the first EMA of a tobacco study that used an app that was integrated into participants' personal mobile phones, as opposed to providing a separate mobile device for data collection. This paper may serve as a guide to other researchers interested in conducting EMA studies in LMIC, but the formative research and procedures must be customized to the specific health behavior and country of interest. Repeated testing of the protocol and software is particularly crucial to studies in foreign settings for two reasons: first, to troubleshoot for technical problems in the data collection and delivery system and, second, to ensure

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that concepts and messages are not lost or misunderstood in translation or culture between researcher and participant.

Recommendations for future studies using a mobile phone EMA include adapting instruments for lower SES populations and developing data collection platforms for basic-feature mobile phones. While it is possible to use momentary prompts, this work suggests the less burdensome approach of end-of-day surveys may be better. Future work should continue to explore methodological approaches, especially as mobile technology access becomes more universal.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

A copy of the questions employed in the momentary and end-of-day surveys in the ecological momentary assessment (EMA) mobile app.

[PDF File (Adobe PDF File), 95KB - resprot_v4i2e76_app1.pdf]

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Abbreviations

CO: carbon monoxide
EMA: ecological momentary assessment
EOD: end of day
GATS: Global Adult Tobacco Survey
GEE: generalized estimating equation
IQR: interquartile range
IRB: Institutional Review Board

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LMIC: low- and middle-income countries
N/A: not applicable
PDA: personal digital assistant
SES: socioeconomic
WHO: World Health Organization

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Original Paper

Internet-Based Birth-Cohort Studies: Is This the Future for Epidemiology?

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Abstract

Background: International collaborative cohorts the NINFEA and the ELF studies are mother-child cohorts that use the internet for recruitment and follow-up of their members. The cohorts investigated the association of early life exposures and a wide range of non-communicable diseases.

Objective: The objective is to report the research methodology, with emphasis on the advantages and limitations offered by an Internet-based design. These studies were conducted in Turin, Italy and Wellington, New Zealand.

Methods: The cohorts utilized various online/offline methods to recruit participants. Pregnant women who became aware volunteered, completed an online questionnaire, thus obtaining baseline information.

Results: The NINFEA study has recruited 7003 pregnant women, while the ELF study has recruited 2197 women. The cohorts targeted the whole country, utilizing a range of support processes to reduce the attrition rate of the participants. For the NINFEA and ELF cohorts, online participants were predominantly older (35% and 28.9%, respectively), highly educated (55.6% and 84.9%, respectively), and were in their final trimester of pregnancy (48.5% and 53.6%, respectively).

Conclusions: Internet-based cohort epidemiological studies are feasible, however, it is clear that participants are self-selective samples, as is the case for many birth cohorts. Internet-based cohort studies are potentially cost-effective and novel methodology for conducting long-term epidemiology research. However, from our experience, participants tend to be self-selective. In marked time, if the cohorts are to form part of a larger research program they require further use and exploration to address biases and overcome limitations.

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KEYWORDS

Internet; epidemiology; birth cohort

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Introduction

Health research is becoming increasingly complex due to the employment of complex protocols (eg, birth and pregnancy cohort studies); large sample sizes; and novel participant retention strategies [1,2] resulting in increased research costs [3] and low response rates. As a consequence, researchers may need to move beyond traditional methods and explore new and innovative means of conducting valid research more efficiently. Some have argued that health researchers have fallen behind the business world in the use of the Internet [4]. There are different forms of electronic-based methods that can be used for health research, namely, (1) low-technology methods, such as e-mails with appended surveys; (2) electronic bulletin boards, such as an electronic message distribution system set up by independent operators; and (3) the World Wide Web, such as free online research tools. The latter approach requires more comprehensive systems, such as software-specific programs for the research, and it is technically more demanding than low-technology systems [5]. To date, it is clear that using Web-based research methodologies is an emergent trend among a variety of health research disciplines [6-8]. The aim of this paper is to describe 2 Internet-based birth cohort studies as potential models to learn how to develop and conduct, in the future, better Internet-based epidemiological research.

For epidemiological research purposes, utilizing the Internet is currently considered a novel approach. However, its use could become more widespread, at least for longitudinal studies, for the following reasons: (1) the Internet is becoming more accessible and it is globally used[9,10]; (2) in many situations, Web-based research is relatively inexpensive to set up and maintain[5,11,12];(3) the Internet allows for a greater sampling frame for a wider target population, including populations in areas that typically could not be accessed using traditional methods for recruitment [9,12];(4) automated data entry allows the data to be collected in a format suitable for analysis while avoiding data entry errors [5];and (5) combined or individual use of low- and high-technology systems offers a variety of data collection methods that may increase participation rates [13-15].As discussed in recent papers [7,16],baseline selection introduced by recruitment via the Internet may alter the confounding patterns originally present in the source population, but this does not necessarily translate into selection bias in the exposure-outcome estimates obtained in longitudinal studies [17].In this paper, we describe the methodological collaboration between 2 Internet-based birth cohort studies designed to investigate the association between early life exposures and the health of babies through to young adulthood, an international first. The Nascita e INFanzia gli Effetti dell'Ambiente (NINFEA) cohort was established online in Italy in 2005 [7]. From this study, the Early Life Factors (ELF) cohort was designed and implemented online in New Zealand (NZ) in 2008.

The goal for the NINFEA and ELF birth cohorts was to investigate the association between early life factors, early environmental exposures, and noncommunicable diseases. A life-course epidemiology approach was used to investigate exposures at various time points, including the prenatal and early postnatal periods and subsequent postnatal life. This approach assessed the effects of exposures at several stages during the life-course [18], and their interactions, in order to fully understand the causes of a variety of health conditions. For both cohorts, the first 3 phases consisted of similar questionnaires to allow for pooled analyses between the 2 countries. Cohort discrepancies are related to differences in social and cultural aspects relevant to each country and differences in research expertise and interests between the research groups.

Methods

Overview

Since recruitment through the Internet is less intensive compared with traditional methods, an advantage of the online approach is that cohorts can recruit for many years. Accordingly, NINFEA is a dynamic cohort with ongoing recruitment and a minimum target of 7,500 participants; however, we report data last downloaded in March 2015. The ELF cohort was a feasibility study and obtained a minimum target of 5,000 participants; recruitment ended at the end of 2012.

NINFEA Study

The NINFEA cohort started as a pilot study in the city of Turin, Italy, in July 2005 and has been gradually extended to the rest of Italy. The original study protocol and subsequent amendments have been approved by the Ethical Committee of the San Giovanni Battista Hospital—CTO/CRF/Maria Adelaide Hospital, Turin, Italy. Members of the cohort are children of mothers who have access to the Internet, have enough knowledge of the Italian language to complete an online questionnaire, and volunteer to participate at any time during the pregnancy. They register through the project Web site and complete the first questionnaire that lasts approximately 30 minutes. While the Web site has always been public and accessible from any part of Italy (and the world), the methods for advertisement of the existence of the study have changed over time.

All women participate online, although NINFEA is advertised using both offline and online methods. Offline methods involve the collaboration of health personnel and, therefore, target a prespecified catchment population. Currently, the NINFEA study is actively advertised in the city of Turin, in the Tuscany Region and, with a lower intensity, in the Piedmont Region (of which, the city of Turin is the capital). In these areas, leaflets and posters were distributed, and the study was introduced to pregnant women when they attended hospitals or family clinics for reasons related to their pregnancy. Online recruitment includes recruitment through the Internet (eg, Web sites, forums, social networks) and the media.Until March 2015, approximately 16% of participants were recruited via a passive mode, 82% were recruited actively, and 2% of participants comprised both modes. A total of 7003 pregnant women were recruited in the study as of March 2015. The 3 most represented Italian Regions in the NINFEA cohort are the Piedmont Region (62% of the participants), the Tuscany Region (22%), and the Lombardy Region (4%), while the most represented municipality is Torino (45%). About one-third of the participants are from central urban

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areas, almost 50% from peripheral urban areas, and the remaining 20% are from rural areas.

ELF Study

The primary location for the ELF cohort is Wellington, New Zealand, but additional study sites are located in the other main city centers (eg, Christchurch and Auckland). Ethical approval was obtained in 2007 from Massey University, New Zealand (MUHEC Application 07/62). Pregnant women who were 16-years-or older were eligible to participate in the study. The ELF cohort recruited pregnant women at "parent and child shows" located in the main urban centers. Parent-child shows are large-scale events, marketed at expecting and experienced parents. People pay a small fee to enter these shows because it is a "1 stop shop" destination to purchase standard and newly available products (eg, food), services (eg, child-care), recreation and education programs (eg, developmental courses), and specialist advice (eg, child psychologist). The shows are attended by more than 22,000 people annually. The ELF study used other recruitment avenues including: information inserted in antenatal care booklets, promotional posters in hospitals and sonography clinics, and participants who enrolled through an Internet search engine. Thus, the study population included any expecting mothers, new and experienced, recruited through parent-child shows and other avenues, with access to the Internet. Participants were offered a "postal" option (offline) if they did not have access to the Internet, or if they preferred the offline option.

A final total of 2197 women were recruited in the study from September 2008 to September 2012. A large proportion of the participants were from Wellington (43.5%) with the other participants from Auckland (37.5%) and Canterbury (11.8%). A small proportion was from other regions (7.2%); and for less than 1% we had no current address. From the 2197 pregnant women recruited, 1,155 (52%) were categorized as lost to follow-up. The reasons were: (1) attrition to follow-up (81%); (2) participants who later declined to take part (12%); (3) missing information (1%); and other reasons (4%) such as miscarriage, nonviable pregnancy or death of the baby, and moved to another country and subsequently withdrew from the study. The final study sample analyzed in this paper is 1,042 participants. The majority of respondents (55%) took part via an offline mode, compared to 44.9% of online participants, and most women were recruited from the parent-child shows (73.2%), as described earlier.

Follow-Up Measures

NINFEA Study

When it is time to complete a follow-up questionnaire, participants are invited to access the Web site using their username and password. The follow-up questionnaire remains accessible for a number of months after the first invitation, while women are reminded of the questionnaire via e-mail, telephone calls, short message service (SMS) texts, and regular mail. For example, the 6-month questionnaire can be completed until the child turns 15 months old; after that, the questionnaire is closed and the woman is considered as "lost to follow-up." Based on this definition, the attrition proportions for each of the follow-up questionnaires were estimated on the NINFEA database version 15.03. Out of all pregnant women recruited at baseline, 88% completed the 6-month questionnaire, 83% completed the 18-month questionnaire, and 78% completed the 4-year questionnaire. These proportions refer to the overall participation, including, for example, miscarriages and stillbirths in the denominator.

ELF Study

As described earlier, in an attempt to reduce the attrition rate, we sent out quarterly reminders and newsletters and made the follow-up online questionnaires available for an indefinite period. Based on the ELF database version 13.08, out of all the pregnant women recruited at baseline, 47.4% completed the Phase I questionnaire and 52.5% participants were identified as lost to follow-up, as defined by the proportion of participants that did not submit the questionnaire after at least 3 follow-up reminders in Phase I of the study. Of those that participated, the participation of onliners (44.9%) as compared to offliners (55%) was proportionately less. A specific focus on recruiting only online participants may have reduced the attrition rate of the ELF cohort.

Cohort Measures

NINFEA Study: Questionnaires

The cohort is multipurpose and collects information on a broad range of exposures and outcomes. NINFEA involves 3 main questionnaires and subsequent short questionnaires targeting specific outcomes and/or exposures. Further follow-up questionnaires will be added in the future. Table 1 summarizes the domains that are currently investigated in the NINFEA study. Further information is available on the inventory of European birth cohorts.

After the first baseline questionnaire (completed during pregnancy), participants complete 2 other main (30 minutes long) online questionnaires at 6 months and 18 months after delivery. Long-term follow-up continues with short online questionnaires focusing on specific outcomes and linkage with health-related databases (eg, inpatient registry, prescription registry, etc).

When it is time to complete a follow-up questionnaire, mothers are contacted by e-mail asking them to access the Web site and complete the questionnaire. Nonresponders are additionally contacted first by e-mail and then by telephone, SMS texts, and regular mail. Contact between participants and the research team is also maintained using the NINFEA Facebook page, which is updated weekly.

NINFEA Study: Biological samples

The NINFEA study also involves collection of saliva samples from the mothers and the children, which commenced in 2009. At the time of the Phase II questionnaire, when the child is aged 6 months, women are asked if they want to participate in this part of the study. Upon acceptance, they receive 2 self-collection kits, 1 for the mother and 1 for the child. Saliva is then stored at -80°C mainly for extraction of DNA to be used in genetics and epigenetic-based studies. To involve the complete cohort, participants who took part previous to the implementation of

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the biological study were invited to participate in the donation of saliva samples at the Phase III and IV questionnaire stages. As of February 4, 2015, a total of 2,864 mother-child pair saliva samples have been collected.

ELF Study: Questionnaires

Modeling the work from the NINFEA study, the ELF study is also multipurpose and aims to examine a wide range of exposure information collected at important milestone time points, starting at the prenatal stage. Based on our interest in early life exposures, the participants were also asked to report whether they were ever diagnosed with a wide range of medical conditions, including asthma, allergies, high blood pressure, heart conditions, diabetes, stroke, thyroid problems, psychological problems, sexually transmitted infections, diseases of the reproductive system, and more. Table 1 lists each questionnaire and details the information collected at each phase.

Following the completion of the Phase I questionnaire (during pregnancy), regular reminders about the study were e-mailed and postal-mailed to each individual every 3 months. In addition, a quarterly newsletter was sent to all participants to provide an update on the study, and it served as a reminder to renew participant contact details for follow-up purposes. The study Web site includes an electronic inquiry, with a toll-free telephone number that helps participants to maintain contact with the research team.

Presently, ELF includes a short questionnaire on birthing, developmental milestones, sleep patterns, environmental exposures, and respiratory health. Follow-up questionnaires occur at 3 months, 15 months and at 2 years of age. For follow-up, mothers were contacted by e-mail, asking them to access the Web site and complete the questionnaire. Additionally, any nonresponders were contacted first by e-mail and then by telephone and regular mail.

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Table 1. Schedule of questionnaire phases, by Internet cohort.

Questionnaire Phase	Cohort Schedule	Internet Cohort	
		ELF	NINFEA
Phase I	ELF: Prenatal	Social and demographic characteristics	Social and demographic characteristics
	NINFEA: Prenatal	Current and historical occupational exposures	Current and historical occupational exposures
		Domestic environmental exposures	Domestic environmental exposures
		Medical history	Medical history
		Medication use and duration	Medication use and duration
		Reproductive and pregnancy history	Reproductive and pregnancy history
		Maternal weight and diet	Maternal weight and diet
		Lifestyle behaviors	Lifestyle behaviors
		Fitness and physical activity	Fitness and physical activity
		Sleep habits	N/A
		Access to the study	Access to the study
		N/A	Selected information about the partner
Phase II	ELF: 3 mo	Birth outcomes and neonatal tests	Birth outcomes
	NINFEA: 6 mo	Infant anthropometric measures	Infant anthropometric measures
		Infant health	Infant health
		Feeding practices and related behaviors	Feeding practices and related behaviors
		Infant sleep habits	Infant sleep habits
		Contact with other children	Contact with other children
		Domestic environment	Domestic environment
		Work and farming environment	N/A
		Maternal lifestyle factors	Maternal lifestyle factors
		N/A	Update of the baseline questionnaire
Phase III	ELF: 15 mo	Infant anthropometric measures	Infant anthropometric measures
	NINFEA: 18 mo	Feeding practices	Feeding practices
		Health and well-being of the mother	Health and well-being of the mother
		Health and well-being of the infant	Health and well-being of the infant
		Sleep patterns	Sleep patterns
		Contact with other children	Contact with other children
		Domestic environment	Domestic environment
		Farming/animal exposures	N/A
		Work/occupational exposures	Work/occupational exposures
		Smoking	Smoking
		Leisure activities	Leisure activities
		Bonding between child and parent	Bonding between child and parent
Phase IV	ELF: 2 y	Food frequency over a 4- week period	Anthropometric measures
	NINFEA: 4 y	Food habits	Anthropometric/Cognitive development
		Oral health	
		Physical activity	
		Respiratory health	
Phase V	ELF: N/A	N/A	Anthropometric/Respiratory health

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Questionnaire Phase	Cohort Schedule	Internet Cohort	
		ELF	NINFEA
	NINFEA: 7 y		

Results

Subject Characteristics

NINFEA Study

Selected characteristics of the NINFEA study participants are reported in Table 2. Women clearly self-selected; that is, the majority of participants was aged at least 32 years, had a university degree, and most were experiencing their first pregnancy [16]. However, there was still heterogeneity in most of the exposures of interest, as shown by 8% who smoked and 34% who drank alcohol during the first trimester of pregnancy in the cohort.

ELF Study

Selected characteristics of the study participants of the ELF study are reported in Table 3, stratified by method of participation (online or offline). The majority of women were aged between 26-35 years, with an average age of 31 years across both groups. Overall, a large number of women (74%) self-identified their ethnicity as being NZ European, with the remainder identifying either as Māori (indigenous people of NZ; 9.8%) or other (15.9%); while less than 1% did not state their ethnicity. More than half of the participants (54.9%) had 1 or more pregnancies prior to the current pregnancy, and about 57% participated in the study while in their third trimester. Across both groups, 82.8% of the participants had a tertiary level qualification, and an overall 45% earned more than the highest median weekly income in NZ (total average from all sources: $550 per week) [20]. The postal codes and the New Zealand Deprivation Index 2006 (NZDep2006) were used to create a standardized measure of socioeconomic deprivation. Based on the 2006 New Zealand Census, the index combines 9 census variables. The index provides a deprivation score for each small area unit (“meshblock”) in NZ. These meshblocks are defined by Statistics New Zealand as geographical units, which contain a median of 90 people. Each meshblock is categorized between 1 (least deprived) and 10 (most deprived) [19]. For our analyses, deciles were grouped into quintiles: 1-2 (least deprived); 3-4; 5-6; 7-8; 9-10 (most deprived). Approximately 50% of the participants were from the least deprived socioeconomic position.

Currently, the ELF cohort data has been used to conduct quality checks and descriptive analyses, including the comparison of online versus offline participants (Table 4). However, the notable finding from this table indicates a significant difference in women who reported that they had “ever” smoked during pregnancy compared to those women who reported “never” smoking during pregnancy ($P = .002$). Additionally, out of all the women who answered the question about quitting smoking (n=1,019), women were significantly more likely to report “smoked but quit” than to report “no smoking” during pregnancy ($P = .01$).

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Table 2. Selected characteristics of participants in the NINFEA study[a].

Characteristics		N=7003 (%)
Maternal age, y		
	≤25	5.0
	26-31	33.3
	32-35	35.0
	≥36	26.7
	Missing data	0.1
Maternal origin		
	Italian born	95.8
	Non-Italian born	4.2
Maternal residence		
	North Italy	71.3
	Central Italy	25.2
	South Italy	3.5
Maternal educational level		
	Primary school	5.8
	Secondary/college	33.8
	University/tertiary	58.6
	Missing data	1.8
First pregnancy		
	No	32.7
	Yes	63.3
	Missing data	4.0
Stage of pregnancy at recruitment		
	Trimester 1	15.3
	Trimester 2	36.0
	Trimester 3	48.5
	Missing data	0.2
Smoking during pregnancy		
	No	89.3
	Yes	8.4
	Missing data	2.4
Drinking during pregnancy		
	No	64.4
	Yes	33.7
	Missing data	1.9

[a]Database version 15.03 (March 2015).

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Table 3. Selected characteristics of participants in the ELF cohort.

Characteristics		Online n=468 (%)	Offline n=574 (%)	All N=1,042 ($)	*P* values[c]
Maternal age, y	≤25	12.6	15.9	14.4	
	26-31	37.5	34.4	35.8	
	32-35	28.9	31.5	30.3	
	≥36	21.0	18.2	19.4	
	Missing data	n=1	n=3	n=4	*P*= .24
Partner status	No	3.9	5.8	4.9	
	Yes	96.2	94.2	95.1	
	Missing data	n=0	n=1	n=1	*P*= .15
Ethnicity	NZ European	78.6	70.8	74.3	
	Maori[a]	7.9	11.4	9.8	
	Other	13.5	17.8	15.9	
	Missing data	n=0	n=2	n=2	*P*= .01
Regions participating	Auckland	33.6	40.6	37.5	
	Wellington	45.8	41.6	43.5	
	Canterbury	13.1	10.8	11.8	
	Other	7.5	7.0	7.2	
	Missing data	n=3	n=0	n=3	*P*= .12
NZDep06[b]	Quintile 1	26.7	26.5	26.6	
	Quintile 2	25.2	22.3	23.6	
	Quintile 3	22.0	22.0	22.0	
	Quintile 4	16.0	17.7	16.9	
	Quintile 5	10.1	11.5	10.9	
	Missing data	n=4	n=0	n=4	*P*= .75
Highest educational level	Primary school	0.0	0.5	0.3	
	Secondary/college	15.1	18.5	16.9	
	University/tertiary	84.9	81.0	82.8	
	Missing data	n=3	n=5	n=8	*P*= .09
Total household income	$1-$40,000	6.4	10.6	8.7	
	$40,001-$70,000	22.9	21.5	22.1	
	$70,001-$100,000	23.6	24.4	24.0	
	$100,001+	47.0	43.5	45.1	
	Missing data	n=45	n=57	n=102	*P*= .12
First pregnancy	No	56.7	53.3	54.9	
	Yes	43.3	46.7	45.1	
	Missing data	n=1	n=2	n=3	*P*= .27
Stage of pregnancy	Trimester 1	5.3	1.0	3.0	
	Trimester 2	31.0	16.2	22.8	
	Trimester 3	53.6	59.8	57.0	
	Full term	10.1	23.0	17.2	
	Missing data	n=0	n=0	n=0	*P*<.001

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[a]Maori = Indigenous people of New Zealand.

[b]NZDep06 Quintiles = New Zealand Deprivation Index 2006: a scale based on Census information, where 1 represents 10% of the least deprived and 10 represent 10% of the most deprived people in New Zealand.

[c]*P* values = chi-square test

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Table 4. Selected key exposures of online versus offline participants of the ELF cohort.

Characteristics			Online	Offline	All	*P* value
			n=468 (%)	n=574 (%)	N=1,042 (%)	
BMI (kg/m^2)						
	Prepregnancy	BMI<18.5	3.3	3.1	3.2	
		BMI 18.5-<25.0	50.5	57.5	54.3	
		BMI 25.0-<30.0	31.1	25.4	28.0	
		BMI≥30.0	15.1	14.0	14.5	
		Missing data[d]	n=11	n=23	n=34	*P*= .14
Smoking	During Pregnancy	No	94.4	89.0	91.4	
		Yes	5.6	11.0	8.6	
		Missing data	n=0	n=1	n=1	*P*= .002
Quit Smoking	During Pregnancy	Smoked but Quit	95.5	91.7	93.4	
		No Smoking	4.5	8.3	6.6	
		No. of participants reporting	n=463	n=556	n=1,019	*P*= .01
Alcohol	During Pregnancy	No	75.5	67.2	70.9	
		Yes	24.5	32.8	29.1	
		Missing data	n=6	n=0	n=6	*P*=.004
Drugs[a]	During Pregnancy	No	97.4	96.7	97.0	
		Yes	2.6	3.3	3.0	
		Missing data	n=3	n=0	n=3	*P*= .49
Comorbidities[b] (ever vs never)	During Pregnancy	Respiratory Diseases	42.6	43.7	43.2	
		Missing data	n=1	n=0	n=1	*P*= .71
		STI[c]	18.7	21.0	20.0	
		Missing	n=2	n=3	n=5	*P*= .34
		Mental Health Disorders	31.6	29.0	20.0	
		Missing data	n=2	n=2	n=4	*P*= .37
		Reproductive Diseases	38.4	32.8	35.3	
		Missing data	n=2	n=3	n=5	*P*= .058
		High blood pressure	6.2	6.6	6.5	
		Missing data	n=2	n=3	n=5	*P*= .79
		Diabetes	1.1	0.9	1.0	
		Missing data	n=4	n=0	n=4	*P*= .83
		Other	83.7	81.9	82.7	
		Missing data	n=1	n=0	n=1	*P*= .43

[a]Illicit use during pregnancy.

[b]Comorbidities=numbers do not add up to 100 due to coexisting morbidities.

[c]STI=Sexually transmitted infections.

[d]Missing data was not included in the analyses.

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Discussion

Principal Findings

The NINFEA and ELF studies are Internet-based cohorts examining protective and risk factors for a range of noncommunicable diseases in young children. These online birth cohort studies are the first of their kind in Italy and NZ. Both cohorts' participants differed in age structure, with the largest group in the 32- to 35-year-old age group (35.7%) for NINFEA. The ELF cohort's maternal age was predominantly younger (26- to 31-year-old age group). These age groups typically represent the median maternal age for both countries (NZ: 29 years; Italy: 31.3 years) [21,22], which explains much of the changes in the reproductive process (ie, birth delay) and stabilized fertility rates since the 1960s and 1970s [22. A comparison between the NINFEA cohort and the general population revealed that NINFEA participants are mothers with lower parity, higher education level, and lower frequency of smoking during pregnancy [16]. For the ELF cohort, online participants were notable by ethnicity and stage of pregnancy (trimester 3 having the highest participation for both online and offline). The latter characteristic falls in line with the NINFEA's previous analyses, where women in their first trimester of pregnancy have a lower proportion of completed items from the baseline questionnaire [16]. Indeed, these findings are characteristic of Internet-based cohorts being a more self-selective sample of their respective source populations, and the timing (or in this case, the stage of pregnancy) for inviting participants to be take part in an online survey is an important consideration in order to attain complete responses and better respondent rates. Key risk factors of both the NINFEA and ELF cohorts indicated a reasonable comparability of participants who were smokers (8.4% and 8.6%, respectively) and drank alcohol (33% and 29%, respectively) during pregnancy, with clear differences between online and offline users in the ELF cohort. As more health outcomes data becomes available for the ELF cohort (ie, completion of subsequent phases), further analyses—including early life growth trajectory pathways to several health outcomes—will provide meaningful and useful interpretation.

The preliminary findings presented here show that an Internet-based cohort is feasible. Our investigation also highlights 3 major strengths that support the notion that Internet-based cohort studies are feasible and may have advantages in comparison to traditional cohorts: (1) given the prospective longitudinal nature of a cohort study design, an Internet-based approach can provide a significant research resource, particularly in the potential for expanding the breadth of a sampling frame and automated data downloading and cleaning that reduces the costs for administering a project long term; (2) the mode of Internet participation (eg, online questionnaires) has the potential to include multiple geographical sites for a long duration of time and to include large numbers of participants in the study (since recruitment through the Internet is less intensive as compared with traditional methods, an advantage of the Internet approach is that cohorts could recruit for many years; furthermore, there are provisions for identical cohorts to be established in other countries, and the online nature of the study could preclude additional costs for participation of mothers at an international level); and (3) as the protocols and online questionnaires are comparable for some phases of the ELF and NINFEA cohorts, particularly on future analyses on specific exposures and outcomes, this will allow for subsequent pooled analyses (these are currently being planned as the follow-up for each phase becomes more complete and for later phases when the children are of school age).

Limited access to the Internet, particularly for participants from a lower socio-economic background, may result in a selective cohort. Although this selection is not likely to introduce problems of validity in the associations measured, there may be issues of limited exposure heterogeneity in the study subjects. This would happen when the exposure of interest is strongly associated with participation and that there is limited variability in the exposure to investigate its effect on the outcome of interest. However, this problem is likely to be limited as in many countries, including Italy and NZ, the majority of the population not only has access to the Internet, but also access the Internet from a handheld mobile device such as a smartphone or an iPad (Italy: 58%; NZ: 88% in the whole population in 2012 and 2013 [23,24]). In addition, for some exposures, baseline selection may actually increase heterogeneities. For example, if high maternal age were the exposure of interest, having 25% of the cohort aged at least 36 years at delivery would increase the statistical efficiency of the cohort. Moreover, it is important to note that due to the Internet-based design and source population of the NINFEA and ELF cohorts, restricting the source population (like in our cohorts) are more likely to reduce issues of internal validity. This issue has been recently discussed the general consensus is that "representativeness" will depend on the context of a particular study, and thus it is a secondary issue [25]. Other researchers suggest that representativeness should be avoided, particularly if the study design incorporates an intentional nonrepresentative sample for practical reasons (eg, restricting the study to specific participants); minimizing bias by comparing subgroups; and if the focus was on 1 or more population subgroups [26]. This is the case for the cohorts currently presented in this paper, thus restricting the source population and internal analyses should not introduce serious issues of bias.

However, an important characteristic in all birth cohort studies where participants are followed-up is "attrition," and we acknowledge that this is a particular issue for the ELF cohort. Anecdotally, ELF participants provided comments on addressing attrition or lost to follow-up. This included ideas of shorter questionnaires, reducing the interval time for the data collection phases, setting up electronic diary reminders with the participants, being very clear with participants to utilize the offline option if they are "not Internet-savvy," and simplifying the Internet processes for enrollment (ie, there were some technical glitches that prevented participants from registering in a timely manner). These are important learnings from participants' perspectives, and the authors accept that the points highlighted here should be considered for any future Internet-based research. Moreover, there is emerging work examining the follow-up of Internet-based epidemiological studies, and the findings advocate using an offline enrollment

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campaign as a potentially useful aid to achieve higher participation and to limit lost to follow-up. Based on the NINFEA and ELF cohort experiences, we cannot conclude whether attrition is higher or lower in Internet-based cohorts than in traditional cohort studies. As further phases are completed and the cohorts experiment with different online mechanisms (eg, use of social media tools), this issue will become clearer and will produce potential strategies to alleviate attrition at follow-up when using the Internet as a primary method of recruitment and data collection.

Completed and Ongoing Work and Future Directions

The initial work focused on the use of the Internet to conduct cohort studies.

First, some studies demonstrated empirically that baseline selection (or restriction) in cohort studies does not result in biased associations [16]. This has previously been recognized [27], and further support in the context of Internet-based research is needed. Data from the NINFEA study and the population-based birth registry of the Piedmont Region, Italy, were used to show that the confounding pattern in the NINFEA cohort differs from that of the general population, but this difference is not necessarily associated with a stronger overall confounding effect [16]. Simulation studies in which both the exposure of interest and an unmeasured strong risk factor for the outcome of interest, assumed to be independent in the general population, are strong determinants of the probability of participating in the Internet-based cohort were also performed, showing that even in the worst-case scenario, the magnitude of the bias introduced was small [16].

Further work to evaluate methods of recruitment for an Internet-based cohort and their potential effects on the study validity is ongoing. For example, the efficiency of a pilot advertisement campaign in Facebook, estimating a cost of €20 per participant, has been recently studied [30]. In addition, we found that both in the NINFEA and in the ELF cohort, the source of information (offline vs online) was associated with attrition at follow-up.

Studies on specific outcomes are also ongoing, in particular on growth in the first years of life and on wheezing. Data from the NINFEA cohort and 2 other non-Internet-based cohorts have been used to compare different approaches to model growth in the first 4 years of life [28], the association between several maternal prenatal exposures and weight trajectories in infancy were examined [17,28], and the paper highlighted a range of modeling options to estimate salient features of growth in weight in infancy and early childhood. However, the most useful was the SITAR (super-imposition by translation and rotation) model because of its flexible and pragmatic approach for life-course epidemiology inquiries. Finally, the NINFEA cohort participates in several collaborative studies among European cohorts, including those conducted under the CHICOS coordination project [29-34].

The 2 Internet-based cohorts presented in this paper had similar participant characteristics despite the differences in methods, data collection time frames, and source populations. Internet-based recruitment for epidemiological studies has the potential to expand a broader geographical coverage. However, online recruitment could introduce difficulties, particularly in the collection of biological samples, and it limits the capability to take standardized measurements (eg, weight, height). The NINFEA cohort protocol includes collection of saliva samples when children turn 6 months old, but it does not include cord or maternal blood sampling. There is, however, the potential of nesting ad-hoc studies in a subsample of the cohort to mitigate this issue.

Conclusions

There is much to learn about how to include the Internet as a valuable tool in epidemiological research. Over time, technological advances can only further aid in overcoming much of the current shortcomings, particularly in increasing follow-up and reducing the attrition rate. We encourage future studies to incorporate the Internet more strategically to decrease the limitations of individual and population-based approaches in epidemiological study designs.

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Conflicts of Interest

None declared.

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Original Paper

Retrieval of Publications Addressing Shared Decision Making: An Evaluation of Full-Text Searches on Medical Journal Websites

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Abstract

Background: Full-text searches of articles increase the recall, defined by the proportion of relevant publications that are retrieved. However, this method is rarely used in medical research due to resource constraints. For the purpose of a systematic review of publications addressing shared decision making, a full-text search method was required to retrieve publications where shared decision making does not appear in the title or abstract.

Objective: The objective of our study was to assess the efficiency and reliability of full-text searches in major medical journals for identifying shared decision making publications.

Methods: A full-text search was performed on the websites of 15 high-impact journals in general internal medicine to look up publications of any type from 1996-2011 containing the phrase “shared decision making”. The search method was compared with a PubMed search of titles and abstracts only. The full-text search was further validated by requesting all publications from the same time period from the individual journal publishers and searching through the collected dataset.

Results: The full-text search for “shared decision making” on journal websites identified 1286 publications in 15 journals compared to 119 through the PubMed search. The search within the publisher-provided publications of 6 journals identified 613 publications compared to 646 with the full-text search on the respective journal websites. The concordance rate was 94.3% between both full-text searches.

Conclusions: Full-text searching on medical journal websites is an efficient and reliable way to identify relevant articles in the field of shared decision making for review or other purposes. It may be more widely used in biomedical research in other fields in the future, with the collaboration of publishers and journals toward open-access data.

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KEYWORDS

information storage and retrieval; systematic reviews; PubMed; text mining; full-text search; decision making; shared decision making

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Introduction

Full-text searches of articles are known to increase the recall, also called sensitivity, and defined by the proportion of relevant publications that are retrieved [1-3]. Full-text search techniques have already shown many advantages for biomedical research [4], especially in genetic studies [5]. Biomedical search engines, such as PubMed, are essential in the everyday life of researchers and clinicians, and with the exponential growth of the scientific literature [6]. However, full-text searches are rarely used in the medical field, partly due to resource constraints.

In contrast to a PubMed search, a full-text search permits the identification of articles whose keywords appear not only in the title or abstract, but also in the main content (eg, discussion). Furthermore, a full-text search can help to retrieve publications without abstracts. Those articles, such as editorials and debates, have an impact on readers [7,8], and may pave the way for novel concepts, such as shared decision making (SDM). SDM has been defined as a process by which healthcare choices are made jointly by the physician and the patient [9]. It is increasingly advocated as a model of best practice for decision making in the medical encounter [10-12] by combining best evidence with patient values and preferences.

In a recent study [13], we performed a systematic review of publications addressing SDM. We wanted to measure the growth of the SDM concept that seemed to appear increasingly in editorials and article discussions in high-impact medical journals. However, no reliable data could support this assertion. We therefore needed a full-text search method to retrieve publications where SDM does not appear in the title or the abstract.

The aim of the present study was to assess the reliability and efficiency of full-text searches in major medical journals for identifying publications containing the phrase “shared decision making” and to compare the results with a traditional PubMed search. If reliable and efficient, this methodology may be used for retrieving publications for systematic reviews on topics other than SDM.

Methods

We selected the 15 journals with the highest 5-year impact factors in 2010 in the “general and internal medicine” category from the ISI Web of Knowledge Journal Citation Reports [14]. Moreover, the eligible journals had to exist prior to or since 1996 and publish original articles, letters, and editorials.

To identify publications containing the phrase shared decision making, referred to as SDM publications, we built a search strategy combining the following 6 phrases (1) shared decision making, (2) informed decision making, (3) shared medical decision making, (4) informed medical decision making (5) informed and shared decision making, and (6) informed shared decision making. None of the terms exist as a Medical Subject Heading (MeSH) term.

All publications released between January 1996 and December 2011 were eligible, because the concept of SDM began to appear significantly in medical literature in the mid 1990s [15,16]. Moreover, electronic publications only became widely available on journal websites around 1995-1997 due to changes in the publishing framework that permitted the use of automated search engines [17].

Publications were retrieved through the full-text search function on the journals' websites, usually located on the “advanced search” web page or on the publisher website if not available. The search engine of each journal website is handled similarly to that of PubMed, with Boolean operators and filters. It demands no particular informatics competency, but some manpower is required as the operation has to be repeated on each journal website. We refer to this search method as website full-text search. We included publications of any type, with the exception of cover pages, tables of content, and indexes (ie, authors or keywords).

To assess the performance of the website full-text search, we compared it with a PubMed search using a similar strategy (ie, the same 6 SDM-related phrases in the 15 journals from 1996-2011). PubMed searches were limited to titles and abstracts since full texts are usually not directly available on the PubMed platform, but rather through links to the journal websites.

We next compared the type of publications retrieved through website full-text vs. PubMed searches. We categorized the publication type through a bibliometric analysis and then dichotomized the results between research and non-research publications. Research publications included interventional and observational studies, systematic reviews, guidelines, and consensus publications, whereas non-research publications included non-systematic reviews, editorials, comments, letters, book reviews, conference publications, and others.

In contrast to PubMed searches, the website full-text search method relied on journal or publisher websites whose search syntaxes were not explicit. To compare our results with a validation dataset, we contacted the editorial board of each selected journal to request authorization to obtain all published materials since 1996. After receiving their authorization, we collected published material in an electronic version to build a custom-designed database of full-text publications. We designed and launched an automated search script (Python Software, version 2.6, Python Software Foundation, Wolfeboro Falls, NH, USA). We used the same 6 SDM-related phrases for publication retrieval. This text retrieval method on a locally stored full-text corpus is referred to as downloaded full-text search [18]. We assessed the numbers of retrieved publications, and the reliability and concordance between the website and downloaded full-text searches.

Results

Through the website full-text searches, we included 1286 SDM publications out of a total of 229,179 publications in the 15 journals from 1996-2011 (Figure 1).

Through the PubMed searches, 119 SDM publications were included. Of these publications, only 2 were missed by the website full-text searches; one due to unavailable data on the journal website for years 1996-1997, and while the other was

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available on the journal website, the browser failed to retrieve it (Figure 2). The BMJ published the highest number of SDM publications over 16 years with a minority found through PubMed searches (5.8%, 16/274) (Table 1). The Journal of General Internal Medicine and the JAMA followed with high numbers of SDM publications. Over time, the total number of SDM publications increased but the proportion found through the PubMed searches appeared to decrease from 11.5% (22/191) in 1996-1999 to 7.7% (39/505) in 2008-2011. A minority (36.3%, 467/1288) of all found SDM publications were research publications with the proportion of research publications higher through the PubMed search (52.1%, 62/119) compared to the website full-text search (36.2%, 465/1286). However, the PubMed search missed 86.7% (405/467) of the research publications containing the phrase shared decision making.

Of the 15 journals, 6 complied with our request to download all materials published during the study period. When limited to these 6 collaborating journals, 646 SDM publications were found through the website full-text searches, while the downloaded full-text searches retrieved 613 publications (Figure 1). When matching together the publications identified by both full-text searches, the concordance rate was 94.3% (611/648) (Figure 2). As well, 2 research article publications were retrieved by the downloaded full-text search, but not by the website full-text search. The reason for this was a defect in the automated Optical Character Recognition (OCR) of those publications.

Figure 1. Flow chart of the search methods. [a]Canadian Medical Association Journal : publications not available in full text for years 1996-1999, identified through PubMed Central. [b]The 6 journals which collaborated for collecting full-text publications: British Medical Journal; Canadian Medical Association Journal ; Mayo Clinic Proceedings ; American Journal of Preventive Medicine ; Journal of General Internal Medicine ; Journal of Pain and Symptom Management.

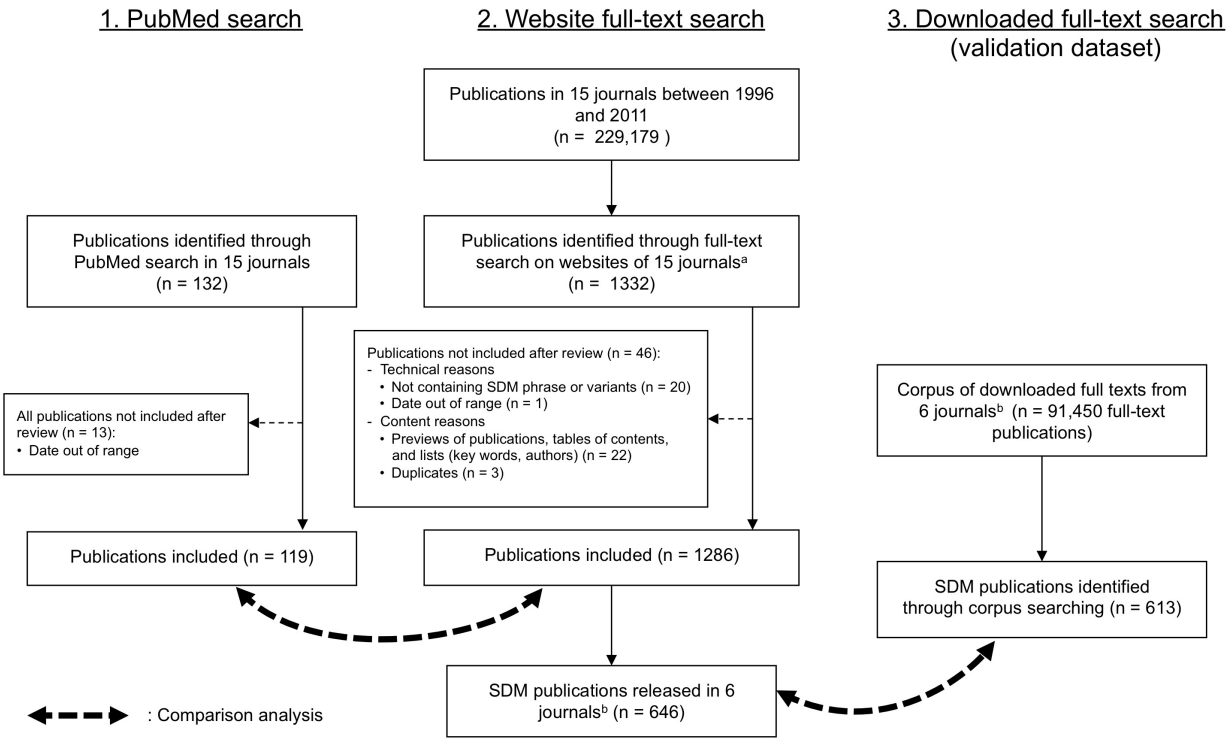

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Table 1. Characteristics of publications containing the shared decision making phrase according to the specific search method (N=1288).

Publication characteristics		Number of publications, n (%)			Total, n
		Found in PubMed only	Found in PubMed and website full-text search	Found in website full-text search only	
Total publications		2 (0.2)	117 (9.1)	1169 (90.7)	1288
Journal					
	British Medical Journal	0	16 (5.8)	258 (94.2)	274
	Journal of General Internal Medicine	0	37 (17.4)	176 (82.6)	213
	Journal of American Medical Association	0	15 (7.3)	191 (92.7)	206
	Annals of Internal Medicine	0	10 (8.5)	107 (91.5)	117
	Archives of Internal Medicine	0	10 (9.5)	95 (90.5)	105
	American Journal of Preventive Medicine	1 (1.2)	11 (13.3)	71 (85.5)	83
	Canadian Medical Association Journal	0	4 (5.6)	67 (94.4)	71
	The New England Journal of Medicine	1 (2.0)	1 (2.0)	47 (95.9)	49
	Journal of Pain and Symptom Management	0	1 (2.1)	47 (97.9)	48
	The Lancet	0	6 (14.6)	35 (85.4)	41
	Preventive Medicine	0	3 (10.3)	26 (89.7)	29
	The American Journal of Medicine	0	1 (3.6)	27 (96.4)	28
	Mayo Clinic Proceedings	0	2 (10.5)	17 (89.5)	19
	Journal of Internal Medicine	0	0	3 (100.0)	3
	Annals of Medicine	0	0	2 (100.0)	2
Publication year					
	1996-1999	2 (1.0)	20 (10.5)	169 (88.5)	191
	2000-2003	0	26 (9.2)	257 (90.8)	283
	2004-2007	0	32 (10.4)	277 (89.6)	309
	2008-2011	0	39 (7.7)	466 (92.3)	505
Publication type					
	[a]Research publications	2 (0.4)	60 (12.8)	405 (86.7)	467
	Non-research publications	0	57 (6.9)	764 (93.1)	821

[a] Research publications are interventional and observational studies, systematic reviews, guidelines, and consensus publications.

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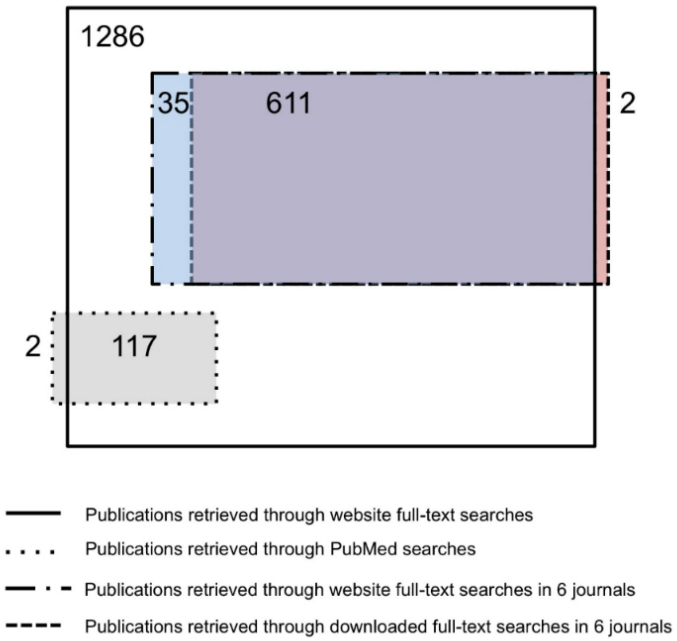
Figure 2. Adapted Venn schematic of the search method results. NB: Areas of the boxes are not exactly proportional.



Discussion

Principal Results

The website full-text searches identified 1286 SDM publications in 15 major medical journals, which was about 10 times more than through the corresponding PubMed searches. The search method was reliable with a good concordance rate when compared with a validation dataset of downloaded publications.

To our knowledge, full-text searches have never been assessed on medical journal websites. Our results are concordant with those of previous studies in other fields (eg, genomics), where the sensitivity of detecting keywords in full-text publications is much higher than when limited to a title and abstract PubMed search [19,20]. This may be especially useful when searching for information about study limitations or adverse drugs reactions [21], which are less likely to appear in abstracts or titles.

In a Cochrane review, handsearching identified more reports of randomized controlled trials than electronic searching through MEDLINE, particularly trials reported as letters, editorials, or journal supplements [22]. In the same way, our study showed that full-text searches found over 86.7% (405/467) of research publications that would have been missed through a simple PubMed search. The website full-text search method could be an efficient alternative to handsearching, where time and resources are limited.

The website full-text searches were fast and simple to perform compared to the downloaded full-text searches. While it took a few days to search the journal websites, it took 10-12 months of long negotiations to sign contracts with copyright holders to gain access to their material. However, we finally reached the goal for less than half of the contacted journals. Unfortunately, similar copyright issues have previously been reported in the text mining field [23].

Limitations

Our study has some limitations. First, we did not develop a comprehensive search strategy, but selected only 6 phrases related to SDM. As a result, we did not assess the performance of an elaborate PubMed search strategy for SDM, compared with a full-text search method. We thought it was reasonable to explore this novel method with a simplified search strategy, as it is closer to the approach used by researchers and clinicians on a daily basis. Further studies should use a more comprehensive search strategy to compare extensively the new search method with PubMed or other search engines. Second, a gold standard search method could not be established, because it was not possible to verify that all publications with inclusion criteria were retrieved. For that matter, all three methods failed to identify all SDM publications, probably due to the lack of consistent indexing mechanisms and technical defects, like in the OCR. Third, for multiple resource constraints, we have not been able to perform the full-content analysis of the 1286 included publications. We are therefore unable to report on the meaning and the potential relevance of each publication. It is possible that some publications mentioned SDM just as a fashionable concept in a sentence or as a replacement term for other terms (ie, patient-centered care or risk communication). From this perspective and without a gold standard, we were unable to measure the proper recall and precision of the search method.

Conclusions

Full-text searching of terms in medical journal websites is a reliable and efficient way to identify relevant articles in the field of SDM for review or other purposes. It may be more widely

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used in medical research in the future, with the collaboration of publishers and journals toward open-access data.

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Conflicts of Interest

None declared.

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Abbreviations

OCR: optical character recognition
SDM: shared decision making

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Original Paper

Recruiting Migrants for Health Research Through Social Network Sites: An Online Survey Among Chinese Migrants in Australia

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Abstract

Background: Traditionally, postal surveys or face to face interviews are the main approaches for health researchers to obtain essential research data. However, with the prevalence of information technology and Internet, Web-based surveys are gaining popularity in health research.

Objective: This study aims to report the process and outcomes of recruiting Chinese migrants through social network sites in Australia and to examine the sample characteristics of online recruitment by comparing the sample which was recruited by an online survey to a sample of Australian Chinese migrants collected by a postal survey.

Methods: Descriptive analyses were performed to describe and compare the process and outcomes of online recruitment with postal survey questionnaires. Chi square tests and *t* tests were performed to assess the differences between the two samples for categorical and continuous variables respectively.

Results: In total, 473 Chinese migrants completed the online health survey from July to October 2013. Out of 426 participants recruited through the three Chinese social network sites in Australia, over 86.6% (369/426) were recruited within six weeks. Participants of the Web-based survey were younger, with a higher education level or had resided in Australia for less time compared to those recruited via a postal survey. However, there was no significant difference in gender, marital status, and professional occupation.

Conclusions: The recruitment of Chinese migrants through social network sites in our online survey was feasible. Compared to a postal survey of Chinese migrants, the online survey attracted different group of Chinese migrants who may have diverse health needs and concerns. Our findings provided insightful information for researchers who are considering employing a Web-based approach to recruit migrants and ethnic minority participants.

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KEYWORDS

Chinese migrants; online survey; recruiting

Introduction

Migrant and ethnic minority groups often have poorer self-perceived health status than the general population, and recruiting participants from those groups for health research is challenging [1]. Migrants and ethnic minorities, especially those who were originally from non-English speaking countries, are likely to be underrepresented in population-based national health

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surveys due to language and cultural barriers and low health literacy [2-4]. With the rapid development of information technology, Internet-based surveys are gaining popularity in health research projects [5]. It is expected that such surveys will become a promising alternative approach for recruiting research participants in health research realms [6].

Conventional population-based sampling is usually costly and time consuming in producing sufficient numbers of minorities [4]. Many health studies in migrants and ethnic minorities have adopted purposeful sampling methods to recruit participants in specific premises including clinics, churches, and community centers [7,8]. In some studies, participants were recruited through a telephone directory by selecting surnames which might indicate the person's ethnic background [9,10]. Nevertheless Smith et al. proposed that a telephone directory sampling strategy was less likely to include subjects born outside of Australia than a door-to-door population census [11].

Web-based or Internet-based data collection methods have been credited for the speed with which data can be collected, low cost, and direct data entry in comparison with traditional paper-based questionnaires [6]. The recent success of Web-based recruiting for young women in Australia shows that using the Internet in medical research presents an opportunity for innovative recruitment modalities [12]. However, a study conducted in the United States successfully recruited a targeted number of white cancer patients from wider Internet communities but failed to recruit a sufficient number of ethnic minority cancer patients from ethnic-specific Internet communities [13].

Social network sites (SNSs) include all types of online social platforms that allow participants to connect and interact within broader Internet communities [14,15]. There are an increasing number of studies using social network sites as a tool or a platform in the public health domain with only a small number describing the use of SNSs among migrants or ethnic minorities. The use of the Internet in recruiting may present broader opportunities to engage ethnic minority groups in health research in order to understand their special health needs and to reduce health inequalities. A previous study found that participants of Web-based surveys were younger and had a higher education level than those of paper-based surveys [16]. It is of interest to understand whether the data collected through the SNSs are comparable to those obtained through traditional data collection methods among migrants and ethnic minorities.

Australia is a culturally-mixed country with more than a quarter of the population born overseas [17]. There is an increasing demand for health research among this growing migrant population. This paper summarizes the outcomes of recruiting Chinese migrants through social network sites and examines the sample characteristics of online recruitment by comparing the sample which was recruited by an online survey with the sample collected by a postal survey respectively amongst the Australian Chinese migrant communities. The findings may provide some insights to researchers who are considering a Web-based approach to recruit migrants and ethnic minority participants.

Methods

Online Survey Procedure

Participants who self-identified as Chinese and had been living in Australia longer than 3 months were recruited through several social websites to complete an online health survey from July to October, 2013. A structured questionnaire with 57 questions regarding demographics, health related risk behaviors, health service use, antibiotic use, and mental problems was uploaded to the University of Queensland server using online survey software [18]. Participants were directed to the survey webpage by clicking a link provided in a series of ads. Before proceeding to the survey, participants were required to provide consent by stating that they understood the provided information and agreed to participate in the study. The opportunity to win 1 of ten $50 gift cards was provided as an incentive for completing the online survey. Participants who completed the questionnaire and provided their name and email address were automatically entered into the draws. The lottery draws occurred five times over the entire survey period when the total number of participants reached 80, 160, 240, 360 and at the endpoint of the survey. Two participants were chosen each time, and were announced as draw winners in the recruiting threads by displaying part of the email address of the winners. At the end of the survey, a brief summary of the survey results was emailed to each participant. This study was approved by University of Queensland School of Medicine Low Risk Ethical Review Committee (2013-SOMILRE-0074).

Our recruitment posts with detailed survey information were initially posted on 3 major Chinese social network sites, including "Oursteps", "Ozyoyo", and "Freeoz". In addition, those notices were also posted on other Chinese social network sites such as "Yeeyi", "ozchinese", QQ instant message, and Weibo. "Oursteps" and "Freeoz" had members Australia-wide while "Ozyoyo" is self-claimed to be the largest Chinese website in Queensland. The primary language of all these sites is Simplified Chinese.

Postal Survey Procedure

The data collected in this online survey were compared with a data set of Australian Chinese respondents collected through a postal survey from November 2005 to February 2006. The process of the postal survey was reported elsewhere [19]. Briefly, an invitation letter and a bilingual (Chinese and English) survey questionnaire along with a self-addressed stamped envelope were mailed to 500 migrants assumed to be Chinese, randomly selected through a Brisbane telephone directory by identifying possible Chinese surnames. No financial incentives were provided in this study; however, a health information pamphlet was included in the mail. In total, 213 participants returned the completed questionnaire. Data were entered manually by the second author (KW).

Data Analysis

The survey software was able to capture some information about participation such as IP addresses of each participants, as well as date and time of starting and finishing the survey. Data were exported directly from the survey software as Excel files. As

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all analyses were performed using Stata 13 [20], Excel files were then converted to a compatible format for analysis. Descriptive analyses were performed to describe and compare the process and outcomes of online recruitment with postal survey questionnaires. Chi square tests for categorical variables and *t* tests for continuous variables were conducted.

Results

Online Recruiting Outcomes

Of the 600 Chinese migrants who visited the survey webpage, 473 (78.8%) completed the online questionnaire. While online recruiting was set to be closed on September 30th, 2013, notices were not removed from the SNSs after the closing date, and we still received a few completed questionnaires, which were included in the final total number of participants. During the total survey period (July-October, 2013), the advertising posts were viewed more than 8000 times including repeated viewings and administrative viewings. By the end of September, 426 out of 473 (90%) participants were recruited through 3 Chinese social network sites "Oursteps", "Freeoz", and "Ozyoyo"; 35 migrants were recruited through other social network sites. There were an additional 12 completed questionnaires received between September 30thand October 30th, 2013. Table 1 provides details of the viewings and respondents through several SNSs. Figure 1 shows the increasing number of participants over the 10-week recruitment period through the 3 SNSs (total recruitment and recruitment by study sites). As we can see in Figure 1, the recruitment outcome through the 3 websites reached over 86.6% (369/426) of the total participants in 6 weeks.

We provided 10 50 Australian Dollar (AUD) gift cards presented as lucky draw winners. Each gift card was mailed to the winner who was randomly selected from the valid participants. The postage for 10 registered mails was AUD44. No additional costs were incurred, as the University of Queensland provided free access to the university's server and the survey software.

Figure 1. Increasing number of participants over the ten-week recruitment period (total recruitment and recruitment by three SNSs).

Identification of the Online Survey Participants

The online survey software enabled us to capture the IP address of each participant. IP addresses identified 94.1% (445/473) of the participants as living in Australia when they undertook the survey. Around 2.5% (12/473) of the participants' IP addresses were outside Australia, and the remaining 3.4% (16/473) of the IP addresses were not detectable. Seven pairs of duplicate IP addresses were detected, which were further verified as different participants (with different personal information such as gender and age).

The selection criteria for our online survey include "self-claimed as Chinese" and "have resided in Australia for longer than 3 months". Out of 473 total participants, 440 (93.0%) were born in Mainland China. Others were born in Taiwan, Hong Kong, Macau, and Malaysia. Among the total participants, 4 of them reported living in Australia for less than three months and another 7 did not answer the question about their length of residence in Australia.

Sample Characteristics and Comparisons With Data From a Postal Survey

Participants of the online survey were spread over of Australia including Queensland, New South Wales, South Australia, Victoria, and West Australia. Fifty-five percent were females. The mean age of participants in the Web-based survey was 33.1 (SD 8.2) years. Table 2 shows the demographic characteristics of the 2 samples of Australian Chinese migrants collected

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through the online survey and the postal survey, respectively. The Web-based survey participants were substantially and significantly younger (by about 12 years) than those of the postal survey. The proportions of participants in different age groups were significantly different between the 2 samples. Of those who completed the Web-based survey, 80.2% (372/464) were under 40 years old, with only 35% of participants in the postal survey being in the same age bracket. The average length of stay in Australia of Web-based survey participants was 5.8 years (ranging from 1 month to 27 years) and was 8.3 years shorter than the postal survey participants (14.1 years, ranging from 6 months to 54 years).

Over 90% of total participants in the Web-based survey (440/473) were born in mainland China versus only 31% in the postal survey. The proportion with an undergraduate or higher degree was significantly higher in the Web-based survey group (85.6%, 405/473) than in the postal survey group (75%). A substantial proportion of the participants had a family doctor in the postal survey (73%) compared to the Web-based survey (47.1%, 223/473). However, there was no significant difference in gender, marital status, BMI, or professional occupation between the 2 samples.

Table 1. Recruiting details in Chinese social network sites from July to October 2013[a].

Study websites	Start	End	Number of viewings[b]	Valid participants
Oursteps	23/07/2013	30/09/2013	2774	146
Freeoz	22/07/2013	30/09/2013	1861	135
Ozyoyo	30/07/2013	30/09/2013	2290	145
Yeeyi	04/09/2013	30/09/2013	2109	22

[a]13 participants recruited from several other websites plus 12 participants recruited after the deadline had passed were not included in the table.
[b]Including duplicated viewings

Table 2. Comparison of demographic characteristics between the 2 samples of Australia Chinese migrants, n (%) or mean (SD).

Characteristics	Online survey mean (SD) or n (%)	Postal survey mean (SD) or n (%)	*P* value
Total participants[a]	473	213	
Age, years, n (%)			
mean (SD)	33.1 (8.2)	45.1 (14.3)	<.001
<30	158 (34.1)	36 (18.5)	<.001
30-39	214 (46.1)	30 (15.5)	
40-49	71 (15.3)	62 (32.0)	
≥50	21 (4.5)	66 (34.0)	
Female	261 (55.2)	116 (56.0)	.84
Born in Mainland China, n (%)	440 (93.2)	66 (31.0)	<.001
Undergraduate or higher degree	405 (86.2)	157 (74.8)	<.001
Professional occupation [b]	206 (43.6)	86 (42.2)	.72
Married or in a partnership	352 (74.7)	144 (78.3)	.34
Length of residing in Australia, years, n (%)			
Mean (SD)	5.8 (4.2)	14.1 (8.8)	<.001
≥5	264 (55.8)	182 (85.5)	<.001
BMI, mean (SD)	23.2 (4.4)	22.6 (3.1)	.08
Have a family doctor, n (%)	223 (48.2)	155 (72.8)	<.001
Family doctor speaks same language, n (%)	133 (59.6)	108 (73.0)	.008

[a]The sum of participants in subgroups may not equal to the total number of participants due to missing values.
[b]Non-professionals include administrative positions, those with home duties, skilled laborers, the unemployed, pensioners, manual laborers, and the self-employed.

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Discussion

Principal Findings

Overall, it is feasible to recruit large numbers of community-based Chinese migrants through social network sites with minimal cost. The majority of participants were recruited within 6 weeks through 3 major Chinese SNSs. Participants of the online survey were younger or had resided in Australia for a relatively shorter time than those of the postal survey. However, participants' gender, marital status, and professional occupations were comparable.

In this online survey, we recruited over four hundred Chinese migrants. Based on a review of the postal codes of participants, we determined that the Chinese migrants resided dispersedly in 5 different states of Australia. The survey was initially designed to recruit Chinese participants through the 3 major Chinese SNSs, where the principal investigator is an active member of the SNS. We then extended our study to include other Chinese SNSs where the principal investigator is a newly registered member. As of September 30th, 2013, 426 participants were recruited from the three social network sites and 35 participants were recruited from other sites. As we can see in Table 1, the recruiting thread was viewed over 2000 times with only 22 valid participations in 4 weeks' time through "Yeeyi". Community coordinators or existing relationships in the community have been proven to be helpful in recruiting ethnic minorities [21]. Our study found similar scenarios among the Internet communities; recruiting outcomes were less satisfactory when the survey initiator was a fresh member in the Internet community.

We noted that the majority (86.6%, 369/426) of participants were recruited within 6 weeks of the survey period and the incoming numbers of respondents slowed down dramatically thereafter. Findings supported the assumption that online survey responses would be quicker compared to traditional mail surveys [5]. Our recruiting message was posted in several social websites as a thread which would be pushed down towards the bottom of the page by new threads or any existing threads which received new replies. In a SNS with a high number of active members, threads are constantly being created or replied to at a fast pace. It is therefore important to ensure the recruiting thread is attended regularly so it will not be ignored [22]. Thus we believe the first few weeks are most important in order to recruit a greater number of participants in social network sites.

We provided incentives to participants in the form of 10 lottery draws for gift cards worth AUD50 each. The marginal cost for this survey was close to AUD1.20 per participant plus organizational expenses, comparable to the cost of the postal survey (AUD0.60 postage plus organizational expenses). Since the financial incentive was relatively small and probability based, it was not likely to be a major factor in deciding to participate in the online health survey. However, by announcing the lottery winners multiple times over the survey period, we were able to attract more attention to the recruiting threads in the SNSs and expand the viewing audience.

The online survey attracted younger participants with a higher educational level than the postal survey, consistent with the existing literature that older participants with lower education might be underrepresented in Web-based surveys due to the disparity in Internet and computer access [23]. Another study comparing Web-based and paper questionnaires also found the Web-based sample to be nearly 9 years younger with a higher educational background than the paper-based sample [16]. In addition, Smith et al reported that samples based on telephone directories are very likely to exclude younger participants and participants who do not own property [11].

As regards migrant health studies, the length of stay in a host country is an important indicator of acculturation. In this study, we found that 85% of participants in the postal survey had been residing in Australia for more than 5 years, compared with about half of participants in the Web-based survey. Similarly, studies amongst US migrants found samples of longer-stay migrants using a telephone directory list [10]. Due to immigration regulations, new arrival migrants are generally young and well educated. They are likely to seek social support through the Internet in the early stage of their immigration [24]. Consequently, Web-based health research could be a promising supplementary method to reach the newly-arrived migrants.

In addition, we found the percentage of the participants having a family doctor was significantly higher in the postal survey than in the Web-based survey. Compared to Web-based survey participants, the postal survey participants were more likely to have a family doctor who could speak the same language as themselves. The findings indicate that health-related behavior may be very different due to various demographic features of the 2 samples. Researchers need to be aware of such differences when interpreting findings from different survey approaches.

Nevertheless, the online survey approach enabled us to quickly recruit Chinese migrants who were living in different states of Australia within a specific limited time and budget. The findings reported here regarding recruiting processes and outcomes are strictly applicable to these specific Chinese social network sites. More studies will be needed to articulate how to effectively recruit migrants or ethnic minorities of various populations using the Internet.

Limitations

We also identified several limitations when we compared the data of these 2 surveys. First, these 2 health surveys adopted different strategies which may have contributed to the discrepancy in the composition of the 2 samples. The participants of postal survey included Chinese who were born in Hong Kong, Taiwan, Malaysia, Singapore, and other countries. The majority of the participants of online survey were born in Mainland China because that is where the majority of the registered members of the study websites were from. Second, the incentive of winning a gift card was offered in the online recruitment, whereas no financial incentives were provided in the postal survey. However, since the incentive is small and probability-based, we believe it is unlikely to be the major motivation of taking part in the health survey. Third, due to convenience sampling, neither sample is representative to the whole Australian Chinese community. Fourth, access to the

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online survey was confined to participants with adequate computer literacy to complete a questionnaire online. Our recruiting through social network sites was likely to overlook those older Chinese migrants who do not use computers and Internet. Last but not least, the postal survey was conducted 7 years prior to the Web-based survey. The demographic composition of migrants might have changed over time. Even so, however, that potential change in demographics is unlikely to account for the observed differences between 2 surveys. A recent study in the United States, using a telephone directory to obtain a sample of Chinese migrants, also showed that the sample population of a postal survey was relatively older and they were longer-stay migrants [10].

Conclusions

Recruiting Chinese migrants through social network sites for health research is demonstrated to be feasible in our online survey. This paper provided detailed processes and outcomes for recruiting Chinese migrants through social network sites in Australia. This online recruitment method is likely to reach younger or shorter-stay Chinese migrants but may miss those older or longer-stay migrants who may not use the Internet. Researchers need to be cautious of this potential sampling bias when interpreting their results. Nevertheless, these findings could be useful for planning and conducting future research or intervention programs among migrants and ethnic minorities.

Acknowledgments

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Conflicts of Interest

None declared.

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Original Paper

Using Facebook to Recruit Young Adult Veterans: Online Mental Health Research

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Abstract

Background: Veteran research has primarily been conducted with clinical samples and those already involved in health care systems, but much is to be learned about veterans in the community. Facebook is a novel yet largely unexplored avenue for recruiting veteran participants for epidemiological and clinical studies.

Objective: In this study, we utilized Facebook to recruit a sample of young adult veterans for the first phase of an online alcohol intervention study. We describe the successful Facebook recruitment process, including data collection from over 1000 veteran participants in approximately 3 weeks, procedures to verify participation eligibility, and comparison of our sample with nationally available norms.

Methods: Participants were young adult veterans aged 18-34 recruited through Facebook as part of a large study to document normative drinking behavior among a large community sample of veterans. Facebook ads were targeted toward young veterans to collect information on demographics and military characteristics, health behaviors, mental health, and health care utilization.

Results: We obtained a sample of 1023 verified veteran participants over a period of 24 days for the advertising price of approximately US $7.05 per verified veteran participant. Our recruitment strategy yielded a sample similar to the US population of young adult veterans in most demographic areas except for race/ethnicity and previous branch of service, which when we weighted the sample on race/ethnicity and branch a sample better matched with the population data was obtained. The Facebook sample recruited veterans who were engaged in a variety of risky health behaviors such as binge drinking and marijuana use. One fourth of veterans had never since discharge been to an appointment for physical health care and about half had attended an appointment for service compensation review. Only half had attended any appointment for a mental health concern at any clinic or hospital. Despite more than half screening positive for current probable mental health disorders such as post-traumatic stress disorder, depression, anxiety, only about 1 in 3 received mental health care in the past year and only 1 in 50 received such care within the past month.

Conclusions: This work expands on the work of other studies that have examined clinical samples of veterans only and suggests Facebook can be an adequate method of obtaining samples of veterans in need of care.

Trial Registration: Clinicaltrials.gov NCT02187887; http://clinicaltrials.gov/ct2/show/NCT02187887 (Archived by WebCite at http://www.webcitation.org/6YiUKRsXY).

(JMIR Res Protoc 2015;4(2):e63) doi:10.2196/resprot.3996

KEYWORDS

alcohol; Facebook; Internet; mental health; online; young adult veterans

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Introduction

Background

Young adult American veterans from the conflicts in Iraq and Afghanistan (Operation Enduring Freedom/Operation Iraqi Freedom, OEF/OIF) are at increased risk of mental health problems such as post-traumatic stress disorder (PTSD), anxiety, and depressive disorders, and/or substance use disorders [1-4]. Rates of these mental health problems are particularly concerning among young adult OEF/OIF veteran samples compared with active duty and civilian samples [2,5-8].

Although mental health problems evident among the growing group of veterans are a cause for concern, the majority of the research that is conducted with young veterans comes from samples recruited through the Veterans Health Care System (Department of *Veterans Affairs or VA*) or from examining VA administrative data [1,4,9]. Although this research is important to understand the needs of veterans in the VA, it excludes hundreds of thousands of veterans who do not seek VA care. Indeed, approximately 50% of OEF/OIF veterans do not seek services at the VA [10,11] and it is estimated that of the over 303,000 OEF/OIF service members and veterans with probable diagnoses of PTSD or depression, only half had sought help for any mental health problems from a medical or specialty provider [2]. Thus, while research on the health of veterans who are in the VA is critical for many reasons, it would be helpful to supplement those samples with research that recruits from other segments of the veteran population.

Facebook Recruitment of Participants

Facebook, a social media website founded in 2004, is a promising—but largely unexplored—vehicle for reaching large numbers of OEF/OIF veterans for research and treatment outreach efforts. Facebook is the second most visited website in the United States [12], with over 165 million regular users from the United States alone [13]. More than half of Facebook users in the United States are under the age of 35 [14] and approximately two thirds to three quarters of all 18-34-year olds have a personal profile on the social media website such as Facebook [15,16].

Facebook allows users to connect with friends online through sharing personal updates or digital content such as pictures or Web pages. It allows users to endorse (by “liking” someone’s picture for example), discuss, or republish content posted by their friends and by organizations, commercial products and brands, media companies, news outlets, and more. Sharing and interacting with Facebook content personalizes a news feed on each user’s main Facebook page and drives an audience targeting engine for Facebook’s paid advertising products.

Compared with traditional forms of recruiting participants outside of a clinical setting (eg, posting flyers, newspaper advertisements), Facebook is well suited to reaching young adults for mental health research and is not biased toward one particular gender [17]. Facebook may also benefit longitudinal retention in research, which is often affected by inability to locate participants who have moved or changed contact information [18,19]. Ads on Facebook have been used successfully to recruit “hard-to-reach” populations such as sexual minorities, veterans interested in PTSD care, and other participants not accessed through traditional recruitment strategies [19-21], as well as young adults and adolescents for sensitive research areas such as substance use behavior [22-24], exposure to violence [25], mental health concerns [17,26], and sexual practices and women’s health issues [27-31]. Overall, Facebook is emerging as a viable and appropriate method of reaching populations for online surveys of a variety of physical and mental health issues [32].

Facebook- and general Internet-based research comes with both benefits and drawbacks [33-35]. For example, Internet-based recruitment is generally cheaper and faster than mailed surveys or interviews and can be used to access populations hesitant to participate in person. Internet surveys and programs enable participants to complete surveys at their convenience. However, lack of Internet and computer/mobile phone access still constitutes a barrier to participation for some classes of individuals in the population, and may effectively exclude the indigent or homeless. However, many of these same concerns hold true for traditional recruitment strategies as well (eg, phone-based interviews, television, and newspaper advertisements). Another potential problem is that, relative to in-person survey research (and to an extent, phone-based surveys), it is easier for respondents to misrepresent themselves; for example, participants misrepresenting eligibility to obtain an incentive (eg, payment, treatment) for which one is not eligible. As interest in Internet-based research (and more specifically the use of Facebook ads to recruit for Web-based research) has grown over the past 10 years, researchers have developed a series of procedures to deter misrepresentation of participants and best ensure validity of the sample obtained [36]. While these procedures help minimize concerns, more research is needed to better understand methods to reduce misrepresentation in Facebook-recruitment studies and ensure adequate representation of the populations targeted.

Study Protocol

This study was the first phase of a larger clinical trial (National Institutes of Health NCT02187887) to provide young adult veteran drinkers with a personalized normative feedback intervention to reduce problematic alcohol consumption. For the first phase, we collected data on drinking behavior and attitude norms for use in the intervention phase of the study. An aim of this first phase of the study is also to examine the feasibility of recruiting a young adult veteran sample using Facebook. Nearly all young adult veterans report access to and use of the Internet, with the majority using the Internet daily and over two thirds reporting routine use for receiving health information or finding services [37-39]. In addition, their family members and friends are on Facebook, and thus, making connection with non-Facebook veterans may be a possibility through these referring sources. For example, Facebook groups tailored toward young adult veterans such as Iraq and Afghanistan Veterans of America have over 500,000 followers, with the most recent report from 2010 indicating that there are about 80,000 OEF/OIF veteran followers [40]. Young adult veterans are online and on Facebook, and thus, this paper describes Facebook recruitment of these individuals and

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provides findings on the cost and speed of using such a strategy to collect young veteran samples. Second, as Facebook is a promising yet novel method of reaching veterans for research, we aimed to look at the representativeness of our obtained sample. We compare demographic information from our sample with veteran population data from the American Community Survey (ACS) and information on the population of discharged military personnel available from the Department of Defense (DoD). Finally, we describe our sample, including health behaviors such as alcohol and marijuana use, mental health status, health care utilization, demographics, and military characteristics to provide a picture of what the young adult veteran sample from Facebook looks like in these areas.

Methods

Facebook Advertising

All procedures for advertising, consent, and survey methods were approved by the Institutional Review Board at the institution where the study was conducted. A series of Facebook ads targeted young adult veterans between the ages of 18 and 34 who had previously served in the US Air Force, Army, Marine Corps, or Navy. These ads targeted young adults likely to be veterans as well as Facebook users that might know a veteran who could be interested in our study. Ads were targeted to a potential audience of about 3.6 million Facebook users in the United States through a series of targeting criteria based on location (United States), age ("18-40"; however, we targeted beyond the 18-34-year-old age group in case a nonveteran family member/friend knew a young adult veteran), and interests (eg, "veteran," names of national veteran service organizations such as Iraq and Afghanistan Veterans of American, movies and TV shows with an OEF/OIF focus such as *Restrepo* and *Generation Kill*, video games such as the *Call of* Duty series, "military spouse"). The study was named the Veterans Attitudes Online Survey Study and the Facebook ads did not specifically target any particular physical or mental health behaviors or problems.

The following 3 types of ads were used: (1) direct promotion of the survey website, (2) promotion of posts we made to our Facebook page, and (3) invitations to "like" (publicly endorse) our Facebook page. Example ads are displayed in Figure 1. Direct survey website promotion ads were displayed on sidebar ad panels and in the personalized news feed that is the home page for Facebook users. These ads briefly described the study and allowed an individual to click through to the survey website. All direct promotion ads mentioned incentives for participation. Post-promotion ads were displayed in news feeds only, and included an option to reach our Facebook page, which contained information about our study and a link to the survey website. One of the 5 post-promotion ads discussed the incentive. Invitations to "like" our Facebook page were displayed in news feeds, with a suggestion that the reader might be interested in our page alongside a button to "like" our page directly from the ad. All of these ads also discussed the incentive. Both post promotions and invitations to like our Facebook page were aimed at cultivating ongoing interest and interactions with our study and to encourage social sharing of the survey info with friends. For all 3 sets of ads, Facebook users could "like" the ad, comment on the ad (eg, "This looks like a great study" would appear in the comments section under our ad), or share it with friends (eg, "Hey, check out this survey for veterans" would display on someone's Facebook wall for their friends to see). All 3 types of ads automatically utilized the social networks inherent to Facebook. For example, when someone liked our ad or our Facebook page, this fact was promoted to that users' friends in their news feed that "[Your friend] liked [our Facebook page] (or [our ad])".

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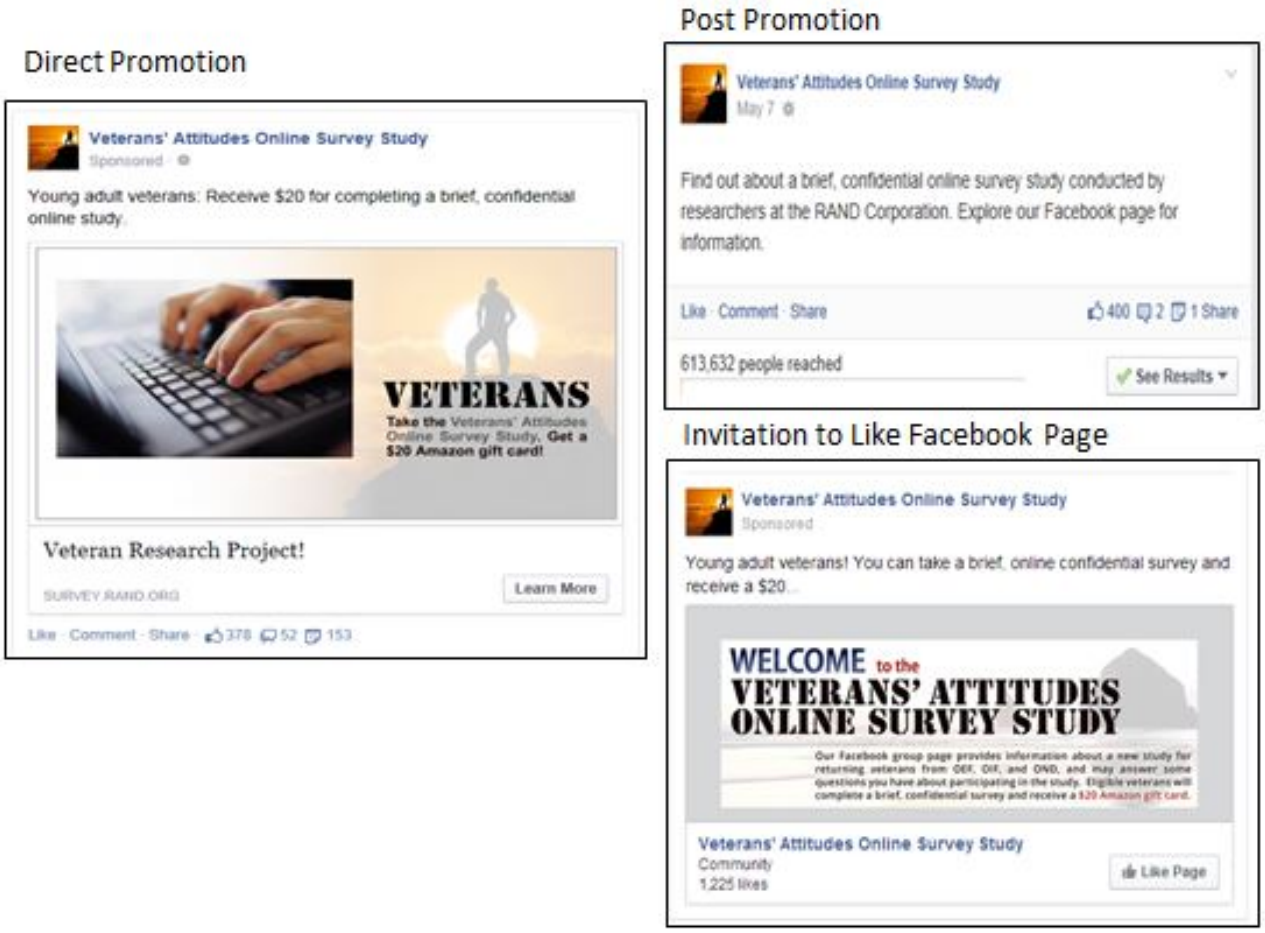
Figure 1. Examples of Facebook ads.



Facebook Recruitment

The number of steps for a potential participant to access the survey from a Facebook promotion differed by the type of ad. If a Facebook user saw a direct survey website promotion ad, they could click on the ad itself and were directed to the survey Web page. The Web page contained a button that said "click here to access the survey" and contained 3 sentences describing that the study was conducted by researchers at RAND, responses were confidential, and contained a link to our Facebook page if the user wanted more information before clicking through. Alternately, if Facebook users saw a post promotion or invitation to like the page, they needed to click on that ad to first reach our Facebook page, where the link to the Web page was displayed.

If participants clicked through an ad directly to the survey Web page, it was anonymously recorded by Facebook as a "website click." Participants reaching the Web page were presented with a consent form at the beginning the survey. If they consented, they accessed the survey. Participants were given a US $20 Amazon gift card for completing the survey. All user actions on our ads, including website clicks, likes, shares, and comments were anonymously recorded for aggregate reporting by Facebook. Facebook ad results reported below were generated from the detailed analytics reports provided by Facebook to all advertisers, for use in evaluating the effectiveness of paid ad campaigns. All reported findings are for unique user counts of each action that exclude any duplicate actions by a given Facebook account.

We followed procedures discussed by Kramer and colleagues [36] to reduce misrepresentation of participants and limit fraudulent responders. These procedures included prohibiting open access to the survey-hosted website, requiring screening questions to prevent and remove noneligible individuals from continuing to complete the survey, asking participants "insider knowledge" questions, examining time stamp of survey initiation and completion, identifying pairs of items that needed to be consistent, and verifying that individuals' responses were consistent with previous research targeting veterans. We also restricted access to the survey website through a single login per Facebook account. That is, to access the survey, participants needed to login via their Facebook accounts, and we limited survey access to one completion per Facebook account. The information technology department at RAND worked with Facebook to ensure we were not collecting any information from a Facebook user's profile (eg, list of friends) or personal information (eg, passwords) and that Facebook had no access to the data collected in our survey.

Once individuals accessed the survey by clicking through to the Web page, they saw an informational statement describing eligibility, confidentiality, and other aspects of informed consent. If interested, they indicated agreement to participate in the study. They began the survey with screening questions of age, veteran status (eg, veteran, active duty, reserves/guard),

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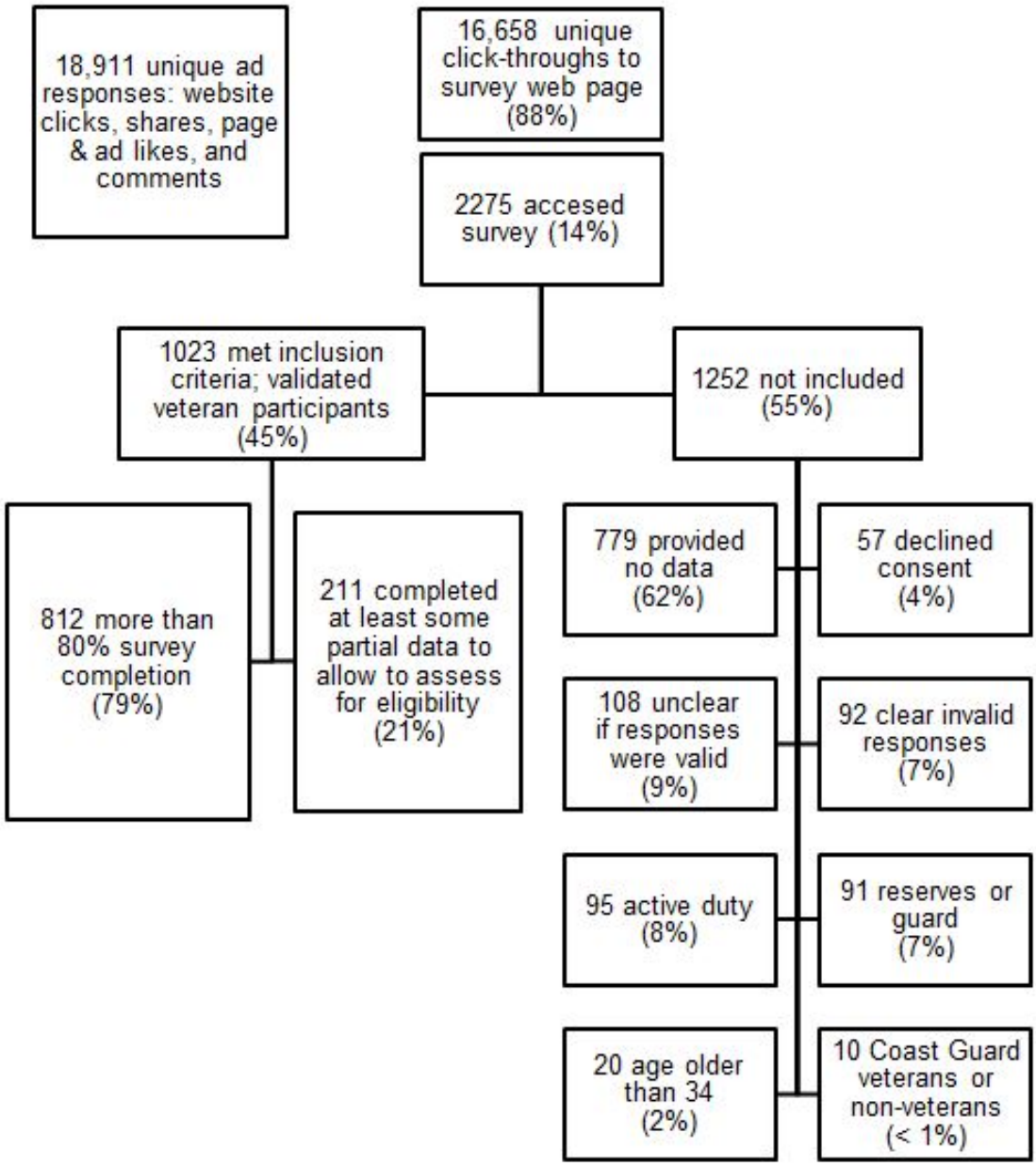
and branch of service. To be eligible, veterans needed to be between 18 and 34 of age and fully separated from the military; thus, not currently in the reserves or guard units. We specified veterans of OEF/OIF in the recruitment documentation, but did not exclude veterans who were not involved in those combat operations. Eligibility criteria were made clear on our Facebook page and in consent. Respondents who were ineligible based on their responses to the screener were exited from the survey without ability to reenter. Figure 2 contains a description of the individuals who were screened out due to ineligibility. Next, participants were presented with questions about pay grade at discharge (eg, E-4); rank at discharge (eg, captain); and occupation code: military occupational specialty for Army and Marine Corps, enlisted classification (for Air Force), or specialty code (for Navy). These items were all open-ended responses. We used these 3 items, branch of service, and age to ensure consistency and verify participants had military knowledge consistent with military service. When it was unclear (eg, if veteran endorsed pay grade at discharge for both pay grade and rank items), we examined the rest of the individual's data to determine whether their data appeared consistent with military service. We excluded participants in cases where data were still unclear or where misrepresentation was likely (Figure 2).

Figure 2. Flow diagram of sample participants.



Comparison and Description of the Sample

We sought to compare our sample with the national population of veterans. Data on the population were obtained from the ACS through the US Census Bureau's online data extraction tool, DataFerrett. The 3-year estimates of population variables from the 2010 to 2012 ACS were selected. From this set of data we

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selected only cases from individuals aged 18-34 who had served in the active duty military in the past (but were not currently serving). In addition to age and military service, we also included gender, marital status, education level attained, income, and race/ethnicity in the data extraction. Because ACS data did not collect information on branch of service, we also examined reports prepared for the DoD [41] to determine the percentages of veterans from each of the 4 branches of service. From these published reports, we determined the average percentage of personnel separated from the US Armed Forces over the past 5 years (2008-2012) for Air Force, Army, Marine Corps, and Navy. Although we were unable to extract data to match veterans aged 18-34 only, we excluded nonmedically retired personnel, as the military requires 20 or more years of service before nonmedical retirement; thus, excluding retired personnel that would be older than 34. Of note, both the ACS and DoD data defined "veteran" as including those in the reserves or guard, whereas we excluded those individuals from our study. Thus, a precise match on demographic characteristics would not be expected.

Measures

Overview

In addition to obtaining demographics to compare our sample with the ACS and DoD data, we sought to describe our sample in greater detail to provide a picture of the Facebook veteran population. Thus, we included measures of health behaviors, mental health, health care utilization, and other demographics and military characteristics.

Health Behaviors

We assessed any alcohol use in the past 30 days with a single item "During the past 30 days, how many days did you have at least 1 drink of any alcoholic beverage such as beer, wine, a malt beverage, or liquor?" Those that indicated at least 1 drinking day received a follow-up question for binge drinking behavior, "Considering all types of alcoholic beverages, how many times during the past 30 days did you have (*5 if male, 4 if female)* or more drinks on an occasion?" Drinking questions were preceded by a graphic depicting standard drinks. Lifetime marijuana use was assessed with a single yes/no question "In your lifetime, have you ever used cannabis (marijuana, pot, hash, hashish)?," which was followed by a single item for past 6 months, "Have you used any cannabis (marijuana, pot, hash, hashish) over the past 6 months?" These items are standard single-item measures used in multiple studies of young adults and veterans to assess health behaviors.

Mental Health

PTSD was assessed with a screener for PTSD, the Primary Care PTSD Scale [42]. Reliability of the scale was adequate in our sample (alpha=.87). The Patient Health Questionnaire-2 item (PHQ-2) [43] was completed as a screener for depression, and the Generalized Anxiety Disorder-7 Item Scale (GAD-7) [44] screened for GAD. Both scales displayed adequate internal reliability (r=.80 for the PHQ-2; alpha=.96 for GAD-7). Lastly, we used a single item included in the *Behavioral Risk Factor Surveillance System* from the US Centers for Disease Control and Prevention to assess for self-reported diagnosis of traumatic brain injury (TBI), which defined TBI and asked participants if a doctor or other health professional ever told them they had suffered from one. These measures are established as valid and reliable when used with military samples in previous work [45-47].

Health Care Usage

Veterans were asked if, since discharge they had ever attended an appointment at a VA (including VA hospitals or VA community-based outpatient clinics), a vet center, or a non-VA/vet center clinic, hospital, or doctor's office for any issue related to (1) physical health care, (2) mental health care, (3) alcohol use concerns, (4) other substance use concerns, (5) a review for service compensation (eg, to receive VA benefits from an injury incurred while on active duty), or for (6) any other reason. For mental health care, participants indicated whether they had attended a mental health care appointment in the past 12 months and if they had attended an appointment in the past 30 days. These items were modified from previous work assessing health care usage among service members and veterans [2].

Other Demographics and Military Characteristics

Participants indicated whether they were currently attending college and if so, what type of college they were attending (community, technical, state university, private college, or university) and whether they were using their GI Bill benefits or not. Participants were also asked how many children they currently had. They were asked how they heard about the study (ie, saw an ad on their computer, saw an ad on their phone, were forwarded a link to the survey from a friend/relative, a friend/relative told them where to find the survey link on Facebook) and on what device they completed the survey (eg, desktop/laptop, phone, tablet). Participants were asked how many times they had been deployed while on active duty. Lastly, they completed a yes/no measure of 11 deployment trauma experiences used in a previous work [2] to determine whether they had experienced trauma while deployed and if so, the severity of that trauma exposure (sum of yes responses to the 11 experiences).

Results

Facebook Advertising

Overview

Overall, the recruitment period lasted 24 days and we funded the Facebook ads for 12 of those days. Unanticipated delays with the advertising account payments, and an unexpected 4-day outage in the in-house server hosting our survey resulted in a total of 7 days during which ads were not actively shown. In addition, we stopped funding the ads 5 days before we took the survey down from our server. During these times, ads were not shown to participants on their Facebook news feeds, but they were still able to access our Facebook page and the see ads their friends shared or commented on from when the ads were running.

Over the recruitment period, 1.58 million Facebook users were shown an ad. On average, each person saw an ad about 2 times

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resulting in a total of about 3.3 million ad impressions. Of these, 18,911 unique individuals engaged with an ad (1.20%) by clicking through to our survey Web page or through liking, commenting on, or sharing the ad. A total of 16,658 users clicked through an ad to our Web page (1.05%) with the information statement and from there 2275 accessed the survey (0.14%). After a series of aforementioned checks, we obtained a total of 1023 verified veteran participants, representing 0.06% of the total targeted population (1023 of the 1,580,000 shown an ad; Figure 2). Overall, we spent US $7209 on ads for an overall cost per validated veteran participant of about US $7.05.

Direct Promotion

Direct promotion included ads that when clicked brought participants directly to the survey website. These ads utilized 72.01% (US $5191) of our budget and yielded 89.00% (16,831) of the 18,911 unique clicks. These cost about US $0.34 per unique click and yielded a 1.7% unique click-through rate.

Post Promotion

Post promotion included status posts on our page that did not have a direct link to the survey website. These utilized 25.00% (US $1802) of the budget and yielded 8.00% (1513) of the unique clicks. This type of ad produced a 0.7% unique click-through rate at a cost of about US $0.66 per unique click. The promotion was effective and reasonably cost effective for producing Facebook page likes, with 1094 likes at US $1.63 per like. Overall, this produced 1084 post likes, 104 post shares, 70 post comments, and 284 page likes, for a total of 1558 actions.

Invitations to like the Facebook Page

Invitation to like our Facebook page cost 3.00% (US $216) of the budget and yielded 3.00% (567) of the unique clicks. This method had the highest click-through rate at 3.00%, and cost about US $0.33 per unique click. This method produced 622 page likes at the lowest cost per like of all ad types.

Facebook Recruitment

Figure 2 displays a flow diagram of the final sample, including reasons for exclusion of participants from the final sample. In total, we had 2275 individuals accessing the first page of the survey. Of these, 1023 (44.97%) were validated veteran participants who met our inclusion criteria and were verified through our validation procedures described earlier. A total of 812 participants completed more than 80% of the survey, whereas 211 completed at least enough partial data to allow for assessment of eligibility (ie, demographic questions at beginning of survey). The remaining 1252 (55.03%) individuals reached the survey but were not included in the sample due to incompletion and ineligibility. Most were not included because they provided no data after reaching the survey page—61.9% (776) of the remaining 1252 individuals. Of interest, 92 individuals endorsed responses that led us to believe they were not actually veterans or had illegitimate responses (eg, indicated impossible rank and pay grade combinations, weight under 50 pounds (22.6 kg), completed survey in less than 2 minutes) and 108 indicated responses that were unclear as to whether they were valid veteran participants.

We asked participants how they learned of our study. Of the 1023 validated veteran participants, 428 (41.8%) saw an ad on Facebook on the computer (eg, on the side bar of their Facebook news feed) and 379 (37.0%) saw an ad on the Facebook app on their mobile phone. A total of 102 (10.0%) reported that a friend/relative emailed them the link to the survey or directed them to the Facebook page where the survey link was hosted. Lastly, 114 (11.1%) indicated they learned about the survey after seeing a Facebook friend had “liked” one of our ads or our Facebook posts.

Participants reported on what device they completed the survey. As much as 21.9% of the participants (225/1023) did not complete this question. Of the remaining 798 who completed the item, 235 (29.4%) completed the survey on a personal desktop or laptop computer, 23 (3%) completed it on a public desktop or laptop computer (eg, a computer at the library), 451 (56.5%) completed it on their personal mobile phone, 72 (9%) completed it on a tablet (eg, an iPad or Samsung Galaxy), 8 (1%) completed the survey on someone else’s mobile phone, and less than 1% each completed it on someone else’s tablet (3 participants), on more than 1 device (ie, started the survey on tablet and finished on a laptop; 1 participant), or on a work computer (5 participants).

Comparison and Description of the Sample

Participant demographics of the 1023 validated veteran participants with at least partial data are displayed in Table 1. As displayed in Table 1, participants were primarily male and white. About three quarters of the participants reported incomes under US $50,000, and about half were married. The sample consisted of veterans primarily from the Army and the Marines (84.9%, 869 participants). To determine how similar our obtained sample was to the general population of veterans, we compared our sample with the ACS data. As can be seen when comparing the first column of Table 1 (Facebook sample) with the ACS data column, our Facebook sample was similar to the broader ACS population on most demographic factors besides race/ethnicity, where our sample contained a higher percentage of Hispanic/Latino(a)s and fewer black/African Americans than might be expected in the general population of young adult veterans. In addition, when compared with the DoD population of separated military personnel, our sample contained substantially more Army and Marines than would be expected in the general separated population (43.1% and 19.8%, respectively), and fewer Air Force and Navy veterans than would be expected (15.3% and 21.8%, respectively). To account for these discrepancies when conducting subsequent analyses, we weighted our sample to match the population on branch of service (from the DoD data) and on race/ethnicity (from the ACS). Weighting on both branch and race/ethnicity appeared to best match our sample to the ACS (Table 1).

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Table 1. Sample demographics of 1023 veteran participants with branch and ethnicity weights compared with American Community Survey and Department of Defense.

Variable		Facebook sample[a] n/N (%)	Facebook sample weighted by branch and race/ethnicity n/N (%)	American Community Survey[b] n/N (%)	Department of Defense[c] n/N (%)
	Age (mean)	28.20 (SD 3.45)	28.24 (SD 3.63)	28.37 (SD 3.91)	
Age (categories)					
	<20	4/1023 (0.4)	20/1023 (2.0)	610/43,602 (1.4)	—
	20-24	155/1023 (15.2)	141/1023 (13.8)	7369/43,602 (16.9)	—
	25-29	485/1023 (47.5)	471/1023 (46.0)	16,482/43,602 (37.8)	—
	30-34	377/1023 (36.9)	391/1023 (38.2)	19,141/43,602 (43.9)	—
Sex					
	Male	905/1023 (88.5)	880/1023 (86.0)	35,143/43,602 (80.6)	—
Race/ethnicity					
	White	723/1023 (70.6)	697/1023 (68.1)	29,867/43,602 (68.5)	—
	Black or African American	37/1023 (3.6)	145/1023 (14.2)	5363/43,602 (12.3)	—
	Other	76/1023 (7.4)	71/1023 (6.9)	3009/43,602 (6.9)	—
	Hispanic/Latino(a)	188/1023 (18.4)	110/1023 (10.8)	5363/43,602 (12.3)	—
Branch					
	Army	616/1023 (60.2)	429/1023 (41.9)	—	334,591/776,313 (43.1)
	Marines	253/1023 (24.7)	193/1023 (18.9)	—	153,710/776,313 (19.8)
	Navy	87/1023 (8.5)	254/1023 (24.8)	—	169,236/776,313 (21.8)
	Air Force	68/1023 (6.6)	147/1023 (14.4)	—	118,776/776,313 (15.3)
Marital status					
	Married	527/1023 (51.5)	498/1023 (48.7)	20,667/43,602 (47.4)	—
	Divorced	177/1023 (17.3)	167/1023 (16.3)	4883/43,602 (11.2)	—
	Widowed	2/1023 (0.2)	1/1023 (0.1)	87/43,602 (0.2)	—
	Separated	54/1023 (5.3)	48/1023 (4.7)	1439/43,602 (3.3)	—
	Never married	247/1023 (24.1)	292/1023 (28.5)	16,525/43,602 (37.9)	—
	Other/member of unmarried couple	16/1023 (1.6)	17/1023 (1.7)	Not available	—
Education					
	Less than grade 12 or general educational development completion	33/1023 (3.2)	15/1023 (1.5)	567/43,602 (1.3)	—
	Grade 12 or general educational development (high-school graduate)	228/1023 (22.3)	207/1023 (20.2)	12,078/43,602 (27.7)	—
	Some college or technical school	610/1023 (59.6)	608/1023 (59.4)	23,414/43,602 (53.7)	—
	College 4 years or more (college graduate)	152/1023 (14.9)	193/1023 (18.9)	7543/43,602 (17.3)	—
Income					
	Less than US $10,000 to US $14,999	183/1023 (17.9)	204/1023 (19.9)	13,037/43,602 (29.9)	—

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Variable		Facebook sample[a] n/N (%)	Facebook sample weighted by branch and race/ethnicity n/N (%)	American Community Survey[b] n/N (%)	Department of Defense[c] n/N (%)
	US $15,000 to US $24,999	219/1023 (21.4)	205/1023 (20.0)	7194/43,602 (16.5)	—
	US $25,000 to US $49,999	357/1023 (34.9)	335/1023 (32.7)	14,040/43,602 (32.2)	—
	US $50,000 or more	264/1023 (25.8)	280/1023 (27.4)	933/43,602 (21.4)	—

[a]Defined veteran as discharged from Army, Marines, Navy, and Air Force. No reserves/guard. Data collected from April 2014.

[b]American Community Survey data from 3-year estimates (2010-2012) of those aged 18-34 only. Defined veteran as follows: "Has this person ever served on active duty in the US Armed Forces, Reserves, or National Guard?" We included those who indicated "Yes, on active duty during the last 12 months, but not now" and "Yes, on active duty in the past, but not during the last 12 months." This sample could include reserves/guard.

[c]Department of Defense data from average of past 5 years separated (2008-2012) excluding those who retired for nondisability reasons (N=776,313 separated between 2008 and 2012). This population could include reserves/guard.

To further describe our sample, we computed means and frequencies of health behaviors, mental health status, health care utilization, and other demographic factors on the unweighted sample and the sample weighted by branch and race/ethnicity. Both the unweighted and weighted samples were similar in their reports of these factors. As can be seen in Table 2, the majority of our sample drank alcohol in the past month and used marijuana within their lifetime, with over half of the drinkers reporting past month binge drinking and nearly half of lifetime marijuana users reporting use in the past 6 months. In addition, the sample appeared to be struggling with mental health concerns, with between one fifth and one half reporting a previous mental health diagnosis of TBI or screening positive for generalized anxiety, depression, or PTSD. About half of the sample reported any use of VA and non-VA services for mental health care and review for service compensation, with about three quarters receiving physical health care since discharge and about 15% (range 118-128) reporting receipt of alcohol or substance use care. As can be seen in Table 3, approximately two fifths were currently attending college and the majority of these students reported use of the GI Bill. Most veterans had at least 1 child. Finally, as might be expected from recruitment of an OEF/OIF sample of veterans, most reported some combat experience and reported a mean of about 2 deployments each.

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Table 2. Health behaviors, mental health status, and health care utilization of the unweighted Facebook sample and the Facebook sample weighted by branch and race/ethnicity.

		Unweighted sample n/N (%)[a]	Sample weighted by branch and race/ethnicity n/N (%)[a]
Health behaviors			
	Alcohol use past 30 days	788/1023 (77.0)	788/1023 (77.0)
	Binge drinking[b] past 30 days (*drinkers only*)	536/788 (68.0)	504/788 (64.0)
	Lifetime marijuana use	582/987 (59.0)	563/987 (57.0)
	Marijuana use past 6 months (*lifetime users only*)	279/582 (47.9)	239/582 (41.1)
Mental health status			
	Post-traumatic stress disorder[c]	385/819 (47.0)	401/819 (49.0)
	Depression[d]	360/819 (44.0)	311/819 (38.0)
	Generalized anxiety[e]	410/820 (50.0)	369/820 (45.0)
	Has a doctor told you that you have traumatic brain injury	221/820 (27.0) indicated "Yes"; 41/820 (5.0) indicated "do not know"	172/820 (21.0) indicated Yes; 49/820 (6.0) indicated do not know
Health care utilization since discharge [f]			
	Physical health care	633/844 (75.0)	616/844 (73.0)
	Mental health care	490/844 (58.1)	439/844 (52.0)
	Past 12 months mental health care	354/844 (41.9)[g]	287/844 (34.0)[g]
	Past 30 days mental health care	17/844 (2.0)[h]	17/844 (2.0)[h]
	Alcohol use care	211/844 (25.0)	118/844 (14.0)
	Substance use care	203/844 (24.1)	127/844 (15.0)
	Review for service compensation	464/844 (55.0)	422/844 (50.0)
	Other (eg, marriage counseling)	203/844 (24.1)	143/844 (16.9)

[a]Denominators in n/N represent the number of participants who completed the item.

[b]Binge drinkers classified as 4 drinks for women, 5 drinks for men at any one time in the past 30 days.

[c]Primary Care Post-Traumatic Stress Disorder Scale score of 3 or higher indicates optimal screener for post-traumatic stress disorder diagnosis [42].

[d]Patient Health Questionnaire score of 2 or higher indicates optimal screener for depression diagnosis [43].

[e]Generalized Anxiety Disorder-7 Item Scale (GAD-7) score of 10 indicates moderate/severe symptoms of anxiety and optimal screener for generalized anxiety disorder diagnosis [44].

[f]Any use of Veterans Affairs Health Care System (VA), Vet Center, or non-VA since discharge.

[g]Percentage reflects entire sample. Of those who reported any mental health care use since discharge (490 unweighted; 439 weighted), 75.9% (372) of the unweighted sample and 69.9% (307) of the weighted sample reported past 12-month usage of mental health care.

[h]Percentage reflects entire sample. Of those who reported any mental health care use since discharge (490 unweighted, 439 weighted), 4.1% (20) of the unweighted sample and 5.0% (22) of the weighted sample reported past 30-day usage of mental health care.

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Table 3. Other demographics including whether the participants are current students, number of children, military characteristics, and combat severity status of the unweighted Facebook sample and the Facebook sample weighted by branch and race/ethnicity.

		Unweighted sample n/N (%)[a]	Sample weighted by branch and race/ethnicity n/N (%)[a]
Current student			
	Not currently attending college	542/1023 (53.0)	593/1023 (58.0)
	Attending community college	133/1023 (13.0)	123/1023 (12.0)
	Attending a technical college	123/1023 (12.0)	61/1023 (6.0)
	Attending a state university	133/1023 (13.0)	133/1023 (13.0)
	Attending a private college or university	92/1023 (9.0)	113/1023 (11.0)
	Use of GI Bill (those attending college only)	352/434 (81.1)	369/434 (85.0)
Children			
	No children	368/1023 (36.0)	390/1023 (38.1)
	1 child	206/1023 (20.1)	235/1023 (23.0)
	2 children	204/1023 (19.9)	215/1023 (21.0)
	3 or more children	246/1023 (24.0)	183/1023 (17.9)
Military characteristics			
	Number of deployments	1.71 (SD 1.53) range 0-14	1.90 (SD 2.07) range 0-14
Combat trauma			
	Combat trauma experiences (any)	795/883 (90.0)	751/883 (85.1)
	Between 1 and 5 combat trauma experiences	453/795 (57.0)	390/751 (51.9)
	Between 6 and 11 combat trauma experiences	342/795 (43.0)	361/751 (48.1)

[a]Denominators in n/N represent the number of participants who completed the item.

Discussion

Principal Findings

This paper describes the methods used to recruit a sample of young adult veterans for a research study using the social media website Facebook. We sought to examine the feasibility of recruiting young veterans via this mechanism by documenting the process of recruitment, describing the sample on a number of demographic and health factors, and comparing the obtained sample with young adult veteran population-level data from national samples available from the ACS and the DoD. In sum, the recruitment period lasted approximately 1 month and yielded a sample of 1023 verified veteran participants for the advertising price of approximately US $7.00 per participant.

Comparison and Description of the Sample

Compared with the ACS population-level data for young adult veterans, we recruited fewer African American/black veteran participants than we would expect given the young adult veteran population. Yet, we recruited a higher percentage of Hispanic/Latino(a)s than would be expected. Regarding branch differences compared with data from the DoD over the past 5 years, we recruited more Army and Marine veterans and fewer Navy and Air Force veteran than would be expected in the general population of separated military personnel. Other work using Facebook to recruit OEF/OIF veterans has similarly reported underrepresentation of Navy and Air Force veterans and African American/black veterans [21]. One of the reasons for this may be the manner in which Facebook targets advertisements, which in our case displayed ads to those whose Facebook posts and interactions suggested veteran status, affiliation with the military, and other interests a veteran might have. It is possible that Army and Marine veterans are more visible with their veteran/military-focused content on Facebook (as are their family members) and were targeted more often by our ads. Observational research using Facebook could help indicate if this is the case, as well as to determine whether African Americans/blacks are disproportionately less likely to have veteran/military-focused content on their pages while Hispanic/Latino(a)s are more likely to display such content. It is also possible that these discrepancies are due to racial/ethnic differences inherent to the US users of Facebook—about 75% white, 11% African American/black, 9% Hispanic/Latino(a)—[14], though statistics for veteran Facebook users by race/ethnicity are unknown. Although other work has looked at nonveteran samples (ie, adolescent girls) and found recruitment of racial/ethnic groups comparable across Facebook and non-Facebook recruitment methods [19], future experiments are needed to compare racial/ethnic minority recruitment rates between traditional recruitment methods and Facebook.

Our sample did not appear to be unrepresentative with respect to most demographic characteristics such as gender, age, income

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level, education level, or marital status. However, we did recruit about 8% more males than expected given the young adult veteran population, which fits with previous Facebook veteran research [21] but not with recruitment of adolescents [17]. In addition, prior work with young women found that Facebook recruitment yielded a sample of women from higher socioeconomic groups compared with lower ones [30]. Yet, we found comparable reports of income in our sample with the general young adult veteran population, which indicates the recruitment method did not exclude those from lower socioeconomic groups. Although we did not assess housing status (eg, homeless) or access to Internet, we did find that about 4% (31) of the sample completed the survey on a public computer or someone else's computer or phone. Thus, it is possible that this method can be used to capture those without computers or Internet access, but more rigorous research on this topic is warranted.

Reaching Veterans in Need of Mental Health Services

Despite not specifically advertising to veterans in need of mental health services, our sample yielded an unusually high number of veterans struggling with a variety of mental health concerns such as depression, PTSD, anxiety, and TBI, as well as those engaging in risky health behaviors such as binge drinking and marijuana use. Despite these high rates, only half had attended any appointment for a mental health concern, with only about 1 in 3 receiving mental health care in the past year and only about 1 in 50 receiving such care within the past month. Our sample appeared to have higher rates of mental health problems than community samples of veterans and service members [2,48,49] and OEF/OIF VA veterans [10,50]. Depending on the intended focus of a research study, obtaining more individuals with mental health concerns than would be expected in the general population could be desirable. More specifically, while this would be a problem for a study designed to estimate the rates of disorder in the population, it is a virtue for studies designed to identify individuals who could benefit from Web-based delivery of care for behavioral health problems, such as our broader intervention study. In general, recruitment of individuals into treatment studies on mental health has traditionally been difficult, with barriers to enrollment related to inconvenient scheduling times, lack of transportation to research sites, and stigma related to discussing sensitive matters with an unknown interviewer in a face-to-face setting [51]. Studies targeting active duty service members and young adult veterans with mental health concerns such as PTSD or TBI have similarly struggled with recruitment [52,53]. Yet, another study using Facebook recruitment has also been successful at obtaining OEF/OIF veteran participants in need of help for PTSD and hazardous alcohol use for an online intervention study [21]. Another study using Facebook has also indicated that those with mental health concerns may be more likely to complete surveys online than through the postal mail [17]. Combined with our findings, it is apparent that young veterans with mental health concerns are on Facebook and are willing to participate in research studies. This represents an important avenue in which to reach and provide outreach to those in need; both those seeking care and those not actively looking for help.

Validation of the Survey Respondents

Lastly, there is a concern that Internet and Facebook studies may attract individuals misrepresenting themselves to receive incentives [36,54]. We included several verification checks to ensure to the best of our ability that we were capturing the young adult veterans we intended to recruit. Our within-survey procedures (eg, screening out those still on active duty or over the age of 34) and validation checks after data collection (eg, checking for consistent data) removed about 20.5% (257) of those who accessed our survey overall. It is unknown why over one third of individuals accessed the survey but decided to not pursue past consent. It is possible at the point of consent they realized the legitimacy of the study and chose to not misrepresent themselves at this point. It is also possible we lost actual potential veteran participants at this point, but we do not have the data to draw meaningful conclusions here.

In this study, 20.6% (211) of the verified veteran sample terminated the survey after initial demographic and health behavior questions. This is somewhat perplexing given the ease of online survey completion. Indeed, in the Millennium Cohort Study, Web-based recruitment was better than traditional paper invitations and surveys at yielding completed surveys from males and younger active duty personnel [55]. Although we do not have these data, we suspect that this rate of partial completion and low survey consent overall may be a product of the survey not being optimized for use on mobile phones. Indeed, over one third of our total sample learned about the study through mobile phone-based ads, about two thirds who completed the survey did so on their phone, and the majority of clicks to the survey website came from ads displayed on phones. While our survey converted adequately from the designed Web version (eg, 1 question per page, large font), it was not optimized for mobile viewing. Thus, it would likely take a participant a longer amount of time to fill out the survey on a phone and thus may explain drop off toward the latter portions of the survey. Online survey research may need to consider mobile phone-adapted surveys that are easy to access on mobile devices in a single sitting.

Areas for Further Research and Recommendations

More research is needed to determine the cost effectiveness of Facebook for recruiting participants in more diverse veteran samples and across different populations. Although some studies have compared costs of different recruitment methods in biomedical and mental health studies [56-58], most journal articles do not include discussions of recruitment costs, and thus, comparisons between recruitment methods for specific targeted groups are difficult. Costs of any recruitment strategy will likely vary greatly depending on the targeted population; for example, recruitment of participants through Facebook has ranged from no cost for adolescent girls [19], about US $4 for young adults [22], about US $11 for pregnant women [31], about US $20 for depressed adults, and up to US $30 for veterans [59]. Comparisons of Facebook and other online advertisements with postal mailing recruitment strategies suggest that Facebook (at US $1.50 per completed survey) was more cost-effective than postal mailings (at about US $19 per completed survey) for recruiting those with mental health

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concerns [17]. Yet, demographics differed between samples (eg, younger people were more likely to be recruited online than by mail), which can have implications depending on the purpose of the study. To our knowledge though, there have been no published comparisons between Facebook recruitment strategies and traditional strategies (eg, mailings, TV, and radio ads) for the veteran population, which is an area for important future research work.

In this study, our sample was relatively inexpensive to recruit (about US $7 per validated participant plus a US $20 gift card incentive) and data collection for the single brief survey was completed rather quickly. Yet, this survey was designed to be completed in a single sitting. Studies requiring more commitment on the part of participants may or may not see similar success. For example, although Brief and colleagues [21] recruited 600 participants in 46 days using Facebook (with a cost of about US $30 per enrolled participant plus US $20 incentive for baseline assessment), attrition at the 2-month follow-up assessment was high (ie, 51.7% of the intervention group, 209/404, and 38.7% of the delayed intervention group, 76/196). Similarly, only about one third of participants completed all 8 modules of the intervention (ie, 33.9% of the intervention group, 137/404, and 38.7% of the delayed intervention group, 76/196). Thus, Facebook recruitment, although established as a viable method of recruiting veterans into research studies, should be tested further to examine how it can be used to retain participants in longitudinal work and if those who sign up for studies via Facebook (vs other recruitment strategies) are more or less likely to drop out of longitudinal studies that expand beyond a one-time brief survey.

We also recommend that studies recruiting from Facebook take steps to validate that participants meeting study eligibility criteria are not misrepresenting themselves (see Kramer and colleagues for guidance [36]). We also recommend researchers compare their Facebook-recruited samples with the best available population-level data to determine representativeness. While most convenience samples are limited in generalizability due to their nature, “Methods” section in journal articles could include information to allow for determination of the extent to which Facebook-recruited samples differ from relevant populations. Weights could be applied if necessary. Lastly, we recommend more research learning how to use other online social media sites to target veterans and other at-risk groups for inclusion in mental health survey and intervention studies. Widely used sites such as YouTube, Twitter, and LinkedIn have options for targeted advertising, as do sites that are focused on specific groups that may be of interest (eg, advertising research studies to men who have sex with men via the Grindr app).

Limitations

There are additional limitations worth noting. First, by design to limit misrepresentation, participants needed a Facebook account, which excludes those who may have had Internet access but not a Facebook account. In addition, we recruited approximately 0.06% (1023/1,580,000) of the targeted Facebook population. Although this seems low, it should be noted that the targeted population included friends/family members of veterans, as well as others who did not have any veteran contacts to refer to the study (eg, someone who “liked” the *Call of Duty* video game but had no connection with US veterans). Still, the majority of users who clicked on our ads but did not click through to access the survey (ie., only 2275 of the 16,658 who clicked on an ad went on to take the survey) suggests a discrepancy between clicks and enrollment for which we do not have data to explain.

Conclusion

The Internet is becoming an increasingly popular venue for reaching young people to deliver informational programs, stand-alone interventions, and adjunct treatments for a variety of mental health problems such as depression and heavy alcohol use [60-63]. This study suggests that the use of Facebook-based recruitment appears to be an inexpensive and practical method to reach young adult veterans for research studies. Understanding how to reach young veterans through Internet-based recruitment can help inform intervention/prevention programs and outreach efforts with this at-risk population. It has applicability to be a means to provide young veterans with resources and information about care seeking, as well as to provide stand-alone or adjunct treatments for mental health concerns. Internet programs and research studies have the ability to reach a widespread audience, can be less expensive than more intensive programs, require less staffing and expertise, can be conveniently accessible at all hours by consumers and, most importantly, can provide outreach and services for individuals who may have never otherwise engaged in such care.

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Conflicts of Interest

None declared.

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Abbreviations

ACS: American Community Survey
GAD: generalized anxiety disorder
GAD-7: Generalized Anxiety Disorder-7 Item Scale
OEF: Operation Enduring Freedom
OIF: Operation Iraqi Freedom
PHQ-2: Patient Health Questionnaire-2
PTSD: post-traumatic stress disorder
TBI: traumatic brain injury
VA: Department of Veterans Affairs

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Original Paper

Effective Strategies to Recruit Young Adults Into the TXT2BFiT mHealth Randomized Controlled Trial for Weight Gain Prevention

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Abstract

Background: Younger adults are difficult to engage in preventive health, yet in Australia they are gaining more weight and increasing in waist circumference faster than middle-to-older adults. A further challenge to engaging 18- to 35-year-olds in interventions is the limited reporting of outcomes of recruitment strategies.

Objective: This paper describes the outcomes of strategies used to recruit young adults to a randomized controlled trial (RCT), healthy lifestyle mHealth program, TXT2BFiT, for prevention of weight gain. The progression from enquiry through eligibility check to randomization into the trial and the costs of recruitment strategies are reported. Factors associated with nonparticipation are explored.

Methods: Participants were recruited either via letters of invitation from general practitioners (GPs) or via electronic or print advertisements, including Facebook and Google—social media and advertising—university electronic newsletters, printed posters, mailbox drops, and newspapers. Participants recruited from GP invitation letters had an appointment booked with their GP for eligibility screening. Those recruited from other methods were sent an information pack to seek approval to participate from their own GP. The total number and source of enquiries were categorized according to eligibility and subsequent completion of steps to enrolment. Cost data and details of recruitment strategies were recorded.

Results: From 1181 enquiries in total from all strategies, 250 (21.17%) participants were randomized. A total of 5311 invitation letters were sent from 12 GP practices—16 participating GPs. A total of 131 patients enquired with 68 participants randomized (68/74 of those eligible, 92%). The other recruitment methods yielded the remaining 182 randomized participants. Enrolment from print media was 26% of enquiries, from electronic media was 20%, and from other methods was 3%. Across all strategies the average cost of recruitment was Australian Dollar (AUD) $139 per person. The least expensive modality was electronic (AUD $37), largely due to a free feature story on one university Web home page, despite Facebook advertising costing AUD $945 per enrolment. The most expensive was print media at AUD $213 and GP letters at AUD $145 per enrolment.

Conclusions: The research indicated that free electronic media was the most cost-effective strategy, with GP letters the least expensive of the paid strategies in comparison to the other strategies. This study is an important contribution for future research into efficacy, translation, and implementation of cost-effective programs for the prevention of weight gain in young adults. Procedural frameworks for recruitment protocols are required, along with systematic reporting of recruitment strategies to reduce unnecessary expenditure and allow for valuable public health prevention programs to go beyond the research setting.

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Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12612000924853; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=362872 (Archived by WebCite at http://www.webcitation.org/6YpNfv1gI).

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KEYWORDS

recruitment; young adults; mHealth; eHealth; weight gain prevention; external validity; cost

Introduction

Younger adults in Australia are gaining more weight and increasing their waist circumference faster than older adults [1]. Research targeting this population of 18- to 35-year-olds has been an emerging area with several recent interventions having been completed [2-5] or underway [6-9], with demonstrated effectiveness at preventing weight gain in the short term. However, engaging young adults in public health research, particularly interventions aimed at the prevention of unhealthy weight gain, remains challenging. There is limited information reported on recruitment strategies, timelines, costs, and alterations to original recruitment protocols in response to any challenges encountered, and limited advice on the application of the recruitment techniques to community settings [10]. Current recruitment evidence is skewed toward older age groups and there is a limited representation of young adults in the literature as they are highly mobile, complicating recruitment efforts [11].

Recruitment for young adults into interventions is often timed with commencement of life events, such as starting tertiary education, moving out of the parental home, or the postpartum period. Interventions are often conducted within tertiary settings and target tertiary students [12]. This suggests that the type of young people engaging in weight gain prevention interventions may not be representative of the young adult population at large, which may reduce the external validity and translation potential [12].

Recruitment strategies reported mainly include multiple strategies, and it is not described whether the multitude of strategies is in response to low uptake from the strategy originally planned or if a combination of strategies is more effective. Traditional strategies in combination, such as posters, flyers, advertisements, email blasts, and/or information stands, are the most commonly reported [12]. In efficacy and effectiveness reporting, inadequate detailed information is provided on the recruitment materials, advertising messages, detail of location of recruitment material placement, quantity and time frame, cost of strategies, and/or the original number of people invited or making initial enquiries to participate who do not proceed to eligibility check [12].

In light of this, current research is recognizing the need for in-depth evaluation of the recruitment process for obesity prevention programs and the implications of this for translation and scalability. Research is emerging on the use of new recruitment avenues, including social media and social media advertising. New studies using Facebook advertising have been shown to be effective in recruiting young adults, particularly young women. The studies are mainly online, lifestyle, weight gain prevention programs and/or evaluations [13,14]. They show promise in recruiting a representative sample of the target population [15] and underrepresented groups [16,17].

Furthermore, little is known about eligible participants who do not engage with prevention research, and the reasons for nonparticipation [18]. There is considerable financial investment in recruiting individuals who do not complete research studies [19]. Systematic reporting of cost and effectiveness of recruitment strategies will enable researchers to select the most appropriate strategies for recruiting participants into health research studies [19]. With limited recruitment information currently reported and the large heterogeneity of studies, research interventions are not easily generalizable [20].

This paper describes the strategies used to recruit young adults to a randomized controlled trial (RCT) of an mHealth program, TXT2BFiT. The progression from enquiry through eligibility check to randomization into the trial and the costs of recruitment strategies are reported. Factors associated with nonparticipation in TXT2BFiT are explored.

Methods

Participants and Eligibility Criteria

The eligibility criteria for the RCT of the TXT2BFiT program included being a young adult aged 18 to 35 years [21]. Furthermore, participants had to meet the following conditions: (1) have a body mass index (BMI) of 25.0 to 31.9 kg/m^2, or 23.0 to 24.9 kg/m^2 with reported weight gain of more than 2 kg over the past 12 months, (2) have a fruit intake of less than two servings per day, a vegetable intake of less than five servings per day, sugar-sweetened beverage intake of at least 1 L per week, energy-dense takeout meals more than once per week, and/or engage in moderate-intensity physical activity of less than 60 minutes per day, (3) own a mobile phone capable of receiving text messages, and (4) have access to the Internet at least once a week. Exclusion criteria included (1) being pregnant or planning to fall pregnant within the next 9 months, (2) enrolled in an alternate weight loss program, (3) had lost more than 10 kg voluntarily in the past 3 months, (4) taking medications that have caused more than 2 kg of weight gain, (5) medical condition that precludes following dietary or physical recommendations, (6) history of disordered eating, and/or (7) does not speak English. The detailed eligibility and study protocol is available elsewhere [21].

Incentives

The participant information statement informed participants that both groups would receive free advice on diet and physical

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activity to help them achieve and maintain a healthy weight, and that they would be compensated for their participation by receiving Australian Dollar (AUD) $10 vouchers for completing surveys and attending an in-person weigh-in (ie, a total of AUD $30 for completion of all measures).

Recruitment

The original protocol was to enroll 354 participants, based on detecting a mean difference of 2.0 kg with $P<.05$ and 80% power, that assumed the standard deviation was 10 kg and the correlation between baseline and final weight was .8. A total of 284 participants were required—142 per arm—and accounting for a 20% dropout rate, an additional 70 participants would be needed. Two phases of recruitment were employed and are detailed below.

Recruitment Phase 1: General Practitioner Letters

The first phase of recruitment involved personal letter invitations (see Multimedia Appendix 1) to young adult patients of participating general practitioners (GPs) recruited from Medicare Locals within the Greater Sydney Area. In July 2011, Australian primary health care services were restructured into independent entities called Medicare Locals, which are responsible for coordinating primary health care over a specified geographic area. GPs can only be recruited for study participation through the assistance of Medicare Locals.

Recruitment Phase 1 commenced in November 2012 (see Figure 1) with three of the seven Medicare Locals in the Greater Sydney Area invited and willing to participate. Our original research and calculations indicated that 3% of patients in a GP practice would be eligible, which meant there would be 60 eligible patients in an average practice. Based on previous research [22,23], if 25% of patients accepted an invitation, it meant that 24 practices would be needed and recruitment was expected to last for 18 months. From these Medicare Locals, 16 GPs from 12 practices—14 (14/352, 4.0%) from Medicare Local A, 2 (2/672, 0.3%) from Medicare Local B, and 0 (0%) from Medicare Local C—agreed to join the study using the latest available GP numbers for each area [24-26]. A total of 5311 letters of invitation were sent to young adult patients. GPs do not routinely collect anthropometric data, including weight and height, and therefore all young adults in the required age range were eligible to receive a letter of invitation, regardless of BMI.

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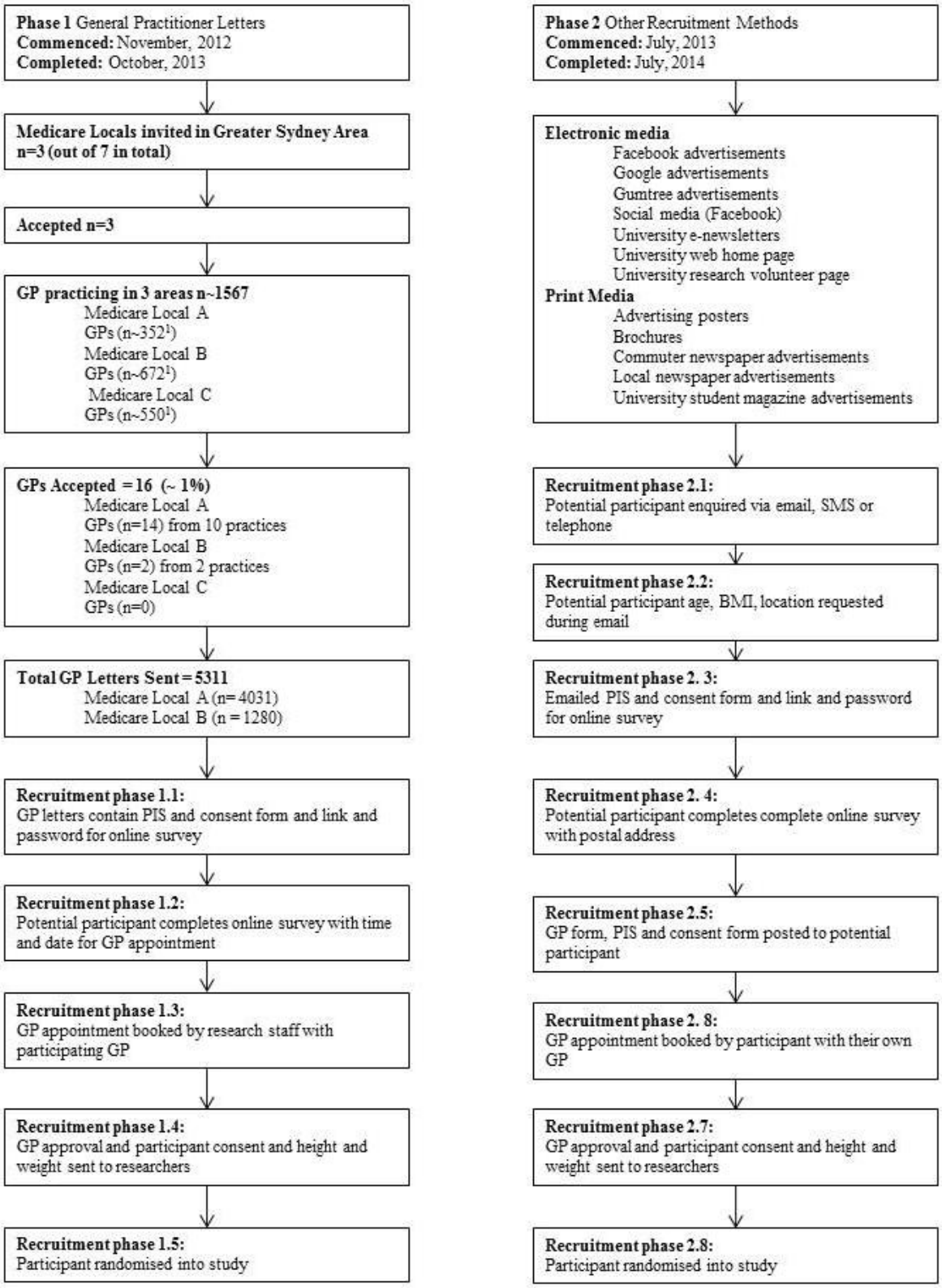
Figure 1. Flow diagram for recruitment phases of the TXT2BFiT study. The number of GPs in each area is approximate. Information obtained from Medicare Local website [24-26].



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Screening for Eligibility: Phase 1, General Practitioner Letters

The invitation letter directed prospective participants to an online survey to screen for eligibility. Questions in the screening survey were structured such that ineligible participants were redirected to a national social marketing website for healthy eating and physical activity promotion [27,28]. Eligible participants reaching the end of the survey were able to nominate dates and times to attend an appointment with the GP—paid for by the study—who had invited them via the letter (see Figure 1 and Multimedia Appendix 1). This 10-minute appointment was booked on the participant's behalf and details sent to the patient by research staff in a confirmatory short message service (SMS) text message. At the appointment, the GP measured the participant's weight (kg) and height (cm), approved their participation, and collected the participant's signed, written informed consent to enter into the trial. Signed consent forms were returned to the researchers with the participants' anthropometric data.

Recruitment Phase 2: Other Forms of Recruitment

Phase 2 of recruitment ran from July 2013 (see Figure 1) until July 2014, involving two main avenues of electronic and print media (see Table 1) because recruitment from Phase 1 slowed. This range of other recruitment strategies and materials using a variety of modalities is described below (see Table 1). Advertising messages were brief, using simple language. Furthermore, advertisements were accompanied by a TXT2BFiT logo, along with healthy and/or unhealthy food images, and/or positive physical activity images (see Multimedia Appendix 1).

Electronic Media Recruitment

Electronic media utilized Facebook and Gumtree advertisements, social media through the use of a TXT2BFiT Facebook page, university e-newsletter, university Web home page news story, and a consistent listing on two university research volunteer pages for the duration of recruitment (see Table 1). Paid Facebook and Google advertising was used three and four times, respectively. To generate these advertisements, the target population was defined, along with a specific budget and time frame. After the duration of the advertisement listing, advertising data were downloaded and interpreted. Free advertising on the Gumtree website—a network of free online classifieds and community websites—was updated 16 times and included two different low-cost advertisements. The TXT2BFiT Facebook page status was updated weekly for the duration of the recruitment period. Anyone interested "requested to be a friend" of the page. Friends were predominantly those of the research staff and their friends and family. Once saturation was reached (ie, no new research staff members to share the page with their "friends"), this avenue provided no further enquiries. The research study was featured in the e-newsletters of two universities, which were sent to all enrolled undergraduate and postgraduate students and staff, and was the topic of a feature story on the Web home page of one university for approximately one week. For the duration of recruitment, the study was listed on two separate universities' research volunteer Web pages and briefly mentioned in lectures at a third university.

Print Media Recruitment

Print media consisted of advertising posters, brochures, commuter and local newspaper advertisements, and university student magazines. Over the 12-month time period (excluding semester breaks), posters were displayed on two university campuses at popular locations and replaced weekly (see Table 1). Posters were also displayed at various community locations and at Technical and Further Education (TAFE) institutions at the beginning of two semesters. Brochures were mostly delivered by research staff and students (n=35,002), but 20,000 brochures were delivered by a distribution company. Suburbs within the Greater Sydney Area with a high percentage of young adults based on census data were targeted. Newspaper and magazine paid advertising was conducted in five local district newspapers and magazines and one newspaper, widely distributed to commuters for free at train stations, on six occasions.

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Table 1. TXT2BFiT recruitment strategy descriptions.

Modality	Recruitment strategy	Recruitment strategy detail
GP[a]	GP letter	5311 letters sent from 12 participating practices (16 participating GPs)
		Personally addressed letter with GP letterhead, TXT2BFiT and university logo, and instructions provided on how to access screener survey
		AUD[b] $500 GP fee per practice paid for time spent to access to their database for potential participants
		Additional AUD $3827.22 for postage and printing
Electronic media		
	Facebook advertisement	Paid advertisements over 22 days
		Link with image accompanying website (Multimedia Appendix 1) on the right-hand advertising column of Facebook—targeted to location and age demographics
		See reach data in Results, Effectiveness and Cost of Different Recruitment Strategies section
	Google advertisement	Paid advertisements over 7 days
		Top-of-page and side-advertisement text
		See reach data in Results, Effectiveness and Cost of Different Recruitment Strategies section
	Gumtree advertisement	16 free advertisements
		Two paid advertisements
	Social media (Facebook)	TXT2BFiT Facebook page
		Weekly updates for 12 months
		Status update examples accompanied by a photo (Multimedia Appendix 1)
	University e-newsletter	Three featured newsletters sent to all students at three universities
	University Web home page	One banner news story on the home page of one university
	University research volunteer Web page	Listed for the duration of the study recruitment (21 months)
Print media		
	Advertising poster	Placed at poster locations at two university campuses during semester (14 months), including a brief advertisement at the end of PowerPoint lectures at one university
		Posters placed at various community locations
		Posters placed at TAFE[c] institutes at the beginning of two semesters
	Brochures	54,872 delivered in total
		19,870 company delivered and 35,002 delivered by research staff
	Commuter newspaper advertisement	Six advertisements
		Handed out during peak hours, 2:30-7:00 PM, on weekdays for train commuters at CBD[d] locations
		663,000 readers, predominantly 18-39 years, in three major capitals in Australia (only advertised in Sydney)[e] and 73.5% of readers live outside inner-city Sydney
	Local newspaper advertisement	Two advertisements in two different local newspapers
	University students' magazines	Two advertisements in two different university magazines
Word of mouth	Friend/family	Heard about the study through friends or family
Other	Unknown	Participant did not respond to email and/or could not recall where they heard about the study

[a]General practitioner (GP).

[b]Australian Dollar (AUD).

[c]Technical and Further Education (TAFE).

[d]Central business district (CBD).

[e]Obtained from the mX website [29].

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Screening for Eligibility: Phase 2, Other Forms of Recruitment

Potential participants registered their interest via email or SMS text message. Researchers screened participants to assess if their age, BMI, and the location of their GP made them eligible. Subjects reported how they heard about the research study (ie, recruitment source). Ineligible participants exited the survey and were redirected to national social marketing sites as detailed above for Phase 1 participants. Eligible participants reaching the end of the survey provided their postal address and received a pack containing a letter explaining the study to the participant, a consent form, a participant information sheet, and a letter explaining the study to the GP with an approval form for the GP to sign as detailed above. However, in this case the participant booked their own appointment, which was paid for by the study (see Figure 1).

Data Collection Procedures

All participant enquiries were recorded in a database. The online survey website, SurveyMonkey [30], collected data on demographics, including gender, postcode—for categorizing socioeconomic data [31]—recruitment modality and strategy, and the eligibility criteria. Detailed data were also collected on the number of GPs in each Medicare Local [24-26]; number of participating GPs; number of GP letters sent and the associated cost; paid advertising costs; number, location, and time frame of brochure deliveries; and time frame of advertising poster distribution and social media updates. All data were recorded in a database.

Statistical Analysis

Descriptive statistics for continuous measures, including counts and percentages for total number of enquiries, total eligible participants, and total participants randomized, are provided for each recruitment modality and strategy. Total costs (AUD $) are reported per recruitment modality and strategy, with the average cost calculated per participant randomized and per eligible participant. Results from each recruitment method are discussed in comparison to each other, as there were not standards or targets defined in the literature for recruitment methodology.

Logistic regression was used to assess any differences in baseline characteristics between eligible participants who were or were not randomized into the study. Characteristics included gender, BMI, postcode—for categorizing socioeconomic data [31]—and recruitment modality and strategy.

Ethics

Materials and methods of the TXT2BFiT RCT were approved by the University of Sydney Human Research Ethics Committee in September 2012 (Approval Number 15226). The trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12612000924853).

Results

Flow of Participants From Recruitment to Randomization

A total of 1181 people enquired from Phase 1 and 2—24.64% (291/1181) male, 53.18% (628/1181) female, and 22.18% (262/1181) remaining unknown (see Figure 2). Of the 1181 people, 349 (29.55%) did not enquire further from their initial enquiry and 118 (9.99%) people were ineligible primarily due to their BMI being below 23 kg/m^2. The remaining 714 (60.46%) were sent links to the screener surveys as detailed above. Of the 714 remaining participants, 119 (16.7%) were ineligible on completion of the screener survey and a further 198 (27.7%) people did not complete it—167 of the 198 (84.3%) did not even attempt the survey. GP appointments were made for 137 people from phase 1, of whom 13.9% (19/137) did not attend. GP information packs were sent to 260 people from Phase 2, of whom nearly half (113/260, 43.5%) did not see a GP to complete screening. A total of 250 out of 1181 (21.17%) participants were randomized, with over half resulting from recruitment methods other than GP letters (see Table 2).

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Table 2. Total enquiries, eligible and randomized, and cost (AUD $) per recruitment strategy for the TXT2BFiT study.

Modality	Recruitment strategy	Total enquiries, n (%)	Total eligible, n (% per enquiry)	Total randomized, n (% per eligible)	Total cost[a], AUD[b] $	Cost per participant randomized[c], AUD $
All modalities	All recruitment methods	1181 (100)	390 (33.02)	250 (64.1)	34,638.96	138.56
General practice	General practice letter	131 (11.09)	74 (56.5)	68 (92)	9827.22	144.52
Electronic media						
	All electronic media	335 (28.37)	118 (35.2)	68 (57.6)	2498.06	36.74
	Facebook advertisement	13 (1.10)	10 (77)	2 (20)	1890.66	945.33
	Google advertisement	4 (0.34)	3 (75)	1 (33)	571.45	571.45
	Gumtree advertisement	50 (4.23)	10 (20)	3 (30)	35.95	11.98
	Social media (Facebook)	7 (0.59)	7 (100)	3 (43)	No cost	N/A[d]
	University e-newsletter	76 (6.44)	43 (57)	23 (53)	No cost	N/A
	University Web home page	164 (13.89)	35 (21.3)	28 (80)	No cost	N/A
	University research volunteer page	21 (1.78)	10 (48)	8 (80)	No cost	N/A
Print media						
	All print media	410 (34.72)	180 (43.9)	105 (58.3)	22,313.68	212.51
	Advertising poster	109 (9.23)	48 (44.0)	29 (60)	No cost	N/A
	Brochures	135 (11.43)	67 (49.6)	41 (61)	13,631.01	332.46
	Commuter newspaper advertisements	163 (13.80)	63 (38.7)	34 (54)	6875.00	202.21
	Local newspaper advertisements	0 (0)	0 (0)	0 (0)	1067.67	No one randomized
	University students' magazines	3 (0.25)	2 (67)	1 (50)	740.00	740.00
Word of mouth	Friend/family	30 (2.54)	8 (27)	5 (63)	No cost	N/A
Other	Unknown	275 (23.29)	10 (3.6)	4 (40)	N/A	N/A

[a]Research staff costs were not included.

[b]Australian Dollar (AUD).

[c]All randomized participants had a AUD $55 general practitioner visit paid for that was not included in this analysis.

[d]Not applicable (N/A).

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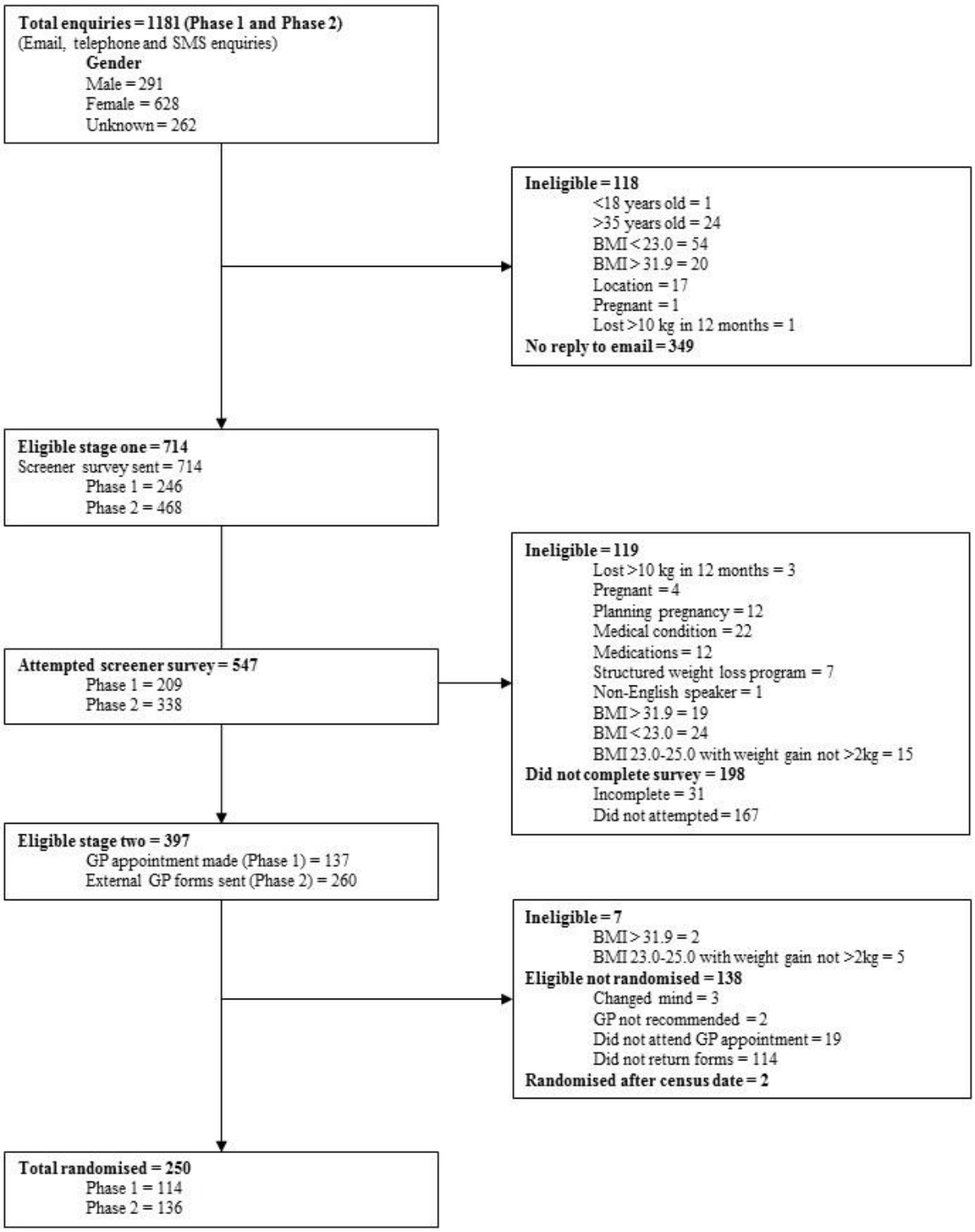
Figure 2. Flow diagram for recruitment of participants into the TXT2BFiT study.



Effectiveness and Cost of Different Recruitment Strategies

Table 2 shows the number of enquiries and eligible participants, the number of subjects enrolled and randomized, and their respective costs stratified by modality type and the strategy subcategories. Letters sent by GPs resulted in 131 enquiries out of a total of 1181 (11.09%), with 74 eligible out of 131 (56.5%). Electronic media resulted in 335 enquiries out of a total of 1181 (28.37%), with 118 eligible out of 335 (35.2%). Print media

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achieved 410 enquiries out of a total of 1181 (34.72%), with 180 eligible out of 410 (43.9%). The conversion of eligible enquiries into enrolments and randomization indicates that GPs (68/74 eligible per strategy, 92%) were highest, followed by print media (68/118 eligible per strategy, 57.6%) and electronic media (105/180 eligible, 58.3%). A total of AUD $34,638.96 was spent, which meant an average of AUD $138.56 was spent per participant enrolled and randomized. This was AUD $144.52 for GPs, AUD $36.74 for electronic media, and AUD $221.51 for print media. When the substrategies within the major modalities were examined, it was found that the university newsletters yielded the second-most enquiries with more than half eligible, and just over half of these enrolled and randomized, and there was no direct cost. For print media, the brochures gave the second-most enquiries with most eligibility and highest enrolment, but the cost was high at AUD $332.46 per person.

Electronic media had a wide range of costs per strategy—AUD $0 to AUD $944 per participant randomized. Targeted paid advertising on Facebook reached 953,007 people (see Table 3 and Table 4), yet only attracted 13 enquiries and made this strategy the most expensive, costing AUD $945 per participant randomized. Likewise, Google advertising was served to 605,504 people over 7 days (see Table 4 and Table 5), at a cost of AUD $571 with four enquiries and one participant randomized.

Print media was the most expensive modality per participant randomized, at AUD $213 (see Table 2) and was the most time-consuming for research staff (ie, brochure distribution and poster placement). It resulted in the most enquiries (410/1181, 34.72%) and provided the greatest proportion of participants randomized (105/250, 42.0%). All print media strategies had similar enrolment rates from eligible participants, despite the advertising materials varying considerably in the information provided (see Multimedia Appendix 1). There were no enquires from paid company-delivered brochures (see Table 1). Brochures delivered individually by the research staff resulted in 136 enquiries. Word-of-mouth (ie, family/friend) recruitment only accounted for 2.0% (5/250) of the total participants randomized.

Table 3. Facebook TXT2BFiT advertisement data for website clicks on right-hand column advertisements on desktop computers over 4 days in 2013 and over 18 days in 2014[a].

Advertisement data	Year and duration						
	2013						2014
	2 days, n, %, or AUD[b]$		1 day, n, %, or AUD $		1 day, n, %, or AUD $		18 days, n, %, or AUD $
Reach, n	72,979	119,661	42,310	79,731	48,525	86,086	503,715
Frequency[c], n	3.16	4.39	2.96	4.28	3.27	4.91	10
Impressions, n	230,500	525,364	125,127	341,109	158,684	422,880	5,196,868
Clicks, n	46	143	34	93	28	108	1061
Unique clicks, n	45	132	34	91	27	105	0
CTR[d], %	0.02	0.03	0.03	0.03	0.02	0.03	0.02
uCTR[e], %	0.06	0.11	0.08	0.11	0.06	0.12	0.21
Spent, AUD $	51.68	148.32	27.03	72.97	21.89	78.11	1490.70
CPM[f],AUD $	0.22	0.28	0.22	0.21	0.14	0.18	0.29
Cost per 1000 people reached, AUD $	0.71	1.24	0.64	0.92	0.45	0.91	N/A[g]
CPC[h], AUD $	1.12	1.04	0.80	0.78	0.78	0.72	1.40
Cost per unique click, AUD $	1.15	1.12	0.80	0.80	0.81	0.74	N/A
Actions, n	47	144	35	93	29	111	N/A
People taking action, n	72,979	119,661	42,310	79,731	48,525	86,086	N/A

[a]Downloaded from Facebook Ads Reporting.

[b]Australian Dollar (AUD).

[c]Frequency is the average number of times the advertisement was served to each person.

[d]Click-through rate (CTR).

[e]Unique click-through rate (uCTR).

[f]Cost per 1000 impressions (CPM).

[g]Not applicable (N/A).

[h]Cost per click (CPC).

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Table 4. Facebook and Google TXT2BFiT advertisement data definitions.

Term	Definition[a]
Campaign, placement	A group of advertisement sets that share the same objective, where the advertisement was served on Facebook and Google
Duration	Length of the advertising
Reach	The number of people the advertisement was served to
Frequency	The average number of times the advertisement was served to each person
Impressions	The number of times the advertising was served. On mobile apps, an advertisement is counted as served the first time it is viewed. On other Facebook interfaces, an advertisement is served the first time it is placed in a person's News Feed or each time it is placed in the right-hand column.
Clicks	The total number of clicks on the advertisement. Depending on what is being promoted, this can include page likes, event responses, or app installs.
Unique clicks	The total number of unique people who have clicked on the advertisement. For example, if 3 people click on the same advertisement 5 times, it will count as 3 unique clicks.
CTR[b]	The number of clicks received divided by the number of impressions
uCTR[c]	The number of people who clicked on the advertisement divided by the number of people you reached. For example, if you received 20 unique clicks and your advertisement was served to 1000 unique people, your unique click-through rate would be 2%.
Spent/cost	The total amount spent so far
CPM[d]	The average cost paid to have 1000 impressions on the advertisement
Cost per 1000 people reached	The average amount paid to have the advertisement served to 1000 unique people
CPC[e]	The average cost per click for the advertisements, calculated as the amount spent divided by the number of clicks received
Cost per unique click	The average cost per unique click for the advertisements, calculated as the amount spent divided by the number of unique clicks received
Actions	The number of actions taken on the advertisement—page, app, or event—after the advertisement was served to someone, even if they didn't click on it. Actions include page likes, app installs, conversions, event responses, and more. For example, 2 page likes and 2 comments would be counted as 4 actions.
People taking action	The number of unique people who took action such as liking the page or installing the app as a result of the advertisement. For example, if the same person likes and comments on a post, they will be counted as 1 unique person.
Average position	Average position of where the advertisement ranks compared to other ads

[a]Definitions available from Facebook Ads Reporting and Google Ads Reporting.

[b]Click-through rate (CTR).

[c]Unique click-through rate (uCTR).

[d]Cost per 1000 impressions (CPM).

[e]Cost per click (CPC).

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Table 5. Google TXT2BFiT advertisement data for top-of-page and side-advertisement text over 7 days in 2013[a].

Advertisement data	Year 2013
Duration, days	7
Clicks, n	601
Impressions, n	605,054
CTR[b], %	0.10
CPC[c], AUD[d]$	0.97
Cost, AUD $	581.95
Average position, rank	2.3

[a]Downloaded from Google Ads Reporting.

[b]Click-through rate (CTR).

[c]Cost per click (CPC).

[d]Australian Dollar (AUD).

Eligible Nonrandomized Participants Versus Randomized Participants

During recruitment, 138 potential participants were identified that were not randomized into the study. Reasons included failure to return their consent form, nonattendance at a GP appointment booked on their behalf, changing their mind, and/or their GP did not recommend the study (not for medical reasons) (see Figure 2). Logistic regression models demonstrated that females were less likely to go on to randomization compared to males—odds ratio (OR) 0.64 (95% CI 0.41-1.00) (see Table 6). Eligible participants recruited through a GP letter were more likely to be randomized than those recruited through all other recruitment modalities—OR 1.8 (95% CI 1.4-2.4) (see Table 6).

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Table 6. Baseline health characteristics, recruitment modalities, and strategies of eligible participants who did not participate in the TXT2BFiT study (n=138) versus randomized participants (n=250)[a].

Characteristic, modality, or strategy	Total eligible not randomized, n (%)	Total randomized, n (%)
Gender		
Male	40 (29.0)	97 (38.8)
Female	98 (71.0)	153 (61.2)
SES quintiles [b]		
0-60%[c]	10 (7.2)	15 (6.0)
61-80%	29 (21.0)	45 (18.0)
81-100% (highest)	99 (71.7)	189 (75.6)
Recruitment modality		
GP[d] letter	6 (4.3)	68 (27.2)
Electronic media	50 (36.2)	69 (27.6)
Print media	73 (52.9)	104 (41.6)
Other	9 (6.5)	9 (3.6)
Recruitment strategy		
GP letter	6 (4.3)	68 (27.2)
Facebook advertisement	8 (5.8)	2 (0.8)
Google advertisement	2 (1.4)	1 (0.4)
Gumtree advertisement	7 (5.1)	3 (1.2)
Social media (Facebook)	4 (2.9)	3 (1.2)
University e-newsletter	20 (14.5)	23 (9.2)
University Web home page	7 (5.1)	28 (11.2)
University research volunteer page	2 (1.4)	8 (3.2)
Advertising poster	18 (13.0)	29 (11.6)
Brochures	25 (18.1)	41 (16.4)
Commuter newspaper advertisements	29 (21.0)	34 (13.6)
Local newspaper advertisements	0 (0)	0 (0)
University students' magazines	1 (0.7)	1 (0.4)
Word of mouth	3 (2.2)	5 (2.0)
Unknown	6 (4.3)	4 (1.6)
BMI [e] **, kg/m** **2**		
23.0-24.9	31 (22.5)	58 (23.2)
25.0-29.9	87 (63.0)	156 (62.4)
30.0-32.0	20 (14.5)	36 (14.4)

[a]All data obtained from screener survey.

[b]Socioeconomic status (SES) by population percentile for Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) (Australian Bureau of Statistics, 2008).

[c]Combined bottom three quintiles.

[d]General practioner (GP).

[e]Body mass index (BMI).

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Discussion

Principal Findings

The TXT2BFiT mHealth study, aimed at preventing weight gain in 18- to 35-year-olds, recruited 250 participants over an 18-month time period, with 21% of those expressing interest randomized into the study. The recruitment protocol originally planned to enroll 354 participants from GP letters (Phase 1) but the inability of two Medicare Locals to fully engage potential participants, and lower than expected response from patients, lead to a second recruitment phase using other means. Free or low-cost electronic media appeared to be the most cost-effective and time-efficient strategy to recruit young adults. However, electronic strategies that had a greater reach (ie, Facebook and Google advertising) achieved low numbers of enquiries. GP letters were a more effective recruitment strategy than print media in terms of cost and eligibility from enquiries. Both GPs and paid print media strategies, including brochures and commuter newspaper advertisements, potentially reached a more diverse population. Men were more likely than women to follow through with enrolment into the study.

Recruitment into a face-to-face, group weight gain prevention intervention in the United States for 18- to 35-year-olds, with a BMI between 21 and 30 kg/m^2 and similar recruitment time frame (19 months), reported 10% of total enquiries were randomized, costing US $233 per participant randomized, which excluded research staff costs [32]. In Australia, a face-to-face individual weight management study recruited 50 overweight or obese (BMI ≥ 27.5 kg/m^2) young women 18 to 25 years over a 2-year period, and cost AUD $308 per person randomized, however, this included research staff costs. If staff costs were removed, this would be reduced to AUD $62 per person randomized [33]. In this study, one full-time research staff member was employed at a cost of AUD $100,000 per annum, but it is estimated that no more than 30% of the time over the 18 months was spent on recruitment, as they also were involved with intervention delivery. In addition, a research student spent 1 day per week on recruitment. Taking this into account would mean recruitment per participant would be estimated at AUD $319. This mHealth study utilized low-cost recruitment strategies with no budget for mass media. Recruitment for young adults to the previously mentioned weight gain prevention program had limited success with mass media television advertising, costing over US $1000 per person randomized, and having a low percentage of the total randomized [32]. However, mass media campaigns have been shown to be an effective method of promoting a telephone-based, state-wide lifestyle program, particularly targeting socioeconomically disadvantaged and overweight participants [34], although no cost data were presented for this program and results included a wide age range of participants. Process evaluation indicated that when developing mass media communications, preference should be given to specifically designed and tailored messaging that explains, models, and displays the relevant contact details for as long as possible to facilitate contact to the program [35]. Secondary referral recruitment, such as GP referral, was recommended as a supplement to the mass media campaigns.

Using Medicare Locals to invite GPs to join in with participant recruitment was included as a feasible method for recruitment in this study due to the reported success in other prevention interventions, although they focused on older adults with existing metabolic risk factors [22]. Targeted recruitment and high enquiry rate (30.6%) was possible in older age groups as anthropometric and metabolic risk factors were documented in a patient's medical records [23]. A fee of AUD $500 per practice for study participants was considered a worthwhile investment by researchers. Young adults had a lower-than-expected enquiry rate to the GP letters (2.5%), with approximately 5.7 participants per practice randomized (range 0 to 18). The study would have required an additional 50 practices—50% greater than anticipated, 62 in total—at the rate observed, costing over AUD $50,000 to randomize the original target of 354 participants. Weight and height are rarely recorded for young adult patients in general practice, and this limited the targeting of invitation letters to patients at risk of weight gain. The transient nature of young adults may suggest that having a long-term GP is less likely, and a proportion of the GP letters may not have been reached by the recipient. For the young adults deemed eligible to participate in Phase 2 of recruitment, the required paid visit to the GP was for ethical reasons, however, this may have been a barrier to enrolment into the RCT.

GPs also showed low interest in engaging young adults into the study, despite being compensated AUD $500 for allowing access to their patient database. Reasons for lack of interest require further research. Primary health care (ie, Medicare Locals) were undergoing extensive restructuring which negatively impacted on cooperation of the Medicare Locals and participation by GPs. Only one of three Medicare Locals recruited the anticipated number of GPs—eight per Local—and one Medicare Local took 12 months to be sufficiently organized to participate and then failed to recruit any GPs. The Medicare Local network has yet again been dissembled with a change of government. This avenue appears to have some degree of instability and may have hindered recruitment efforts. In addition, there is some evidence to suggest GPs believe lifestyle interventions are ineffective [36]. No published RCT aiming to prevent weight gain in young adults utilized the general practice setting to recruit participants. Recruitment strategies are generally poorly reported as we have previously published [12]. Brief descriptions of recruitment methods were reported in only 62% of studies [12], which included using existing databases, mailings, posters, flyers, advertisements, email blasts, and information stands. The effectiveness and cost of traditional strategies in this population have only been reported in two interventions from Western countries [32,33] and other populations at risk of weight gain, such as young families [37]. Formative research into recruitment strategies is providing valuable evidence that may assist in efficient and systematic recruitment processes [32,38].

Among the possible reasons why enquiries were low, focus groups of overweight young adults show health, social image, and self-confidence were reasons identified for pursuing weight loss [38]. However, young adult men, particularly those with reported weight gain and with an overweight BMI (≥ 25.0 kg/m^2), reported needing to gain greater than 6 kg before becoming concerned [39]. This is consistent with Australian

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data showing that overweight men recognize a growing societal concern with many health-related implications with weight gain, but do not feel this was something that affected them personally at their current life stage [40]. It is unclear whether identifying poor behavioral choices associated with weight gain, such as inadequate fruit and vegetable consumption, high intake of sugary soft drinks, increased frequency of takeout meals, and low levels of physical activity, were reasons for young adults to engage in prevention interventions. Thus, advertising for the TXT2BFiT study used images focused on weight gain, depicting an overweight man with central adiposity, as well as scales. Formative research into advertising materials suggested young adults would avoid advertising focusing on images of scales [32], but this was not published at the time TXT2BFiT materials were designed. Now our slogan "gained a few kilos" may be more powerful if the cumulative effect of excess weight gain over time was advertised.

Young adults reported they would be unlikely to click on paid adverting for recruitment to a weight gain prevention program on social networking sites such as Facebook [32]. Facebook paid advertising proved ineffective in the current study, costing approximately seven times the average cost per participant randomized, and had a low enquiry rate despite the high reach. Australian research that has demonstrated recruitment through free advertising on a university Facebook page has been shown to be effective for recruiting young women, 18 to 30 years, to an online weight management survey [13], and was comparable to the e-newsletter strategy used in this study. However, this may limit the representativeness of the sample as the target audience is restricted to the university population. Facebook paid advertising has been shown to be a cost-effective recruitment strategy—US $20 per compliant participant—for online health surveys in 18- to 25-year-old women [15]. Moreover, this has been shown to reach a more representative sample of the population, with success in recruiting nonurban and low-income women [15,16]. Facebook paid advertising was compared to social networking and social marketing for parents of adolescent children and was shown to recruit nearly three times as many participants in less time and at less cost—204 participants over 2 months at AUD $5.94 per participant versus 74 participants over 8 months at AUD $58.70 per participant, respectively [14]. Traditional survey methods for young women such as mailings are becoming costly, with a recent study reporting a three-fold increase—from AUD $30 to just over AUD $100—in the cost to recruit young women aged 18 to 23 years for a national Australian survey [41].

Recent CONSORT (2010) guidelines recommend clearly displaying the flow of participants throughout a study and that studies report the number of eligible participants prior to randomization, yet they do not insist on the need to report the original overall number of responders invited to participate (prior to eligibility) [42]. Despite identifying recruitment as part of their framework, the CONSORT guidelines do not define the actions needed to identify and recruit potential populations of participants. There is an absence of conceptual frameworks for recruitment to intervention studies and also a lack of procedural models. There is a need to identify what factors are effective in engaging eligible participants to improve the external validity of the research study and to establish recruitment goals based on the target population to engage with population subgroups.

Limitations

The cost data reported from this research study is limited to cost per strategy and does not include research staff time. Time spent on recruitment was difficult to calculate due to research staff having multiple roles within the research study. This study had one full-time staff member or less employed at any one time. This needs to be accounted for with future cost analysis. For future translation potential, the recruitment process for this study has areas where improvements can be implemented to attract only eligible participants. No formative research was conducted to inform the development of the recruitment materials nor any focus group discussions of the advertisements employed. In future, it is recommended that formative research be conducted prior to scale-up. The recruitment materials can contain a quick response code for mobile phones, which can provide the potential participant with an instant and direct link to the program website explaining eligibility, which will eliminate the need for prior email correspondence. Self-reported measurements have been shown to accurately identify overweight and/or obesity in young people [43]. The requirement for a GP visit resulted in a large dropout of eligible participants prior to attending an appointment. The visit may have been a potential barrier for participants, and the necessity of this step will be investigated further before translation and scale-up in the wider community. Reasons for eligible participants not participating in research studies requires further exploration. Considerable cost is invested in recruiting participants who drop out and researching the reasons for nonparticipation may lead to future cost saving in population obesity prevention programs. Finally, the recruitment strategies resulted in a sample skewed toward a higher SES advantage, but evidence is lacking and this requires further investigation. Targeted recruitment for socially disadvantaged and minority groups needs to be established for future effectiveness research.

Conclusions

This study is an important contribution for future research into efficacy, translation, and implementation of cost-effective programs for the prevention of weight gain in young adults in general, and in using eHealth. The research indicated that free electronic media was the most cost-effective strategy, with GP letters the most effective of the paid strategies. The results provide guidance for future research, as currently there is limited published research available on the cost and effectiveness of recruitment strategies. The large heterogeneity between published studies shows conflicting information on the best strategies to engage young adults. Procedural frameworks for recruitment protocols are required, along with systematic reporting of recruitment strategies to reduce unnecessary expenditure and allow for valuable public health prevention programs to go beyond the research setting.

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Authors' Contributions

SRP made substantial contributions to the preparation and revision of the manuscript, as well as significant contributions to recruitment for the study, data collection, and analysis. KB, AW, LH, and MAF contributed significantly to recruitment for the study. KB, AW, LH, EDW, MH, PP, and AB were involved in the revision of the manuscript for important intellectual content. KM and MAF were involved in data analysis, and drafting and critical revision of the manuscript for important intellectual content. All authors have contributed and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Examples of the recruitment materials for each modality.

[PDF File (Adobe PDF File), 1MB - resprot_v4i2e66_app1.pdf]

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Abbreviations

AUD: Australian Dollar
BMI: body mass index
CBD: central business district
CPC: cost per click
CPM: cost per 1000 impressions
CTR: click-through rate
GP: general practitioner
HCF: Hospitals Contribution Fund
IRSAD: Index of Relative Socio-economic Advantage and Disadvantage
OR: odds ratio
RCT: randomized controlled trial
SEIFA: Socio-Economic Indexes for Areas
SES: socioeconomic status
SMS: short message service
TAFE: Technical and Further Education
uCTR: unique click-through rate

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