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Protocol

Augmenting Outpatient Alcohol Treatment as Usual With Online Alcohol Avoidance Training: Protocol for a Double-Blind Randomized Controlled Trial

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Abstract

Background: Recent theoretical models emphasize the role of impulsive processes in alcohol addiction, which can be retrained with computerized Cognitive Bias Modification (CBM) training. In this study, the focus is on action tendencies that are activated relatively automatically.

Objective: The aim of the study is to examine the effectiveness of online CBM Alcohol Avoidance Training using an adapted Approach-Avoidance Task as a supplement to treatment as usual (TAU) in an outpatient treatment setting.

Methods: The effectiveness of 8 online sessions of CBM Alcohol Avoidance Training added to TAU is tested in a double-blind, randomized controlled trial with pre- and postassessments, plus follow-up assessments after 3 and 6 months. Participants are adult patients (age 18 years or over) currently following Web-based or face-to-face TAU to reduce or stop drinking. These patients are randomly assigned to a CBM Alcohol Avoidance or a placebo training. The primary outcome measure is a reduction in alcohol consumption. We hypothesize that TAU + CBM will result in up to a 13-percentage point incremental effect in the number of patients reaching the safe drinking guidelines compared to TAU + placebo CBM. Secondary outcome measures include an improvement in health status and a decrease in depression, anxiety, stress, and possible mediation by the change in approach bias. Finally, patients' adherence, acceptability, and credibility will be examined.

Results: The trial was funded in 2014 and is currently in the active participant recruitment phase (since May 2015). Enrolment will be completed in 2019. First results are expected to be submitted for publication in 2020.

Conclusions: The main purpose of this study is to increase our knowledge about the added value of online Alcohol Avoidance Training as a supplement to TAU in an outpatient treatment setting. If the added effectiveness of the training is proven, the next step could be to incorporate the intervention into current treatment.

Trial Registration: Netherlands Trial Register NTR5087; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5087 (Archived at WebCite http://www.webcitation.org/6wuS4i1tH)

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KEYWORDS

cognitive bias modification; alcohol; Alcohol Avoidance Training; Approach-Avoidance Task; treatment as usual; cognitive behavioral treatment

Introduction

Background

Alcohol misuse is a key public health concern and is associated with a high burden of disease, which in turn contributes to considerable economic costs for both individuals and society [1]. Although addicted people are aware of the negative consequences, most continue this self-destructive behavior. This paradox can be explained by models that conceptualize addictive behavior as a "dual process": an imbalance between relatively automatic processes and conscious/cognitive processes [2].

Recent research provides evidence that addictive behaviors are partly guided by relatively automatic processes that occur outside conscious control, making the individual respond impulsively to cues associated with the addictive substance, rather than displaying inhibitory control [3,4]. Multiple implicit cognitive biases have been shown to play a role in alcohol addiction, such as an attentional bias for alcohol-related stimuli [5], a memory bias for the automatic activation of alcohol-related associations [6], and a bias toward automatically activated action tendencies to approach alcohol [7].

Cognitive behavioral therapy (CBT) is an evidence-based treatment for a variety of disorders including alcohol use disorders. Various meta-analyses show a large effect size in treatment outcomes of patients with alcohol disorders compared to no treatment and a small but clinically significant effect when compared to other active treatments [8,9]. Although effective, CBT programs primarily target the reflective, voluntary system and leave the automatic, impulsive system mostly unaffected [10,11]. This suggests that treatment of alcohol use disorder could be improved by also focusing on those processes that are primarily automatic. Over the past decade, a set of computerized training programs have been developed with the aim of reducing automatic biases in information processing and thereby reducing psychopathology. Collectively, these programs are termed Cognitive Bias Modification (CBM) training [12-15]. Alcohol-related CBM programs have been shown to be effective in changing attentional bias [16-18], memory bias [19,20], and approach bias [21-23], which in turn is often associated with reductions in drinking behavior or reduced relapse into drinking behavior.

The current study focuses on retraining the automatically triggered behavioral tendency to approach alcohol, by using online Alcohol Avoidance Training. In a preliminary test with this CBM training among heavily drinking students, it was shown to be successful in modifying the automatic action tendencies and related memory associations, and students who were successfully trained to avoid alcohol drank less alcohol in a taste test directly after the training [22]. The first clinical trials with German alcohol-dependent inpatients showed that this training reversed the patients' approach bias into an avoidance bias for alcohol with generalization of the training effects to other experimental tasks [21].

More importantly, compared to patients in the placebo condition, patients in the training condition showed significantly less relapse after a year. A second study in the same clinic replicated the main findings and showed that the effects on relapse were mediated by change in approach bias [23]. While these studies tested the added effect of CBM training on top of treatment as usual (TAU), recent studies examined the effect of the training as a stand-alone intervention and failed to observe positive training effects [24,25].

Because TAU for alcohol use disorders often comprises of outpatient treatment, it is relevant to study the added value of CBM outside the clinical setting. Effectiveness of CBM in an outpatient setting may be attenuated by a lower adherence as compared to an inpatient setting. However, offering CBM online at home seems to generate high adherence rates. Combining Internet-based CBM with Internet-based CBT was found to be an acceptable form of treatment delivery for patients with depression, showing full adherence to the seven CBM sessions by 81% of participants [26]. Similarly, Salemink and colleagues showed an adherence rate of 85% among patients with different anxiety disorders, completing all 8 online training sessions (45 min each) in a period of 11 days [27]. Delivering CBM online in an outpatient setting may even generate stronger effects than in a clinical setting. There is preliminary evidence that training in a relevant context improves the effectiveness of CBM training. Kuckertz et al [28] showed improved results for CBM training in anxiety patients when patients were in a state increased anxiety while undergoing the CBM training. In case of alcohol addiction, training in a relevant, real-life context might lead to better results.

We, therefore, are interested in whether the positive added effects found in clinical inpatient samples [21] with the CBM training on local desktop computers in the clinic is possible to reproduce when the CBM is administered online in an outpatient sample.

Aims and Hypotheses

The aim of the current study is to investigate the effectiveness of online CBM Alcohol Avoidance Training as an adjunct to TAU in an outpatient treatment setting. Patients receive eight sessions of either the active or placebo version of the CBM Alcohol Avoidance Training during their TAU. The primary goal is to test the effects of this adjunct CBM on alcohol use immediately after finishing the intervention and three and six months later, by looking at the changes in the level of alcohol consumption over a week. The primary outcome measure is the percentage of the patients reaching the low-risk drinking level, defined as <22 standard units/week for men and <15 for women [29]. It is expected that more patients in the experimental condition will reach low-risk drinking level. Furthermore, it is hypothesized that the CBM intervention decreases or reverses the approach bias, and these changes are expected to mediate the effects on alcohol use [23]. An improvement in health status and a decrease in depression, anxiety and stress for patients in the training condition, compared to the placebo condition, are expected as secondary outcomes. To investigate who benefits most from the training, possible moderators will be examined. Automatic impulses may be controlled by cognitive capacity available to inhibit these impulses. Refusal self-efficacy is considered such a cognitive resource. Following this assumption, CBM interventions can yield benefits, especially for those with

a relatively weak cognitive control over their impulses to drink [12,30-32]. In line with the predictions from dual process models and prior CBM trials [12], it is expected that for patients with a low baseline self-efficacy, the additional effect of the Alcohol Avoidance Training will be stronger. Similarly, time-varying self-efficacy is expected to partially mediate the CBM effect as repeated experiences of successful coping due to stronger avoidance responses will enhance refusal self-efficacy. Patients' adherence and perceptions of treatment acceptability, and credibility will also be examined.

Methods

Trial Design

This study is a double-blind randomized placebo-controlled trial in a real-world setting. Patients receive TAU, consisting of outpatient personalized care

All patients with a primary alcohol problem enrolled for TAU are invited by their therapist to participate in the Alcohol Avoidance Training. After giving informed consent, patients are randomly assigned to one of the two training conditions: CBM Alcohol Avoidance Training or CBM placebo training. Patients begin the training simultaneously with the start of the behavioral change part of their treatment. Patients are recommended to follow a 15-minute CBM session twice a week for a period of five weeks. The CBM training includes eight sessions, preceded and followed by an assessment session, the preassessment and postassessment, respectively. Patients will be rewarded with a € 20 voucher if they complete all ten sessions. Three and six months after the TAU there will be follow-up assessments. Figure 1 shows the participant flow chart of the study.

The study has been approved by the Ethics Committee of Amsterdam Academic Medical Centre in January 2015 (reference number 2014_154#C20141463) and has been registered at the Netherlands Trial Register (NTR5087).

Participants and Procedure

The study population consists of patients aged 18 years or older with a primary alcohol problem, who are currently following TAU at Tactus Addiction Treatment Institute in the Netherlands. One general inclusion criterion is accessibility and ability to use the Internet, since patients will need to access CBM-training online. Two exclusion criteria apply for the TAU: (1) serious psychiatric illness with a risk to decompensate while decreasing alcohol consumption; and (2) the possibility of severe physical illness as a consequence of decreased alcohol consumption. There are no additional criteria for participation in this study.

Patients for the training are recruited by therapists at Tactus Addiction Treatment Institute. After the regular intake procedure, including baseline questionnaires, the TAU starts. Before the patient reaches the goal-setting assignment, the therapist will inform the patient about the CBM training and provide the patient with further information about the study. If the patient wants to participate, an informed consent form will be provided to patients by the therapist. After signing the form, the patient receives login credentials for the CBM training from the researcher.

After finishing registration, the patient is randomly assigned to the Alcohol Avoidance Training or to the placebo training, and receives an email with a link to the CBM training website. After logging in, the patient receives instructions about the training. At the start of each session, the patient is asked to complete the additional questionnaires for the purpose of this study, consisting of self-reported weekly alcohol consumption and desire for drinking. Each of the eight training session takes about 10-15 min. The first training session is preceded by an (online) preassessment and the final training session is followed by an (online) postassessment. Three and six months after the postassessment, each patient will receive online follow-up questionnaires. In case of nonresponse, the patient will be reminded by email or phone to complete the questionnaire.

Interventions

Treatment as Usual

TAU in this outpatient treatment setting is based on principles of CBT [33] and motivational interviewing [34]. The specific form of the TAU is tailored to the individual needs of the patient, in terms of treatment modality (Web-based or face-to-face) and intensity (brief 5-week version or intensive 3-month version). Study participants, therefore, receive an individualized version of treatment, as is common in regular real-world treatment settings. However, the basic ingredients for all versions are identical: daily registration, the analysis of the functions of the patients' drinking behavior, behavioral change components, and motivational interviewing. Table 1 provides an overview of the main treatment ingredients. Sessions in face-to-face and Web-based treatment are identical. The only difference is that the contact with the therapist is synchronous in face-to-face treatment, and asynchronous via the Internet in the Web-based treatment [35]. The intensive version of the treatment takes approximately three months with (online or face-to-face) sessions once or twice a week and daily self-reporting of alcohol intake during the whole program. This treatment consists of two parts: a first part focusing on the analysis of the patients' drinking habits, and a second part starting with the goal setting assignment, followed by sessions geared towards helping the patient reach the set goals and desired behavioral change. The brief 5-week version of the treatment focuses solely on behavioral change (part 2) and is intended for patients who already gained insight into their drinking habits when starting with treatment.

As we are interested in the effectiveness of online CBM Alcohol Avoidance Training as an adjunct to TAU, we do not differentiate between these four treatment "subgroups." Due to the randomization, the experimental and control group are expected to be balanced concerning treatment modality and intensity.

Therapists have either a bachelor's degree in social work or a master's degree in psychology, and received a 2-day training on the treatment protocol of the TAU. Therapists can obtain expert advice from a multidisciplinary team consisting of treatment staff, an addiction physician specialized in addiction, a psychologist, and a supervisor. This multidisciplinary team also provides quality assurance through monitoring of client

files and discussing treatment fidelity with counselors during weekly review of clients.

CBM Training

The intervention used in this study is the Alcohol Avoidance Training [21,23], based on the Approach-Avoidance Task (AAT) [36]. In this training, pictures of alcoholic beverages or soft drinks are presented, which are tilted 3 degrees to the left or right. Patients are instructed to respond to the tilted format of the picture, and not to the picture itself. This so-called irrelevant-feature version of the training (ie, responding to the format of the picture and not the subject of the picture itself) is used [21,23] because it is more indirect [37], and therefore blinds condition allocation (training vs placebo). Another advantage is that it is possible to change from measurement to training without changing the content of the picture set [38]. Striking the selected "u" key causes an avoidance movement of pictures in one format (eg, tilted left), while striking the selected "n" key causes an approach movement of pictures in the other format. The approach movement increases the size of the picture, and the avoidance movement decreases the size. This zooming effect generates a sensation of approach or avoidance, respectively. The combination of the format of the picture and the response (left=avoid and right=approach, vs left=avoid and right=pull) is counterbalanced across patients.

Figure 1. Participants flow chart. TAU: treatment as usual; CBM: Cognitive Bias Modification.

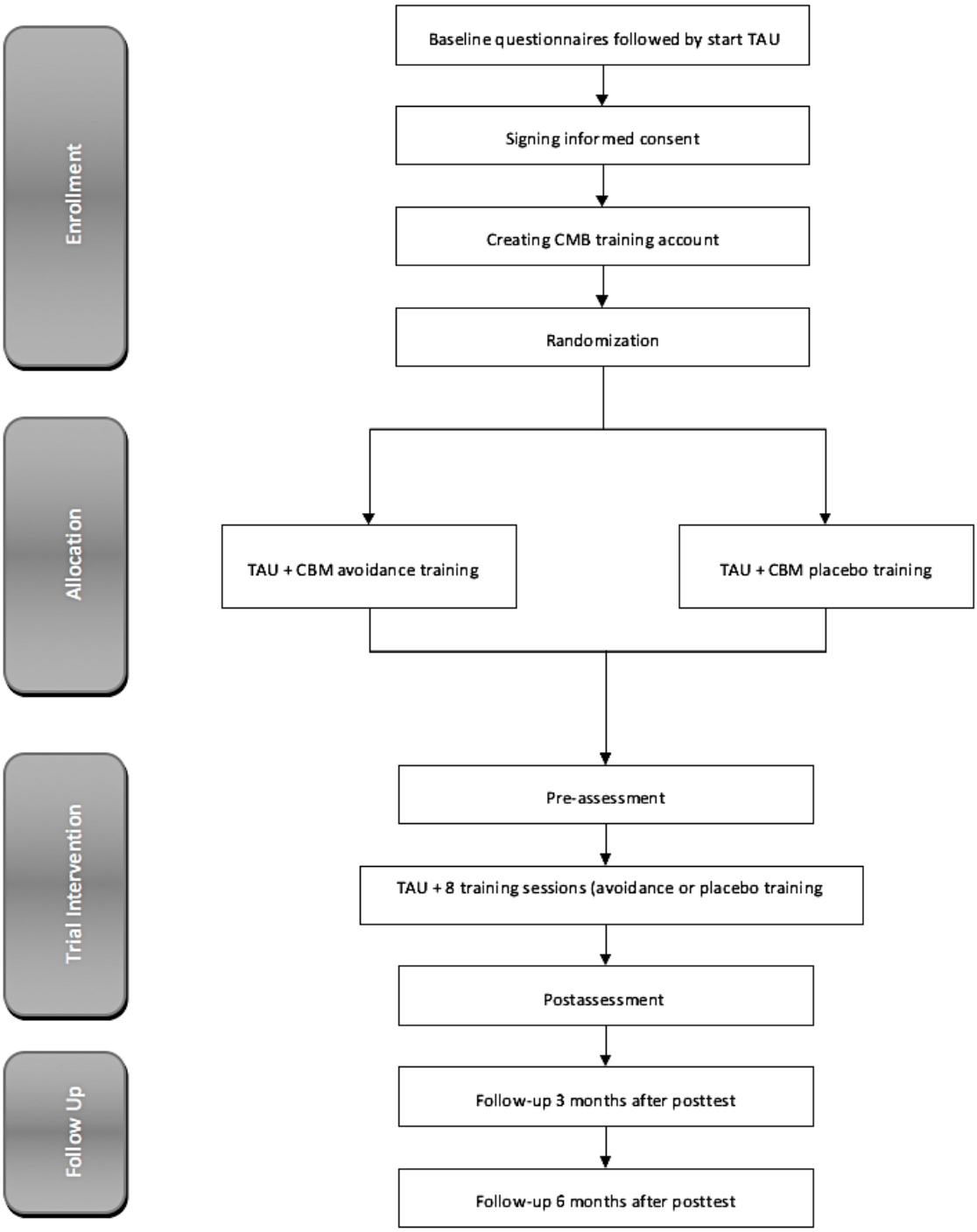

Table 1. Overview of the main treatment ingredients in intensive and brief treatments.

Session[a]	Content	Intensive (face-to-face/Web)	Brief (face-to-face/Web)
1	Baseline assessment	✓	✓
2	Advantages and disadvantages	✓	
3	Daily drinking diary	✓	
4	Description of drinking moments	✓	
5	Analysing drinking situations	✓	
6	Goal setting	✓	✓
7	Helpful thoughts	✓	✓
8	Helpful behavior	✓	✓
9	Decision moments	✓	✓
10	Action plan	✓	✓

[a]Part 1 is comprised of sessions 1-5 and part 2 is comprised of sessions 6-10.

The complete training program consists of eight sessions. Each session starts with a practice block of 12 trials with gray squared pictures followed by 160 trials divided into 4 blocks. The use of blocks was adopted to make the task less monotonous and to provide a short break. Two sets (A and B) of 40 stimuli each are used of which 20 are for alcoholic beverages and 20 for soft drinks [39]. Patients randomly received either set A or set B for assessment and the other set for training to be able to test generalization to untrained stimuli. In the training condition, all 40 stimuli are repeated 4 times (alcoholic beverages in avoid format, soft drinks in approach format) to train patients to avoid alcohol by exposing them only to alcohol/push and soft drink/pull trials. In the placebo condition, all 40 stimuli are presented 4 times: 2 formats (tilted to the left or right) x 2 repetitions. Alcoholic beverages and soft drink pictures are presented equally often in both formats. Figure 2 shows an example of the Alcohol Avoidance Training. Stimuli stay on the screen for a maximum of 3000 ms. In the case of no response, the trial is restarted after repeating the instructions. Each trial starts with a fixation cross to keep patients' attention focused.

Measures

An overview of all measurements instruments along with the randomized controlled trial measurement time-points are presented in Table 2.

Demographic characteristics like gender, age, educational level, employment and clinical case history details (duration of alcohol dependence, previous detoxifications and treatments, duration of current abstinence and medication intake) will be collected during the baseline assessment of the TAU.

Alcohol Consumption

Weekly alcohol consumption will be assessed using the Alcohol Timeline Follow Back (TLFB) method [40]. For every day of the previous week, patients provide retrospective estimates on the number of standard units alcohol they consumed.

Alcohol Dependence

The type and severity of alcohol dependence will be assessed by using the Diagnostic and Statistical Manual of Mental Disorders IV criteria, by means of the Substance Abuse Module (SAM) of the Composite International Diagnostic Interview (CIDI) [41].

Craving

The 5-item Obsessive Compulsive Drinking Scale (OCDS) [42] assesses obsessionality and compulsivity related to craving and drinking behavior, and is derived from the original 14-item OCDS scale [43].

Health Status

Health status is evaluated using the Maudsley Addiction Profile, Health Symptom Scale (MAP-HSS). The MAP-HSS is a 10-item questionnaire that was adapted from the health scale of the Opiate Treatment Index [44]. Because the MAP-HSS measures only general physical complaints, eight additional alcohol-specific physical complaints were added: hyperventilation, sweating, diarrhoea, heart palpitations, headache, memory problems, sexual problems and epileptic seizures.

Depression, Anxiety and Stress

The 21-item Depression Anxiety Stress Scale (DASS-21)[45] is a self-report questionnaire designed to measure depression, anxiety and stress at baseline.

Drinking Motives

The baseline drinking motives will be measured using the modified Drinking Motives Questionnaire Revised (mDMQ-R) [46]. The mDMQ-R is a 28-item self-report inventory that assesses the frequency of drinking for each of the original four motives in Cooper's model [47] with coping motives subdivided into coping-anxiety and coping-depression factors.

Self-Efficacy

Using eight items of the Drinking Refusal Self-efficacy Questionnaire (DRSEQ), participants will be asked whether they feel sure they can refuse alcohol on the three subdimensions of self-efficacy: social pressure, emotional relief and opportunism [48].

Figure 2. An example of Approach-Avoidance Training.

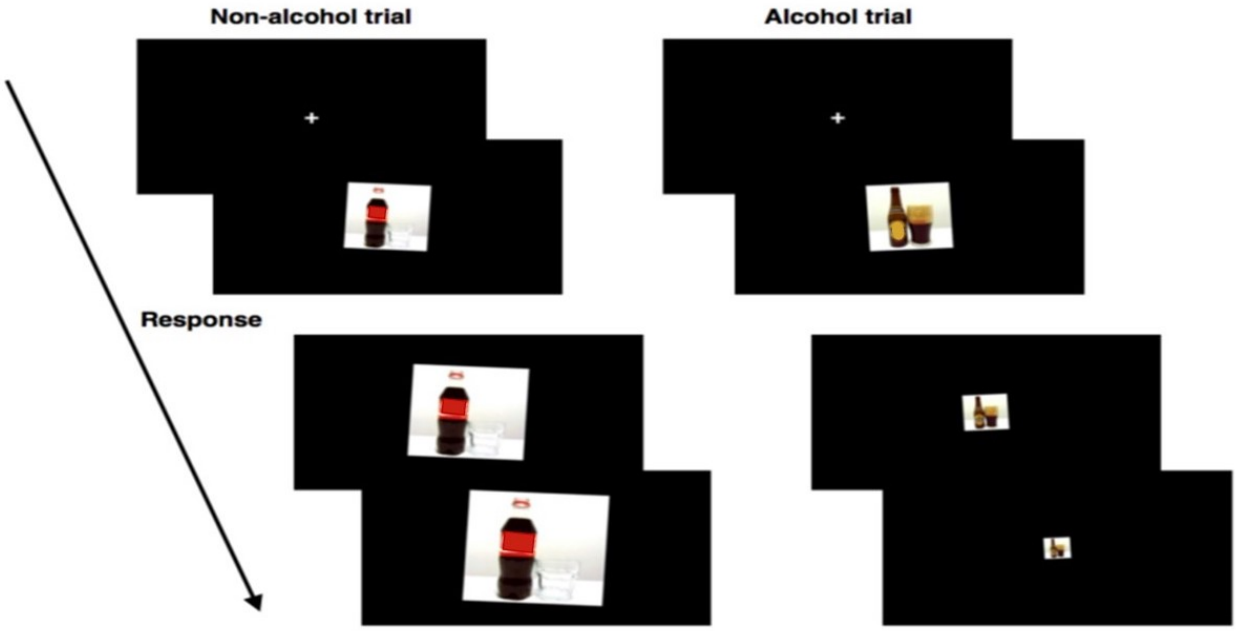

Table 2. Measurement instruments: purpose, measures and time points.

Purpose and measure[a]	Baseline TAU[b]	Preassessment	Training	Postasssessment	Posttest TAU	Follow-up
Cognitive bias assessment						
AAT		✓	✓	✓		
Baseline measures						
Demographics	✓					
MAP-HSS	✓				✓	✓
DASS	✓				✓	✓
OCDS	✓				✓	✓
DMQ-R		✓				
CIDI	✓					
Drinking refusal self-efficacy	✓					
Primary outcome measure						
Weekly alcohol consumption	✓	✓	✓	✓	✓	✓
Secondary outcome measures			✓			
CEQ[c]			✓			
CSQ				✓		

[a]AAT: Approach-Avoidance Task; MAP-HSS: Maudsley Addiction Profile; DASS: Depression Anxiety Stress Scale; OCDS: Obsessive Compulsive Drinking Scale Depression; DMQ-R: Drinking Motives Questionnaire (Revised); CIDI: Composite International Diagnostic Interview; CEQ: Credibilty Expectancy Questionnaire; CSQ: Client Satisfaction Questionnaire.

[b]TAU: treatment as usual.

[c]CEQ will take place in session 2.

Credibility of the Intervention

In the second training session intervention, credibility will be assessed using the Credibility and Expectancy Questionnaire (CEQ) [49]. It contains six items and differentiates between a patient's thoughts and his or her feelings regarding the CBM training.

Client Satisfaction

The patient satisfaction regarding the CBM training will be assessed using the Client Satisfaction Questionnaire (CSQ) [50]. It contains 8 items and answers are given on a 4-point scale.

Approach-Avoidance Tendencies

Approach-avoidance tendencies are assessed with the AAT pre- and posttraining [23]. The tests consist of 172 trials; 12 practice trials (gray squared pictures) and 160 assessment trials, the latter subdivided into four blocks of trials. Participants randomly receive either set A or set B during assessment. Each set consists of 40 pictures (20 depicting alcoholic beverages and 20 soft drinks) and those are presented 4 times: 2 formats (tilted to the left or right) x 2 repetitions. Alcoholic beverages and soft drink pictures are presented equally often in both formats.

Primary and Secondary Outcome Measures

The primary outcome measure for this study will be *the proportion of patients reporting alcohol consumption below low-risk drinking limits* (<22 standard units/week for men and <15 for women) [29], since achieving safe drinking is the primary aim of alcohol addiction care. This will be assessed using the TLFB method [40]. As it was not feasible to verify whether all participants met this threshold at the start of treatment and with the knowledge that a previous trial with a similar target group showed that enrolled participants only very rarely report below-threshold consumption levels at baseline [35]-, we allowed all patients to enroll in the study. If necessary, corrections will be made in the analyses.

Secondary outcome measures include changes in approach bias measured by an AAT in the preassessment and postassessment. An AAT bias index is calculated as the difference between the median reaction time scores for pushing pictures of one category (alcoholic beverages or soft drinks) and the median reaction time score for pulling pictures of that category. Median scores are used to minimize the influence of outliers. Positive scores indicate approach tendencies whereas negative scores indicate avoidance tendencies. Furthermore, it is investigated whether the added effect on treatment outcome is mediated by the amount of change in approach bias and who benefits most from training by identifying patient characteristics that moderate the outcome of the training. Other secondary outcome measures are general health condition, depression, anxiety and stress, intervention credibility and patient satisfaction.

Randomization

Patients will be automatically assigned to one of the two conditions (Alcohol Avoidance Training or placebo training, as described in the Intervention section) with an equal likelihood, using the method of minimization [51] in order to balance for type of TAU (online vs face-to-face). The randomization will be computer-generated without any involvement by the investigators. Patients will be randomly allocated to the condition to which the fewest participants of that type of treatment have so far been assigned.

Blinding

The trial has a double-blind design because neither patients nor therapists know to which condition patients are assigned. To ensure anonymity, patients receive an email with a user ID to create their personal research account. If necessary, patients can contact the researcher for help. Patients complete the training at their own computer. To keep patients blind to their intervention condition, patients respond to an irrelevant feature (orientation of the picture) instead of the content of the picture (alcoholic beverage vs soft drink beverage) [23]. During the postassessments, patients' awareness of the experimental condition is assessed by means of a manipulation check.

Sample Size Calculation

An a priori statistical power analysis (G-power) was conducted to determine the necessary number of participants. The primary outcome measure is a reduction in alcohol consumption. To obtain an estimate of the effect size to be expected, studies describing previous Alcohol Avoidance Training interventions were inspected [21,23]. In both these studies, a relative increase of 20% was observed in effectiveness of TAU + CBM as compared to TAU. The proportion of patients reaching long-term abstinence increased by 13% from 41%-54% [23]. Although in these studies a different dependent measure was used (prolonged abstinence from alcohol), we assume a similar increase in success rate of +13 percentage points as effect size. It has been shown that the Web-based treatment resulted in a 68% success rate (ie, reaching the low-risk drinking criterion) [52]. When extrapolating that to this study, a +13 percentage points additional effect of the Alcohol Avoidance Training is predicted to result in 81% achieving the safe drinking criterion (beta>.80; alpha (one-tailed) <.05). Based on these parameters, 152 patients are needed within a condition to show the hypothesized effects using a Fisher's exact test for proportions in two independent samples.

Statistical Analyses

Analyses will be conducted in agreement with intention-to-treat principle. Missing data points will be handled using multiple imputation [53]. One-way ANOVAs and χ^2-tests will be performed to see if there are any significant differences at baseline between the two CBM training conditions (Avoid Alcohol vs placebo) for any of the demographic variables or outcome measures. Nonsignificant differences will indicate successful randomization. To determine the primary outcome, a logistic regression analysis will be used to test the differences in the proportion of patients reaching the low-risk drinking criterion between the CBM Alcohol Avoidance Training and CBM placebo condition, both at posttest and at follow-up. If necessary, baseline confounders will be controlled for, and significant interaction effects will be further investigated using post hoc *t*-tests (independent samples *t*-test and paired samples *t*-test). Effect sizes on clinically relevant outcomes at postintervention and follow-up will be calculated by Cohen's d using the means and pooled standard deviations of the measurements of the conditions. Effect sizes of .56-1.2 are considered large, .33-.55 are considered moderate, and less than .33 are considered small [54]. Repeated measures ANOVAs will be conducted to test for differences between the CBM Alcohol Avoidance Training and the CBM placebo condition on the secondary outcomes general health condition, depression, anxiety and stress. Mediation analyses will be conducted by applying the analytic procedure according to Preacher and Hayes [55] and Hayes [56] to examine whether a change in approach bias is mediating the Alcohol Avoidance Training effects on our primary outcome measure. Logistic regression analyses will be used to assess whether patient characteristics moderate the

effect of the Alcohol Avoidance Training on our primary outcome measure. The procedure proposed by Baron and Kenny [57] will be adopted. Descriptive statistics will be used to investigate to what extent patients adhered to the Alcohol Avoidance Training (in terms of timing, frequency, and duration of sessions) and to what extent patients found the Alcohol Avoidance Training both acceptable and credible (testing adherence, acceptability, credibility).

Ethics, Consent, Permissions, and Funding

Written informed consent to participate in the study will be obtained from all participants.

The study has been approved by the Ethics Committee of Amsterdam Academic Medical Centre in January 2015 (reference number 2014_154#C20141463) and has been registered at the Netherlands Trial Register (NTR5087).

The study was funded by Saxion University of Applied Sciences, Enschede.

Results

The trial was funded in 2014 and is currently in the active participant recruitment phase (started on May 2015). Enrolment will be completed in 2019. First results are expected to be submitted for publication in 2020.

Discussion

This study protocol design describes a double-blind randomized controlled trial to assess the added value of an online Alcohol Avoidance Training as adjunct to TAU for outpatient alcohol patients. Previous studies involving alcohol dependent patients in inpatient addiction treatment have shown promising results for Alcohol Avoidance Training in addition to TAU [21,23]. The present study wants to test whether the positive added effects found in a more controlled, clinical setting, with training on local desktop computers, are replicated when the training is administered in a less controlled, ambulatory setting with online delivery.

The online delivery of CBM training enables patients to conduct the sessions at a preferred location, which may entail some threats to treatment fidelity. The preferred environment might bring distractions like ambient sounds or the interaction with other people present, which could influence the concentration level and responsiveness to the training [57]. Therefore, patients will be instructed to avoid distractions and that concentration, accuracy and speed during the sessions is required. Another aspect to take into consideration is that online interventions typically have a high dropout rate [58]. Therefore, treatment adherence is encouraged by: (1) emails from the research assistant to the therapists to enable them to monitor the progress of their patients when, for example, the patient has not finished a training session for some time; (2) emails or oral messages from the therapist to the patient to reinforce motivation; (3) emails to invite, remind and praise patients regularly. These messages are generated automatically by the training program whenever a patient can start a new training session, or when patients do not start with a new training session after the designated time; (4) a gift voucher of €20 from an online shop (Bol.com) when upon completion of all 10 study sessions (8 training sessions, and pre- and postassessment).

The strength of this study is the combination of online Alcohol Avoidance Training with TAU in an ambulatory setting. CBM training in an outpatient setting might be extra effective, because patients work on the training in their own relevant context with the presence of alcohol-related cues and challenges (eg, craving), that are not (or less) available in a clinical setting. So, patients can practice and apply their skills directly into the relevant setting. We are interested in investigating the impact of CBM training in the ambulatory setting. In addition, the ambulatory TAU is much less intensive than TAU in a clinical setting [23]. Therefore, the CBM training covers a proportionally greater part of the total treatment, and we will investigate whether this might have more impact. Additionally, the ambulatory and online delivery of the training will give us a first impression of the possibilities and concerns of the broader dissemination of CBM training.

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Authors' Contributions

MB-vdW, ES, MGP and MEP constructed the design. MB-vdW and MCL were responsible for the data collection and drafted the manuscript. ES, MGP, MEP, SBA, ETB and RW are supervisors and revised the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AAT: Approach-Avoidance Task
CBT: cognitive behavioral therapy
CBM: Cognitive Bias Modification
DASS: Depression Anxiety Stress Scale
DMQ-R: Drinking Motives Questionnaire Revised
MAP-HSS: Maudsley Addiction Profile, Health Symptom Scale
mDMQ-R: modified Drinking Motives Questionnaire Revised
OCDS: Obsessive Compulsive Drinking Scale Depression
TAU: treatment as usual
TLFB: Time Line Follow Back

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Protocol

Evaluation of Technology-Based Peer Support Intervention Program for Preventing Postnatal Depression: Protocol for a Randomized Controlled Trial

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Abstract

Background: Multiple international agencies, including the World Health Organization and the International Monetary Fund, have emphasized the importance of maternal mental health for optimal child health and development. Adequate social support is vital for the most vulnerable to postpartum mood disorders. Hence, an urgent need for sustainable social support programs to aid mothers ease into their new parenting role exists.

Objective: This study protocol aims to examine the effectiveness of a technology-based peer support intervention program among mothers at risk for postnatal depression in the early postpartum period.

Methods: A randomized controlled 2-group pretest and repeated posttest experimental design will be used. The study will recruit 118 mothers from the postnatal wards of a tertiary public hospital in Singapore. Eligible mothers will be randomly allocated to receive either the peer support intervention program or routine perinatal care from the hospital. Peer volunteers will be mothers who have experienced self-reported depression and will be receiving face-to-face training to support new mothers at risk of depression. Outcome measures include postnatal depression, anxiety, loneliness, and social support. Data will be collected at immediate postnatal period (day of discharge from the hospital), at fourth week and twelfth week post childbirth.

Results: The recruitment and training of peer support volunteers (N=20) ended in June 2017, whereas recruitment of study participants commenced in July 2017 and is still ongoing. The current recruitment for new mothers stands at 73, with 36 in the control group and 37 in the intervention group. Data collection is projected to be completed by May 2018.

Conclusions: This study will identify a potentially effective and clinically useful method to prevent postnatal depression in new mothers, which is the top cause of maternal morbidity. Receiving social support from others who share similar experiences may enhance the positive parenting experiences of mothers, which in turn can improve the psychosocial well-being of the mothers, tighten mother-child bond, and enhance overall family dynamics for mothers and infants.

Trial Registration: International Standard Randomized Controlled Trial Number ISRCTN14864807; http://www.isrctn.com/ISRCTN14864807 (Archived by WebCite at http://www.webcitation.org/6xtBNvBTX)

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KEYWORDS

anxiety; loneliness; peer group; postpartum depression; social support; technology

Introduction

The mental well-being of women is highly vulnerable after childbirth, with postpartum mood disorders being the top cause of maternal morbidity [1,2]. The severity of these postnatal affective disorders can range from early maternity blues [3] to postpartum psychosis, which affects less than 1% of mothers [4,5]. Among these affective disorders, postnatal depression (PND) is the most common [5]. Women who have suffered PND often report feelings of inadequacy [6-8], disconnection from others [9,10], role conflicts [8,9,11], loneliness [9], anxiety [11-13], dissatisfaction with life [6,14], insomnia [14], and for severe cases, suicidal ideation [10,15]. Women are susceptible to PND in the first 12 weeks postpartum [16], with the duration dependent on severity [17] and time to onset of the treatment [18]. A total of 50% of clinically depressed mothers have experienced PND symptoms for at least 6 months postpartum [19,20], whereas approximately 25% of untreated mothers experience the symptoms for at least a year [21].

PND poses a huge mental health threat for women, with recent literature reporting an estimated prevalence rate of 10% to 15% for major PND [22,23]. Despite the insufficient statistics in the Singapore context, a recent local study by Shorey et al has discovered that the prevalence of PND symptoms at 4 weeks post birth is at 13% [24]. Additionally, the national G *rowing up in Singapore Towards Health Outcomes* (GUSTO) study [25] has revealed that across the general population, the increased maternal emotional difficulty during pregnancy has adverse effects on child neurodevelopment, in particular, brain regions associated with cognitive and emotional function. These results are supported by other studies that have examined how PND affects the quality of mother-child interactions [26] and has a significant adverse effect on the development of a child [13]. Mothers suffering from PND tend to be more hostile toward the infant [27,28], display disengaged parenting behaviors [27], and are unresponsive toward their infants' cries [29]. These tendencies increase the risk of attachment anxiety, social behavioral problems [28], and psychopathology [30] in the affected child. Therefore, curbing the risk for depression and anxiety is necessary not only at an individual level but also for the general public health and societal capacity.

Causes of Postnatal Depression

To date, the causes of PND remain uncertain, with considerable amount of literature suggesting a multifactorial etiology [3,9,31]. However, many studies can identify the primary risk factors for PND. Apart from a history of psychopathology [9,32,33] and demographic variables, such as young age [3], single marital status [32], and low socioeconomic status [3,32], psychosocial variables, such as insufficient social support [14,34], low maternal self-esteem [11,32], marital conflict [14,35], life stress [11,33,34], and childcare stress [9,22,32], are also major predictive factors of PND. The detailed analysis of predictive studies has further revealed underlying issues commonly faced by mothers, which can increase the risk of PND. Common social deficiencies experienced by mothers include insufficient initiated support by others [3,7,22,33], the lack of a close friend to confide in [9], and the inability to find a nonjudgmental person that can listen and empathize with them [36,37].

Prevention of Postnatal Depression

In previous studies [6,7,14,36,38], emotional and instrumental support have been shown to be important in preventing PND. A previous study has revealed that instrumental support is preferred by mothers more than emotional support [7]. In a study by Gebuza [39], relationship between perceived instrumental support and actual support provided have also been found to be significant, as compared with emotional and informational support. Moreover, the mean social support received from significant others has helped mitigate the decline in mothers' quality of life after childbirth [39]. Social support through companionship from significant others [6,14,36,38] and family members [3,36,38,40], as well as group belongingness with other identical individuals [36], have also been shown to serve as a protective barrier against PND. Alternatively, in the study of Leahy-Warren et al, no protective relationship was observed between professional support and PND [38]. In addition to social support from family and significant others, the study of Dennis et al also revealed the importance of support from other experienced mothers [36]. New mothers who share experiences with other mothers feel a sense of belonging and reassurance [6,10], which has helped boost their confidence in child rearing and reduced negative feelings [36]. The results from this study suggest that simple intervention means, such as talking to an experienced mother with similar stressors or situation, can act as a buffer against PND [6,10,41].

In addition, numerous randomized controlled trials [42-45] have been conducted to evaluate the effectiveness of psychosocial support interventions to prevent PND. These trial interventions are mostly conducted immediately after post birth [46,47] and primarily targeted high-risk women in professionally led antenatal groups [48,49]. Methodological limitations for these trials include poor measurement of PND and premature timing of outcome assessment. In a large scale Australian trial [47], postoperation debriefing by midwives are not only found ineffective in improving the psychological well-being of mothers but also has actually worsened the emotional health of mothers at 24 weeks. A local trial [50], which evaluated the success of a postpartum psychoeducational program, also found a significant effect in reducing PND. This intervention is administered by midwives paying home visits; therefore, the sustainability of this program is limited by the scarcity of midwives.

Gaps in the Literature

The scarcity of resources and advancement of technology has led to an increasing trend in telemedicine, which is a previously underutilized platform in the health care sector [51-55]. Technology-based interventions are not only accessible and cost-effective; they also enhance privacy, flexibility, and reduce stigmatization [56,57]. These interventions are especially important for a multiracial, conservative society, such as Singapore, where traditional views and homebound confinement practices restrict new mothers from seeking the necessary help after childbirth [58,59]. Therefore, technology-based support

will be the most practical alternative form of support for local mothers. Previous studies have successfully implemented technology-based support intervention for new mothers [51,60]. Technology-based peer support has effectively helped mothers maintain breastfeeding for 3 months postpartum as compared with those in the control group [60]. In another technology-based peer support study [51], pregnant mothers who received support were shown to have decreased anxiety and depressive traits. The risk of PND was also reduced to half of those in the control group. From these studies, we can deduce that the use of technology-based support may be effective in reducing the risk of depression for high-risk mothers.

The aim of this study is to examine the effectiveness of a technology-based peer support intervention program among mothers at risk for postnatal depression in the early postpartum period. This study has 3 objectives:

1. To evaluate the peer support intervention program on maternal outcomes, including PND (primary outcome), anxiety, loneliness, and social support (secondary outcomes)
2. To analyze mothers' evaluations of their peer support experience
3. To analyze peer volunteers' evaluations of their peer support experience

We hypothesized that when compared with those in the control group receiving routine care, mothers receiving the peer support intervention program will report a significantly lower level of PND, lower level of anxiety, lower level of loneliness, and higher level of social support received.

Methods

Design

A randomized controlled, single-blinded, 2-group pretest and repeated posttest experimental design will be used. Mothers (n=118) recruited from the postnatal wards of a tertiary public hospital will be randomly allocated to 2 groups (intervention group receiving the peer support intervention program and routine perinatal care from the hospital or control group receiving only routine perinatal care from the hospital). Data will be collected at immediate postnatal period (on day of discharge from the hospital), at the fourth week, and the twelfth week post childbirth using Web-based questionnaire surveys that include locally validated and reliable instruments, semistructured face-to-face interviews, and telephone interviews.

Participants

Potential participants must be mothers who (1) are at least 21 years old, (2) can speak and read English, (3) own a telephone and are willing to share their number, and (4) plan to stay in Singapore for the first 3 months post childbirth. The inclusion criteria for the peer volunteers are mothers who (1) are at least 21 years old, (2) can speak and read English, (3) have delivered healthy baby in the past, (4) have self-reported history of and recovery from PND, (5) have a phone and are willing to share their number and call needy mothers as instructed by the research team, and (6) plan to stay in Singapore for next 6 months from the time of recruitment to participate in the mother-to-mother peer support intervention program. The exclusion criteria for the participants are mothers who (1) have a history or existing psychiatric illnesses, cognitive impairment, "and" or "or" major medical conditions that can interfere with their ability to participate in the study, (2) have had a vacuum- or forceps-assisted delivery with fourth-degree perineal tear; and/or (3) has given birth to a stillborn or a newborn with birth defects and/or medical complications. The exclusion criteria for the peer volunteers are as follows: (1) they have any physical or mental disorders that can interfere with their ability to participate in the study and (2) do not want to share their number and call needy mothers as instructed by the research team.

Components of the Peer Support Intervention Program

Mothers who participate in the intervention group will receive technology-based peer support alongside routine postnatal care by the hospital, including follow-ups by the obstetrician, nurses, and lactation consultant. Mothers in the control group will only receive standard routine postnatal care provided by the hospital. Research assistant one (RA1) will match the participant to the peer volunteer based on availability [61] and demographics they have provided, especially in the mode of delivery. RA1 will then provide the name and contact details of the participants to the volunteer and inform the participant of the pairing. Each peer volunteer will not only be paired with 1 participant at a given point of time but will also be required to correspond with at least 3 mothers in total. The peer volunteer will initiate contact with the participant within 2 to 3 days post childbirth to discuss suitable timings for future correspondence. On the basis of the effectiveness of previous trials [60,61], peer volunteers will be encouraged to make a minimum of 4 phone contacts in 4 weeks. However, if the dyad cannot compromise on a time for a follow-up call, they will be allowed to correspond through messages or other mobile communication apps such as WhatsApp as frequently as they deem necessary. Frequency and duration will be tailored to maternal needs, which have been found to be effective in the previous trial. As shown in Figure 1, a Peer Volunteer Activity Log will be used to assess the intensity and duration of each intervention session. Additionally, peer support volunteers will be encouraged to maintain a free-text journal on their conversations with the new mothers. Semistructured interviews with peer volunteers and mothers will be conducted to evaluate the nature of the interaction.

Figure 1. Peer Voluntary Activity Log. Overall rating: 1 least satisfied; 5 most satisfied.

S. No.	Duration of Call/No. of Messages	Topics Covered	Any important points to take note of before next call/message	Overall Rating of this experience 1-5
1				
2				
3				
4				
N				

Sample Size Determination

Psychosocial and educational interventions in perinatal period often result in a medium to large effect size on outcome variables [62], such as parenting self-efficacy [24]. Therefore, we can reasonably regard the peer support intervention to have a medium-size effect on the outcome variables. In our study, a 2 sample *t* test will be used to test for differences between the 2 groups. The required sample size to detect a medium effect size of 0.6 (*t* test) at a power of 80% and a significance level of 5% (2-sided) is 45 in each group [63]. In addition, when considering the dropout rate of 30% based on a previous similar study [62] and a preliminary study [24], a minimum sample size of 118 (45×2+45×2×30%=90+28=118) participants, with 59 in each group, is required for this study.

Randomization

After confirming the eligibility criteria and obtaining the consent of the participants, all mothers will be randomized into 2 groups. Mothers who give consent to participate will be asked to choose a number from 1 to 118 from an opaque envelope. The research randomizer [64] will be used to generate 1 set of 59 numbers. Participants whose picked number matches with any number in the set will be assigned to the intervention group (PIP intervention), and the remaining will be assigned to the control group. The principal investigator, who is not involved in recruitment, intervention, and data collection, will generate the random numbers and will pass them to RA1, who is not involved in data collection.

Process Evaluation

After the peer support intervention (between 4 and 12 weeks post childbirth), an approximate purposive sample of 20 mothers, 10 each from intervention and control groups (actual number will depend upon data saturation), and all (N=20) peer support volunteers will be selected to participate in the interview to obtain their opinions and comments on the receipt and delivery of the peer support intervention program, respectively. Participation in the interviews will be voluntary. The process evaluation of each interview will take approximately 30-60 min. Participants will be given pseudonyms during the interviews to protect their actual identities. As part of the presentation of the results, their own words will be used in text and will be made anonymous. The interview will be audio-recorded and transcribed into text form. The recruitment will continue until the proposed number is achieved or data saturation is achieved, whichever occurs earlier.

Outcome Measures and Instruments

The demographic data of mothers (eg, age, gender, ethnicity, education) will be collected. The following instruments will be used to measure the outcomes.

Edinburgh Postnatal Depression Scale

The Edinburgh Postnatal Depression Scale (EPDS) [65] is a 10-item scale that has been widely used to measure postnatal depression in international [66,67] and local studies [24,68]. On the basis of previous trials [61,69], the recommended cutoff score of 9 will be used to screen the mothers. A score of >13 is recommended to be used as probable diagnosis for PND. The sensitivity of EPDS ranged from 68% to 80% with specificity of 77% and Cronbach alpha of .88 [65].

Patient Health Questionnaire

The Patient Health Questionnaire (PHQ-9) [70] is a shortened 9-item questionnaire extracted from the full PHQ used to diagnose and measure the severity of major depression. It is scored from 0 to 27, with higher scores indicating high severity. An additional item was added to the diagnostic portion for patients who indicated on the questionnaire that they faced problems: “How difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?” The PHQ-9 is well tested and validated in international [71,72] and local [73] studies. The Cronbach alpha in a previous local study was .87 [73].

State Trait Anxiety Inventory

The State Trait Anxiety Inventory (STAI) [74] is a 40-item, self-administering 4-point Likert scale used to assess parental anxiety state. This instrument is well tested for its psychometric properties in international [75-77] and local setting [78]. The Cronbach alpha value of the instrument is .8 in local setting [78].

University of California, Los Angeles Loneliness Scale

The University of California, Los Angeles (UCLA) Loneliness scale [79] is a 10-item self-report instrument used to measure loneliness. Items are rated on a 4-point Likert-type scale to produce a summative score ranging from 10 to 40, with higher scores indicating higher degrees of loneliness. In a previous study, the Cronbach alpha value was .90 [61].

Perceived Social Support for Parenting

This 4-item instrument developed by Leerkes and Crockenberg [80] will be used to measure the satisfaction of parents with the social support from partners and from others. The 5-point scale ranges from 5 to 20 each for the support received from partners or others. The instrument has shown high internal consistency with Cronbach alpha value of .81 in a previous study [80].

A semistructured interview guide will be used for process evaluation. Individual telephone or face-to-face interviews with mothers and peer volunteers will be conducted (4-12 weeks post childbirth) to identify the strengths, weaknesses, and effectiveness of the intervention (from the mothers’ and peer volunteers’ perspectives) as well as on the delivery process from the peer volunteers. All interviews will be audio-recorded.

Study Procedure

The study will be composed of 2 phases:

Phase 1: Planning intervention strategies for intervention group, including recruitment of peer volunteers, development of peer volunteer training manual, and training the peer volunteers.

Phase 2: Implementing the PIP and investigating its effectiveness on maternal outcomes.

The recruitment of peer volunteers in phase 1 was conducted before the recruitment of participants. Recruitment was done through the blasting of emails to the study venue working community and through word of mouth. On the basis of a previous study [61], 20 peer volunteers were recruited. The recruitment of ethnically diverse peer volunteers was ensured by RA1. RA1 (1) coordinated the peer volunteer recruitment and acquired their informed consent, (2) participated in peer volunteer training sessions, (3) has been pairing mothers with a suitable peer volunteer based on the availability of the volunteer, (4) monitoring the intervention implementation, (5) providing support to peer volunteers as required, and (6) assisting in setting up peer volunteer meetings.

Peer volunteers were required to attend a 4-hour training session conducted by the psychiatrist (one of the study team member). The training for all recruited volunteers was completed in one session in June 2017 to maintain standardization. The training session included roleplaying and discussions to provide necessary skills for the peer-volunteers to successfully deliver the intervention. Peer volunteers were also trained in assessing and conducting the appropriate referrals to relevant health care professionals should the need arise. A peer volunteer training manual was distributed during training to facilitate and guide the intervention process. The trial was introduced during training sessions, and all peer volunteers who agree to participate were required to fill a demographic form and were provided activity logs to account for their sessions with the mothers.

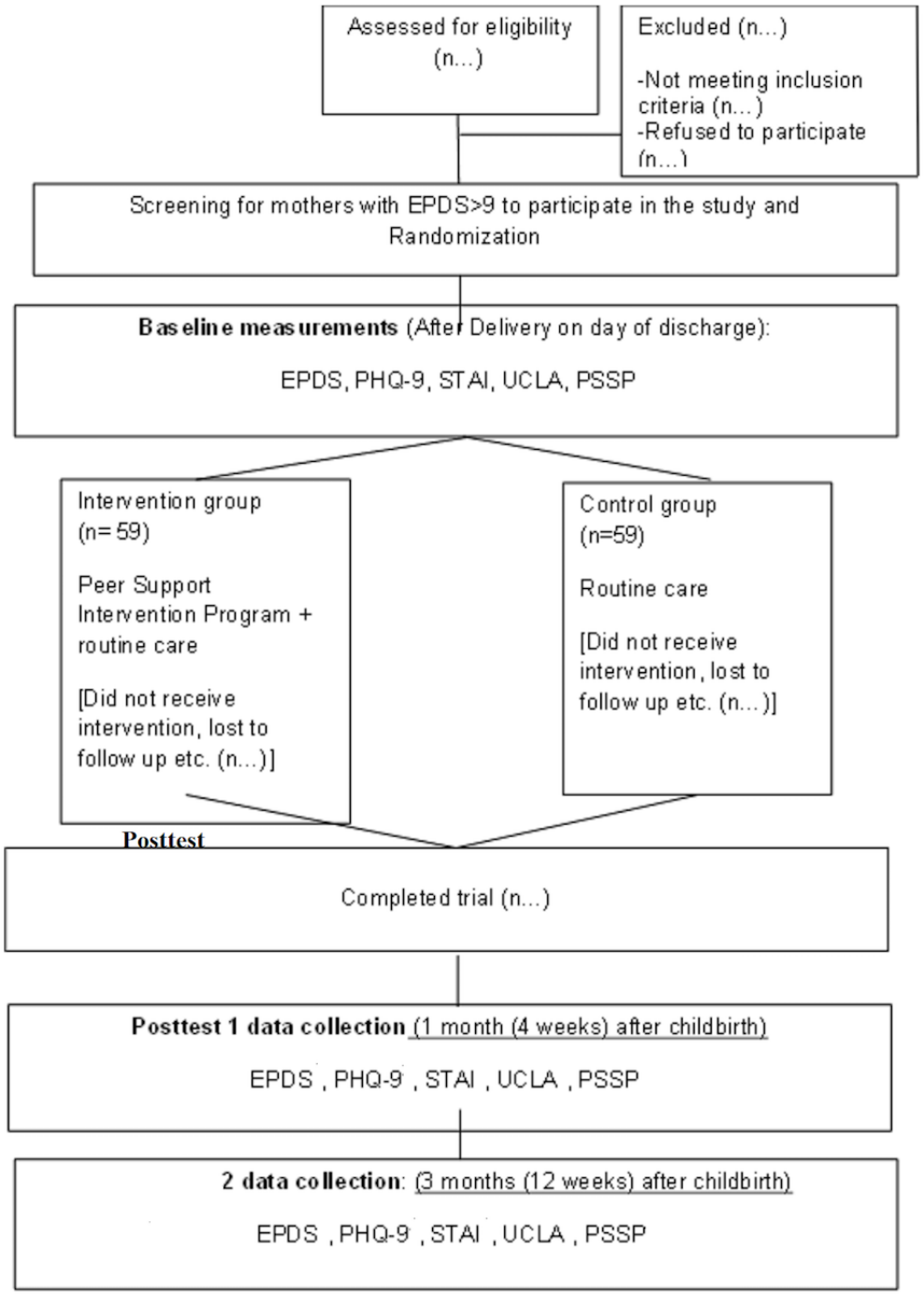
For phase 2, ethics approval has been granted (NHG DSRB: 2017/00815), and participant recruitment has commenced in the postnatal clinics at the study venue. RA1 has informed the nurse managers and clinicians of the respective postnatal wards of the study. The nurse in charge creates a short list of eligible participants based on the selection criteria and verifies the overall physical and psychological well-being of the women. RA1 then approaches those women who meet the inclusion criteria and explains the study purpose and details to them. Voluntary participation is emphasized. Those who are keen to participate are screened using EPDS. On the basis of previous studies [60,61], only mothers with an EPDS score of at least 9 are recruited. After RA1 obtains their written consent, the participants are randomized and grouped into the intervention or control groups accordingly. Participants are then asked to fill a baseline questionnaire, a demographics form, as well as to provide their name and contact information for future data collection and correspondence purposes.

Data Collection

A single-blinded technique is used. Research assistant two (RA2), who is not part of the randomization and is not involved

in the intervention, collects all data and will conduct the process evaluation interviews to avoid bias. Outcome measures of depression, anxiety, loneliness, and perceived social support are collected by RA2 primarily through a Web-based questionnaire, unless the mothers request for an alternative mode, such as through phone call, face-to-face, or via mail. Follow-up time points for all mothers are as follows: (1) immediately after the post birth when discharged from the hospital (baseline), (2) 4 weeks postpartum, and (3) 12 weeks postpartum. Between week 4 and week 12 postpartum, RA2 will invite mothers each from the intervention and control groups to participate in a semistructured process evaluation interview either face-to-face or by telephone. Participation is strictly voluntary. RA2 will also conduct process evaluation interviews with peer volunteers once they are done administering technology-based support to the assigned mothers. The activity logs will also be collected by RA2 for further evaluation. The PND at 12 weeks is chosen as the primary outcome because the results suggest that most PND develop within this time period [19], and we hope to give value to other PND prevention trials [48,49,81-83] by providing comparable results. The 4-week period is chosen for data collection because most of the mothers will be ending their confinement practices, which may alter their support needs [58]. The consolidated standards of the reporting trial flowchart are presented in Figure 2.

Figure 2. Consolidated Standards of Reporting Trial Flowchart. EPDS: Edinburg Postnatal Depression Scale; PHQ-9: Patient Health Questionnaire 9; STAI: State Trait Anxiety Inventory; UCLA: UCLA Loneliness Scale; PSSP: Perceived Social Support for Parenting.



Data Analysis

All quantitative data will be analyzed using the latest version of IBM SPSS. Missing data will be replaced for intention-to-treat analysis. Both intention-to-treat and per-protocol analyses will be conducted to compare the differences between groups. Descriptive statistics, such as mean, standard deviation, and range for continuous data and frequency as well as percentages, will be used for the nominal and ordinal data. Cronbach alpha value will be used to examine the internal consistency of the questionnaires. Inferential statistics, such as independent sample *t* test or analysis of variance (ANOVA), will be used to compare outcome differences among or between the demographic subgroups. Presuming that the outcomes are normally distributed, parametric tests will be used. Repeated measures analysis of covariance (ANCOVA) adjusted for confounding variables (eg, age, education level) will be used to test the effect of intervention on outcomes, including postnatal depression, anxiety, loneliness, and social support across 3 time points in the data collection. The percentage changes in the postnatal depression, anxiety, loneliness, and social support scores from baseline will be calculated for repeated measures ANCOVA. The ANCOVA will be used to test the differences in each outcome among 2 groups at 2 posttests separately.

Qualitative data from the interviews will be analyzed using the thematic analysis [84,85]. The audio interview data will be transcribed verbatim by RA2 concurrently with data collection to capture nonverbal information. Transcribed data will then be sorted into different categories, with similar ideas in a category highlighted in the same color. Related codes or categories will be collated to form subthemes, which will be reviewed and combined to form overarching themes [84] that will describe the opinions of mothers on strengths and weaknesses of the intervention and ways to improve the intervention or on the routine postnatal care. A total of 2 investigators will be involved in the analysis process and will compare and discuss the categories, subthemes, and themes generated and achieved in the consensus. Rigor or trustworthiness, including credibility, transferability, dependability, and conformability, will be considered in the study process [85].

Ethical Considerations

Ethics approval has been obtained from the National Health Group Domain Specific Review Board before the commencement of the study (Ref number: NHG DSRB: 2017/00185) in April 2017. All mothers who meet the inclusion criteria (EPDS≥9) will be given a set of participant information sheet consisting of a brief introduction, purpose, as well as the advantages and disadvantages of the study conveyed clearly. A written informed consent will be obtained from mothers who agree to participate. The participants are guaranteed anonymity and are informed of their right to withdraw at any point without affecting the subsequent care received. A token of appreciation will be given to all participants.

Results

Phase 1 of the study has been completed. The peer volunteer manual has been developed, and peer volunteers have been trained. For phase 2, the recruitment of study participants was commenced in July 2017 and is still ongoing. The targeted aim of recruiting 118 mothers will continue for a year. Thus far, a total of 909 participants have been approached and 542 were screened (including those not interested and EPDS score of less than 9). The current sample size to date is 73 mothers (for both the intervention [n=37] and control [n=36] groups). The projected timeline for the completion of data entry and analysis for investigating the effectiveness of the technology-based peer support intervention program to prevent postnatal depression is around May 2019.

Discussion

Previous local [24,59,86] and international studies [7,10,33,61,87] have shown that mothers have unmet needs during the early postchildbirth period. Given the insufficient support received, many of these mothers are potentially at risk of developing postnatal depression [7,14,24,34]. Results from a systematic review by Dennis [36] on psychosocial intervention methods for postpartum depression have shown that social support is one of the most preferred and effective intervention method to reduce the risk of PND. Previous studies [6,10,36,41] have also shown that additional support from similar other peer volunteers who have also suffered similar symptoms of depression has been proved beneficial for these at-risk, needy mothers. Hence, this study aims to provide technology-based peer support from mothers (peer volunteers) who have suffered and recovered from postnatal depression for mothers at risk of depression with EPDS score more than or equal to 9.

We hope to assess the effectiveness of this peer support intervention program. Optimistically, if the program is effective, it can then be implemented by health care professionals to aid at-risk mothers and reduce the prevalence of postnatal depression. This intervention program may not only be able to introduce a positive parenting experience to new mothers but may also mitigate the adverse psychosocial effects that PND has on the individual, the family, and society in general.

To ensure treatment fidelity, peer volunteers have undergone training to build rapport with their paired mothers, such as through daily text greetings and regular contact through mobile phone or email. Peer volunteers are also trained to contact and reply to the mothers quickly. On the other hand, constant messages and reminders are being sent to the peer volunteers by the research assistant to establish better rapport with them as well.

This study only recruits English-speaking Singaporean mothers, thus limiting its transferability to international settings. However, being set in a multiracial environment can increase international relevance. Additionally, due to practical reasons, the data collection is based on a self-report questionnaire, which is subject to response bias. Recruitment of peer mothers with prior history of postpartum depression also posed as a challenge due to the stigmatization of such mental illnesses in a conservative Asian society. Initial recruitment using posters was ineffective; therefore, recruitment of peer volunteers was mainly done through word of mouth. Despite these challenges and limitations, similar intervention methods in other studies have been shown to be effective.

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Conflicts of Interest

None declared.

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Abbreviations

ANCOVA: analysis of covariance
ANOVA: analysis of variance
EPDS: Edinburg Postnatal Depression Scale
GUSTO: Growing Up in Singapore towards Health Outcomes
IBM SPSS: International Business Machines Statistical Package for the Social Sciences
IMF: International Monetary Fund
NHG DSRB: National Health Group Domain Specific Review Board
PHQ-9: Patient Health Questionnaire
PND: postnatal depression
PSSP: perceived social support for parenting
STAI: State Trait Anxiety Inventory
UCLA: University of California, Los Angeles
WHO: World Health Organization

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Protocol

Uterine Artery Embolization Versus Hysterectomy in the Treatment of Symptomatic Adenomyosis: Protocol for the Randomized QUESTA Trial

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Abstract

Background: Adenomyosis is a benign uterine disease characterized by invasion of endometrium into the myometrium resulting in heavy menstrual bleeding and pain (dysmenorrhea). Hysterectomy is established as the final treatment option when conservative treatment fails. Uterine artery embolization (UAE) in patients with symptomatic adenomyosis has demonstrated to reduce symptoms and improve quality of life. However, randomized controlled trials are lacking.

Objective: With this study, we aim to evaluate the impact of UAE on Health-Related Quality of Life (HRQOL) in a randomized comparison to hysterectomy in patients with symptomatic adenomyosis.

Methods: This is a multicenter non-blinded randomized controlled trial comparing UAE and hysterectomy. Eligible patients are symptomatic premenopausal women without the desire to conceive and who have symptomatic magnetic resonance imaging (MRI)–confirmed pure adenomyosis or dominant adenomyosis accompanied by fibroids. After obtaining informed consent, patients will be randomly allocated to treatment in a 2:1 UAE versus hysterectomy ratio. The primary objective is HRQOL at 6 months following the assigned intervention. Secondary outcomes are technical results, pain management, clinical outcomes, HRQOL, and cost effectiveness during 2 years of follow-up. In addition, transvaginal ultrasound (TVUS) and MRI will be performed at regular intervals after UAE.

Results: Patient enrollment started November 2015. The follow-up period will be completed two years after inclusion of the last patient. At the time of submission of this article, data cleaning and analyses have not yet started.

Conclusions: This trial will provide insight for caretakers and future patients about the effect of UAE compared to the gold standard hysterectomy in the treatment of symptomatic adenomyosis and is therefore expected to improve patients' wellbeing and quality of life.

Trial Registration: Netherlands Trial Register NTR5615; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5615 (Archived by WebCite at http://www.webcitation.org/6xZRyXeIF)

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KEYWORDS

adenomyosis; uterine artery embolization; hysterectomy; randomized trial; quality of life

Introduction

Adenomyosis is described as the benign presence of ectopic endometrial glands and stroma causing reactive hypertrophy of the smooth muscle fibers of the myometrium [1,2]. The prevalence of adenomyosis is estimated to be 5%-8% in some studies, whereas others find even 40%-70% [3-5]. Approximately one-third of women with adenomyosis are symptomatic [2]. Symptoms associated with the presence of adenomyosis are abnormal menstrual bleeding, pain (dysmenorrhea) and an enlarged uterus. About 40%-50% and 15%-30% of patients will suffer from heavy menstrual bleeding and/or dysmenorrhea, respectively [3]. Fibroids are present in up to 55% of the patients diagnosed with adenomyosis [6]. Therefore, it can be difficult attributing symptoms to one or the other [7,8]. Adenomyosis can be diagnosed with transvaginal ultrasonography (TVUS) or magnetic resonance imaging (MRI) [9,10]. Adenomyosis can be treated conservatively (hormonal/non-hormonal). When conservative management fails, a hysterectomy is the most common surgical solution, since surgical removal of adenomyosis is difficult given its diffuse aspect.

Uterine artery embolization (UAE) has been a minimally invasive treatment for symptomatic uterine fibroids since 1995 [11]. Since then, much research has been conducted including several randomized controlled trials establishing UAE as a valuable treatment option for women with symptomatic fibroids [12-14].

During the last fifteen years, several case series and cohorts evaluated UAE as a treatment for patients suffering from symptomatic adenomyosis. These cohorts show promising results [15-26]. Randomized data, comparing this new treatment modality with the gold standard (ie, hysterectomy) are lacking though. The "Quality of Life after Embolization vs Hysterectomy in Adenomyosis" (QUESTA) trial was set up to fill this knowledge gap comparing UAE with hysterectomy in patients with symptomatic adenomyosis. In this paper, we present the design of the trial.

Methods

Design

The QUESTA trial is a multicenter nonblinded randomized controlled trial, performed within selected hospitals in the Netherlands containing experienced interventional radiologists qualified to perform UAE. The study is performed in a network infrastructure in which radiologists and gynecologists collaborate. This trial will be conducted in accordance with the Consolidated Standard of Reporting Trials [27-29], the principles of the Declaration of Helsinki, and the Medical Research Involving Human Subject Act.

This study is approved by the ethics committee of the VU Medical Centre Amsterdam (Reference Number 2015/211) and by the boards of all participating hospitals. The trial is registered at the Netherlands Trial Registry (Netherlands Trial Register NTR5615).

Participants and eligibility criteria

Eligible adult women are asked to participate when they meet the following inclusion criteria:

1. Premenopausal women with symptomatic pure adenomyosis or dominant adenomyosis (with concurrent uterine fibroids). Symptoms are defined as heavy menstrual bleeding, dysmenorrhea, and/or cycle independent pain and bulk-related symptoms.
2. Women with an indication for hysterectomy. These women had or have unsuccessful medicinal treatment or decided that such treatment is no option.

The exclusion criteria are:

1. Patients younger than 18 years of age
2. Patients with a pelvic infection
3. Suspicion or presence of a malignancy
4. Current pregnancy or desire to conceive in the future
5. Absolute contraindication for angiography
6. Deep infiltrating endometriosis requiring surgery or risks on intestinal stenosis
7. Concurrent hysteroscopic removable submucous fibroids

Procedures, recruitment, and randomization

When adenomyosis is suspected on TVUS (see criteria in Table 1) and MRI is performed to confirm adenomyosis (see criteria in Table 2), eligible patients will be informed about the study by the gynecologist, resident, research nurse or study coordinator and will be informed about the website for additional information and an introduction video (Multimedia Appendix 1). If the patient declines randomization, she will be asked to participate in the cohort group. The patients in the cohort study group will be offered standard care (ie, hysterectomy, since embolization is not available outside the trial). Afterwards, participants with written informed consent are randomly allocated (2:1) to the experimental intervention (UAE) or the standard care control group (hysterectomy). Randomization is computer-based and stratified for the participating hospitals. The study is not blinded since uterine artery embolization is performed either under conscious sedation or epidural anesthesia in contrast to a hysterectomy which is performed in the operating room under full narcosis. Therefore, it is not possible to blind the patients or the physicians.

Intervention group

A specific UAE particle protocol for adenomyosis will be delivered to the interventional radiologist of each center and, if needed, our experienced interventional radiologist will be present during the first UAE procedure (PNM Lohle).

Table 1. Criteria for diagnosing adenomyosis on transvaginal ultrasonography (TVUS).

Criteria	eCRF[a] answers
Uterus (cm)	Height*length*width
Asymmetrical thickening[b]	Yes/no/I don't know; Measurements uterine walls
Cysts[b]	Yes/no/I don't know
Fan-shaped shadowing[b]	Yes/no/I don't know
Myometrial aspect[b]	Homogenous/inhomogeneous/I don't know
Inhomogeneous endometrial-myometrial zone (endometrial lines/buds)[b]	Yes/no/I don't know
Diffuse flow[b]	Yes/no/I don't know
Adenomyosis type	Diffuse/Focal/Combined diffuse>focal/Combined focal>diffuse
Fibroids	Yes/no/I don't know
Fibroid count	Number
Size biggest fibroids (cm)	Height*length*width
Occurrence of pedunculated fibroid	Yes/no
Pedunculated fibroid count	Number

[a]eCRF:electronic clinical report forms.

[a]Adenomyosis criteria. If 3/6 are recognized, adenomyosis is suspected.

Table 2. Criteria for diagnosing adenomyosis on magnetic resonance imaging (MRI).

Criteria and types	Definition
Adenomyosis	Junctional zone[a]>12mm diameter
Cysts (hyper intense foci T2)	Yes/no
Asymmetric myometria	Yes/no
Adenomyosis category 1	Focal: 25% or less of endometrial interface
Adenomyosis category 2	Regional: Entire endometrial surface of the anterior wall, posterior wall or fundus
Adenomyosis category 3	Diffuse: Entire or most of the endometrial surface • Moderate: 20-29mm • Severe: ≥30mm
Dominant adenomyosis in combination with fibroid	Volume domination: Adenomyosis>fibroids

[a]Adenomyosis is confirmed.

UAE is carried out under epidural anesthesia or patient controlled analgesia (PCA). A catheter is introduced in the femoral artery and positioned selectively into the uterine arteries under fluoroscopic guidance. Microspheres are then injected through the catheter into the uterine artery. The bloodstream will move the microspheres towards the small uterine artery branches in the area of adenomyosis (and fibroids if present). Microspheres consist of a hydrogel core with polymethylmethacrylate (PMMA) and a flexible shell of polyphosphazene (Polyzene-F), which is a synthesized inorganic biostable and biocompatible polymer (Embozene microsphere). This embolic agent establishes reduction and cessation of blood flow to the area of adenomyosis resulting in ischemia and infarction. The embolization protocol sets out the provisions regarding the microsphere size (Embozene 500 μm) for use and the angiographic embolization end-point until full stasis at the distal end of the uterine artery.

A second protocol will include: administration of antibiotics, drip infusions, Foley bladder catheters, PCA pump usage with strict protocols for pain management, and a nursing protocol for the ward.

Control group

Hysterectomy is preferably performed by vaginal hysterectomy (VH) or total laparoscopic hysterectomy (TLH). A TLH or abdominal hysterectomy is always performed under general anesthesia. No protocol will be provided for surgical standardization. Adhesiolysis will be performed when necessary. Planned concomitant endometriosis surgery serves as an exclusion criterion. However, during surgery, coagulation of mild endometriosis is allowed. In case of laparoscopic or vaginal hysterectomy, the uterus will be removed vaginally or by the use of (in bag) morcellation. Supra cervical hysterectomy is allowed.

Data collection

All electronic clinical report forms (eCRF) and patient questionnaires are digitally online secured and filled out in the study website with the use of a patient-specific study number [30]. The patient and physician receive this study number at time of informed consent. Figure 1 shows the study flowchart.

Baseline

At time of inclusion and randomization, baseline medical history, obstetric history, and laboratory work up (hemoglobin, renal function (eGFR), CA-125, Anti-Mullerian hormone (AMH) in a subset of centers) are reported in the eCRF. The imaging characteristic displayed in Table 1 will all be registered.

Patients will fill out validated Health-Related Quality of Life (HRQOL) and symptom questionnaires (see "outcome measures")

Procedure

At procedure, data about the course of the intervention (UAE or operation), any particularities or complications are reported in the eCRF. At discharge from the hospital the eCRF will report the total of admitted days and complications during hospital stay.

Follow-up

The research investigator will send invitations for the digital online secured patient questionnaires by email at baseline, 6 weeks, 3 months, 6 months, 12 months and 24 months of follow-up. All patients will also specifically be asked at baseline to give their consent to be approached for long-term follow up. Validated questionnaires will be filled out to report on HRQOL, symptoms, clinical outcomes, return to normal activities, absence of work, medication use, costs, medical consultation/consumption, and additional received therapy (see “outcome measures”). The patients who underwent UAE will receive a TVUS at 6 weeks and 6 months with an MRI at 6 months to compare the adenomyosis features with baseline results. In the hysterectomy group, pathology outcomes are also registered. All the eCRFs will report complications.

Outcomes measures

The primary outcome is quality of life at 6, 12 and 24 months after index procedure as measured by a combination of the World Health Organization Quality of Life Scale (whoqol-Bref) and Short Form-12 (SF-12) Questionnaire.

Secondary outcomes at 6 weeks and 3, 6, 12, 24 months after treatment consists of:

1. Clinical outcomes: technical failure rate, clinical failure arte as defined by secondary hysterectomy, additional therapy or reinterventions, complications.
2. Recovery related outcomes (6 weeks, 3 and 6 months): hospital stay, return to normal activities (Recovery Index-10).
3. Symptom and quality of life outcomes: menstrual characteristics (pictorial blood assessment chart), validated pain-questionnaire (Numeric Pain Rating Scale 0-100 scale, Facet 1: Pain and discomfort WHOQOL-100), sexual functioning (WHOQOL-100, sexual activity domain), satisfaction (Likert-scale, vignettes preference), quality of life (WHOQOL-Bref, SF-12).
4. Cost utility analysis (European Quality of Life 5 Dimensions) after 12 months.
5. Laboratory outcomes (baseline, 6 weeks and 6 months): hemoglobin, CA-125 and AMH in specific predefined centers.
6. Pathology outcomes (6 weeks): pathological finding of uterus in hysterectomy group.

Also, imaging outcomes will be investigated in order to identify potential predictive parameters for therapy effect.

1. TVUS (baseline, 6 weeks and 6 months): imaging parameters described in Table 1, uterine size reduction and reduction of fibroid volume in case of concomitant fibroids. In specific predefined centers, we will measure vascular index (3D power Doppler).
2. MRI (baseline and 6 months): imaging parameters described in Table 1, uterine size reduction, junctional zone reduction, infarction rate, reduction of fibroid volume in case of concomitant fibroids, presence of endometriosis.

Sample size

This study has a noninferiority design, where UAE is considered noninferior to hysterectomy when HRQOL at 6 months does not differ (delta) more than 5 points (scale 0-100). When the following assumptions are used: SD of 9 points (scale 0-100), alpha 0.10, power 0.80, using a one-sided two-sample equal-variance *t* test, a sample size of 1 x 52 patients (embolization) and 1 x 34 patients (hysterectomy) is needed. Excluding 10% dropout, in total 96 patients are needed for the primary outcome. Assumptions are based on the Embolization versus Hysterectomy (EMMY) trial outcomes [13].

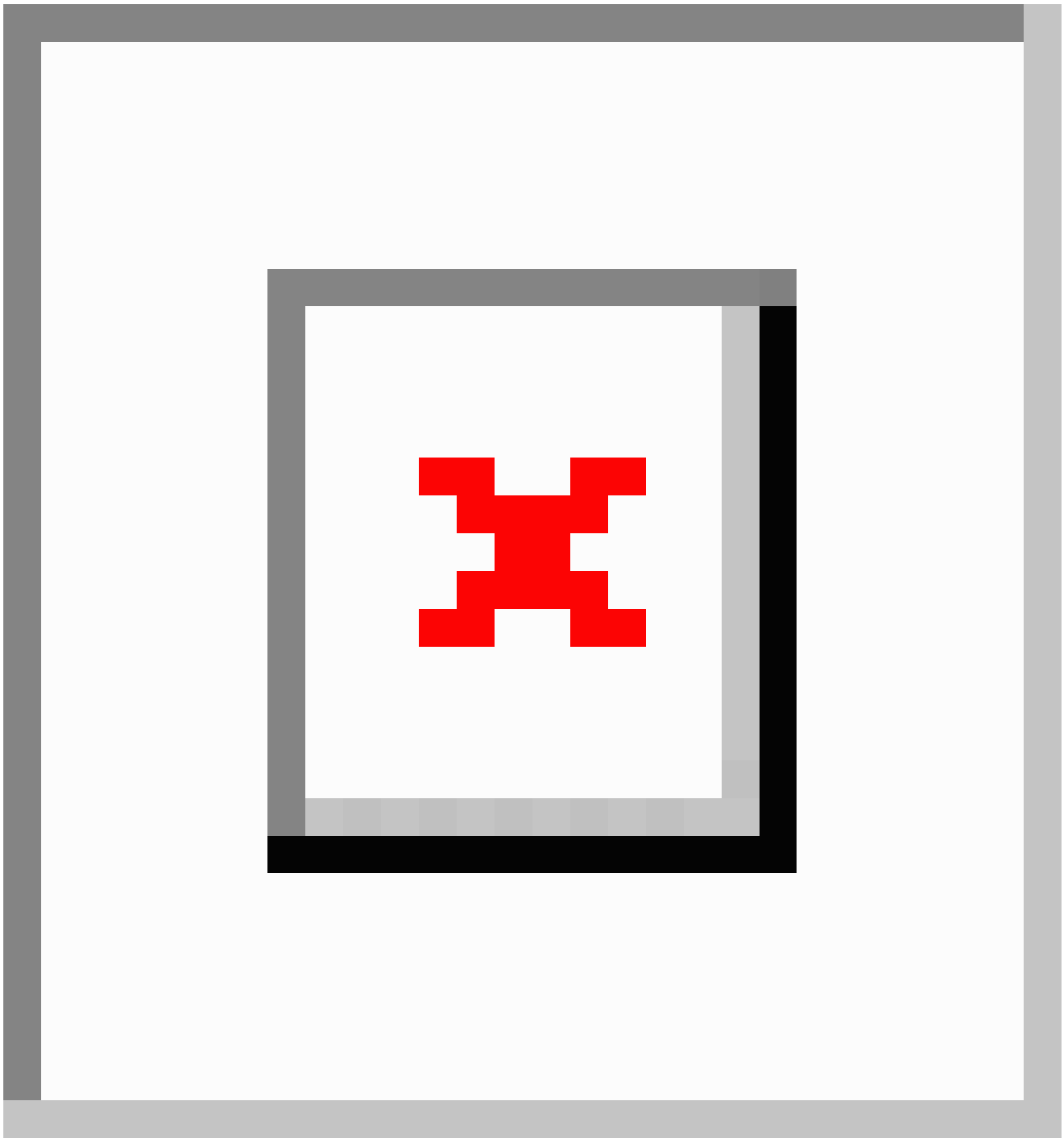
Statistical analysis

Analysis of the study will be based on the intention-to-treat and per protocol analysis. With regard to the primary outcome variable (WHOQOL-Bref, SF-12), non-inferiority is established between UAE and hysterectomy when the mean difference does not exceed 5 points (with a SD of 9 points).

The primary outcome will be analyzed using linear mixed modeling, applying transformation if necessary, adjusting for, if necessary, clinically relevant baseline imbalances. With regard to the secondary outcomes, we will use the appropriate nonparametric and parametric statistics to evaluate statistically significant differences between the two treatments. A *P* value <.05 will be considered as statistically significant. In all analyses, statistical uncertainties will be expressed in 90%CI.

The database will be locked 6 months after the last surgical procedure in order to obtain the short-term outcomes. These data will be analyzed and published in a “short term results” manuscript. The long-term results (HRQOL and costs) will be analyzed 12 months after the last procedure, when the last patient returned her last questionnaire.

Figure 1. Study flowchart. Patient data includes the following questionnaires: Pictorial Blood Assessment Chart (PBAC), Numeric Pain Rating Scale (NRS), Facet 1:Pain and discomfort WHOQOL-100, World Health Organization Quality Of Life-Bref (WHOQOL-Bref), Short Form-12 (SF-12), Facet 15: sexual activity domain WHOQOL-100, recovery (RI-10), Euro-QOL 5D (EQ-5D), patient preference (vignette), and patient satisfaction (Likert-scale).



Safety Monitoring and Interim Analysis

Since both treatment options have proven their safety, no specific risks apply. This study is conducted to determine the efficacy of the treatment. However, safety monitoring without direct involvement in the trial (clinical research bureau, VUMC) will be installed to monitor the setup and conduct of the trial. No interim analysis is planned because of the relatively small sample size.

All serious adverse events (SAEs) will be reported to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events. SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur no later than 48 days after the responsible investigator has first knowledge of the adverse event. In case of more than one SAE, the METC will be notified. This committee can advise to terminate the trial due to safety reasons.

Results

Inclusion of patients started in November 2015. The expected end date is November 2019. Data collection for the primary outcome will be expected to last until May 2020. Data collection concerning the secondary outcomes are expected two years

following the last included patient. Analysis has not yet started as of this article's submission.

Discussion

Summary

With this randomized controlled trial, we aim to evaluate the impact of UAE on HRQOL in a randomized comparison to hysterectomy in patients with symptomatic adenomyosis.

Strengths and Limitations

This is the first randomized controlled trial evaluating effectiveness of UAE versus hysterectomy in patients with symptomatic adenomyosis. The QUESTA trial uses a web-based randomization program with the use of allocation concealment which reduces the chance of selection bias. The study is not blinded for the patient or health care worker which could possibly influence the outcomes. Blinding is impossible considering the nature of the treatments. Earlier studies reported on UAE being more cost-effective compared to hysterectomy, however these studies were conducted in patients with fibroids and mostly carried out through abdominal hysterectomies [31]. Over the years hysterectomy techniques have changed and the more cost-effective laparoscopy has become available. No studies have yet reported on cost effectiveness of UAE versus laparoscopic hysterectomy. We expect UAE to be more cost effective since the procedure itself is less expensive and recovery time is shorter [32], however we do expect consultation to be more frequent in the UAE group. We note that we allow all hysterectomy techniques in this study due to the intention to treat analysis. It will be registered and corrected for in analysis.

Disease specific questionnaires for adenomyosis have not yet been developed. Used questionnaires are validated in terms of quality of life, pain, heavy menstrual bleeding, sexual functioning, recovery, and allocation satisfaction and proved to be disease specific in the EMMY trial [13].

The follow-up in this trial is set at 24 months. This could be a limitation since 5- and 10-year follow-up of the EMMY trial showed additional hysterectomies in the UAE group [33,34]. Depending on the result of this trial a possibility to extend follow-up was included in the informed consent.

In the last 15 years, 30 cohorts and case series [15-26,35-52] described UAE in the treatment of symptomatic adenomyosis. The lack of level 1 evidence, heterogeneous particle use and UAE techniques make the development of a national guideline for standardized UAE in the treatment of adenomyosis challenging. We provide a mini-protocol on the usage of the standardized microspheres, however we do not provide a specific UAE technique protocol because we assume general UAE techniques will be followed [28]. In addition, we wish to maintain the intention to treat analysis of the Dutch population treated in the UAE centers.

Potential Impact and Implications

Results of the QUESTA trial will provide knowledge for the most optimal treatment regimen in terms of HRQOL, side-effects, complications and satisfaction with allocated treatment. Hysterectomy requires hospitalization of 2 to 4 days, depending on the approach [31]. On the other hand, the source of adenomyosis is removed and might provide a more definite solution. An embolization is less invasive and in general, requires hospitalization of only 1 night [31]. Meanwhile, the uterus is preserved and complaints may continue (possibly to a lesser extent). How these pros and cons relate between the two strategies is unknown. If embolization proves to be comparable in terms of HRQOL, this can be offered to patients as a less invasive alternative, in particular in women that would like to preserve the uterus. These study outcomes could inform future patients about the expected effect of UAE and hysterectomy in the treatment of symptomatic adenomyosis and could therefore support shared decision making. These results are expected to improve patients' wellbeing and quality of life.

Acknowledgments

The members of the QUESTA Trial Group are as follows: Initiators: PNML and WJKH; Steering committee: WJKH, JAFH, PNML, JdV; Monitoring Committee: Clinical Research Bureau, VU Medical Centre; Data management and analysis: AMdB, WJKH; Executive and Writing Committee: AMdB, WJKH, PNML and JAFH. Clinical Centers (13) who contribute to the QUESTA trial and QUESTA-trial group members are as follows: Academic Medical Center: Amsterdam —W Ankum, M de Lange, A, Timmermans, A, Thurkow; Albert Schweitzer Hospital, Dordrecht: G van Hoecke, O Elgersma; Albert Schweitzer Hospital, Dordrecht: G van Hoecke, O Elgersma; Amphia Hospital, Breda: J van Bavel; Catharina Hospital, Eindhoven: H van Vliet, L Yo; Leids Univestity Medical Center, Leiden: D Twijnstra, F Jansen, A van Erkel, C van Rijswijk; Leids Univestity Medical Center, Leiden: D Twijnstra, F Jansen, A van Erkel, C van Rijswijk; Maxima Medical Center, Veldhoven: J Maas, H Kruimer; University Medical Center Nijmegen (Radboud), Nijmegen: S Coppus; M Arntz; OLVG-oost, Amsterdam: P van Kesteren, E Bakkum, J Blomjous; OLVG-west, Amsterdam: J Kwee, C Radder, A Wust; Tweesteden Hospital location Elisabeth, Tilburg: M Smink, PF Janssen, PNML; Tweesteden Hospital location Tweesteden, Tilburg: I van Rooij; VU Medical Center, Amsterdam: WJKH, JAFH, R Lely; Ziekenhuisgroep Twente, Almelo, Hengelo: L van Boven, H van de Hout.

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Conflicts of Interest

PNML has a consultancy agreement with Boston Scientific. AMdB, PNML, JAFH and WJKH received a grant from Boston Scientific.

Multimedia Appendix 1

Text and animations on the website.

[JPG File, 1MB - resprot_v7i3e47_app1.jpg]

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Abbreviations

AMH: Anti-Mullerian hormone
eCRF: electronic clinical report forms
EMMY: Embolization versus Hysterectomy
HRQOL: Health-Related Quality of Life
MRI: magnetic resonsnce imaging
PMMA: polymethylmethacrylate
QUESTA: Quality of Life after Embolization vs Hysterectomy in Adenomyosis
SF-12: Short Form-12
TLH: total laparoscopic hysterectomy
TVUS: transvaginal ultrasound
UAE: uterine artery embolization
VH: vaginal hysterectomy
WHOQOL-bref: World Health Organization Quality Of Life-Bref

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Protocol

Treatment with Creatine Monohydrate in Spinal and Bulbar Muscular Atrophy: Protocol for a Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Although spinal and bulbar muscular atrophy (SBMA) has been classified as a motor neuron disease, several reports have indicated the primary involvement of skeletal muscle in the pathogenesis of this devastating disease. Recent studies reported decreased intramuscular creatine levels in skeletal muscles in both patients with SBMA and transgenic mouse models of SBMA, which appears to contribute to muscle weakness.

Objective: The present study aimed to examine the efficacy and safety of oral creatine supplementation to improve motor function in patients with SBMA.

Methods: A randomized, double-blind, placebo-controlled, three-armed clinical trial was conducted to assess the safety and efficacy of creatine therapy in patients with SBMA. Patients with SBMA eligible for this study were assigned randomly in a 1:1:1 ratio to each group of placebo, 10 g, or 15 g daily dose of creatine monohydrate in a double-blind fashion. Participants took creatine or placebo orally 3 times a day for 8 weeks. Outcome measurements were results of neurological assessments, examinations, and questionnaires collected at baseline and at weeks 4, 8, and 16 after a washout period. The primary endpoint was the change in handgrip strength values from baseline to week 8. The secondary endpoints included the following: results of maximum voluntary isometric contraction tests of extremities; tongue pressure; results of the 15-foot timed walk test and the rise from bed test; modified quantitative myasthenia gravis score; respiratory function test results; activities of daily living assessed with the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale and the Spinal and Bulbar Muscular Atrophy Functional Rating Scale; skeletal muscle mass measured with dual-energy X-ray absorptiometry; urinary 8-hydroxydeoxyguanosine levels; and questionnaires examining the quality of life, swallowing function, and fatigue.

Results: Participant enrollment in the trial started from June 2014 and follow-up was completed in July 2015. The study is currently being analyzed.

Conclusions: This is the first clinical trial evaluating creatine therapy in SBMA. Given that creatine serves as an energy source in skeletal muscles, recovery of intramuscular creatine concentration is expected to improve muscle strength.

Trial Registration: University Hospital Medical Information Network Clinical Trials Registry UMIN000012503; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000014611 (Archived by WebCite at http://www.webcitation.org/6xOlbPkg3).

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KEYWORDS

spinal and bulbar muscular atrophy; creatine; randomized controlled trials

Introduction

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is an adult-onset, X-linked neuromuscular disease characterized by limb, trunk, and facial weakness [1-3]. Most of the patients with SBMA experience finger tremor or muscle cramp before the onset of muscular weakness. In general, the progression of neurological dysfunction is slow, with the average interval between the onset of muscular weakness and death being approximately 20 years [4]. Patients at a terminal stage of SBMA are certainly bound to be in a wheelchair or bedridden state, and some of these patients develop recurrent aspiration pneumonia due to bulbar palsy [4]. SBMA is caused by the expansion of a CAG trinucleotide repeat, encoding a polyglutamine tract, within the first exon of the androgen receptor (AR) gene [5]. The ligand-dependent accumulation of the pathogenic AR proteins in the nucleus is fundamental to the molecular pathogenesis of this disease, providing a potential target for therapy development [6-8].

Although motor neurons are the primary target of polyglutamine-mediated toxicity, several studies have implied skeletal muscle involvement in SBMA pathogenesis. Serum levels of creatine kinase are higher in patients with SBMA than in those with amyotrophic lateral sclerosis (ALS) [4,9,10]. Patients with SBMA demonstrated both neurogenic and myopathic features in the muscle biopsy [11]. Moreover, it has been demonstrated that skeletal muscle pathology preceded neurodegeneration in knock-in and transgenic mouse models of SBMA [12-15]. In skeletal muscles, the polyglutamine-expanded AR induces transcriptional alterations of several genes that are implicated in muscle function [12,16]. Recent studies showed transcription alterations in skeletal muscle energy metabolism that are a consequence of mutant AR expression in SBMA muscle [17,18]. These findings imply a direct involvement of the skeletal muscle in SBMA pathogenesis [19].

We previously identified the serum creatinine level as a sensitive serological biomarker for motor dysfunction in patients with SBMA [20]. Serum creatinine is produced from creatine, which is mostly present in skeletal muscle tissues. Serum creatinine levels are, therefore, construed as an index of skeletal muscle mass. However, we recently reported that serum creatinine levels in patients with SBMA are markedly decreased due to the decreased muscular uptake of creatine resulting from the pathogenic AR-mediated downregulation of SLC6A8, a creatine transporter [21]. In addition, both animal and clinical studies indicated glycolytic-to-oxidative fiber type switch in the skeletal muscle of SBMA [17,18,22], which may also contribute to the decreased intramuscular creatine in SBMA, given that type 1 slow-twitch fibers have lower phosphocreatine contents compared with type 2 fast-twitch fibers [23].

Creatine is converted to creatine phosphate by creatine kinase and exists as a storage material of high energy phosphate in skeletal muscle [24]. It has been reported that orally ingested creatine increases the amount of creatine phosphate in the skeletal muscle [25]. Intramuscular creatine phosphate functions as an energy source when energy demand is increased by rapid movement. Creatine also regulates intramuscular calcium homeostasis and mitochondrial ADP-stimulated respiration in both slow- and fast-twitch fibers [26,27].

Based on these findings, we hypothesized that supplementation of creatine will attenuate muscle weakness in patients with SBMA. Hence, we designed the CREatine Complemental medication for Kennedy's disease in Eight weeks Trial (the CRECKET study), a randomized controlled trial (RCT) that examines the efficacy and safety of creatine therapy in patients with SBMA. Although the efficacy of creatine replacement therapy has been demonstrated in certain muscular diseases such as Duchenne muscular dystrophy [25,28,29], its effectiveness in SBMA has yet to be validated. This study is the first attempt to evaluate the efficacy and safety of creatine supplementation in patients with SBMA.

Methods

Ethical Approval and Trial Registration

This study was conducted in compliance with the Helsinki Declaration and approved by the Ethics Committee of Nagoya University Graduate School of Medicine. The study was registered with the University Hospital Medical Information Network clinical trials registry (UMIN000012503) before the start of the recruitment period.

Study Design

This study is a randomized, double-blind, placebo-controlled, three-armed, phase II trial to assess the safety and efficacy of creatine monohydrate in patients with SBMA in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guideline. After obtaining informed consent, a primary assessment (T^{-1}) of the potential participants was performed, whereby participants were screened for eligibility within 4 weeks prior to the start of the study medication by measuring their blood parameter values and serum testosterone levels. Patients with SBMA eligible for this study were allocated randomly in a 1:1:1 ratio to receive placebo, 10 g daily of creatine monohydrate (SAVAS; Meiji Co, Ltd, Tokyo, Japan), or 15 g daily of creatine in a double-blinded fashion. The duration of the intervention was 8 weeks. The study participants underwent four assessments (T^0, T^1, T^2, and T^3) composed of neurological assessments, examinations, and questionnaires (Figure 1 and Table 1). The study intervention was initiated after baseline assessment (T^0). For the purpose of safety assessment and compliance, participants were assessed again after 4±1 treatment weeks (T^1). Efficacy assessments were scheduled after 8±1 treatment weeks (T^2). Follow-up assessments were performed after the 8-week washout period (T^3). All assessments were performed at Nagoya University Hospital.

Intervention

Participants took creatine or placebo orally after every meal, 3 times a day, for 8 weeks. In the high-dose creatine group, participants took 5 g of creatine monohydrate powder daily after every meal (total 15 g). In the low-dose creatine group,

participants took powder medicine containing 3.33 g of creatine monohydrate powder and 1.67 g of lactose daily after every meal (total 10 g). In the placebo group, powder medicine containing 5 g of lactose was taken daily after each meal (total 15 g). Participants started the oral administration within 3 days after the baseline assessment (T^0). Participants were instructed to pay attention to the following points when taking the medicine: (i) To take powder medicine suspended in sufficient water or juice; (ii) take the powder medicine always after meals, and not before meals; (iii) avoid warm water to suspend powder medicine; and (iv) take all the medicine including the precipitated powder.

To avoid the influence of other treatments on the evaluation of the effectiveness of creatine, participants were prohibited to use the following medicines until the end of the evaluation period; luteinizing hormone-releasing hormone (LH-RH) agonists, LH-RH antagonists, testosterone drugs, 5-alpha-reductase inhibitors, anti-androgen drugs, protein anabolic hormone, progesterone drugs, estrogen drugs, unapproved drugs, and creatine supplements. Participants were also prohibited to start rehabilitation of extremities or undergo castration until the end of the evaluation.

Participants

Patients with SBMA were eligible for participating in the study. All participants were recruited from the Department of Neurology at Nagoya University according to the inclusion and exclusion criteria. The inclusion criteria were as follows: (1) Male patients who present one or more of the following motor symptoms: (i) muscle weakness of extremities, (ii) muscle atrophy of extremities, and (iii) bulbar palsy; (2) Patients whose genetic testing results showed that they bear at least 38 CAG repeats within the AR gene; (3) Patients who were twenty (≥ 20) to eighty (< 80) years of age at the time of informed consent; (4) Patients who can visit the hospital regularly as outpatients; (5) Patients whose renal function meets the following criteria: creatinine at < 1.5 × Upper Limit of Institutional Reference Value; (6) Patients who provided written informed consent by themselves.

Figure 1. Flow chart of design and enrollment procedures. SBMA: spinal and bulbar muscular atrophy.

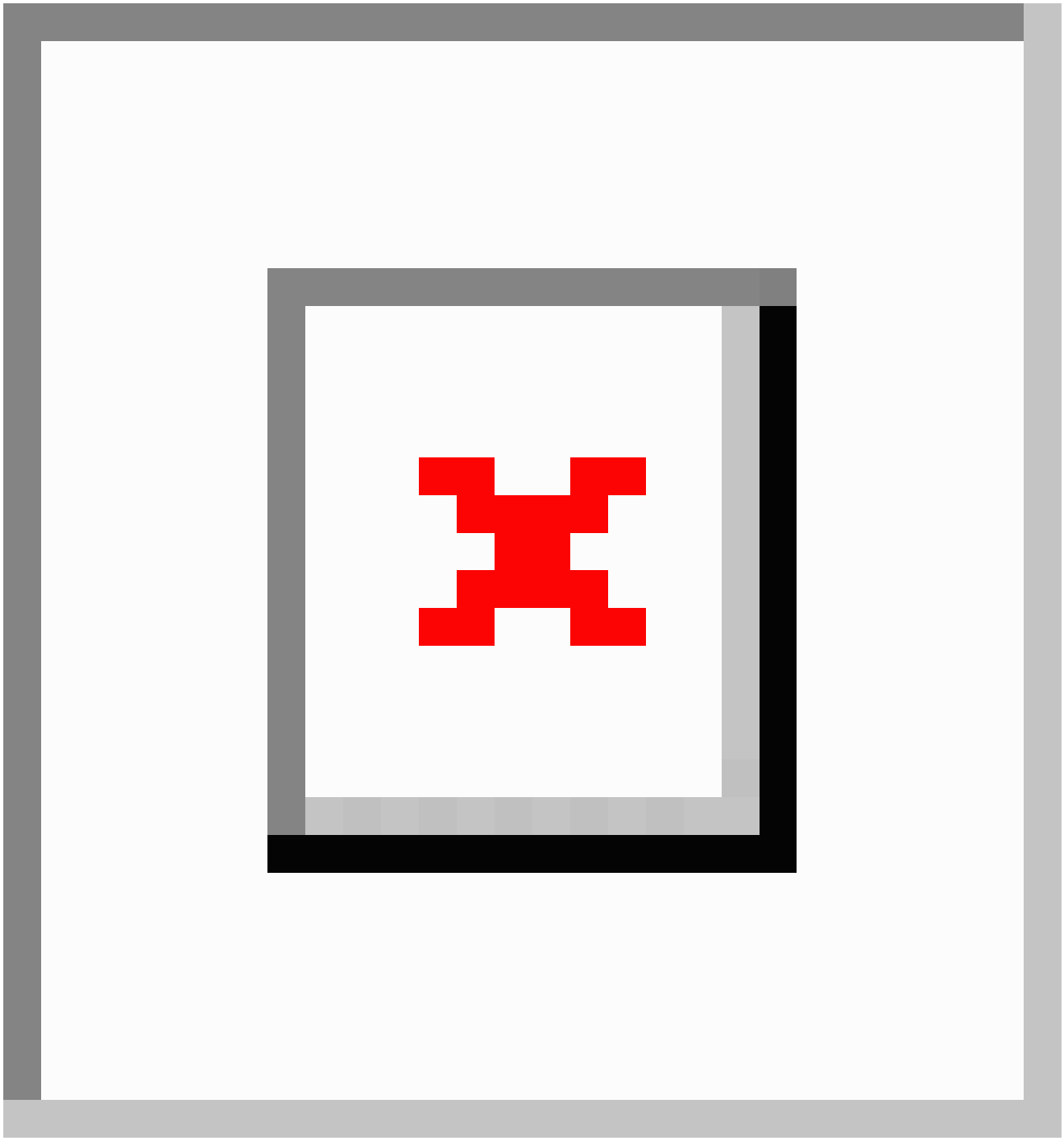

Table 1. Study schedule and assessments.

Item	Prestudy		Double-blind, placebo-controlled study			Washout	Early termination
	Screening (T^{-1})	Registration	T^0 (0 week)	T^1 (4 weeks)	T^2 (8 weeks)	T^3 (16 weeks)	
Enrollment							
Written consent	✓						
Patient characteristics	✓						
Screening tests	✓						
Registration		✓					
Assessment							
Handgrip strength			✓	✓	✓	✓	✓
Quantitative muscle test			✓	✓	✓	✓	✓
Timed walk test			✓	✓	✓	✓	✓
Rise from bed test			✓	✓	✓	✓	✓
Tongue pressure			✓	✓	✓	✓	✓
Modified QMG score[a]			✓	✓	✓	✓	✓
Dual-energy X-ray absorptiometry			✓		✓	✓	✓
Respiratory function test			✓		✓		✓
ALSFRS-R[b] (Japanese version)			✓		✓		✓
SBMAFRS[c]			✓		✓		✓
SDQ[d] (Japanese version)			✓		✓		✓
SWAL-QOL[e] (Japanese version)			✓		✓		✓
ALSAQ-5[f] (Japanese version)			✓		✓		✓
MFI-20[g] (Japanese version)			✓		✓		✓
Urinary 8-OHdG[h]			✓		✓	✓	✓
Serum creatine/creatinine			✓	✓	✓	✓	✓
Urinary creatine/creatinine			✓		✓		✓
Subjective/objective concomitant symptoms			✓	✓	✓	✓	✓
Laboratory test							
Blood test			✓	✓	✓	✓	✓
Biochemical test	✓		✓	✓	✓	✓	✓
Urine test			✓	✓	✓	✓	✓
Blood pressure, body weight			✓	✓	✓	✓	✓
Serum testosterone	✓						
Genetic test[i] (CAG repeat length)			✓				

[a]QMG score: Quantitative Myasthenia Gravis score

[b]ALSFRS-R: Revised Amyotrophic Lateral Sclerosis Functional Rating Scale

[c]SBMAFRS, Spinal and Bulbar Muscular Atrophy Functional Rating Scale

[d]SDQ: Swallowing Disturbance Questionnaire

[e]SWAL-QOL: Swallowing Quality of Life Questionnaire

[f]ALSAQ: Amyotrophic Lateral Sclerosis Assessment Questionnaire

[g]MFI: Multidimensional Fatigue Inventory

[h]8-OHdG: 8-hydroxydeoxyguanosine

[i]Re-examination under the same conditions.

Patients who met any of the following criteria were excluded from the study: (1) Patients who have taken LH-RH agonists, LH-RH antagonists, testosterone drugs, anti-androgen drugs, estrogen drugs, or unapproved drugs within 48 weeks and 5-alpha-reductase inhibitors within 24 weeks before agreement acquisition; (2) Patients whose serum testosterone level is below the lower limit of normal; (3) Patients who have taken creatine supplementation within 8 weeks before agreement acquisition; (4) Patients who have severe complications, such as malignancy, heart failure, and renal failure; (5) Patients who were determined ineligible for this study by the investigator or coinvestigators.

Recruitment and Settings

Neurologists, ie, investigator or coinvestigators, identified patients with SBMA and provided them with sufficient information about the explanatory statement and the informed consent form before their participation. All participants gave their written informed consent for trial participation prior to the screening. After the screening assessment for eligibility, neurologists evaluated the eligibility of the patients using a checklist and register patients for this trial.

Randomization and Blinding

Randomization was performed centrally with the use of an online system (Waritsuke-kun; Mebix, Inc, Tokyo, Japan). Dynamic random allocation was done with minimization on the basis of the patients' disease duration (0–9 or ≥ 10 years from onset) and past history of LH-RH agonist treatment to reduce the bias. A double-blind study was conducted to achieve a higher standard of scientific rigor in evaluating the efficacy and safety of creatine. A biostatistician from an external facility (MG) was delegated to the "Allocator" who was responsible for treatment allocation. The Allocator ensured that it was impossible to determine whether the study agent was creatine monohydrate or placebo by its appearance or package and randomly allocated patients to the study agents in a repeatable manner. The Allocator ensured that the allocation code/list has been kept in a sealed envelope before opening it, and that the allocation has been concealed before unblinding. During the study period, serum creatine, serum creatinine, urinary creatine, and urinary creatinine were measured by a clinical laboratory measuring institution (LSI Medience Corporation, Tokyo, Japan) to maintain the blindness in this study. The results of the examination were kept at the clinical laboratory measuring institution without disclosure. After unblinding, the examination results of these items were reported to the investigator.

Outcome Measures

The primary endpoint of this trial was the change in handgrip strength values from baseline to week 8 (T^2). Handgrip strength values were measured using an electronic hand dynamometer. For measurement, the patients were instructed to keep their elbows at an angle of 90°, their forearms in a neutral rotation, and their wrists not flexed or pronated. The grip power was measured twice on each side, and the average of the maximal power of both sides was recorded. Secondary outcome measures included muscle strength measured by tongue pressure [30], maximum voluntary isometric contraction (bilateral shoulder flexors and extensors, elbow flexors and extensors, knee flexors and extensors, and ankle flexors and extensors), five components of the Quantitative Myasthenia Gravis score (excluding the ptosis and diplopia sections) [31], 15-foot timed-walk test [32], and rise-from-bed test, which measures the time in changing the position from the supine position on the bed to the sitting position. We also measured changes in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) [7,33,34] and the Spinal and Bulbar Muscular Atrophy Functional Rating Scale, which is a validated, disease-specific scale with a high sensitivity to disease progression in SBMA [35]. We evaluated muscle mass with dual-energy X-ray absorptiometry (DXA) using the fan-beam technology (Discovery A; Hologic Inc, Bedford, MA). The sum of the appendicular lean soft tissue mass measured with DXA has been validated by the measurement of the skeletal muscle mass using magnetic resonance imaging and computed tomography [36-38]. As other outcome measures, we analyzed the subjective assessment of swallowing function (Swallowing Disturbance Questionnaire and Swallowing Quality of Life Questionnaire) [39,40], respiratory function values (vital capacity, forced vital capacity [FVC], forced expiratory volume one second percent, peak expiratory flow, and V50/V25), 5-item Amyotrophic Lateral Sclerosis Assessment Questionnaire [41], the Multidimensional Fatigue Inventory [42], and urinary 8-hydroxydeoxyguanosine (8-OHdG) as a marker of oxidative stress [43].

Efficacy, Safety, and Tolerability Data Analyses

Efficacy Data Analyses

The primary endpoint of the efficacy analysis was the change in grip strength at 8 weeks of administration from baseline. In the primary analysis, we examined the superiority of 10 g/day and 15 g/day of creatine administration groups over the placebo-treated group using the Dunnett's multiple comparison test with the placebo treated group as the control. In the secondary analysis, we also estimated a dose-response relationship among the 3 groups using the linear contrast test. The mixed model for repeated measures and random slope mixed effect model were also applied. All the analyses were conducted based on the intent to treat principle that included all randomly assigned patients who received the study medication and provided at least one postbaseline efficacy datum, as well as the per-protocol set that included all intent to treat patients with no important protocol violations relevant to assessing the study agent efficacy. A two-sided $P<0.05$ was considered to be statistically significant. All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc, Cary, NC, USA).

Safety/Tolerability Data

Safety was evaluated in all patients who received the study agent. In each patient, safety and tolerability assessments including vital signs, medical examination findings, clinical laboratory data, and intensity of adverse events (AEs) were evaluated. Severe AEs were defined as incapacitating or causing inability to work or undertake usual activities. Each AE was coded to a preferred term and associated organ system according

to an established and validated adverse reaction dictionary (MedDRA/J, version 18.0); AEs were monitored by an independent data and safety monitoring board.

Sample Size Calculation

In this study, we intended to enroll 45 patients with SBMA. This was based on previous studies that examined the efficacy of creatine therapy for muscular dystrophy. In those placebo-controlled trials, intergroup differences of the change from baseline were 6.4 to 16.2% (SD 19.8 to 30.7%) in the maximum voluntary muscle strength [25,28,29,44]. The pharmacological mechanism of increasing intramuscular creatine concentration is common in SBMA and muscular dystrophy. In addition, in our preliminary examination, patients with SBMA displayed a lower intramuscular creatine concentration compared with disease controls including muscular dystrophy, suggesting that a larger creatine efficacy may be expected in SBMA. Based on the above, the number of required participants was calculated assuming that the intergroup difference of the change rates of the muscle strength is 28.0% and the SD is 20.0%.

Results

All 45 participants have been enrolled starting in June 2014 and follow-up was completed in July 2015. The study is currently being analyzed.

Discussion

This trial is the first randomized control trial evaluating the efficacy and safety of creatine monohydrate in patients with SBMA. Currently, there is no treatment available for counteracting muscle weakness in patients with SBMA. Restoration of the muscle creatine concentration may be a candidate therapeutic strategy for SBMA.

To be eligible for randomization, we set the patients' disease duration from the onset of muscle weakness as the allocation factor because SBMA is a slow progressive disease and clinical symptoms worsen with the disease progression. In addition, since prior LH-RH agonist administration may influence the evaluation of the efficacy, we set the past treatment history of LH-RH agonists as the other allocation factor.

We used the handgrip strength as a primary endpoint. Muscle weakness in patients with SBMA is known to stem from the cytotoxicity of mutant AR in both motor neurons and skeletal muscles. In SBMA, handgrip strength decreases gradually over the course of the disease progression [20]. Furthermore, in a randomized, double-blind comparative study of creatine therapy for Duchenne muscular dystrophy, the grip strength was reported to improve significantly compared with the placebo group [29]. In the Cochrane Collaborative Plan systematic review of creatine therapy for muscular diseases, creatine therapy has been shown to be effective for muscle strengthening when using quantitative strength measurements including hand grip strength as the primary endpoint [45]. Therefore, we chose the handgrip strength as the primary endpoint in our trial. In the previous clinical trials of creatine therapy, other outcome measures such as quantitative muscle testing of extremities, pulmonary function testing, body composition measured by DXA, subjective assessment of improvement of muscle weakness, and urinary 8-OHdG as a marker of oxidative stress to DNA were adopted [28,29,44,46]. In our trials, we added five components of the Quantitative Myasthenia Gravis score as a secondary outcome to evaluate muscular endurance.

Although it was suggested that creatine may have a neuroprotective effect in ALS animal model [47], it was reported that creatine did not have a statistically significant effect on survival, ALSFRS-R progression, or percent predicted FVC progression in the Cochrane Collaborative Plan systematic review (although creatine 5 to 10 g per day was well-tolerated with no serious adverse events in all studies [48]).

In a systematic review of creatine therapy for muscle disorders with meta-analysis of 14 RCTs [45], the median creatine administration period was 8 weeks (3-6 months). Since the pharmacological mechanism anticipated for creatine therapy in SBMA is similar to that in other muscle disorders, the administration period in this study was also set at 8 weeks.

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Authors' Contributions

YH was responsible for drafting the manuscript. YH, MK, and GS were involved in study design and concept, statistical analysis, and revising the manuscript. Analysis and interpretation of the data were carried out by YH, MK, KS, A Hashizume, AA, A Hirakawa, and GS. YH, MK, KS, A Hashizume, AA, SY, TI, and DI were involved in the acquisition of data and research project execution. FK was involved in data management. MG was responsible for assigning patients to treatment groups and patients allocation. Research project organization was carried out by GS.

Conflicts of Interest

None declared.

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Abbreviations

8-OHdG: 8-hydroxydeoxyguanosine
AE: adverse event
ALS: amyotrophic lateral sclerosis
ALSFRS-R: the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale
AR: androgen receptor
DXA: dual-energy X-ray absorptiometry
FVC: forced vital capacity
LH-RH: luteinizing hormone-releasing hormone
RCT: randomized controlled trial
SBMA: spinal and bulbar muscular atrophy

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Protocol

Outcome of Critically ill Patients Undergoing Mandatory Insulin Therapy Compared to Usual Care Insulin Therapy: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Observational and interventional studies in patients with both acute medical conditions and long-standing diabetes have shown that improved blood glucose control confers a survival advantage or reduces complication rates. Policies of “tight” glycaemic control were rapidly adopted by many general intensive care units (ICUs) worldwide in the mid 00’s, even though the results of the studies were not generalizable to mixed medical/surgical ICUs with different intravenous feeding policies.

Objective: The primary objective of the study is to assess the safety of mandatory insulin infusion in critically ill patients in a general ICU setting.

Methods: This protocol summarizes the rationale and design of a randomized, controlled, single-center trial investigating the effect of mandatory insulin therapy versus usual care insulin therapy for those patients admitted for a stay of longer than 48 hours. In total, 109 critically ill adults predicted to stay in intensive care for longer than 48 hours consented. The primary outcome is to determine the safety of mandatory insulin therapy in critically ill patients using the number of episodes of hypoglycaemia and hypokalaemia per unit length of stay in intensive care. Secondary outcomes include the duration of mechanical ventilation, duration of ICU and hospital stay, hospital mortality, and measures of renal, hepatic, and haematological dysfunction.

Results: The project was funded in 2005 and enrolment was completed 2007. Data analysis is currently underway and the first results are expected to be submitted for publication in 2018.

Conclusions: This protocol for a randomized controlled trial investigating the effect of mandatory insulin therapy should provide an answer to a key question for the management of patients in the ICU and ultimately improving outcome.

Trial Registration: International Standard Randomized Controlled Trial Number ISRCTN00550641; http://www.isrctn.com/ISRCTN00550641 (Archived at WebCite: http://www.webcitation.org/6xk8NXxNv).

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KEYWORDS

intensive care; insulin; glycaemic control

Introduction

Background

Observational and interventional studies in patients with both acute medical conditions and long-standing diabetes have shown that improved blood glucose control confers a survival advantage or reduces complication rates [1-4]. In 2001, Van den Berghe and colleagues extended this to critically ill patients with no history of diabetes when they published the results of a study of "tight" blood glucose control compared with conventional blood glucose control in Dutch intensive care unit (ICU) patients following surgery [5]. They showed a corrected relative reduction in intensive care mortality of 32% in the "tight" control group, with the benefits primarily seen in the patients who required a prolonged ICU stay. A reduced ICU length of stay and a reduction in the incidence of renal dysfunction and nosocomial infections were also seen in the "tight" glucose control patients.

Tight glycaemic control therapy necessitates increased insulin administration to achieve euglycaemia. This raises the possibility that any patient benefits may be a result of the insulin delivered rather than the glycaemic control attained, and that further improvements in patient outcomes might be possible with increased insulin administration [6]. However, intensive insulin therapy is a complex intervention. The effects depend upon the protocol used, feeding strategies, staff training and availability, and the method of near-patient glucose concentration measurement used. Separation of the effects of insulin infusion from those of euglycaemia could be achieved by comparing two groups receiving substantially different quantities of insulin, but achieving similar glycaemic control. However, mandatory continuous insulin infusion (to achieve higher insulin infusion rates than those required simply for glycaemic control) has not been undertaken in ICU patients for the prolonged periods utilized in studies of tight glycaemic control, although previous studies have shown much higher insulin rates to be safe in intensive care patients over short periods [7-9]. This trial aims primarily to determine if insulin infusions of 96 units/day can be achieved safely in a UK mixed general adult ICU, and what short-term biochemical effects occur with these infusions.

Mechanisms by Which Insulin Might Alter Intensive Care Unit Mortality

Whilst it has long been known that chronic derangements of lipid profile are associated with long-term increases in mortality, more recent studies in the critical care environment suggest they also have an impact on acute survival [10]. The lipid profile of the critically ill patient is frequently abnormal, most commonly showing increased triglycerides combined with low levels of high-density lipoproteins (HDLs) and low-density lipoproteins (LDLs) cholesterol. This is partly due to the insulin resistance caused by acute illness or trauma. Observational studies suggest that the severity of these abnormalities correlate with an increased mortality [11].

By inhibiting hormone-sensitive lipase, insulin would be anticipated to decrease free-circulating triglycerides, which have been linearly correlated with mortality [12]. Excess triglycerides are thought to be toxic to the cell membrane and also increase oxygen consumption in an already ischemic environment.

Conversely, there is a body of animal work and some human studies that suggest that hypertriglyceridaemia is protective in gram negative sepsis because triglyceride-rich lipoproteins absorb endotoxin, thus preventing CD14 positive monocyte mediated cellular activation [13].

It may be that insulin, whilst reducing the amount of triglyceride available to absorb endotoxins, increases absorption by other mechanisms. It has been shown to ameliorate the decrease serum HDL levels in the critically ill. HDL has been shown to absorb the majority of endotoxins incubated with whole blood, and infusing reconstituted HDL has been shown to prevent endotoxin stimulated TNF-α production [14]. Moreover, HDL has been shown to provide endothelial protection by both antiapoptotic and antioxidative mechanisms [15].

Initially, this work seems contradictory to retrospective studies which showed a decreased mortality and incidence of sepsis in patients treated with long-term (lipid-lowering) 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitors (statins) prior to their critical illness [16,17]. However, whilst reducing LDL cholesterol, statins, in common with insulin, cause moderate elevation of serum HDL [18]. The above mechanisms may therefore be similarly applicable, as statins are also known to have a range of other anti-inflammatory actions [19].

Critical illness is associated with increased protein catabolism that is relatively resistant to nutritional support [20]. The consequent loss of skeletal muscle leads to respiratory muscle weakness and a prolonged need for mechanical ventilation [21,22]. Small studies, mainly of burn patients, suggest insulin causes a decrease in protein catabolism, but have not shown morbidity or mortality benefits [23-25]. Work has suggested that the negative nitrogen balance that occurs is partly attributable to growth hormone resistance and decreased production and action of insulin-like growth factor 1 (IGF-1) [21]. Administration of high levels of growth hormone has been shown to improve nitrogen balance, but two large European randomized trials demonstrated increased mortality rates in the critically ill [26]. This was thought to be due to a combination of immunomodulatory and hyperglycaemic effects. Many of the effects of growth hormone are mediated via insulin-like growth factors (formerly somatomedins), modulation of which may avoid these unwanted effects.

Infusion of exogenous insulin into volunteers causes an increase in IGF-1 by inducing a reduction in the concentration of its binding protein insulin-like growth factor binding protein 1 (IGFBP-1) [27]. Serum IGF-1 levels have been consistently reported as low in acutely ill patients [28-31] and high IGFBP-1 levels have been associated with increased mortality in similar patients [32]. A longitudinal study of 18 heterogeneous critically ill patients showed initially low-circulating concentrations of IGF-1 and increasing IGF-1 values on recovery [33]. IGF-1 is both antiapoptotic and anabolic, and so might reduce the muscle wasting that leads to prolonged ventilator dependence. The vast majority of insulin-like growth factors in the circulation exist in a ternary complex with IGFBP-3 and an acid-labile subunit

(ALS). This complex is too large to traverse the capillary endothelia and stimulate insulin or IGF receptors. ALS is also essential in sustaining plasma levels of IGF's as it extends their half-life from 10 minutes to twelve hours. Levels of ALS are reduced in critical illness due to growth hormone and insulin resistance. The effect of mandatory insulin infusion on these aspects of the somatotrophic axis in the critically ill is unknown. Work from a subgroup of the original Van den Berghe trial has, somewhat surprisingly, shown a decrease in IGF-1 in the "tight glycaemic control" arm of the study [19].

The overall results of all these studies would seem to indicate that there may be a benefit from "tight glycaemic control". A trial designed to clearly delineate insulin dose between two arms should provide more evidence for the science behind this new "therapy" if this feasibility trial can show that recruitment of ICU patients is possible and the therapy is shown to be able to be delivered safely.

Objectives

The primary objective of the study is to determine the safety of mandatory insulin infusion in critically ill patients in a general ICU setting. This will be assessed by the number of episodes of hypoglycaemia and hypokalaemia per unit length of stay in intensive care.

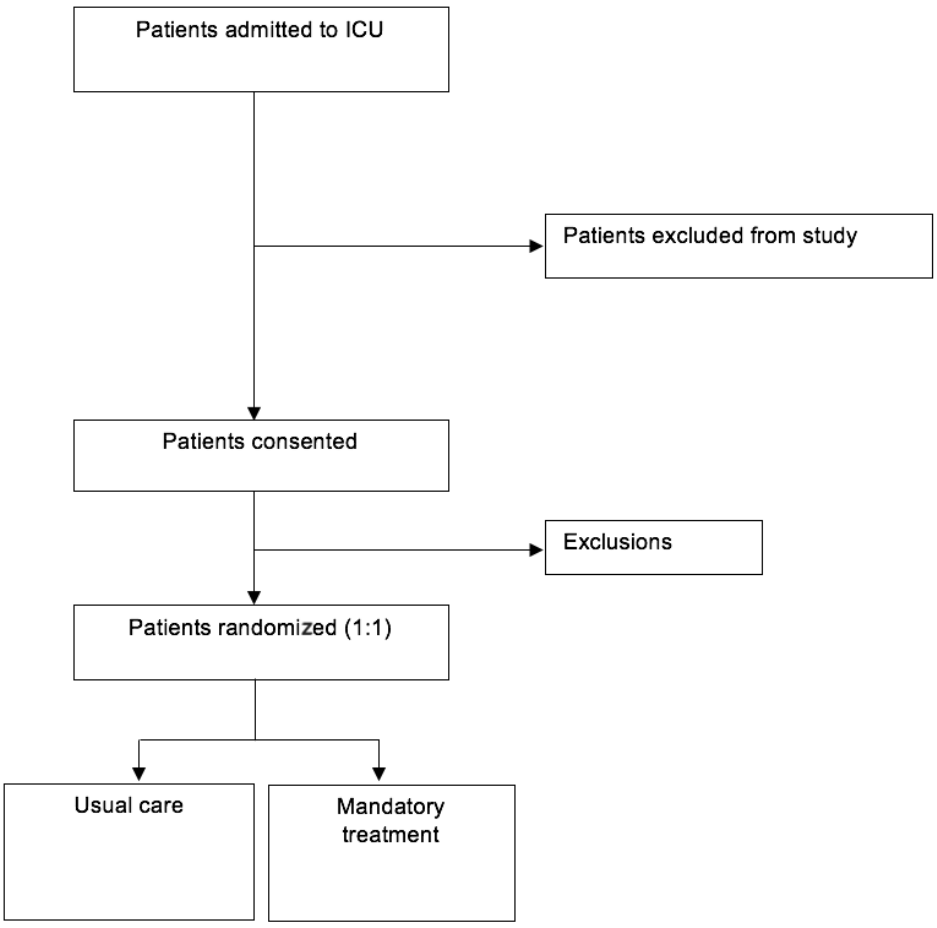
The secondary objectives are to investigate four mechanisms by which exogenous insulin might alter outcome: (1) effects on lipid profiles (to include free fatty acids profiles, triglyceride, HDL, and LDL levels); (2) effects on nitrogen balance; (3) effects on the somatotrophic axis; and (4) effect on oxidative damage by measuring protein carbonyls.

Methods

Trial Design, Setting, and Patient Population

This is a randomized, controlled, open-label, single-centre trial comparing two strategies for the management of blood glucose in the ICU. The study will be conducted in one General (noncardiac) ICU at a UK university teaching hospital. All patients admitted to the ICU will be screened for eligibility. The study sponsor is the Oxford University Hospitals NHS Trust. A SPIRIT figure showing the schedule of enrolment, assessment of outcome measures, allocation, and interventions is shown in Figure 1. Those that were not diabetic, had not had hepato-biliary surgery or had a diagnosis other than pancreatitis, and who were expected to stay in the ICU for at least 48 hours were eligible for inclusion. The full inclusion and exclusion criteria is listed in Textbox 1.

Figure 1. SPIRIT flowchart.



Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- 16 years or older
- Deemed by the attending physician to require 48 hours or more days of critical care treatment

Exclusion criteria:

- Known diabetes mellitus
- Admitted with diabetic ketoacidosis
- Current diagnosis of pancreatitis
- Undergone hepato-biliary surgery in the current admission
- Insulinoma or pituitary tumour
- Currently on, or likely to require, total parenteral nutrition
- Pregnant or breast-feeding
- Primary diagnosis of head injury
- Primary diagnosis of intracranial haemorrhage
- Primary diagnosis of stroke
- Inclusion in another study
- Currently placed under a section order
- Learning disability
- Unable to speak English and without a suitable translator
- Already on higher than 4 units of insulin per hour and have been so for at least 3 out of the last 24 hours
- No central line access
- Had cranial neurosurgery within the past 4 weeks
- Spent more than 24 hours on another ICU directly before this ICU admission
- Prisoners
- Undergone kidney-pancreas transplant in the current admission
- Failure to synthesise glucose

Study Definitions

Hypoglycaemia is defined as a blood glucose measurement taken that is less than 2.2 mmol/L (this low level is set to be in agreement with other completed and in-progress trials [5,34-38]). *Hypokalaemia* is defined as a blood potassium measurement taken that is less than 2.6 mmol/L.

Treatment

Line Management for Both Arms

A central line port should be dedicated to study use (as well as with Total Parenteral Nutrition). This port can be used for both insulin and glucose infusions. Both insulin and glucose infusions need priming (2 mls) for central infusion.

Potassium Measurement and Monitoring

Serum potassium should be monitored at least every 4 hours (by blood gas analysis or laboratory).

Mandatory Insulin Therapy (Intervention Arm)—4 Units of Actrapid Insulin Infusion per Hour

As soon as possible after randomization, an infusion of Actrapid (Novo Nordisk) should be prepared (50 units of Actrapid should be made up to 50 mls with 0.9% normal saline). This should be attached to an infusion pump to enable the patient to receive a mandatory insulin infusion of 4 units of Actrapid per hour. The syringe should be changed every 24 hours. A bag of 50% glucose should also be set up and the rate of this infusion is as per Table 1 to maintain normoglycaemia. Normoglycaemia will be maintained by sliding scale 50% glucose infusion with the rate of glucose infusion being dependent upon the blood glucose measurement as per Table 1.

If a patient has blood glucose measurements greater than 8 mmol/L after initial stabilisation (meaning the first 5 hours of treatment, or after initiation or change of feeding) on 3 successive occasions after stopping glucose infusion, they should be transferred to standard (insulin sliding scale) treatment. It should be checked that nutrition is not being given incorrectly prior to this decision being made.

Table 1. 50% glucose infusion rates for mandatory insulin therapy arm

Blood glucose measurement (mmol/L)	Glucose infusion rate
<2.6	1. Stop insulin infusion 2. Bolus patient with 25ml of 50% glucose 3. Seek medical advice 4. Repeat blood glucose measurement in 30 minutes 5. Once the blood glucose is back in the normal range the insulin infusion should be recommenced with the 50% glucose solution infusion rate increased by 8 mls per hour
<4.1	1. Increase 50% glucose infusion rate by 8 mls per hour 2. Measure blood glucose again in 30 minutes
4.1 – 7	1. No change to infusion rate 2. Measure blood glucose again in 60 minutes[a]
>7	1. Decrease 50% glucose infusion rate by 4 mls per hour 2. Measure blood glucose again in 60 minutes[a]

[a]If blood glucose levels are changing rapidly, more frequent measurements may be necessary. If blood glucose levels remain in the desired range (and do not alter by more than 0.7 mmol/L each time) for 2 consecutive hours without alteration of glucose infusion, blood glucose measurement may be reduced to 2 hourly.

Table 2. Insulin infusion rates for usual care insulin therapy arm.

Blood glucose measurement (mmol/L)	Insulin infusion rate (units per hour)
0 – 4	0.5
4.1 – 7	1.0
7.1 - 11	2.0
11.1 – 17	4.0
17.1 – 27	7.0
>27	10.0

If changes to a patient's feed- or glucose-containing intravenous fluid regimes occur or if a feeding break occurs, hourly monitoring of blood glucose should be recommenced until the levels are again stable. Immediately after the stopping of feed, increase the glucose infusion rate by 8 mls per hour.

As soon as it is known a patient will be discharged the patient should have both glucose and insulin stopped. A blood gas (arterial or venous) should be taken just prior to departure to check that blood glucose and potassium levels are within the normal range.

Usual Care Insulin Therapy (Control Arm)

Only the frequency of blood glucose and potassium monitoring was changed for these patients (to be more frequent, every hour) and the standard unit guidelines for insulin administration should be followed. Actrapid should be made up as per the treatment arm. The unit guidelines are for the target range of 4-7 mmol/L blood glucose which should be achieved with insulin doses as per Table 2.

Therapy Administration

Once a patient is entered into the trial, either the patients' attending nurse, the trial physician, or research nurse will set up the assigned therapy. The patients nurse will then follow either Table 1 or Table 2, depending upon allocation, to adjust the insulin and glucose infusions accordingly. As per the unit protocol and trial protocol, a physician should be called for any patients that has a blood glucose measurement of less than 2.6 mmol/L and the patient must be treated immediately for hypoglycaemia.

Trial Protocol

Description of Trial Flow

Patients will be identified in the ICU through twice daily surveillance by the research coordinator or treating ICU physicians. Each patient's eligibility will be verified by the use of a screening form that summarizes the inclusion and exclusion criteria. The patient needs to have been randomized within 24 hours of their admission to the ICU.

Outcomes

The primary outcome is to determine the number of episodes of hypoglycaemia and hypokalaemia, and compare this with the usual treatment (control) group.

Additional outcome measures used to determine safety will be duration of mechanical ventilation, duration of ICU and hospital stay, hospital mortality, and measures of renal, hepatic and haematological dysfunction. Antibiotic use will be used as a surrogate marker for nosocomial infections. Biochemical markers as specified in the protocol will also be measured to compare between groups.

Sample Size Justification

The study duration will be limited by funding, so a formal power calculation has not been performed. Instead, a recruitment target of 120 patients is set. It was felt that as the recruiting ICU had admitted 912 patients in the 12 months prior to the start of the trial, of which 270 stayed for 5 or more days this would be a realistic recruitment target.

Informed Consent

Wherever possible, informed consent will be obtained from patients prior to randomization. It is recognized that in the majority of cases the patients will be unable to give informed consent due to alterations in level of consciousness caused by illness and therapeutic sedation. Although a relative cannot provide consent on behalf of a patient whose consent cannot be obtained, a written agreement stating no objection will be obtained from the patient's relative. The relative will be given the information sheet making them aware that they can only offer an opinion as to whether they know if the patient would not have objected to taking part in medical research.

In the event that the relative cannot be spoken to in person, a verbal "no objection" will be obtained by telephone and randomization will be undertaken. Verbal assent will be obtained by the recruiting consultant or an individual with appropriate experience he/she nominates. The quality of consent will be ascertained from the responses given by the relative. Questions will be encouraged and the relative will have the opportunity to clarify any of the information given. Signed confirmation of the verbal assent will be sought, retrospectively, if practical.

Once the patient regains the capacity to comprehend the details of the study, they will be asked for permission to include their data in the study. If a patient or relative refuses consent/assent then the patient will receive the usual treatment as defined by the clinician responsible for the patient's care.

If a patient dies before regaining consciousness and the relative has given assent, the patient's data will be included in the study. The person taking consent will ensure that the patient (or the relative) receives a copy of the Consent/No Objection Form, and that a copy is placed in the patient's notes. The original will be filed in the Trial Office. This process is in line with the Mental Capacity Act 2005 and has been approved by a UK Research Ethics Committee.

Randomization

Allocation to a treatment arm will be made randomly. A Web-based specialist randomization service will be used (www.thesealedenvelope.com). Randomization will occur once a patient meets the inclusion criteria and has either consented to the trial or his/her relative (Personal Legal Representative) has provided verbal or written assent. When a member of the trial team logs onto the randomization service, basic descriptive information will be requested. The allocation will be minimized according to the patient's gender. The requirement to titrate an infusion of insulin in one group and an infusion of glucose in the other group, using two different schedules, precludes blinding.

Data Collection

Clinical data will be collected in a standardized way on a trial specific data form. Data will be transcribed from the patient's notes or the clinical information system (Philips CareVue) by members of the PERMIT research team. Baseline measures of severity of illness (Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment score) will be collected on admission, along with the demographics required to demonstrate equivalent groups.

All estimations of blood glucose and serum potassium, whether performed in the central laboratory or using near patient testing, will be collected from the clinical information system (CareVue). The doses of insulin, potassium, glucose, and antibiotics will also be collected. Nitrogen input will be estimated from the documented feed rates. Blood glucose levels will be monitored hourly, and 3-hydroxybutrate levels daily, using the Abbott system.

Blood and urine samples will also be taken from all randomized patients whilst they remain in the ICU. Specifically, blood samples will be taken at baseline (Day 1), Day 3, Day 5, Day 7 and Day 14. Urine collections will be taken over the preceeding 24-hour period on Days 3, 5, and 7.

Data are collected for the entire period of the patient's stay in ICU. The hospital discharge date will be obtained from the local patient administration system (PAS) by the Trial Office. When a patient is transferred to another acute hospital, the discharge date will be requested from the receiving hospital. To enable collection of patient status 30 days after randomization, the PAS will be interrogated to determine the patient's location at 30 days. For those patients that have been discharged, the patient's General Practitioner will be contact by telephone to establish their location. There is no planned long-term follow up.

Statistical Analysis

The principal comparisons will be between those allocated to usual care and those allocated to mandatory insulin (the "intention to treat principle"). The primary outcome variable will be the differences in the number of hypoglycaemic and hypokalaemia events between groups which will be compared by chi-squared tests. Differences between multiply measured continuous variables will be compared using analysis of variance. To allow for differences in length of stay between patients, wherever possible, variables will be converted to time-weighted averages if they are used as a single, between-group measure.

Data Safety and Monitoring

Data relating to the safety of patients will be reviewed by an independent statistician (Dr Tony Brady) once 40 patients have been randomized to the trial. The data reviewed will specifically relate to: (a) serious unanticipated events (SAEs) and (b) deaths at 30 days (any cause)

Ethical Considerations

This trial protocol was approved by a research ethics committee (Oxfordshire Local Research Ethics Committee C) (REC REF: 05/Q1606/103) and by the UK Medicines Healthcare Regulatory Agency as competent authority (CTA No. 21439/0207/

001-0001). The protocol adheres to principles of the Declaration of Helsinki and Good Clinical Practice.

Results

The project was funded in 2005 and enrolment was completed 2007. The trial was suspended after recruiting 109 patients and all patients were followed up as per this protocol. Data analysis is currently underway and the first results are expected to be submitted for publication in 2018.

Discussion

This protocol for a randomized controlled trial will allow further investigation of the impact of mandatory insulin infusions and determine if a powered trial would be feasible. The trial aims to determine if the insulin is the biological effector that alters mortality in these patients. This requires similar blood glucose control in two groups of patients, but a different insulin dose. This can be achieved with a mandatory insulin infusion in one group and an "as needed" insulin infusion in the other, with a variable glucose infusion in the mandatory group to maintain euglycaemia. This should allow us to determine the safety of mandatory insulin infusions of this dose in this patient group. Secondly, we aim to determine whether insulin or euglycaemia is the biological effector that alters outcome to inform and plan future research. Euglycaemia in the absence of additional insulin may be ineffective in reducing mortality and so the routine adoption of "tight" glycaemic control, as is happening at present, will be largely ineffective.

This study should allow us to further interpret the Van den Berghe study as their study design necessarily resulted in two differences between the arms, the blood glucose level and the insulin dose. The authors linked the reduction in mortality to changes in the blood glucose level; in essence proposing that hyperglycaemia per se has some ill effect that increases the chance of death, and so elevated blood glucose carries an attributable mortality. The biological pathway for this was thought to be related to impaired leukocyte function in the presence of high glucose concentrations. However, the proposal that maintenance of normoglycaemia led to the benefits seen by improving immune function is belied by the relatively small difference in median glucose values between the two groups compared with the levels of plasma glucose required in previous studies to cause immune dysfunction (39, 40).

There are potential risks from this study as a mandatory insulin infusion will have two main effects that might lead to patient harm: an excessive reduction in blood glucose level and an excessive reduction in serum potassium concentration. In a modern ICU with an appropriate staffing ratio and close monitoring, the risk of both of these events would be expected to be low. In the Van den Berghe study 5.1% of the patients in the "tight" glucose control group had one or more blood glucose determination of less than 2.2 mmol/l. The number of episodes of hypokalaemia were not reported.

Conflicts of Interest

None declared.

Multimedia Appendix 1

SPIRIT checklist.

[PDF File (Adobe PDF File), 41KB - resprot_v7i3e44_app1.pdf]

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Abbreviations

ALS: acid-labile subunit
HDL: high-density lipoprotein
ICU: intensive care unit
IGF: insulin-like growth factor
IGFBP: insulin-like growth factor binding protein
LDL: low-density lipoprotein
PAS: Patient Administration System

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Protocol

Symptomatic Treatment of Vascular Cognitive Impairment (STREAM-VCI): Protocol for a Cross-Over Trial

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Abstract

Background: People with vascular cognitive impairment (VCI) constitute a clinically heterogeneous group, but previous symptomatic drug trials in VCI did not take this clinical heterogeneity into account. Executive dysfunction and memory impairment are the cognitive domains that are most frequently impaired in VCI, and these impairments are likely to reflect vascular damage to specific neurotransmitter systems, which opens the possibility for targeted symptomatic treatment directed at specific neurotransmitters.

Objective: Here we describe the design of the "Symptomatic Treatment of Vascular Cognitive Impairment" (STREAM-VCI) trial. In this proof-of-concept study, we investigate whether people with VCI with executive dysfunction due to vascular damage to the monoaminergic neurotransmitter system differentially respond to a monoaminergic challenge, whereas people with VCI with memory dysfunction associated with vascular damage to the cholinergic system will in turn respond to a cholinergic challenge.

Methods: The STREAM-VCI is a single center, double blind, three-way cross-over trial among 30 people with VCI, in which subjects received a single dose of galantamine, methylphenidate, or placebo on separate occasions. The most important inclusion criteria were a diagnosis of VCI with a Mini-Mental State Examination score of ≥16 and a Clinical Dementia Rating of 0.5-1.0. For each person, the challenges consisted of a single 16 mg dose of galantamine, 10 mg of methylphenidate, and placebo, in random order on three separate visits. Change in performance in executive functioning and memory was assessed directly after the challenge using standardized neuropsychological tests. We will correlate a positive response to the cholinergic and monoaminergic treatment with differences in structural and functional connectivity at baseline using structural magnetic resonance imaging (MRI), diffusion tension MRI, and resting-state functional MRI.

Results: The protocol of this study is approved by the Medical Ethics Committee of VU University Medical Center and the competent authority. The first participant was enrolled in April 2014. In September 2017, enrolment for the study was completed. We expect to publish the results in 2018.

Conclusions: STREAM-VCI is the first study to investigate the association of a response to a cholinergic and monoaminergic treatment with structural and functional connectivity of the monoaminergic and/or cholinergic systems on MRI. We aim to predict on an individual basis which individuals show a positive response to a cholinergic and/or monoaminergic challenge in people with VCI. This may be instrumental in moving in the direction of individually-tailored pharmacological interventions based on MRI measures in people with VCI.

Trial Registration: ClinicalTrials.gov NCT02098824; https://clinicaltrials.gov/ct2/show/NCT02098824 (Archived by WebCite at http://www.webcitation.org/6xhO7Ya1q)

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KEYWORDS

Vascular cognitive impairment; dementia; methylphenidate; galantamine; cognition; Magnetic Resonance Imaging; small vessel disease; vascular disease; clinical trial

Introduction

The two most prevalent cognitive symptoms in people with vascular cognitive impairment (VCI) are executive dysfunction and memory impairment [1,2]. However, the presence and extent of these symptoms varies largely between people with VCI. Previous intervention studies did not take this into account, and until now, there is no approved symptomatic treatment for people with VCI.

Recent insights in the neuropharmacological basis of cognitive symptoms in VCI suggest that executive dysfunction is largely related to dysfunction of the monoaminergic systems (noradrenergic and dopaminergic) that project mainly from the locus coeruleus. Memory impairment is thought to be related to dysfunction of the cholinergic system projecting form the nucleus basalis of Meynert [3-5]. Also, neuronal networks, such as the default mode network (DMN), is assumed to be involved in attention, concentration, and executive function. Vascular damage is thought to cause impairment of the cholinergic and monoaminergic neurotransmitter systems by damaging specific white matter tracts and cause disturbances in the neuronal networks such as the DMN [6-8], resulting in cholinergic and/or monoaminergic deficits.

Galantamine is a drug that increases the availability of acetylcholine in the synaptic cleft and previous studies have shown positive results on memory in people with probable Alzheimer's disease [9-14]. Executive functioning might be improved by increasing norepinephrine and dopamine transmitters with methylphenidate. This drug can increase the concentrations of dopamine and norepinephrine in the synaptic cleft [15-17]. Two previous studies have shown a slight improvement on cognition, based on Mini-Mental State Examination (MMSE) scores, in people with dementia following methylphenidate use [18,19].

Here we describe the design of the trial "Symptomatic Treatment of Vascular Cognitive Impairment" (STREAM-VCI). In this proof-of-concept study, we aim to study the individual change on performance on executive function and/or memory function after a single dose of methylphenidate and galantamine, compared to placebo, in people with VCI. We will correlate the change on performance after the pharmacological challenge with functional and structural connectivity of the damaged monoaminergic and cholinergic neurotransmitter systems using a structural magnetic resonance imaging (MRI) and resting-state functional magnetic resonance imaging (rs-fMRI) [20-24]. Based on this information we aim to understand and predict which individuals will benefit from a certain pharmacological treatment. This could be a step forward towards personalized drug treatment based on MRI measures.

Methods

Study Design

The STREAM-VCI is a single center, double-blind, three-way, case cross-over pharmacological challenge study, in which participants received a single dose of galantamine, methylphenidate, or placebo on separate occasions. Participants were primarily recruited from the Alzheimer Center of the VU University Medical Center (VUmc). Also, subjects were recruited after referral from the Department of Neurology of the Utrecht University Medical Center (Utrecht) and the outpatient clinic of the following hospitals: Groene Hart Ziekenhuis (Gouda), Spaarne Gasthuis (Haarlem), and Tergooi (Blaricum). Subjects were enrolled between April 2014 and September 2017. The trial is registered at the clinical trial register: NCT02098824.

Subjects

Subjects were people with VCI ranging from vascular mild cognitive impairment to vascular dementia, according to the definitions of the American Heart Association/American Stroke Association [25]. Eligible people who satisfied the inclusion and exclusion criteria were selected (Textbox 1). Individuals fitting the inclusion and exclusion criteria were given the study information and at least one week's time to consider participation in the study. The enrolment of 30 subjects was complete in September 2017.

Randomization

Eligible subjects who fulfilled the inclusion and exclusion criteria were given the study medication in a randomized order. Latin squares balanced for first-order carry-over effects were used, called Williams squares. Because of the uneven number of treatments, a pair of squares was required to ensure balance for first-order carry-over effects. Randomization was carried out by an independent researcher. Medication was identified by project and protocol number, packing number, expiration date, storage requirement, and contents.

Textbox 1. Inclusion and exclusion criteria for Symptomatic Treatment of Vascular Cognitive Impairment.

Inclusion criteria

- Outpatients
- Objective executive dysfunction and/or memory impairment on neuropsychological tests
- Imaging evidence of cerebrovascular disease (white matter changes (Fazekas ≥2), (lacunar) infarcts, and/or (micro)hemorrhages)
- Mini-Mental State Examination score of ≥16
- Clinical Dementia Rating of 0.5-1
- No contraindication for treatment with a cholinesterase inhibitor or methylphenidate
- Assessed by the treating neurologist as mentally capable of understanding the implications of study participation
- Presence of an informant/caregiver at the information visit and signing of informed consent

Exclusion Criteria

- Clinically-relevant history of abnormal physical or mental health interfering with the study as determined by medical history taking and physical examinations obtained during the screening visit and/or at the study day as judged by the investigator
- Clinically-relevant abnormal laboratory results, electrocardiogram (ECG) and vital signs, or physical findings at screening and/or at the start of the study day (as judged by the investigator)
- Unwilling or unable to stop smoking on the study day until the end of the study day
- Other causes that can explain cognitive symptoms including but not limited to: delirium, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, mental retardation, infectious encephalitis that led to persistent cognitive deficits or head trauma with loss of consciousness that led to persistent cognitive deficits
- Use of neuroleptics
- Use of celiprolol and sotalol
- Use of doses of corticosteroids that may interfere with the pharmacodynamic measurements performed in the study
- Use of Monoamine oxidase A/B inhibitors
- Current use of centrally acting anticholinergics
- Use of benzodiazepine within 48 hours before a study day
- Current use of a cholinesterase inhibitor
- Alcohol abuse (defined as use of alcohol despite significant areas of dysfunction, evidence of physical dependence, and/or related hardship due to alcohol)
- Use of recreational drugs
- Concomitant use of inhibitors of CYP2D6 or of CYP3A4 (unless on a stable dose without any recent or upcoming changes)
- Any other condition that in the opinion of the investigator would complicate or compromise the study or the wellbeing of the subject
- Any contraindication for magnetic resonance imaging

Procedures

Prior to any study-related procedures, written informed consent for the study was obtained from each subject. The study consisted of a screening visit, followed by three study visits (challenge phase). The screening visit occurred at approximately 1 to 6 weeks prior to the first study visit. After inclusion, the study lasted a maximum of 9 weeks until the end of the third study visit. Between each study visit, a wash-out period of at least one week was scheduled. About 7 days after the end of the third study visit, participants were contacted by telephone to inquire about possible side effects. An overview of the study can be seen in Figure 1.

Screening Visit

A full medical screening (medical history, physical examination, vital signs in supine position, 12-lead electrocardiogram (ECG), urinalysis and routine hematology, biochemistry and electrolytes) was performed to assess a subject's eligibility for this study and to assess possible safety concerns of administrating the study medication. Extensive information of the medical screening can be found in Multimedia Appendix 1. All participants were thoroughly trained and familiarized with the central nervous system (CNS) tests on the screening visit in order to minimize learning effects during the study. The tests were performed in a quiet room with ambient illumination with only 1 participant in the room per session. When a person met the criteria for inclusion, an MRI was performed on the same day. An overview of the screening visit can be seen in Table 1.

Study Visit

On each study visit, safety measures were performed prior to drug administration, consisting of vital signs, 12-lead ECG and urinalyses. Vital signs were checked again halfway through the

visit and at the end of the occasion. During a study visit, 5 rounds of CNS tests were performed. Table 1 shows an overview of the assessments during a study visit.

Intervention

During three separate study visits, subjects received a single pharmacological challenge with galantamine, methylphenidate, or placebo in a random order. The Department of Clinical Pharmacology and Pharmacy of the VUmc manufactured galantamine capsules, methylphenidate capsules, and its matching placebo for oral use and guarded stability of the products.

Galantamine

In this trial, a dose of 16 mg was administered (2 tablets of 8 mg). Galantamine is a reversible competitive inhibitor of acetylcholinesterase and also has activity as an allosteric modulator of nicotinic acetylcholine receptors [14]. In several randomized, double-blind, placebo controlled clinical trials, galantamine was effective in people with probable Alzheimer's disease [9-13]. The usual starting dose of galantamine treatment is 8 mg per day [26]. In a previous study the dose was upgraded to 16 mg per day to objectify a good clinical effect [27-29]. Adverse events of galantamine are particularly cholinergically mediated events affecting the gastrointestinal system such as nausea and vomiting which occur in >10% of the people [26].

Methylphenidate

Methylphenidate (MPH) is an indirectly working sympathicomimetic drug with effects comparable to amphetamines and a potent dopamine, norepinephrine, and serotonin releaser that also inhibits the uptake of the released biogenic amines into presynaptic neurons [15-17]. The dose of MPH was chosen at 10 mg (2 tablets of 5 mg), taken orally. This dose and administration of MPH was chosen based on strategies used in previous trials in the elderly depressed, open-label administration guidelines in the demented population and because a preliminary study of MPH for apathy provided data on the safety and efficacy of 10 mg of methylphenidate administered two times a day [30]. The main adverse effects of MPH are agitation, sleep problems, reduced appetite, and palpitations. MPH is also associated with a modest rise in blood pressure and heart rate [31].

Measures

Pharmacodynamic Assessments

A series of CNS tests were administered using the 'NeuroCart' to study the acute effects of the intervention on a set of the CNS drug responsive domains (Table 2) [32].

Figure 1. Schedule diagram of the study. During the screening visit, a magnetic resonance imaging (MRI) is performed. After randomization, a person is placed in one of the 6 study arms. One week after the last study visit, follow-up by telephone will take place. Between each study visit, a wash-out period of one week is scheduled.

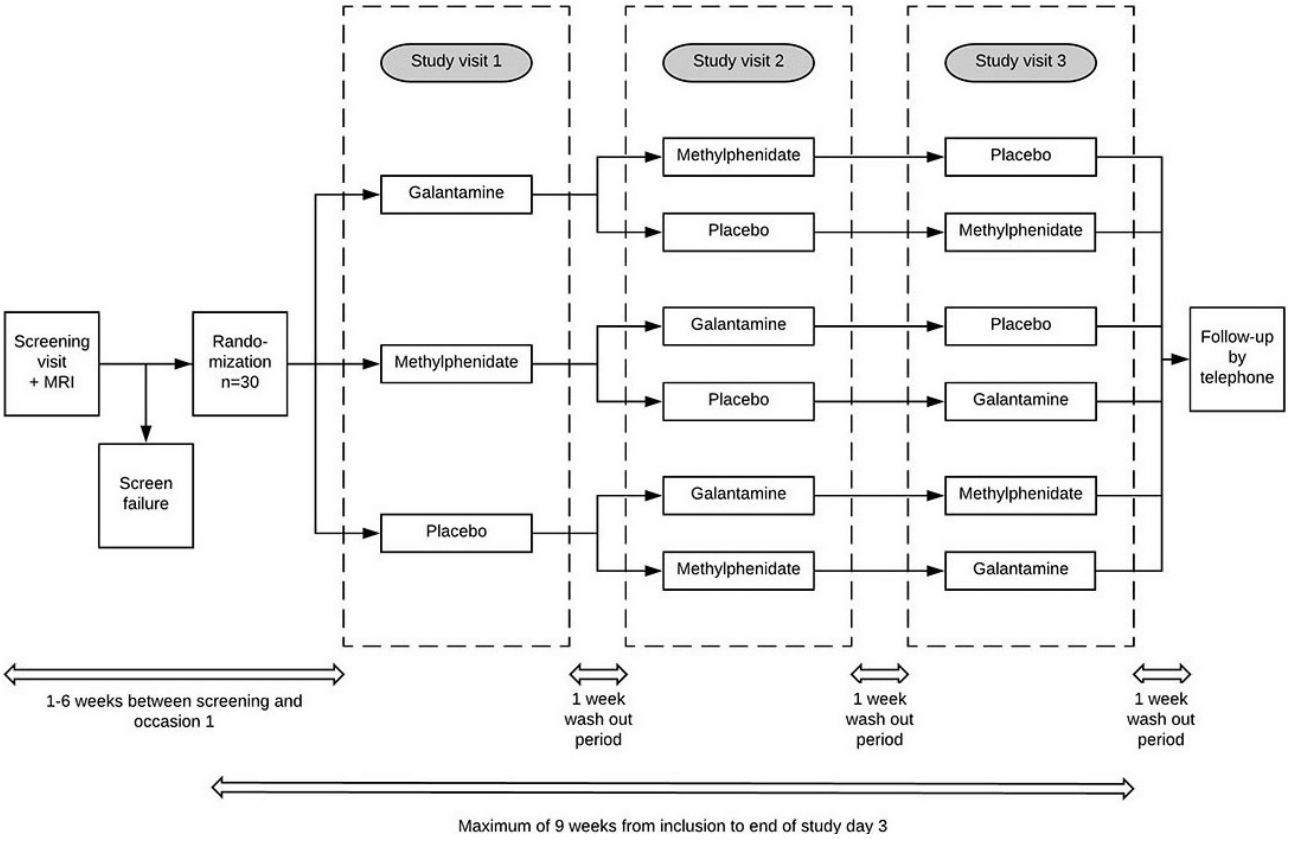

Table 1. Overview of the screening and the study visits. On the study days, the pharmacological challenge is administered at time point 0.

Assessments	Screening visit	Study visits (1, 2, 3) with time points (hours)							
		-1.5	0	1.0	1.5	2.0	2.5	3.0	3.5
Clinical measures									
Clinical procedures[a]	X[b]								
Vital signs	X	X			X				X
12-lead electrocardiogram	X	X							
Urinalysis	X	X							
Clinical laboratory[c]	X								
Pharmacokinetics blood sampling		X		X			X		X
Drug administration			X						
Central nervous system tests									
Eye movements	X	X		X			X		X
Adaptive tracker	X	X		X			X		X
Visual Analog Scales	X	X		X			X		X
Pharmaco-electroencephalography		X		X			X		X
Visual Verbal Learning Test-15	X					X	X	X	
Facial recognition task	X						X		
N-back task	X	X		X			X		X
Stop Signal test	X	X		X			X		X
Magnetic resonance imaging	X								

[a]Clinical procedures include medical history and medication use, Mini-Mental State Examination, Clinical Dementia Rating scale, and physical examination.

[b]X: the assessment was performed.

[c]Clinical laboratory includes hematology and blood biochemistry.

Table 2. Functions measured by each task.

Task	Function				
	Executive Functioning	Memory	Psychomotor speed	Vigilance	Subjective Drug Effects
N-back task	X[a]	X			
Stop Signal Task	X				
Adaptive tracking	X		X	X	
Visual Verbal Learning Test–15		X			
Facial encoding and recognition task		X			
Eye movements			X		
Pharmaco-electroencephalography			X		
Bond and Lader Visual Analog Scale					X

[a]X: task belongs to the function in the column.

Executive functioning was measured by the tasks adaptive tracking [33-35], Stop Signal Task [36,37], and N-back task [38-40]. Memory was assessed by Visual Verbal Learning Test-15 (VVLT-15) [41], N-back task and the Facial Encoding and Recognition Task [38,42]. The VVLT-15 contains 3 different subtests. The immediate word recall test was performed first; after an interval of approximately 60 minutes, the delayed word recall test and then the delayed word recognition test were performed. Our main outcome is defined as the change in performance after a pharmacological challenge on the VVLT-15 and the adaptive tracker.

Besides executive functioning and memory the following functions were measured: psychomotor speed, vigilance, and

subjective drug effects. The following Neurocart tests were used for the measurement of these functions: saccadic and smooth pursuit eye movements [33,34], adaptive tracking, and Bond and Lader Visual Analog Scale [43,44]. In Table 2, the tests with corresponding cognitive functions can be seen.

MRI measurements

The MRI was acquired on 3T whole-body MR system (Discovery; GE Medical Systems Milwaukee, WI, USA), using an eight-channel head coil at the VUmc. The following sequences were applied: T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR), Diffusion Tensor Imaging (DTI) MRI and resting-state functional MRI (rs-fMRI). In total, the imaging took about 40 minutes. There was no intravenous contrast administration. All scans were checked by a neuroradiologist for unexpected gross abnormalities.

Medial temporal lobe atrophy was rated on the coronal reconstructions of the T1-weighted images with scores ranging from 0-4 [45]. Posterior atrophy was rated on the combination of T1-weighted and FLAIR sequences and global cortical atrophy was rated on FLAIR sequences using a 4-point visual rating scale (0–3) [46-48].

White matter hyperintensities (WMH) were rated using the Fazekas scale, with scores ranging from 0-3, on the FLAIR images [49]. Microbleeds were defined as small round hypointense foci on T2*-weighted images, with a maximum diameter of 10 mm located in brain parenchyma. Lacunes were defined as deep lesions (3-15 mm) with cerebral spinal fluid—like signal on all sequences. A rater who was blinded for all clinical information assessed the scores.

We are currently preprocessing all images. They will be normalized to standard Montreal Neurological Institute (MNI) space with FSL software [50,51]. Presence and location of lacunar infarcts in each subject will be assessed and the severity and location of WMH will also be measured using automated segmentation [52]. Structural connectivity will be assessed using DTI “fiber tracking” with FSL software. We will segment specific white matter tracts part of the cholinergic and monoaminergic systems, by means of probabilistic tractography. Diffusion properties (fractional anisotropy and mean diffusivity) will be investigated along the tract pathways. Functional connectivity will be assessed using rs-fMRI. Individual connectivity maps will be identified using standard resting state network maps from FSL. These maps include eight resting state networks, including the DMN and executive control network.

Pharmacokinetic assessments

Blood samples (4mL) for plasma concentrations of galantamine and methylphenidate were collected repeatedly. According to protocol, blood samples were taken before administration of the medication and 1 hour, 2.5 hours and 3.5 hours after administration (Table 1). The exact dates and times of blood sampling were recorded. Samples were centrifuged at 2000G during 5 minutes at 4 degrees Celsius. Plasma was transferred into 2 mL Sarstedt tubes by pipette. The plasma was stored at -20 degrees Celsius for the most optimal stability until analyses. For the analysis of galantamine and methylphenidate, two dedicated liquid chromatography—mass spectrometry / mass spectrometry methods were developed. Each method was specific and sensitive for the analysis of interest. Bioanalysis was performed by the Pharmacy at the VUmc, Amsterdam. ADAPT II Release 4 software was used [53]. Pharmacokinetic parameters will be estimated using compartmental analysis.

Statistical analyses

Sample size

Based on a recently performed study at the Centre for Human Drug Research in people with Alzheimer’s disease, acute effects of galantamine on Neurocart tests have been measured (CHDR0915). In this study, the difference in adaptive tracking performance between galantamine and placebo occasions was 2.07% with a standard deviation of 3.35. Assuming that a comparable efficacy can be seen in people with VCI and monoaminergic neuronal dysfunction supplemented with methylphenidate, and assuming a similar standard deviation, we would need at least 24 subjects with VCI to show a mean difference of approximately 2.0% (on adaptive tracker) with a power of 80%. For the galantamine challenge, the VVLT-15 was used to calculate the sample size. In this study, the difference in VVLT-15 between galantamine and placebo was 3 words with a standard deviation of 3.0. Assuming that in people with VCI and cholinergic neuronal dysfunction supplemented with galantamine, a 2-word difference should be possible, and assuming a similar standard deviation, we would need at least 24 people with VCI. Taking into account a 25% drop out rate, we enrolled 30 subjects.

Planned analyses: Pharmacodynamics

The main outcome of this study is the individual change on the CNS tests after a pharmacological challenge. Participants will be categorized as a responder or nonresponder (defined as a significant difference on Neurocart tests) on both active conditions. Statistical analyses of outcome measures will be performed by using mixed-model analyses of variance (ANOVA) with treatment, period, time, and treatment by time as fixed factors; participant, participant by treatment, and participant by time as random factors; and the average baseline measurement as covariate for each test on each time point. Single-measured parameters without pre-value measurement will be analyzed with a mixed-model ANOVA with treatment and period as fixed factors and subject as random factor. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and model parameters will be estimated using the restricted maximum likelihood method. The general treatment effect and specific contrasts are reported with the estimated difference and the 95% confidence interval, the least square mean estimates, and the *P* value. For repeated measures, graphs of the Least Squares Means estimates over time by treatment will be presented with 95% confidence intervals as error bars, as well as change from baseline Least Square Means estimates. All statistical hypothesis tests are conducted at alpha=0.05 (two-sided). No adjustments for multiple comparisons will be applied.

Furthermore, we will correlate the location and severity of the cerebrovascular lesions to the derived white matter fiber tracts

and neuronal networks. ANOVAs adjusted for age, sex, and baseline cognition will be performed to associate MRI measures for structural and functional connectivity with a positive response to the cholinergic and to monoaminergic challenge. Subsequently, we will use logistic regression to identify the most optimal combination of MRI measures to predict response.

Planned Analyses: Pharmacokinetics

Where appropriate and possible, the relationship between plasma concentrations of galantamine/methylphenidate and a corresponding selection of relevant pharmacodynamic measurements will be defined and the data will be plotted to evaluate the relationship graphically. If deemed appropriate and possible, a suitable pharmacokinetic/pharmacodynamic model may be applied to describe the exposure/concentration-effect relationship.

Ethical Considerations

The protocol of this study was approved by the Medical Ethics Committee of VU University Medical Center (protocol number 2013.393) and the competent authority (number NL45933.029.13). The trial is registered at the European Union Clinical Trials Register (2013-003396-35). The study was conducted according to the Dutch Act on Medical Research involving Human Subjects. An independent monitor (quality manager) of the Centre of Human Drug Research monitored the study data according to Good Clinical Practice.

All adverse events reported spontaneously by the subject or observed by the investigator or his/her staff were recorded. The occurrence of an adverse experience that was fatal, life-threatening, disabling, required or prolonged in-patient hospitalization, or caused congenital anomaly was described as a serious adverse event (SAE). A Suspected Unexpected Serious Adverse Reaction (SUSAR) was defined as an unexpected serious adverse reaction in subjects given a drug that may or may not have been dose related, but was unexpected, as they were not consistent with current information.

Results

The first participant was enrolled in March 2014. Participant enrolment was completed in September 2017. After data-cleaning and locking of the database, we will start analyzing the results. We expect to publish the results in 2018. No SAEs or SUSARs have occurred during the study.

Discussion

The STREAM-VCI is a double-blind, three-way, case cross-over trial, in which people with VCI received methylphenidate, galantamine, or placebo in a random order. With this trial, we aim to improve executive function and memory in people with VCI using pharmacological interventions aimed at the enhancement of monoaminergic and cholinergic neurotransmitter systems.

VCI is one of the most important subtypes of cognitive impairment [1,2,54,55], and as of date, there is no approved symptomatic treatment for people with VCI. Evidence suggests that executive dysfunction and memory complaints in VCI are caused by damage to monoaminergic and cholinergic neurotransmitter systems, respectively [8,20-24]. In the past, several studies have investigated the effect of pharmacological intervention with methylphenidate and a cholinesterase inhibiter. However, the results of these studies were contradictive with some studies showing a positive effect of the intervention and other studies showing no effect [16,19,56]. A possible explanation for the lack of conclusive results may be the heterogeneity in symptoms displayed by people with VCI. Previous studies did not take this interpatient variability into account. By using structural and functional connectivity measures of the cholinergic and monoaminergic tracts, we aim to visualize how vascular damage affect these tracts in each person. By doing so, we aim to understand why some people respond to the challenge and some people do not. In this proof-of-concept study, we expect that people with VCI with executive dysfunction due to vascular damage to the monoaminergic neurotransmitter system will respond to a monoaminergic challenge and that people with VCI with memory dysfunction caused by vascular damage to the cholinergic system will have a positive response to a cholinergic challenge.

STREAM-VCI is the first study to take the heterogeneity of people with VCI into account by correlating the cognitive symptoms with structural and functional connectivity in monoaminergic and cholinergic systems measured with structural and functional MRI and by correlating these changes with a positive response to a challenge with galantamine or methylphenidate. Based on this information, we aim to develop a prediction model that estimates a positive response to a cholinergic and/or monoaminergic challenge in people with VCI. This could be a major step forward towards individually-tailored pharmacological interventions aimed at the affected neurotransmitter systems.

Acknowledgments

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Conflicts of Interest

None to declare

Multimedia Appendix 1

Safety measurements on screening day.

[PDF File (Adobe PDF File), 41KB - resprot_v7i3e80_app1.pdf]

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Abbreviations

ANOVA: analyses of variance
CNS: central nervous system
DMN: default mode network
DTI: Diffusion Tensor Imaging
ECG: electrocardiogram
FLAIR: fluid-attenuated inversion recovery
MMSE: Mini-Mental State Examination
MNI: Montreal Neurological Institute
MPH: Methylphenidate
MRI: magnetic resonance imaging
rs-fMRI: resting-state functional magnetic resonance imaging
SAE: serious adverse event
STREAM-VCI: Symptomatic Treatment of Vascular Cognitive Impairment
SUSAR: Suspected Unexpected Serious Adverse Reaction
VCI: vascular cognitive impairment
VUmc: VU University Medical Center
VVLT-15: Visual Verbal Learning Test-15
WMH: white matter hyperintensities

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Protocol

Investigating the Impact of Hearing Aid Use and Auditory Training on Cognition, Depressive Symptoms, and Social Interaction in Adults With Hearing Loss: Protocol for a Crossover Trial

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Abstract

Background: Sensorineural hearing loss is the most common sensory deficit among older adults. Some of the psychosocial consequences of this condition include difficulty in understanding speech, depression, and social isolation. Studies have shown that older adults with hearing loss show some age-related cognitive decline. Hearing aids have been proven as successful interventions to alleviate sensorineural hearing loss. In addition to hearing aid use, the positive effects of auditory training—formal listening activities designed to optimize speech perception—are now being documented among adults with hearing loss who use hearing aids, especially new hearing aid users. Auditory training has also been shown to produce prolonged cognitive performance improvements. However, there is still little evidence to support the benefits of simultaneous hearing aid use and individualized face-to-face auditory training on cognitive performance in adults with hearing loss.

Objective: This study will investigate whether using hearing aids for the first time will improve the impact of individualized face-to-face auditory training on cognition, depression, and social interaction for adults with sensorineural hearing loss. The rationale for this study is based on the hypothesis that, in adults with sensorineural hearing loss, using hearing aids for the first time in combination with individualized face-to-face auditory training will be more effective for improving cognition, depressive symptoms, and social interaction rather than auditory training on its own.

Methods: This is a crossover trial targeting 40 men and women between 50 and 90 years of age with either mild or moderate symmetric sensorineural hearing loss. Consented, willing participants will be recruited from either an independent living accommodation or via a community database to undergo a 6-month intensive face-to-face auditory training program (active control). Participants will be assigned in random order to receive hearing aid (intervention) for either the first 3 or last 3 months of the 6-month auditory training program. Each participant will be tested at baseline, 3, and 6 months using a neuropsychological battery of computer-based cognitive assessments, together with a depression symptom instrument and a social interaction measure. The primary outcome will be cognitive performance with regard to spatial working memory. Secondary outcome measures include other cognition performance measures, depressive symptoms, social interaction, and hearing satisfaction.

Results: Data analysis is currently under way and the first results are expected to be submitted for publication in June 2018.

Conclusions: Results from the study will inform strategies for aural rehabilitation, hearing aid delivery, and future hearing loss intervention trials.

Trial Registration: ClinicalTrials.gov NCT03112850; https://clinicaltrials.gov/ct2/show/NCT03112850 (Archived by WebCite at http://www.webcitation.org/6xz12fD0B).

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KEYWORDS

sensorineural hearing loss; hearing aids; crossover design

Introduction

Background and Rationale

Hearing loss is a common experience for older adults and is one of the leading causes of nonfatal disease burden for Australians aged 65 years and older [1,2]. Sensorineural hearing loss or presbycusis is the most prevalent hearing-related chronic condition affecting this population; however, it is often underdetected and undertreated. This type of hearing loss cannot be medically or surgically treated [3-6]. The number of adults who suffer from sensorineural hearing loss worldwide is likely to increase rapidly as the population ages [7].

Recent studies have reported that hearing loss among older adults is strongly and independently associated with accelerated cognitive decline [8-13]. Epidemiologic and longitudinal studies have demonstrated that older people aged between 70 and 79 years with hearing impairment, who live in the community, have a 24% increased risk of a decline in cognitive function and may experience a 30% to 40% higher rate of cognitive decline over a 6-year period than those without hearing loss [9,14,15]. The proposed theories to explain the above association relate to the effects of hearing loss on cognitive load and cognition reserve, and the effects of hearing impairment on brain structure and shared pathologic etiology, social isolation, and depressive symptoms [13]. Social isolation and communication impairments caused by hearing loss are known to lead to loneliness and depression in older adults [16,17], often resulting in a negative perception of one's own health and a decline in daily activities, with associated declines in cognitive performance.

In aural rehabilitation, hearing aid use and auditory training strategies contribute to improving auditory abilities. The basic function of hearing aids is acoustic amplification of sound signals with the aim of restoring the audibility of sounds, thus helping to improve speech perception [18]. Studies have examined the effects of hearing aid use by older adults on a broad range of cognitive functions, such as information-processing speed, memory, and verbal fluency. Preliminary research evidence has suggested that hearing aids may improve the cognitive abilities, social, emotional, psychological, and physical well-being of people [18-21]. Some studies reporting the cognitive and psychological benefits of using hearing aids in elderly people have shown that the effects of hearing aid use are most distinctive in the early periods of use [6]. Despite the high prevalence of hearing loss in older adults, and the consequences for health outcomes, people are generally slow to acquire hearing aids [22]. Less than 25% of people who would benefit from hearing aids actually own them [23]. Existing research in this area, attempting to describe the effects of hearing aids on cognition, often assessed global mental status rather than cognitive performance and often examined only a single measure of hearing [6,19,24], thus limiting the insights gained. These studies also lack data on the duration of hearing impairment and loosely define hearing aid use as the self-reported use of a hearing aid in either or both ears, thus making it unclear about how hearing loss may affect performance on measures of cognition.

Auditory training is the use of instruction, drill, or practice, designed to increase the amount of information that hearing contributes to a person's total perception [25]. For example, a person with a hearing impairment who is fitted with a new hearing aid may benefit from instruction and practice in recognizing sounds through the aid. Research has shown that new hearing aid users show greater benefit from auditory training than experienced hearing aid users [26]. Auditory training also shares processes in common with cognitive training for improving working memory, attention, and communication. Studies have shown that auditory training can produce prolonged cognitive performance improvements [27,28] and improve speech understanding [29,30]. Other studies have shown that the benefits of training for people with hearing loss in terms of improved speech understanding are best achieved if an integrated auditory-cognitive training approach is adopted [31].

Although the concept of auditory training is not new, its popularity has declined in recent years, and only a small proportion of audiologists (fewer than 10%) offer auditory training to patients with hearing impairment [32]. Also, limited auditory training effort has been directed toward adults with impaired hearing, and the focus of auditory training has historically been directed toward young children with profound or severe to profound hearing loss [33,34].

Studies have investigated the effects of auditory training with laptops and computers, such as with the Listening and Communication Enhancement (LACE) software, on generalization to speech perception, self-report of communication difficulties, and cognition [27,28,33]. The results of these studies have often demonstrated the efficacy of auditory training, despite the computerized method of auditory training perhaps resulting in lower compliance with training protocols [32]. In addition, Saunders et al [35] found that LACE training did not result in improved outcomes over a standard-care hearing aid intervention on its own. Furthermore, according to research studies [36,37], there are still a large number of outstanding questions on the benefits of auditory training, such as which aspects of auditory training protocols contribute to learning, how auditory training generalizes to benefits in everyday communication, how individual characteristics interact with training outcomes to identify candidacy for auditory training, and the identification of outcome measures that are appropriate and sufficiently sensitive.

Research has shown that hearing aid devices alone do not always adequately compensate for sensory losses despite significant technological advances in digital technology [38]. Therefore, the focus of intervention will consider face-to-face auditory training in conjunction with a hearing aid device, whereas the comparator (control) group will consider individualized face-to-face auditory training on its own.

Study Objective

Extending upon preliminary findings [27,28,36], the objective of this study is to investigate whether wearing hearing aids will improve the impact of individualized face-to-face auditory training on cognition, depression, and social interaction for adults with sensorineural hearing loss in a crossover intervention trial.

The study is based on the following hypotheses:

1. In adults with sensorineural hearing loss, hearing aids in combination with face-to-face auditory training will be more efficient for improving cognition than face-to-face auditory training on its own.
2. In adults with sensorineural hearing loss, hearing aids in combination with face-to-face auditory training will be more efficient for improving depression and social interaction than face-to-face auditory training on its own.

Methods

Trial Design

This study has a randomized crossover trial design. It attained ethics approval on July 22, 2016 (Swinburne's Human Research Ethics Committee protocol number SHR Project 2016/159).

All participants will undergo an individualized face-to-face auditory training program for a period of 6 months and will be randomly allocated to one of the following groups:

1. Participants who will be fitted with hearing aids only for the first 3 months of the auditory training program—*Group A.*
2. Participants who will be fitted with hearing aids only for the last 3 months of the auditory training program—*Group B.*

Participants will be tested at baseline, and at 3 and 6 months in terms of cognition, depressive symptoms, social interaction, and hearing satisfaction.

A crossover design is chosen to allow each participant to serve as their own control [39]. Group A participants will have the option to withdraw from the study after 3 months if they decide to purchase hearing aids immediately. Similarly, group B participants will also have the option of withdrawing from the study at any time. As all participants will receive auditory training for the entire duration of the study to address their hearing loss, participants will benefit from the study even when the hearing aid intervention is not in place.

Study Setting

This study is set in Melbourne, Australia. The study will recruit men and women who are living independently—both in supported independent living accommodation and living independently in the community.

Eligibility Criteria

To be eligible to participate in the study, participants must satisfy all of the following criteria:

1. Be aged between 50 and 90 years
2. Have a good working knowledge of English
3. Have mild (26-40 dB) or moderate (41-70 dB) symmetric sensorineural hearing loss with a pure-tone average threshold of 0.5 to 4 kHz in both ears
4. Have never worn hearing aids previously
5. Be willing to wear hearing aids for 3 months
6. Be willing to undergo weekly auditory training for a period of 6 months
7. Be willing to provide written consent to participate in the study

Exclusion Criteria

Participants will be unable to participate in the study if they have any significant visual impairment that would prevent reading or performing computer-based tasks requiring color recognition. Additionally, study participants with severe or profound hearing loss will not be eligible to take part in the study. Finally, participants with suspected cognitive impairment (defined as a score ≤24 on the Mini-Mental State Examination [MMSE]) will be excluded.

Intervention

Fitting of Hearing Aids for Group A and Group B Participants

Participants will be loaned and fitted with 2 Blamey Saunders hearing aids known as LOF (LOF is the current trade name used by the manufacturer for the model of hearing aid in this study. The name LOF was derived from its original name, Liberty Open-Fit). The hearing aids will be fitted to participants according to the Blamey and Saunders protocol and using the prescription procedures from the National Acoustics Laboratories (NAL) protocol for fitting hearing aids as a guide [40]. Explanation of the hearing aid usage, insertion of the aids and batteries, along with a step-by-step guide on how to use the hearing aid will also be provided. To increase hearing aid compliance, support will be provided post fitting (after 1 month) to make sure that each participant is progressing with his or her hearing aid. Counseling and other compliance-improving policies [41-43] will be provided when participants receive their new hearing aids and at their postfitting appointment. An automatic internet-based data logging function installed in the hearing aids will be used to assess hours of hearing aid use.

Auditory Training

Historically, auditory training has been provided in a face-to-face setting that centered on a range of auditory skills, including detection, discrimination, identification, and comprehension. Training often incorporated both drill-like activities, described as analytic therapy activities, and paragraph comprehension activities, which were synthetic in nature. For both activities, the auditory skills that were trained used various

stimuli such as syllables, words, phrases, sentences, and continuous discourse [38].

All participants enrolled into the study will undergo weekly individualized face-to-face auditory training for a period of 6 months. Over the 6-month period, each participant will participate in two 12-week individualized speech tracking programs. Participants living in supported independent living accommodation will attend their auditory training sessions at their place of residence, once per week for the 6-month period. Participants living independently in the community will attend their auditory training sessions once per week at Swinburne University of Technology. Each auditory training session will last for approximately 15 min.

The type of counseling intervention that will be provided to participants is called Continuous Discourse Speech Tracking [44]. A key aspect of this approach is that the training will involve interaction (a vital component of real-life communication) between the researcher and the participants. In this process, the researcher will articulate a sentence or phrase in a novel or short story, and the task of the participant will be to repeat back verbatim the sentence or phrase. If the repetition is correct, the researcher will articulate the next phrase or sentence. If the repetition is incorrect, the researcher will repeat the phrase or sentence, or a portion of it, or may use other repair strategies, until the sentence or phrase is correctly repeated in its entirety. The procedure will be timed for 15 min and scored in number of words per minute transmitted. Tracking rate will be calculated as the number of words correctly repeated divided by the time elapsed.

This program is adopted for this sample population because training materials could be tailored to the personal interests of participants. The materials chosen for the speech tracking program will consist of short stories, which will be long enough to last for a full 12-week program. A new story will be started at the beginning of each 12-week program.

Outcome Measures

The primary outcome measure will be changes in cognitive performance as measured by the spatial working memory component of the Swinburne University Computerized Cognitive Assessment Battery (SUCCAB). Reliability and validity assessment has demonstrated that the SUCCAB, especially the spatial working memory component of this battery, is sensitive to aging and intervention and correlates strongly with memory subsets in the Wechsler Adult Intelligence Scale –Fourth Edition [45-47].

Secondary measures include the other SUCCAB cognition measures, social interaction measured using the Berkman-Syme Social Network Index, and depressive symptoms measured using the Geriatric Depression Scale (GDS). Hearing satisfaction (with or without hearing aids) will be measured using the Abbreviated Profile of Hearing Aid Benefit (APHAB) Inventory.

All outcomes will be measured at baseline, after 3 months, and after 6 months (Table 1).

Table 1. Schedule of enrollment, interventions, and assessments for study.

Time points	Prescreening telephone call	Baseline assessment T_0 (<24 days following screening)	Study assessment T_1 (3-month follow-up)	Study assessment T_2 (6-month follow-up)
Enrollment				
Explain study	X[a]			
Screen eligibility criteria	X			
Outcome measures				
SUCCAB[b] testing		X	X	X
GDS[c]		X	X	X
Berkman-Syme		X	X	X
APHAB[d]		X	X	X
Randomization after completion of all baseline assessment		X		
Interventions				
Auditory training				
Hearing aid for Group A participants				
Hearing aid for Group B participants				

[a]X: Task to be completed.

[b]SUCCAB: Swinburne University Computerized Cognitive Assessment Battery.

[c]GDS: Geriatric Depression Scale.

[d]APHAB: Abbreviated Profile of Hearing Aid Benefit.

Participant Timeline

Participant prescreening and assessment will take place at information sessions that will be held at several independent living aged care facilities located in Melbourne and at Swinburne University of Technology. Independent living aged care facilities with existing relationships with Swinburne University of Technology will be chosen. Participants attending information sessions at Swinburne University will be individuals in the community who have expressed interest in assisting with research projects run by the university, and have therefore provided their contact information to be stored in Swinburne's Centre for Human Psychopharmacology (CHP) database. After providing informed consent, eligible participants will be randomized into 2 equal groups (A and B) for the study, as described in Figure 1.

Sample Size

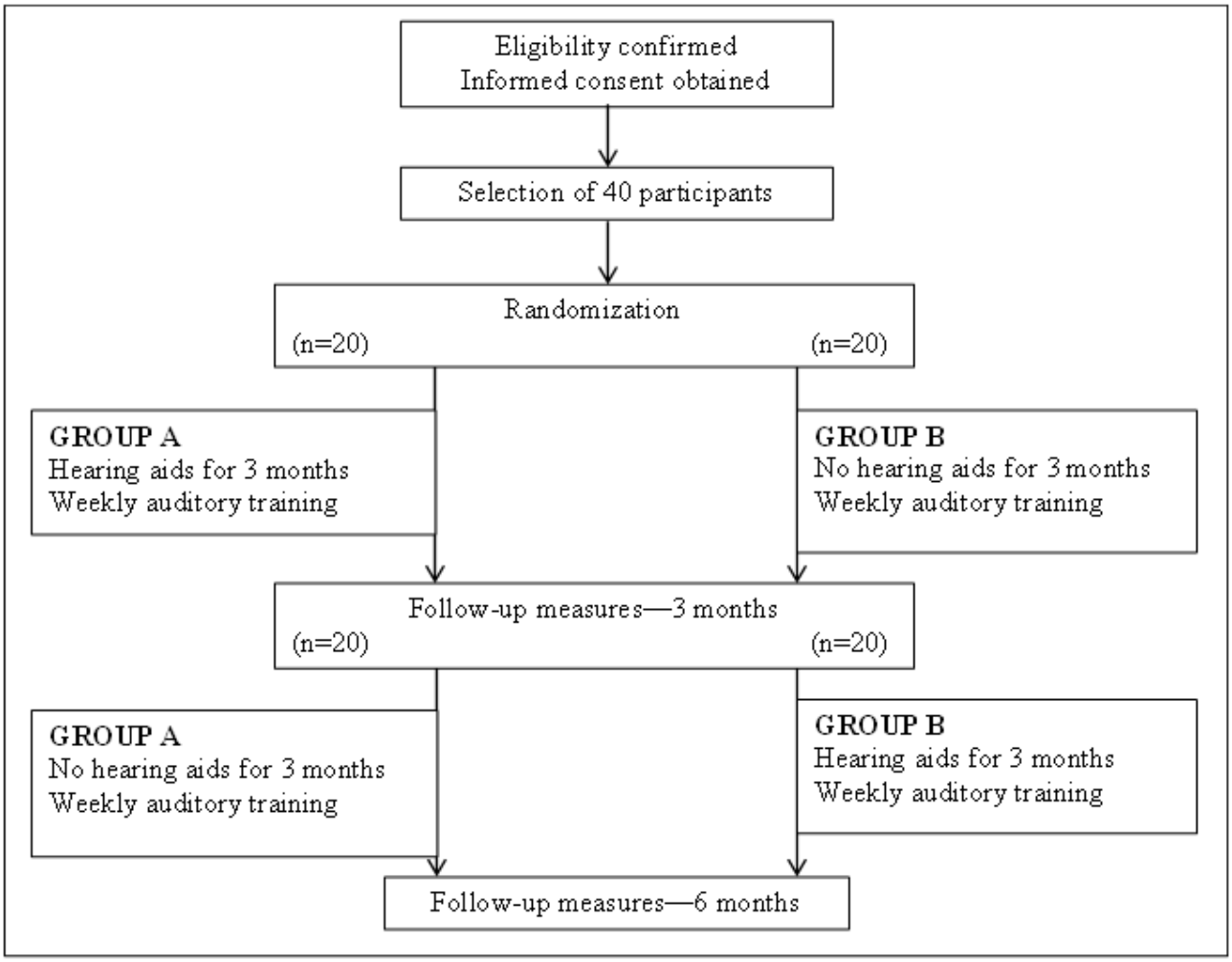
Allowing for 2.5% significance, 80% power, and a moderate effect size (f=0.25), a power analysis indicated that a repeated measures mixed effects design with 3 repeated measures required a total sample size of 34 participants, split evenly between the 2 groups. This allows for the comparison of changes from baseline to 3 and 6 months for the 2 groups. Except for participants from Swinburne's CHP database who will need to travel to attend their auditory training sessions at Swinburne University, all other participants will attend their appointments at their facilities. As a result, only a 10% allowance was made for attrition resulting in an overall sample size of 40.

Recruitment

Aged care facility managers will be contacted by telephone to explain the study. If an aged care facility shows interest in the study, researchers will visit the facility to provide the facility manager with more detailed written and oral information. If the facility manager consents for their facility to participate in the study, the study will be advertised at the facility and promotional materials will be distributed to all the residents, inviting them to an information session. Participants from the CHP database will be contacted by the researchers either by telephone or email to explain the study, and participants who express interest will be invited to attend an information session.

At the information session, researchers will explain the purpose and significance of the study. At the same time, a preselection screening will be conducted to identify participants who are willing to wear hearing aids and undergo auditory training to address their hearing loss. Selected participants will be sent a Participant Information and Consent Form package that includes detailed information on the study procedure, a consent form, and a return prepaid envelope. Once written consent is received, participants will be invited to complete baseline measures before enrollment into the study. Recruitment commenced in December 2016.

Figure 1. Participant flow diagram.



Assignment of Interventions

Allocation

Groups will be matched in terms of the degree of hearing loss (mild or moderate) with 1 member from each matched pair randomly assigned to *Group A* and the other member of each matched pair assigned to *Group B*. Allocation will be performed using a system of envelopes prepared and opened by the researcher at the time of recruitment.

Blinding

Given the nature of the intervention, this study will not be blinded as both investigators and participants will know who is wearing hearing aids in each 3-month period.

Measures

Screening

All enrolled participants will not be cognitively impaired and will be screened for adequate cognitive functioning using MMSE. Participants scoring 24 or lower on MMSE will not be eligible for participation.

Swinburne University Computerized Cognitive Assessment Battery

SUCCAB is a validated computer-based cognitive battery consisting of 8 measures that were developed, based on cognitive and neuroimaging literature, to focus on cognitive domains that were most likely to decline with increasing age [45]. Studies using this battery have shown cognitive changes sensitive to interventions in 5 to 16 weeks [47,48]. The SUCCAB battery uses a simple 5-button interface and has been validated in other studies involving the elderly [49,50]. The 8 measures of cognitive tests assessed by SUCCAB consist of Simple and Choice Reaction Times, Immediate and Delayed Recognition, Congruent and Incongruent Stroop color-words, Spatial Working Memory, and Contextual Memory.

A performance score for each task will be calculated as the ratio of accuracy and reaction time. This approach takes into account variations in accuracy and response time because of speed versus accuracy trade-offs in performance.

Hearing Assessments

Participants will undergo the following hearing assessments:

Otoscopy and Tympanometry

Following otoscopy, all participants will undergo tympanometry and acoustic reflex testing to assess the status of the middle ear.

Pure Tone Audiometry in Each Ear

To understand the degree of hearing impairment and classify participants according to the type of hearing loss, hearing ability will be measured at threshold frequencies 0.5, 1, 2, 3, 4 kHz in both ears. The choice of frequency to be tested corresponds to the amplification range of most modern hearing aids and is consistent with capturing sensitivity at frequencies affected by sensorineural hearing loss and noise-induced damage. Only participants with either mild or moderate symmetric sensorineural hearing loss will be included in the study.

Blamey Saunders Speech Perception Test

A Web-based Speech Perception Test (SPT) will be used in addition to the standard audiogram for the purpose of measuring hearing loss. SPT is a monosyllabic word test used to characterize the form and degree of hearing loss [23]. There will be 5 SPT evaluations altogether: SPT will be performed without hearing aids at baseline, after 3 months, and then at 6 months for all participants included in the trial. It will also be performed with hearing aids immediately after participants are fitted with hearing aids for the first time and at the end of 3 months of auditory training while wearing a hearing aid.

Paper-Based Questionnaire

Participants will complete a paper-based questionnaire, which will be structured in the following sections:

Demographics

Information on a variety of demographic variables will be collected to describe the characteristics of the study sample.

Geriatric Depression Scale

GDS is a self-rating screening scale for measuring levels of depressive symptoms in elderly population [51]. The short version of GDS will be used [52]. The GDS has been found to be a reliable and valid measure of depressive symptoms [53] and to be highly correlated with other measures of such symptoms. GDS was designed for older adults. Items are scored dichotomously (respondents answer “Yes” or “Not” to 5 items). Items assess nonsomatic aspects of depression, thus allowing for discrimination between respondents with depressive symptom and those with medical problems. A cut-off GDS score of 7 will be used, with a score greater than 7 indicating the presence of depression. Participants will answer GDS at baseline, after 3 months, and then at 6 months.

Social Interaction Measure

The Berkman-Syme Social Network Index [54] will be used to assess participants’ social interaction and connections with families and friends. Participants will answer the Berkman-Syme Social Network Index at baseline, after 3 months, and then at 6 months.

Abbreviated Profile of Hearing Aid Benefit

APHAB [55] is a self-assessment inventory that will be answered by each participant to assess hearing satisfaction (with or without hearing aids). Participants will answer APHAB at baseline, after 3 months, and after 6 months. Four scales of the APHAB will be assessed, namely, (1) ease of communication, (2) effects of background noise, (3) effects of reverberation, such as listening to sounds across a large room, and (4) aversiveness, which will look at uncomfortable loudness of background sounds such as traffic and alarm bells.

Statistical Analysis

The following statistical analyses will be performed:

1. Baseline comparison of the 2 groups in terms of demographics, cognition, depression, social interaction, hearing loss, and hearing satisfaction by reporting descriptive statistics of each group as randomized, and an effect size of the difference using Cohen's d.

2. Comparison of the 2 groups in terms of changes in cognition, depression, and social interaction from baseline to 3 months and 6 months, using a per protocol approach for the crossover analysis [39] and an intention-to-treat, multilevel model analysis [56]. These methods will be used to estimate any carryover effects [57].
3. Analysis of SPT results with and without hearing aids as a measure of the efficacy of hearing aids and auditory training with and without hearing aids using multilevel models and again allowing for carryover effects.
4. Analysis of the speech tracking rates from the two 12-week programs of speech tracking using a learning model as described by Blamey and Alcantara [25]. This analysis will yield learning and forgetting rates with and without hearing aids. These learning and forgetting rates are valid measures of cognitive processes that are likely to be affected by the use of hearing aids. These data will also be analyzed using multilevel models again allowing for carryover effects.
5. Analysis of the aided and unaided scores from APHAB will be used to assess how the benefit of hearing aids differed between groups and over degree of hearing impairment (mild/moderate hearing loss).

Results

This investigation was funded by the Australian Research Council and Blamey and Saunders Hearing Pty Ltd under the Industry Transformation Training Centre Scheme (ARC Project No. IC140100023). The study protocol was reviewed and approved by Swinburne's Human Research Ethics Committee (SUHREC) on July 22, 2016, protocol number SHR Project 2016/159. The trial is registered in ClinicalTrials.gov with identifier NCT03112850. Recruitment commenced in December 2016 and was completed in June 2017. Researchers obtained written consent from all participants before participating in this trial.

The integrity of the trial, including data collection and monitoring, trial progress, adverse events, and compliance with SUHREC reporting procedures will be overseen by the chief (DM) and associate investigators. No serious adverse events are anticipated. The study coordinator (JN) is responsible for communicating protocol changes to relevant stakeholders, including ClinicalTrials.gov registry.

Data analysis is currently under way and the first results are expected to be submitted for publication in June 2018.

Discussion

Chronic hearing loss can have a negative impact on several domains of aging such as social engagement, activity, vitality, physical mobility, and cognitive health. Interventions that can significantly delay the onset of sensorineural hearing loss or slow its progression are being actively pursued; however, no disease-modifying treatment is currently available. Understanding the best strategies for aural rehabilitation in older people in whom hearing could compensate for other physical or sensorial limitations may help mitigate cognitive decline.

A limitation of the study is that, it will recruit community-dwelling adults who are not cognitively impaired; hence, they may not show improvement in cognitive functioning because of their high baseline scores. However, by focusing on community-dwelling adults, this research will be able to examine the efficacy of programs aimed at minimizing cognitive decline and reducing the rate of transfer to low- and high-care accommodation.

For the study intervention, auditory training is being used as the comparator rather than hearing aids, which is popularly known as the main clinical management approach for addressing hearing loss. Although this may be a limitation, the concept of auditory training is not new for addressing hearing loss, as its inception can be traced back to the birth of audiology decades ago, when aural rehabilitation programs were first created for people who had suffered hearing loss [58]. Today, auditory training is a common intervention that is effective and is still used in routine practice for pediatric clients who receive rehabilitation services [59] and with clients who receive cochlear implants [60,61]. It is hoped that with individualized face-to-face auditory training as the comparator for this study, participants will be actively involved in the rehabilitation process, leading to increased compliance in terms of hearing aid usage. Auditory training plus hearing aids will also allow us to know whether hearing aids provide any added benefit to face-to-face auditory training.

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Authors' Contributions

JN conceived the study. DM, JN, and PB designed the study. All authors were involved in drafting the protocol. All authors read and approved the final protocol.

Conflicts of Interest

JN, DM, AP, and SB declare that they have no competing interests. PB is co-owner of Blamey & Saunders Hearing Pty Ltd, the company that sells the hearing aids used in this study. Blamey & Saunders is a profit-for-purpose company with an interest in improving benefits and outcomes for hearing aid users.

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Abbreviations

APHAB: Abbreviated Profile of Hearing Aid Benefit
CHP: Centre for Human Psychopharmacology
GDS: Geriatric Depression Scale
LACE: Listening and Communication Enhancement
LOF: Liberty Open-Fit
MMSE: Mini-Mental State Examination
SPT: Speech Perception Test
SUCCAB: Swinburne University Computerized Cognitive Assessment Battery

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Protocol

Improving Transplant Medication Safety Through a Pharmacist-Empowered, Patient-Centered, mHealth-Based Intervention: TRANSAFE Rx Study Protocol

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Abstract

Background: Medication errors, adverse drug events, and nonadherence are the predominant causes of graft loss in kidney transplant recipients and lead to increased healthcare utilization. Research has demonstrated that clinical pharmacists have the unique education and training to identify these events early and develop strategies to mitigate or prevent downstream sequelae. In addition, studies utilizing mHealth interventions have demonstrated success in improving the control of chronic conditions that lead to kidney transplant deterioration.

Objective: The goal of the prospective, randomized TRANSAFE Rx study is to measure the clinical and economic effectiveness of a pharmacist-led, mHealth-based intervention, as compared to usual care, in kidney transplant recipients.

Methods: TRANSAFE Rx is a 12-month, parallel, two-arm, 1:1 randomized controlled clinical trial involving 136 participants (68 in each arm) and measuring the clinical and economic effectiveness of a pharmacist-led intervention which utilizes an innovative mobile health application to improve medication safety and health outcomes, as compared to usual posttransplant care.

Results: The primary outcome measure of this study will be the incidence and severity of MEs and ADRs, which will be identified, categorized, and compared between the intervention and control cohorts. The exploratory outcome measures of this study are to compare the incidence and severity of acute rejections, infections, graft function, graft loss, and death between research cohorts and measure the association between medication safety issues and these events. Additional data that will be gathered includes sociodemographics, health literacy, depression, and support.

Conclusions: With this report we describe the study design, methods, and outcome measures that will be utilized in the ongoing TRANSAFE Rx clinical trial.

Trial Registration: ClinicalTrials.gov NCT03247322: https://clinicaltrials.gov/ct2/show/NCT03247322 (Archived by WebCite at http://www.webcitation.org/6xcSUnuzW)

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KEYWORDS

telemedicine; mhealth; transplant; clinical trial; errors; adherence

Introduction

Kidney transplantation is considered the preferred treatment option for patients with end-stage renal disease, with more than 140,000 patients living in the U.S. with a functioning transplant [1]. The use of potent contemporary immunosuppression has significantly decreased acute rejection rates, with current one-year rates of <10%, compared to 30%-40% three decades prior [2-4]. Despite this, long-term renal allograft survival remains largely unchanged during this time period. Studies have demonstrated that predominant causes of graft loss are driven by immunosuppression adverse drug events (ADE) (patient harm related to a medication) and rejection from medication nonadherence (MNA) [5-7]. These origins of graft loss encompass issues directly related to medication safety. Current immunosuppression regimens are highly effective but carry the burdens of considerable toxicities and exceeding complexity [8]. These attributes place a transplant patient at high risk of developing ADEs and medication errors (ME). Several studies suggest that ADE, particularly surrounding infection from over-immunosuppression and calcineurin inhibitor nephrotoxicity, may be a predominant cause for the discordance noted between reductions in acute rejection and lack of improvements in graft survival. In 2006, Parasuraman, et al. demonstrated that infectious etiologies surpassed rejections as the leading cause of death-censored graft lost [7]. Despite this, there are limited studies analyzing the incidence, etiologies, and outcomes associated with medication safety issues [9,10].

Our formative research has demonstrated that MEs (taking a med in a manner not intended), predominantly due to patient-related factors, occur in nearly two-thirds of kidney transplant recipients, leading to hospitalization in 1 out of every 8 recipients [11,12]. Further, we found that recipients that develop clinically significant MEs are at considerably higher risk of deleterious clinical outcomes, most significantly graft loss; these patients also develop substantially more ADEs, readmissions, and acute rejections [11,12]. We have also demonstrated that immunosuppressant ADEs are correlated with MEs; patients that experience MEs leading to hospitalization have 2.3 times the risk of developing at least three ADEs (P=.02, Table 1) [12]. In other chronic disease states, ADEs have clearly been established as a major risk factor for MNA [13-15]. Therefore, early recognition of ADEs in kidney transplant recipients will likely help prevent downstream clinical sequelae, including MNA and irreversible immunosuppressant toxicities. Research demonstrates that clinical pharmacists have the unique education and training to identify these events early, as well as developing strategies to mitigate or resolve the associated sequelae [16-21].

Objectives

Due to the complexities and toxicities associated with their immunosuppressive medication regimens, kidney transplant recipients are at high risk of developing medication safety issues which can lead to hospitalization, increased healthcare expenditures, and ultimately graft loss. Founded on preliminary information, the use of pharmacists and mobile health (mHealth) technology provide a promising and innovative approach to improve medication safety in high-risk patients. The ultimate goal of this research is to demonstrate how patients, pharmacists, and technology can work hand-in-hand to optimize medication-related outcomes and reduce healthcare expenditures.

Methods

Study Design

TRANSAFE Rx is a 12-month, parallel, two-arm, 1:1 randomized controlled clinical trial involving 136 participants (68 in each arm) and measuring the clinical and economic effectiveness of a pharmacist-led intervention which utilizes an innovative mHealth application to improve medication safety and health outcomes, as compared to usual post-transplant care. This study has been approved by the local Institutional Review Board (IRB) and conforms to the clinicaltrial.gov guidelines.

Aims

The primary aim of the TRANSAFE Rx study is to compare the incidence, severity, and etiologies of MEs and ADEs in kidney transplant recipients under normal care with recipients randomized to a pharmacist-led innovative mHealth intervention. Secondarily, we will compare the total resources utilized to provide care between the cohorts and measure the impact of MEs and ADEs on clinical outcomes.

Recruitment, Screening, and Enrollment Procedures

Adult (≥18 years old at the time of transplant) solitary kidney transplant recipients 6 to 36 months posttransplant that meet study eligibility will be identified through review of patients visiting the kidney transplant clinic as part of usual care and approached by research personnel for consideration for participation. Patients will be required to complete an informed consent document to ensure they understand the goals, risks, and potential benefits of the study before any research related activities occur. Patients will be randomized into one of the two groups by random selection using a random number generator in a simple blocked manner (blocks of 8). Due to the nature of the intervention, complete blinding of the subject and research staff is unable to be performed. In order to minimize bias, data for MEs, ADEs and clinical outcomes will be collected by blinded study coordinators and clinical pharmacists.

Eligibility

Inclusion criteria

Participants must be adult (≥ 18 years of age) kidney transplant recipients between 6 and 36 months posttransplant and their primary transplant physician must agree that they may participate.

Exclusion criteria

We will exclude multi-organ transplant recipients and any patient that is incapable of measuring their own blood pressure and blood glucose (if applicable); self-administering medications; speaking, hearing and reading English; or utilizing the mHealth application after sufficient training.

Table 1. Televisit schedule based on patient risk.

Risk Level	Definition	Scheduled Televisits	Triggered Televisits
High	Meets 2 or more of the following High-Risk Criteria: • <80% adherence to medications • Missed clinic visits • Blood pressure outside of 20% of goal • <80% of blood sugars within goal range • Moderate to severe side effects	Twice Monthly	• Patient-reported medication change or initiation • New severe medication side effect • Critical home values of blood pressures or glucoses • Any transition in care
Moderate	Meets 1 of the High-Risk Criteria	Monthly	
Low	Does not meet any of the High-Risk Criteria	None Necessary	

Sample Size Requirements

Based on previous studies conducted by our research collaborative, we estimate that approximately 64% of kidney transplant recipients in the control group will experience at least one ME during the one year study (defined using the Overhage criteria) [12,17]. Our previous research demonstrates that pharmacist-led initiatives can reduce these MEs by approximately 50% [14,15]. Using these estimates, enrolling 104 participants (52 in each cohort), will provide 92% power in detecting a statistically significant difference in ME event rates, with a two-tailed α=0.05. We will also have 94% power (two-tailed, α=0.05) to detect a 33% reduction in significant ADEs (CTCAE grade 3 or higher), given an estimated incidence rate of 87% in the control cohort and the strong association between MEs and ADEs [12-15]. From previous analyses, we expect that the control cohort will have a mean of 18.4 (SD 2.6) healthcare encounters (clinic visits, acute care/ER visits and hospitalizations) during the one year study. We estimate the intervention group will see an 8% absolute reduction in total encounters, to a mean 17.0 encounters, with an estimated 33% relative reduction in the mean number of hospital readmissions (1.2 vs 0.8, respectively). A previous study demonstrated a 47% reduction in 30-day readmission rates with a pharmacist-led intervention that improved admit and discharge medication reconciliation accuracy [16]. Although the current study employs a different intervention in a population at lower risk of readmission, we estimated that we could expect a 33% reduction in hospital readmissions within a year based on the previous data. Given these estimates (two-tailed, α=0.05), enrolling 52 patients in each arm will provide 80% power to detect a statistically significant difference. It is estimated that the intervention will also produce a mean cost savings of at least US $2489 per patient (US $7658 in the control cohort and US $5169 in the intervention cohort, with a SD estimated at US $4,530) [12]. This study is expected to have >80% power to detect a statistically significant difference in total posttransplant costs between cohorts, given these estimates.

For the exploratory outcomes of acute rejection, infections, graft function, graft loss, and death, this study is not powered to detect statistically significant differences in these clinical events between groups. However, we expect to demonstrate meaningful clinical signals, particularly with a reduction in acute rejection. Our previous study demonstrated an acute rejection rate that was 1.8 times higher in patients experiencing a significant medication error (13.7% vs 7.7%, respectively) [11]. Thus, we expect an overall acute rejection rate of 12% in the control cohort and 9% in the intervention cohort, corresponding with a 25% relative reduction in acute rejection rates. Based on previous randomized controlled trials conducted within the study institution, we expect to maintain an 85% retention rate. We adjusted our total sample size to 136 patients (68 in each cohort) to account for dropouts, thus maintaining adequate sample size to produce at least 80% power to detect statistically significant differences in the primary outcome measures.

Intervention

Patients randomized to the intervention cohort will be provided the same usual care as the control cohort. In addition, this cohort of participants will receive clinical pharmacist-led supplemental medication therapy monitoring and management, utilizing a smartphone-enabled mHealth app, integrated with televisits and home-based monitoring of blood pressures and glucoses (when applicable). Patients in this cohort will be provided with a mobile device/data plan if they are not current owners of an iPhone version 4 or later (Apple, Cupertino, CA). All will also be provided with a Bluetooth-enabled, automated, cuff-style bicep home blood pressure monitor and a Bluetooth-enabled digital home blood glucose monitor (if the patient has diabetes; ForaCare, Moorpark, CA). On the mobile device, a HIPPA compliant app developed by our collaborative group will be installed that displays the patient's medication list and alerts them when it is time to take each medication, requiring them to indicate if the medication was taken for adherence tracking. Through the app, medication regimen-specific symptom surveys will be pushed to patients that ask the frequency and severity of common side effects of their medications on a monthly basis and on-demand by the subject. The intervention will include a clinical transplant pharmacist telemonitoring subject medication; medical appointment adherence; weekly blood pressure/glucose readings (if applicable); and scheduling telehealth visits with patients, as outlined in Table 1.

The clinical transplant pharmacist will be alerted by the patient if there are medication changes made by outside providers, through a patient-initiated notification on the app in addition to prescription refill monitoring (SureScripts, Arlington, VA). At this point, the patient will be contacted to evaluate the medication change and determine if the adjustment to the regimen is safe and effective. If the pharmacist deems this change to be of concern, they will work with the patient and

prescribing physician to alter the regimen in an appropriate manner. In addition, the pharmacist will be alerted if the patient has evidence of significant nonadherence (≥20% missed self-reported medication doses in the course of a week), if they have blood pressure or glucose values that fall into critical ranges or if there are alarming trends in their readings or symptom assessments from surveys. Upon receiving these alerts, the pharmacist will communicate with the patient, determine the root cause, and coordinate care with other care providers as delineated at the bottom of Figure 1. During televisit encounters, the transplant pharmacist will conduct a thorough medication review, evaluate for signs and symptoms suggestive of medication safety issues, screen for drug-drug and drug-disease interactions and provide recommendations to resolve identified issues to the patient and/or provider, when applicable. The clinical pharmacist will be alerted and evaluate each patient when making a transition of care (emergency room visit, inpatient admission or discharge) to ensure accurate medication regimens are communicated to accepting teams and to the patient. The process used to resolve medication safety issues during distant monitoring is outlined in Figure 2. Once the clinical pharmacist identifies an issue, they will develop a management plan using the algorithm detailed in Figure 2, discuss the recommendations with the providers, agree on a plan, and implement the plan with direct patient follow-up. The algorithm in Figure 2 encompasses the major medication safety issues, including side effects, adherence, drug interactions and less than optimally controlled comorbid disease states. This algorithm is a guideline, and the transplant pharmacist will use this, as well as their clinical judgment and professional experience, to develop the medication safety issue resolution plan.

mHealth Medication Safety Monitoring and Management Tool

Patients in the intervention cohort will have enhanced medication safety monitoring utilizing an integrated mHealth system, coalescing the EHR (EPIC, Verona, WI) with an application developed by our research collaborative and FORACare telehealth systems to provide a seamless, bidirectional, patient-centered, home-based monitoring tool that will allow for early, effective, and efficient identification of medication safety issues by the clinical transplant pharmacist. The application will provide patients with useful tools to conduct self-care monitoring and management, including timely reminders to take medications; automated messages when patients miss multiple medication doses or scheduled health monitoring; tracking of medication side effects; and reporting of trends in blood pressures and glucoses (when applicable). Using our foundational research and through previous collaborations, we have partnered with Technology Applications Center for Healthful Lifestyles (TACHL) to incorporate monitoring tools and patient questionnaires that will minimize intrusions, while maximizing the potential of identifying medication safety issues, including MEs, nonadherence and ADEs, early in their course (Figure 3).

Figure 1. Pharmacist process to resolve medication safety issues.

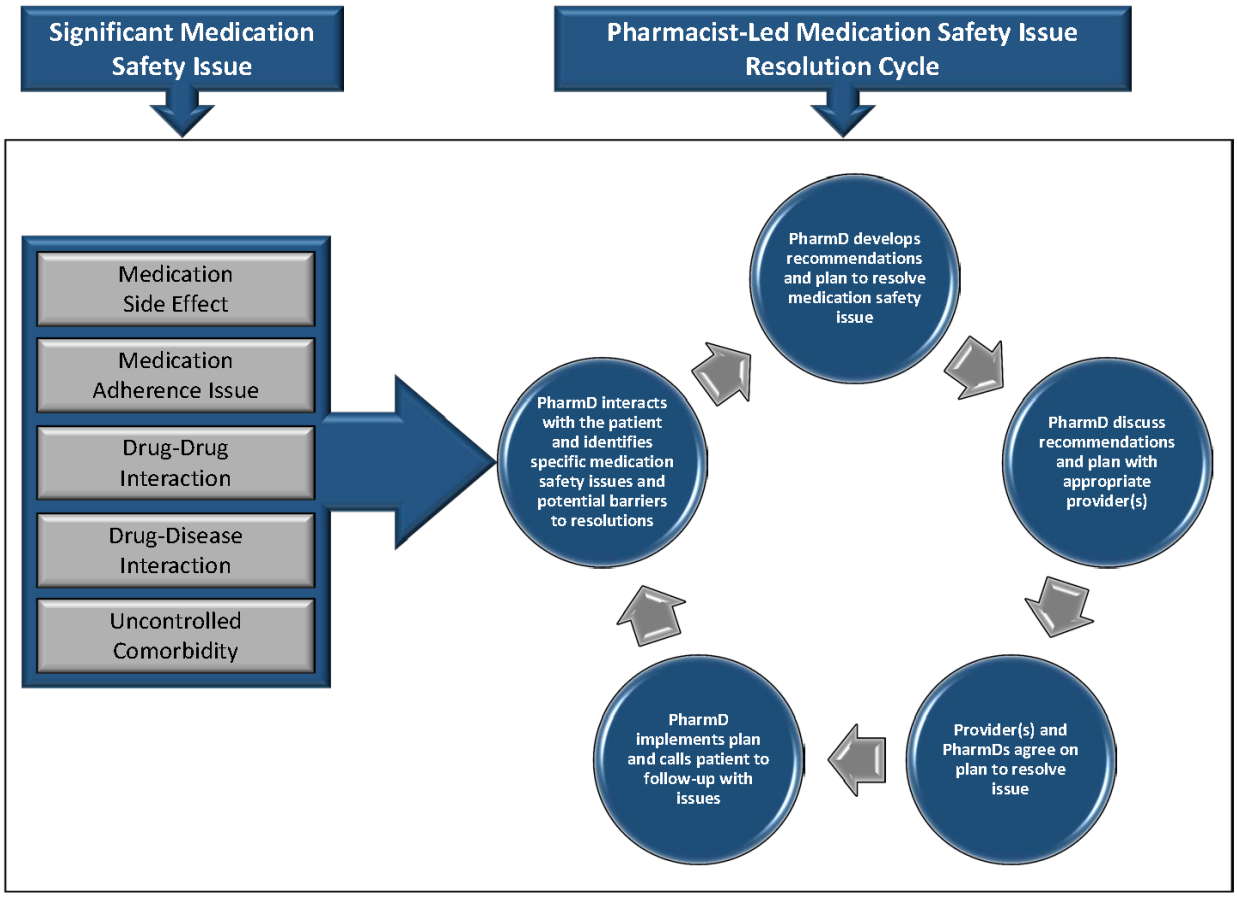
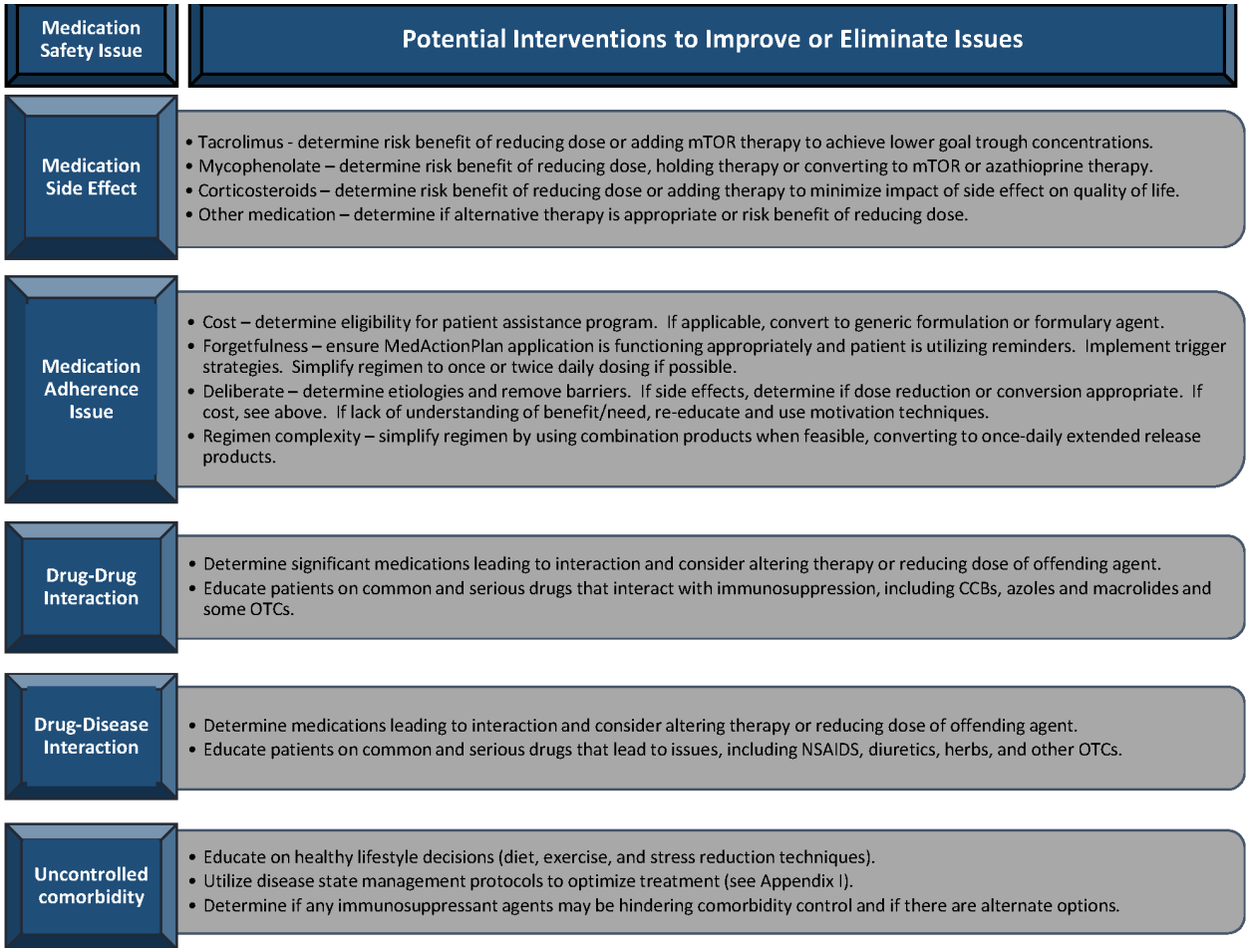


Figure 2. Predominant medication safety issues with mitigating interventions.



Safety Monitoring

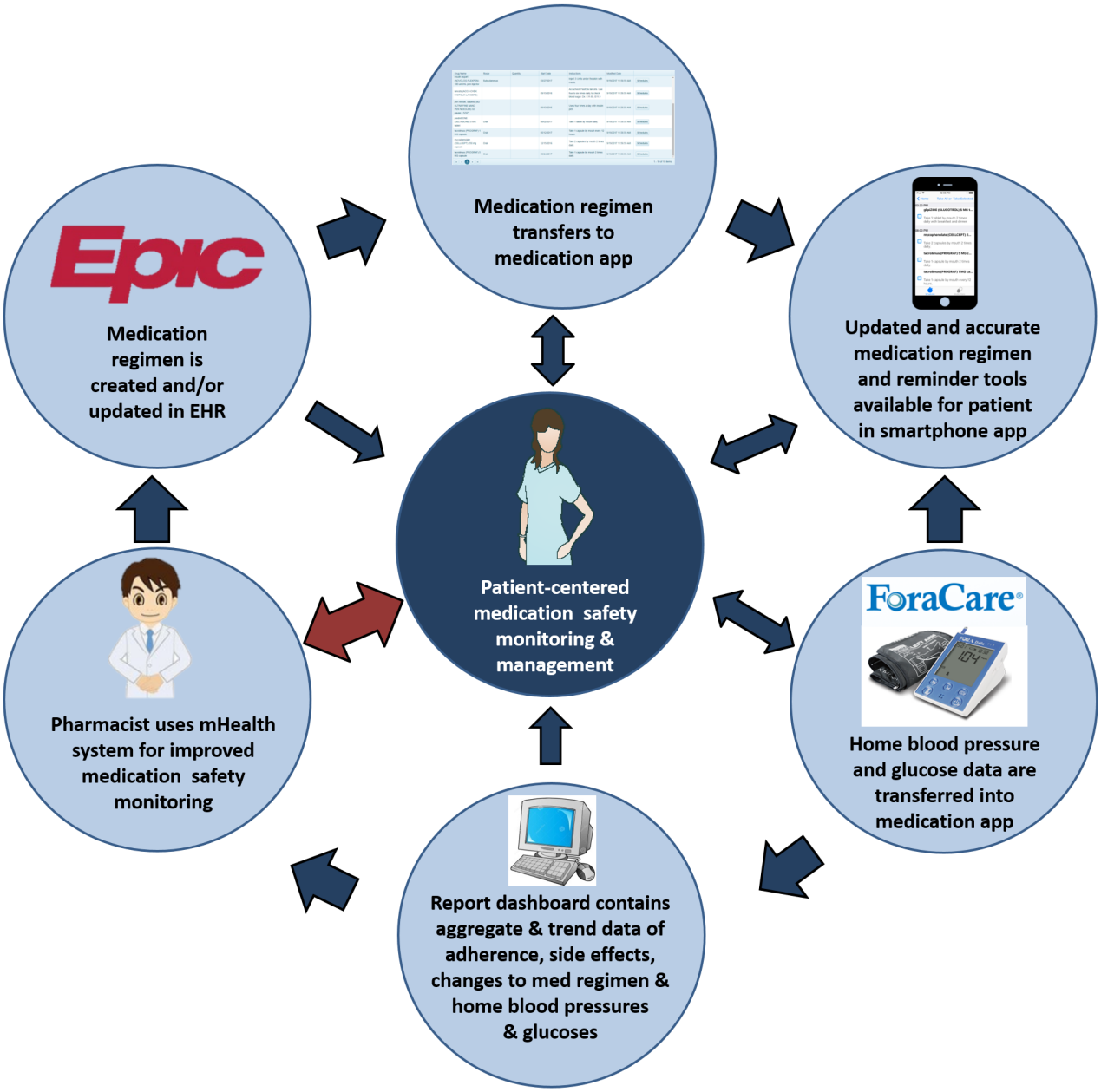
The data safety monitoring plan (DSMP) includes the use of a safety officer, with overarching IRB oversight, to monitor the study-related clinical outcomes, medication side effects, and adverse events. Additionally, the DSMP will utilize the study statistician to review the data generated by the TRANSAFE Rx study and ensure data integrity. Summaries of adverse event reports and patient safety concerns raised by the safety officer will be made to AHRQ in yearly progress reports unless the nature of a particular event is such that it bears reporting to the NIH immediately.

Both the safety officer and the biostatistician will coordinate data review and analysis and work closely with the study Principle Investigator (PI) and the co-investigators. The functions of the designated safety officer are to: 1) provide scientific oversight; 2) review all adverse effects or complications related to the study; 3) monitor accrual; 4) review summary reports relating to compliance with protocol requirements; and 5) provide advice on resource allocation.

The safety officer and statistician will meet at the following seven predesignated study milestones: each time 34 patients have received at least 6 months of study follow-up care (four meetings); once 68 patients have completed the study (one meeting); once 102 patients have completed the study (one meeting); and at study close-out. The team will also meet on an as-needed basis for any unexpected serious adverse events or significant study findings. Data will be provided at these meetings by the investigators on key variables that may indicate harm, including significant medication safety events leading to hospitalization or intervention. Study patient clinical events, including hospitalizations, emergency room visits, acute rejections, life-threatening infections, graft loss and patient death will also be reviewed during these sessions. The biostatistician will evaluate confidentiality and integrity of the database, and the procedures for recording and storing confidential files. The safety officer will also review the elements of the research plan to deal with emergencies. At the conclusion of these meetings, the recommendations of the safety officer will be reviewed and the PI and co-investigators will take appropriate corrective actions as needed.

The safety officer will have the authority to halt the trial if he/she perceives that harm is occurring due to the interventions.

Figure 3. Conceptual diagram of mobile health (mHealth) system.



Intervention Protocol Adherence

Monitoring for adherence with medications, clinic visits, blood pressure and glucose monitoring (if applicable) is a part of the intervention in the intervention cohort. If patients are not adhering to data monitoring in the intervention cohort, they will be contacted by the study pharmacist to encourage use of the smartphone and any relevant Bluetooth-enabled devices. If this does not resolve the nonadherence, the subject will be contacted by the study PI to discuss continued involvement in the study. These data will not be monitored real-time in the usual care cohort.

In both cohorts, adherence with study data capture will be monitored by the study coordinators, who are completely independent of the pharmacists providing the interventions. Data that will be gathered by the coordinators includes blood pressures and laboratories measured at clinic visits, number of clinic visits, hospital admissions, infections, rejections, graft loss, and number and type of medication errors. They will gather data via direct subject interview and through review of the subject's electronic medical records.

Statistical Analysis Plan

This analysis will incorporate the intent-to-treat principle, namely, all randomized participants will be included in the analysis according to their intervention assigned at baseline. The two groups will be compared using standard statistical analyses. Data will be reported using percentages for nominal and ordinal variables and compared using Fisher's exact test or Pearson's chi-squared test as appropriate. This includes baseline demographic and transplant characteristic variables, as well as the outcome variables of the incidence and severity of medication errors and adverse drug events, acute rejection, and infections. For continuous variables with normal distribution, results will be reported using means and SDs with statistical

comparison using Student's *t* test for two independent samples. For nonnormally distributed variables, the results will be reported using medians and interquartile ranges, with statistical comparison conducted using the Mann-Whitney U test. Normal distribution of continuous variables will be assessed using normality plots and the Shapiro-Wilk test. Normal variance will be assessed using Levene's test for equality of variances. Results for graft and patient survival will also be reported using Kaplan-Meier survival curves and compared using the Log Rank test.

If it is determined that there are significant imbalances in baseline demographics or characteristics known to influence any of the outcome measures, multivariable modelling will be used to adjust for these differences. For nominal outcomes, binary logistic regression will be used in a standard entry fashion, which will include both the grouping variable and all known risk factors. For continuous outcomes that demonstrate linearity in the relationship between dependent and independent variables, with a lack of serial correlation between covariates, homoscedasticity of the errors, and normality of the error distribution, linear regression will be utilized in a similar manner. We will adjust for baseline values if the interventions are discrepant at baseline. This model will include the intervention arm and baseline response as fixed effects and is known to lead to very precise inference [22]. If any of the four aforementioned assumptions are violated, then the data variables will either be transformed or appropriate substitute multivariable modelling will be used. Cox proportional hazard regression analysis will be used for time-dependent survival analyses involving the outcomes of graft and patient survival. For count outcomes, such as health care encounters, we will use Poisson regression; if the assumption of equal mean and variance is violated (over dispersion), we will use Negative Binomial regression. In all models, we will adjust for correlation of outcomes by including random effect terms. For all models that belong to the generalized linear model (linear, logistic, Poisson), we will use generalized estimating equations, and for survival outcomes, we will use frailty Cox regression [23]. We will use multiple imputation techniques to deal with missing data that is at random (MAR) [24]. MAR assumes that the probability that an outcome is missing depends on observed outcomes. While mechanisms for missingness are likely to be MAR, we will also do sensitivity analysis for data missing not at random (MNAR) using methods from Little and Rubin [24].

Results

The primary outcome measure of this study will be the incidence and severity of MEs and ADRs, which will be identified, categorized, and compared between the intervention and control cohorts. The exploratory outcome measures of this study are to compare the incidence and severity of acute rejections, infections, graft function, graft loss, and death between research cohorts and measure the association between medication safety issues and these events. Additional data that will be gathered includes sociodemographics, health literacy, depression, and support. These are important variables that may modify or confound the impact of the intervention.

Study Endpoint Definitions and Assessment Plan:

The following will be used to define and capture data and events within this study:

1. MEs are defined as documentation that a patient is taking a medication in a manner that was not intended; synonymous with the definition developed by Overhage and utilized within our previous research [12,17].
2. ADEs are defined according to the AHRQ Patient Safety Network, in which it describes an adverse drug event as "an adverse event (ie, injury resulting from medical care) involving medication use" [25]. The severity of the ADE will be defined according to a modified version of the CTCAE developed by the National Cancer Institute and utilized in our previous research. In both the usual care and intervention arms, a highly trained clinical research coordinator will independently interview all participants at bimonthly intervals and review their medical records to capture and record all MEs and ADEs, including timing, likely cause, and severity of each event. To assess for ME, the research coordinator will review and compare the patient's documented medication regimen in the electronic health record (the regimen intended to be taken) to the medication regimen actually being taken by the patient. To assess for ADEs, the research coordinator will review patient symptomology, vital signs and laboratory values.
3. Acute rejection will be defined as a renal allograft biopsy demonstrating at least grade 1A rejection by Banff '97 criteria or higher or treated borderline rejection [26]. All patients will be required to have biopsy confirmation of rejection episodes within 24 hours of onset of treatment for acute rejection, as per our protocol and usual care. It is standard care that all kidney allograft biopsies performed for transplant recipients occur at the transplant center (study institution). Biopsies will be read by the local pathologist, as per usual care. This pathologist will not be informed of participant participation in the study and will be blinded to cohort assignment. The study coordinator capturing clinical event data, different from the screening and randomizing coordinator (to ensure blinding is maintained), will review the medical record at regular intervals to determine the incidence, timing, severity, treatment regimen, and reversibility of each acute rejection episode for all study participants.
4. Infections will be defined as any diagnosed and treated infection, and will be subclassified as bacterial, viral, or fungal etiologies. Flu-like illnesses and viral syndromes NOT requiring antimicrobial therapy will not be defined as infections for this study. Opportunistic infections will also be subclassified for this study as viral, bacterial or fungal and defined as infections not seen in immunocompetent individuals; the most common opportunistic infections in kidney transplant recipients include cytomegalovirus (CMV), BK virus, Ebstein-Barr virus (EBV) and candidiasis [27,28]. The study coordinator capturing clinical event data will review the medical record at regular intervals to determine the incidence, timing, severity, treatment regimen, and cure timing of each infection episode for all study participants.

5. Graft function will be defined using the 4-variable Modification of Diet in Renal Disease equation to estimate glomerular filtration rate (GFR). This equation has been validated as an accurate reflection of true GFR within kidney transplant recipients [29]. Routine serum creatinine concentrations, which are measured as part of usual care, will be utilized to estimate GFR at these approximate time points: baseline, 3, 6 and 12 months postenrollment.
6. Graft failure will be defined as return to chronic dialysis, transplant nephrectomy, retransplantation or death. The study coordinator capturing clinical event data will review the medical record at monthly intervals to determine if a study subject has developed graft failure. The timing and cause of each graft loss will be recorded for comparative analysis. Patient death will also be captured in a similar fashion, with timing and cause recorded as well.
7. Healthcare encounters will be defined as any direct encounter (face-to-face) between the study patient and a physician or advance practice provider occurring within a licensed healthcare facility and occurring during the 12-month study. These encounters will be categorized as ambulatory clinic visits, ambulatory procedure visits, acute care/emergency room visits, and hospitalizations. Hospitalizations will be defined as an admission to a hospital with at least one overnight stay. Length of stay within the hospital for readmissions will also be captured. Healthcare encounters will be captured through direct study subject interviews with patients at bimonthly intervals. The study coordinator will record all healthcare encounters that have occurred. If the patient has a health care encounter outside of the study institution, the research coordinator will document the type of encounter to estimate costs, as detailed below.
8. Costs associated with care will be assessed based on data from hospital accounting at the study institution, once the study is completed. Costs will be measured from the time of randomization up until the end of the 12-month follow-up period. Analyses will include all costs associated with inpatient and outpatient care, including hospitalizations, ambulatory care visits, ambulatory procedure visits, acute care/emergency room visits, and laboratory assessments. Costs uniquely associated with the intervention group will include the costs of the devices and data plan provided to the patients; time necessary for training patients on use of the technology; and research pharmacist time associated with the intervention. Total costs will be calculated for each cohort. These data will be electronically captured by providing a list of patients' medical record numbers to hospital accounting after the completion of the study to allow for accurate and complete billing information to accrue. Costs associated with healthcare encounters that occur outside the study institution will be estimated by acquiring information from the patient regarding the type of encounter and using this data to estimate cost based on cost/charge ratios from the study institution. This will be a cost-consequences analysis, using cost effectiveness methodology, taken from the societal perspective.

Discussion

Due to the complexities and toxicities associated with their immunosuppressive medication regimens, kidney transplant recipients are at high risk of developing medication safety issues which can lead to hospitalization, increased healthcare expenditures, and ultimately graft loss. Founded on preliminary information, the use of pharmacists and mHealth technology provide a promising and innovative approach to improve medication safety in high-risk patients. The ultimate goal of this research is to demonstrate how patients, pharmacists, and technology can work hand-in-hand to optimize medication-related outcomes and reduce healthcare expenditures.

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Conflicts of Interest

None declared.

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Abbreviations

ADE: adverse drug events
DSMP: data safety monitoring plan
GFR: glomerular filtration rate
IRB: institutional review board
ME: medication errors
MNA: medication nonadherence

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Protocol

Strengths-Based Behavioral Intervention for Parents of Adolescents With Type 1 Diabetes Using an mHealth App (Type 1 Doing Well): Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Supportive parent involvement for adolescents' type 1 diabetes (T1D) self-management promotes optimal diabetes outcomes. However, family conflict is common and can interfere with collaborative family teamwork. Few interventions have used explicitly strengths-based approaches to help reinforce desired management behaviors and promote positive family interactions around diabetes care.

Objective: The aim of this protocol was to describe the development of a new, strengths-based behavioral intervention for parents of adolescents with T1D delivered via a mobile-friendly Web app called Type 1 Doing Well.

Methods: Ten adolescent-parent dyads and 5 diabetes care providers participated in a series of qualitative interviews to inform the design of the app. The 3- to 4-month pilot intervention will involve 82 parents receiving daily prompts to use the app, in which they will mark the diabetes-related strength behaviors (ie, positive attitudes or behaviors related to living with or managing T1D) their teen engaged in that day. Parents will also receive training on how to observe diabetes strengths and how to offer teen-friendly praise via the app. Each week, the app will generate a summary of the teen's most frequent strengths from the previous week based on parent reports, and parents will be encouraged to praise their teen either in person or from a library of reinforcing text messages (short message service, SMS).

Results: The major outcomes of this pilot study will include intervention feasibility and satisfaction data. Clinical and behavioral outcomes will include glycemic control, regimen adherence, family relationships and conflict, diabetes burden, and health-related quality of life.

Conclusions: This strengths-based, mobile health (mHealth) intervention aims to help parents increase their awareness of and efforts to support their adolescents' engagement in positive diabetes-related behaviors. If efficacious, this intervention has the potential to reduce the risk of family conflict, enhance collaborative family teamwork, and ultimately improve diabetes outcomes.

Trial Registration: ClinicalTrials.gov NCT02877680; https://clinicaltrials.gov/ct2/show/NCT02877680 (Archived by WebCite at http://www.webcitation.org/6xTAMN5k2)

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KEYWORDS

adolescence; type 1 diabetes; parenting

Introduction

Background and Rationale

Type 1 diabetes (T1D) is one of the most common pediatric chronic conditions [1]: between 2001 and 2009, the prevalence among people under 20 years of age in the United States approached 1 in 500 youths. Diabetes management demands include frequent daily blood glucose monitoring, precise insulin calculations and adjustments, multiple insulin administrations via injections or subcutaneous insulin pump, and consideration of nutritional intake and physical activity. Difficulty in adhering to these demanding self-management tasks contributes to suboptimal glycemic outcomes and increased risk for serious complications [2]. Difficulties with self-management and elevated glycemic outcomes are common during adolescence [3,4], when youths are often expected to take increasing responsibility for daily management [5,6]. Supportive parent involvement promotes optimal diabetes outcomes [7], yet maintaining positive, collaborative parent-adolescent interactions can be challenging in the context of normative adolescent development and diabetes-related stressors. Many families describe escalating conflict and difficulty in working together for T1D management [8,9], which increases the risk for poor clinical, behavioral, and glycemic outcomes [10,11]. Negative interactions stemming from parents' frustration and fears about the consequences of poor glycemic control can interfere with positive family teamwork [9].

Several interventions for adolescents with T1D report improvements in family collaboration, youths' quality of life (QOL), self-management behaviors, and prevention of deteriorations in glycemic outcomes [12,13]. Existing interventions often target behavioral risk factors for poor diabetes outcomes such as diabetes-related conflict, ineffective family management, and maladaptive coping [12]. Unfortunately, effect sizes compared with control groups are modest and in-range glycemic outcomes (ie, glycated hemoglobin A_{1c} [HbA_{1c}] <7.5% [14]) are not consistently achieved or maintained [12].

Diabetes Resilience is defined as the achievement of optimal diabetes outcomes (ie, good QOL, high engagement in self-management behaviors, and close to target glycemic outcomes) despite the numerous challenges inherent to having T1D [15]. New interventions that use positive psychology strategies and aim to promote resilient outcomes in pediatric populations are gaining attention as an approach to extend the impact of existing behavioral interventions [16-19]. Strengths-based interventions for other populations have increased gratitude, happiness, and self-control; decreased psychological symptoms and behavior problems; and improved subjective well-being [20,21]. However, relatively few interventions promote optimal diabetes outcomes by explicitly reinforcing youth and family strengths [22], or positive diabetes-related attitudes and behaviors (eg, confidence, seeking support [15]) that have demonstrated associations with resilient outcomes [23,24].

Existing behavioral interventions are often multicomponent programs delivered by trained interventionists at multiple in-person sessions in the medical setting [12]. Time and space requirements for intervention delivery, families' ability to attend multiple sessions, and the expenses of hiring and training behavioral interventionists limit the potential for widespread dissemination. Although behavioral support is consistently recommended by international diabetes care guidelines [14,25,26], few practices have the resources to employ behavioral care providers or routinely provide such services [27,28]. Limited resources must be prioritized for patients at the highest level of psychosocial need, leaving many without access to potentially helpful behavioral interventions [29].

Mobile health (mHealth) technologies address many of these limitations by reducing barriers to dissemination [30-32]. For example, intervention automation and delivery via mobile devices minimize the need for space, time, and specialized interventionists to deliver behavioral care [33-35]. Mobile health interventions for people with diabetes have included text message–based (short message service, SMS) reminders to perform diabetes self-management activities (eg, blood glucose monitoring, insulin administration, physical activity), automated reinforcement for engaging in self-management activities via text message, diabetes education via mobile phone or email, and guidance for making diabetes care decisions (eg, insulin dosing calculators, advice for managing low blood glucose); these interventions have generally been well received but have reported only modest results [35-38]. Previous mHealth interventions have largely targeted adolescents with T1D and adults with T1D or type 2 diabetes, but have not been delivered directly to parents of youths with T1D. Multicomponent, evidence-based behavioral interventions for adolescents with T1D and their parents have begun to be adapted for delivery via websites or mobile phone apps, and initial results suggest high acceptability and at least short-term improvements in adherence [36,39]. On the basis of previous research, recommendations for mHealth interventions in diabetes include minimizing demands and burden for participants (eg, patients, family members, providers), providing timely feedback about the targeted outcome, and relying on behavior change theory to inform the intervention/app design [35,38].

Study Overview and Aims

This paper describes the study design and protocol for the Type 1 Doing Well pilot intervention study, which aims to address the need for brief, low-burden, and easily translatable behavioral interventions to facilitate positive family interactions and ultimately strengthen resilient diabetes outcomes during the challenging adolescent period. The purpose of the Type 1 Doing Well study is to develop and evaluate the feasibility of a

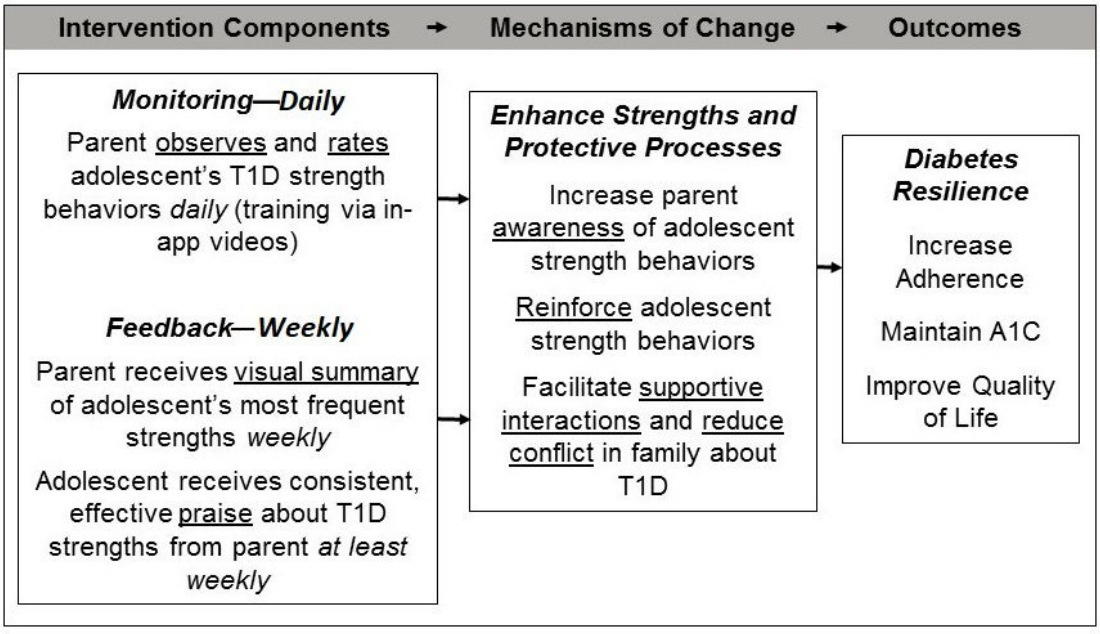
strengths-based behavioral intervention for parents of adolescents with T1D, delivered via a mobile-friendly Web app that parents use for approximately 3 to 4 months, the standard period of time between quarterly diabetes clinic visits. The app uses a monitoring plus feedback design to help parents recognize and reinforce what their adolescents are doing well for diabetes management. Intervention components include the following: (1) *monitoring* by the app prompting parents to record observed strength behaviors (eg, asking an adult for help with insulin calculation, managing a difficult diabetes-related problem) their adolescents engage in each day; (2) *feedback* to parents by providing personalized weekly summaries of the adolescents' most frequent strengths; and (3) *feedback* to adolescents by teaching and encouraging parents to reinforce their teens' diabetes strengths. Theorized intervention mechanisms include enhancing protective behavioral and family processes by increasing parents' awareness and reinforcement of diabetes actions that adolescents are doing well and facilitating positive family interactions in the context of everyday diabetes management, the ultimate goals of which are to improve adolescent QOL, self-management, and glycemic outcomes.

This protocol describes the process of developing and pilot testing the Type 1 Doing Well app. To develop the app, we employed user-centered design processes [40] to ensure the app would be engaging, easy to use, and meet families' needs and preferences. The pilot intervention tests the resulting app with 82 adolescent-parent dyads. Each family will be randomized to either use the app (in addition to their usual diabetes care) or to a usual care control condition, in which they do not use the app, using a 2:1 randomization scheme. This exposes twice as many participants to the app; for a pilot study, this approach maximizes the amount of feedback received about the intervention to learn about its feasibility and acceptability, and generates more suggestions for refinement. The aims of the pilot intervention study are to evaluate the feasibility, acceptability, and preliminary impact of the intervention. Feasibility will be demonstrated by participant consent rates >70% and at least twice-weekly app use rates >75%. Acceptability will be demonstrated by high adolescent and parent satisfaction ratings >80%. To evaluate impact, it is hypothesized that adolescents will increase self-management behaviors and maintain or improve glycemic control pre- to postintervention. Because glycemic control often worsens during this period, either improvement or maintenance from baseline to follow-up is hypothesized to be better than the usual trend. It is also hypothesized that adolescents and parents will report improvements in diabetes strength behaviors, family conflict, diabetes burden, and health-related QOL from pre- to postintervention.

Theoretical Framework

Type 1 Doing Well has its theoretical foundation in the Diabetes Resilience Model [15], which posits that diabetes outcomes are influenced by the individual's and family's risk factors and assets, and that enhancing positive protective processes that maximize diabetes-related strengths can buffer the negative impact of risks and amplify the positive impact of strengths, leading to resilient outcomes. By targeting positive family processes (eg, supportive parent involvement) and positive adolescent behaviors (eg, diabetes strengths: expressing confidence, seeking support), the Type 1 Doing Well intervention aims to enhance these protective factors, reduce the impact of risk factors (eg, diabetes burden, family conflict), and ultimately promote resilient diabetes outcomes (Figure 1). This approach represents a shift in tone from routine diabetes care (which by necessity focuses on identifying and solving problems with diabetes management) and from existing behavioral interventions (which seek to reduce behavioral barriers to optimal outcomes).

Figure 1. Conceptual model of strengths-based intervention components and theoretical mechanisms of change to reduce risk factors and promote resilient diabetes outcomes. T1D: type 1 diabetes; A_{1c}: glycated hemoglobin A_{1c}.



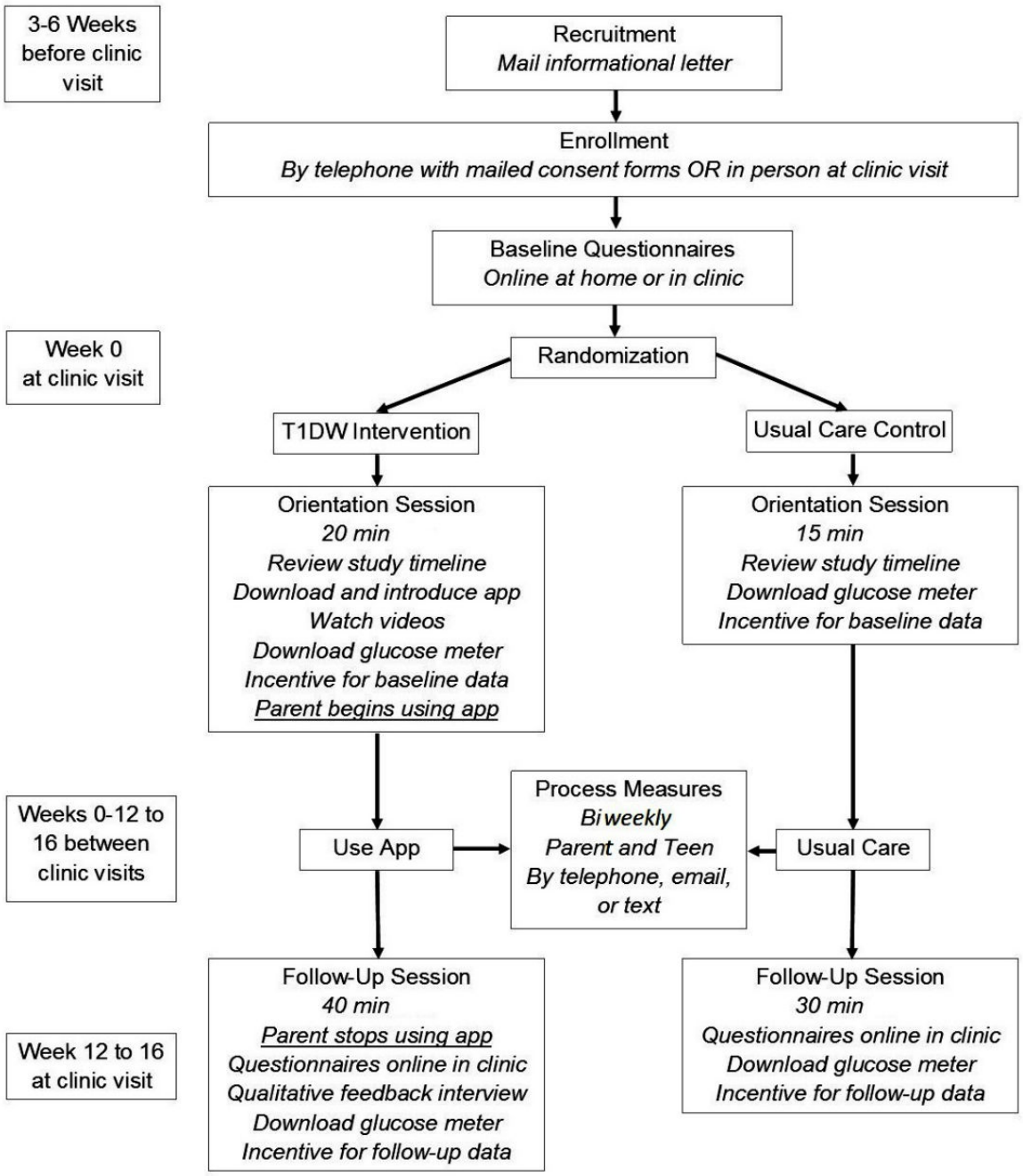
Compared with in-person interventions, a primary benefit of mHealth is ecological validity: data are collected and participants experience the intervention in the context of everyday activities [30,41,42]. Ecological validity can enhance intervention impact through increased proximity and relevance to the everyday behaviors being targeted and can reduce barriers to engagement. By making daily contact for strengths monitoring and weekly contact for feedback and to encourage parents to offer praise, this intervention is designed to increase their ability to apply strengths-based behavioral strategies in vivo. The focus on monitoring adolescents' strengths rather than risks or problems throughout the day in this study may also increase the intervention's appeal, and thus boost participant engagement, all noted challenges in existing interventions [21].

Methods

Design Overview

Participants will be randomized 2:1 to the intervention and comparison groups, respectively, to maximize feasibility data and feedback from the intervention group. The intervention group will use the app for 3 to 4 months, between 2 outpatient diabetes clinic visits. The control group will receive usual care and will not use the app during the study period. Data collection will occur at baseline and follow-up for both the groups. The schedule of participant activities is outlined in Figure 2.

Figure 2. Schedule of participant activities. TIDW: Type 1 Doing Well.



Participants in both the groups will receive US $25 per person for completing both baseline and follow-up questionnaires. They will also receive an additional US $5 per person for each biweekly survey they complete (described below). At each of 2 study visits (1: baseline data collection, randomization; 2: follow-up data collection), the family will receive US $13 to cover parking and/or transportation expenses. Adolescents will receive an additional US $5 per study visit for bringing all actively used blood glucose meters for download. Parents and adolescents in both the groups will also receive a small silicone wallet embossed with the study logo that adheres to the back of a mobile phone as an additional incentive, which also serves as a visual reminder to participants about the study. Because intervention feasibility is a primary study aim, incentives will be provided for completing data collection procedures but not for participation in the intervention. Intervention group participants will receive US $10 per month to offset data usage charges from using the app.

The protocol was approved by the institutional review board and is registered on ClinicalTrials.gov (NCT02877680). Data monitoring committees are not required for pilot studies; however, annual review by the institutional review board monitors for adverse participant events and conducts random audits. Protocol amendments are processed through the institutional review board, and significant changes are approved by the study sponsor.

Recruitment

The target sample is 82 parent-adolescent dyads. Inclusion criteria are as follows: adolescent aged 12 to 17 years at enrollment, treated for T1D at the children's hospital diabetes clinics where recruitment is taking place, and diabetes duration of at least 6 months. Parents (female or male) who self-identify as the primary caregiver will be eligible. Because the validated questionnaires and app are not available in other languages, fluency in English for parents and adolescents is required. Because the intervention is delivered via an app, parents must have a mobile device (ie, mobile phone or device that can receive text messages and access the Internet) with a data plan. Adolescents are not required to have a mobile device, as they will not be interacting directly with the app, and parents have the option to praise their adolescent by a text message or in person. Exclusions include serious medical, cognitive, or mental health comorbidity in parents or adolescents that would preclude the ability to participate. Recruitment takes place at 2 diabetes clinics serving patients of the Pediatric Diabetes and Endocrinology Service at a large tertiary children's hospital affiliated with an academic medical center in the Southern United States. The 2 clinics were selected based on the size of the patient load at each clinic and to maximize study staff availability to be present for recruitment and study activities most days of the week. Following established diabetes clinic research processes, research staff review clinic schedules and mail informational letters to potentially eligible families and follow up by telephone call to introduce the study and conduct eligibility screening. Staff meet potentially eligible families in clinic for recruitment, informed consent, data collection, and enrollment. When possible, participants provide written consent and are sent a weblink to complete questionnaires before the clinic visit. When that is not possible, families are sent the weblink to complete questionnaires immediately following the in-clinic meeting, and participation in the intervention begins at the subsequent clinic visit. Families who decline participation will be asked to share the reason for choosing not to participate.

Randomization

After consenting, enrolling in the study, and completing baseline questionnaires, participants will be randomized to the intervention or control group. A 2:1 randomization scheme with random block sizes will be used to maximize feasibility data and feedback from the intervention group (n=55 for intervention, n=27 for comparison). Following randomization, the intervention group will begin the intervention immediately. Research staff will help the parent install the app, register a username and password to access the app, and demonstrate app use. Staff will show the family 3 instructional videos within the app that teach participating parents about the importance of praise, how to identify strength behaviors, and how to provide developmentally appropriate praise to adolescents. Participants in this group will be instructed to begin using the app that day.

Type 1 Doing Well Intervention: Development and Design

Semistructured qualitative interviews were conducted with 10 adolescents (mean age 15.4 [SD 1.9] years, 50% (5/10) female, 60% (6/10) non-Hispanic white, mean diabetes duration 7.0 [SD 3.8] years, 90% (9/10) privately insured) and their parents (70% (7/10) mothers) and 5 pediatric diabetes care providers (100% (5/5) physicians, 60% (3/5) faculty, 40% (2/5) postdoctoral fellows, 60% (3/5) female) to inform app design and intervention content. Parent and adolescent interviews asked about their perspectives on what positive diabetes-related behaviors adolescents tend to engage in and what adolescents wish their parents appreciated about their lives with diabetes, and how parents communicate with adolescents about diabetes management. Diabetes strengths described by parents and adolescents included adolescents performing diabetes self-management tasks without reminders, planning ahead for diabetes management during meals or activities, prioritizing diabetes management even when other events are occurring (eg, school, sports), using a positive tone during family communication about diabetes, and talking openly about diabetes with friends. Adolescents highlighted their desire for their parents to notice "small" everyday behaviors (eg, doing blood glucose checks), to provide specific rather than generic (eg, "good job") praise, and to focus more on the adolescents' efforts than on blood glucose values. The interviewer also sought parents' and adolescents' input on the app content and structure, including parents' preferred frequency of contacts from/with the app, desired features of the app, for how long they might use the app, and recommendations to make the app appealing and usable. Feedback included asking parents to use the app no more than 1 to 2 times per day to rate their adolescents' behavior over the previous 12 to 24 hours, and providing the strengths summary once a week (on the weekend) in a simple and easy-to-interpret list or graph, preferably using visually appealing colors. Parents and teens indicated that they communicate frequently via text message and thought that would

be a useful way to provide praise. Some parents wanted the app to provide brief template praise texts that they could personalize and others wanted the option to create their own text messages. Adolescents were open to receiving texts from parents about what they did well and wanted the texts to be simple and straightforward, without adding comments about problems, concerns, or tasks that the adolescents needed to do. Several parents and adolescents noted that they would like to include emojis in the texts.

Diabetes care provider interviews focused on their observations of adolescents' diabetes strengths and parent-adolescent interactions, and their perspectives on how the app could potentially be integrated into routine diabetes care practices. Strengths identified by providers included adolescents taking initiative to complete some diabetes tasks independently/with few parent reminders, using positive communications strategies with parents, seeking support from peers, and establishing diabetes self-management routines or habits. Their suggestions for the app included minimizing burden on app users by keeping the app format simple and the questions brief, introducing the app not as a punishment for poor parenting but rather as a tool for all parents, and having the option to add new strengths or text messages into the app. Providers highlighted the importance of helping parents focus on praising their adolescents more, and they suggested incorporating a summary of strengths-oriented data from the app into clinical conversations at later clinic visits.

After developing a prototype of the app based on this input, 4 families were shown screenshots of various features of the app, and they gave feedback (eg, ranked their preferences for strengths summary formats, commented on unclear or irrelevant strengths or text message templates). After finalizing the app design and components, research staff and software developers conducted extensive usability testing with the app to ensure optimal functionality.

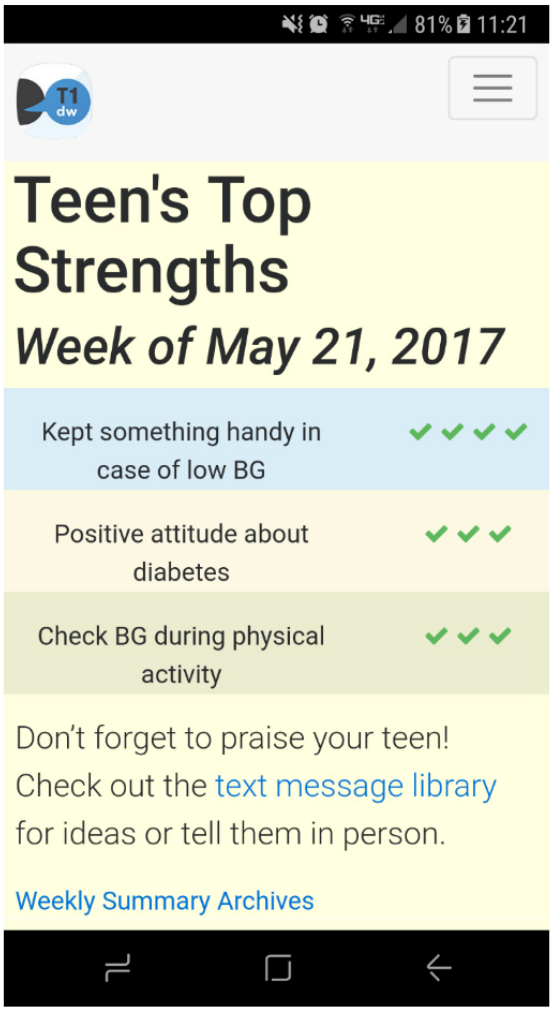
On the basis of parent preferences and provider recommendations to limit parent burden in using the app, the app prompts parents by SMS and/or email (parent chooses method) to use the app once each day in the evening. A second prompt is sent 90 min later if the parent has not yet logged into the app. After logging in, parents are asked to select from a list of diabetes strength behaviors that their adolescent engaged in during the previous day. The strength behaviors were developed based on review of the literature and input from parents, adolescents, and providers about positive actions and attitudes that adolescents tend to engage in around diabetes self-management. Example strengths include the following: "Checked blood glucose without being asked," "Discussed diabetes in a calm or positive way," and "Took care of diabetes when he/she had a lot of other things going on." In response to suggestions to incorporate new, personalized content to the app, if no response options apply, parents can select "other" and provide a written description of other positive behaviors observed, which are added to the list of strengths and can be selected by the parent again at a later time. Parents can also log into the app at other times and provide additional reports of their adolescent's strength behaviors. Once a week, parents receive an additional prompt to view a summary of the top 3 strength behaviors they reported their adolescent engaged in over the previous week. On the basis of parent feedback, the summary is presented graphically as a list with checkmarks indicating how frequently each strength behavior was reported (Figure 3). The summary tab of the app links to a library of sample text messages that parents can copy into their mobile phone's text messaging or email program to send to their child. The text wording was guided by adolescent suggestions. Parents have the option to edit the texts, write their own, or provide praise in person. In response to participant suggestions to include emojis, a collaboration was formed with Joyce Lee, MD MPH, who developed the "Diabetes Emoticons" emojis. Because the emoji pack can be used only on Apple devices, it could not be incorporated into the T1 Doing Well app (which was designed to be accessible on any device, described below). However, study staff inform participants that the emojis can be downloaded by Apple users and may be used to personalize their praise text messages, and the app includes a link to the free sticker pack in the iTunes store. The app also includes 3 videos described above, the content of which was informed by parent and adolescent input about which positive behaviors to track and how to offer praise in an adolescent-friendly way. The videos also address frequently asked questions (eg, how to respond when it is difficult to identify any positive behaviors). Parents watch these videos after being randomized to the intervention group and can access them at any time for a refresher.

The app was created and is maintained by faculty, staff, and software developers at the Center for Behavioral Intervention Technologies Development Core Facility at Northwestern University School of Medicine. To maximize the number of people who could use the app and not limit eligibility by platform (eg, Android vs Apple products), the app was created as a mobile-friendly website that is optimized for Android (with Chrome, Firefox, or Android v5.0+ Web browsers), iOS (with Chrome, Firefox, and Safari Web browsers), and Windows 10 (with Microsoft Edge) mobile devices and Mac (with Chrome, Firefox, Safari, and Opera Web browsers) and Windows (with Chrome, Firefox, IE10+, Microsoft Edge, and Opera Web browsers) desktop, laptops, and tablets. To increase app accessibility for participants, Android and iOS home screen app icons were developed so that users can save the icons to their home screen and access the Web app as if it were a mobile app. In addition to the participant-facing app, there is also a researcher-facing dashboard that allows research staff to add content (eg, new praise texts or strengths), manage participant access to the app and support requests, and export app usage data and participant summaries in real time.

Usual Care Comparison Condition

Participants in both groups will receive usual care for T1D, which includes approximately quarterly visits with a multidisciplinary (ie, physician and advance practice nurse, nurse/medical assistant, registered dietician and certified-diabetes educator, and social worker) diabetes care team. The diabetes care team also includes a licensed clinical psychologist with expertise in diabetes who is available for treatment referrals based on provider concern or family request. Usual care without app use was selected as the comparison condition, given the early phase of development of the study.

Figure 3. Screenshot of weekly strengths summary. BG: blood glucose.



Measures

Data are collected at 2 times: parents and adolescents complete questionnaires at baseline following consent and before randomization, and at the diabetes clinic visit following randomization (approximately 3-4 months later). Questionnaires are collected via secure, HIPAA (Health Insurance Portability and Accountability Act)-compliant Web survey hosted through the institution's clinical trials management system. Adolescents and parents have unique log-ins and passwords and are instructed to complete the surveys independently. Participants have the option to not answer any questions that they chose not to answer; if 3 or more questions are unanswered on a questionnaire, the system provides the following prompt: "You have not answered some questions in this survey. Click ok to continue or cancel to answer those questions." Study data are identified with randomly generated participant numbers, and any paper materials are stored separately from documentation of identifiable health information, including informed consent.

To assess the process of the intervention's impact, adolescents and parents each provide biweekly ratings of their relationship quality throughout the 3- to 4-month study period. These items can be answered via email, phone, or text message. Medical chart data are also collected during this period. Attempts are made to collect follow-up data from all participants, including those who stop using the app, to assess the impact of intervention dose.

Feasibility

Recruitment data will be used to calculate the percent of eligible families who enroll in the study. Usage data from the software platform (accessed via the research dashboard) will be used to calculate parent engagement with specific app features (eg, response rate to prompts, frequency of opening feedback summaries, frequency of using provided texts) and the percent of participants who interact with any app feature at least twice weekly.

Participant Characteristics

At baseline, parents will report their relationship to the adolescent, parent and adolescent's racial and ethnic backgrounds, number of parents/caregivers living in the home, the adolescent's insurance status (private, public, or none), and the highest level of parental education. Adolescents' gender, date of birth (to calculate age), date of diabetes diagnosis (to calculate duration of diabetes), and current diabetes treatment regimen will be extracted from the medical record.

Clinical Diabetes Outcomes

Glycemic control (HbA_{1c}) and blood glucose monitoring frequency are collected routinely at diabetes clinic visits and will be extracted from the electronic medical record. Trained phlebotomists draw blood samples by fingerstick and analyze assays immediately using the DCA 2000 Hemoglobin HbA_{1c} system (Siemens-Bayer). Blood glucose meters are routinely downloaded to calculate mean daily blood glucose monitoring frequency (previous 14 days).

Behavioral Outcomes

Adolescents self-report on the frequency of resilience-promoting attitudes and behaviors (ie, strengths) via the Diabetes Strengths and Resilience measure [23], a 12-item measure of perceived mastery over T1D management demands and accessing social/family support for T1D needs. They also complete the Monitoring Individual Needs In Diabetes (MIND)-Youth Questionnaire [43], a 33-item measure of diabetes health-related QOL. Parents rate youth engagement in diabetes self-management behaviors using the appropriate version (based on the youth's insulin regimen) of the 24-item Diabetes Self-Management Profile Self-Report [44] and adolescents using the 15-item Self-Care Inventory-Revised [45].

Intervention Mechanisms

To assess the process of intervention impact, parents complete the PedsQL Family Impact Module (36 items) [46] and the Diabetes Family Impact Scale (14 items) [47], which measure the impact of diabetes on family activities and relationships and parent QOL. Diabetes-specific burden will be assessed via the Problem Areas in Diabetes measures for adolescents (26 items) [48] and parents (18 items) [49], both of which demonstrate good psychometric properties. Parents and youths complete the Diabetes Family Conflict Scale-Revised [50], a 19-item scale of family conflict surrounding diabetes issues, which has good reliability and validity. Parents and youths also complete the Helping for Health Inventory [51], a 15-item measure of unhelpful parental attention to the adolescent's diabetes management. In addition to the questionnaire batteries at baseline and follow-up, every 2 weeks, parents and adolescents are asked to each rate their relationship quality using 3 items adapted from the Parent-Youth Relationship Index of the National Longitudinal Study of Youth-1997 [52].

Intervention Satisfaction and Feedback

Postintervention, parents in the intervention group complete the USE Questionnaire [53], a 32-item measure of the users' perceived usefulness of, satisfaction with, and ease of use of a particular technology. Semistructured interviews with participants (separately with parents and adolescents) will be conducted to discuss experiences with the app (eg, intrusiveness of prompts, clarity/relevance of response options, usefulness and appeal of strength behavior feedback charts) and obtain suggestions for improvement.

Planned Statistical Analyses

Intervention feasibility will be determined if the upper bound of the two-sided 95% exact, binomial CI is ≥95% for downloading the app and ≥70% for using the app at least twice per week. Acceptability will be measured as the proportion of participants who rate the intervention as acceptable (somewhat to very much) with 95% exact, binomial CIs (upper bound should be ≥80%).

Baseline participant demographics and clinical characteristics will be summarized with descriptive statistics, stratified by treatment group. Group differences will be assessed using two-sided, two-sample *t* tests, Wilcoxon rank sum tests, or Fisher exact test as appropriate. Statistical significance for univariate analysis will be assessed at the .05 level. However, this is a randomized clinical trial; therefore, significant group differences must be due to chance **,** and those variables will be adjusted for in a multiple regression model to confirm the magnitude of the effect.

The analysis of preliminary impact of this pilot intervention on the primary outcomes will compare mean blood glucose monitoring frequency, survey measures of self-management behaviors, and HbA_{1c} at follow-up between groups using an independent, two-sample *t* test. Equal variances will be assumed, unless the *F* test rejects the null hypothesis of equality at the .05 level. Quantile-quantile plots and Shapiro-Wilk tests, stratified by group, will be used to test for approximate normality, and data transformations (eg, natural logarithm) will be used if needed. Statistical significance will be assessed at the two-sided alpha=.05 level. A separate analysis will be used for each primary outcome **,** and no adjustments for multiple hypothesis tests will be made in this pilot study.

A general linear mixed model will also be used to compare follow-up measures between groups, adjusting for baseline response and baseline characteristics that are unequally distributed between groups. The generalized linear model will allow for the use of all available data, including participants with incomplete sets of observations. The model will include fixed effects for treatment group, time (discrete), baseline response, and a group-time interaction term. The model will also assume an unstructured matrix of correlated error terms to account for repeated observations. Statistical significance will be assessed at the .05 level for all hypothesis tests. All analyses will assume intention to treat. Missing data will not be imputed for the main analysis of primary or secondary outcomes. We anticipate very little missing data for these outcomes. Total scores will be calculated based on each measure's scoring instructions (including instructions for handling missing item responses) and used in analyses. Analysis of secondary behavioral outcomes will be analyzed using a similar approach.

Power

A total sample size of n=66 with complete data would be required to detect a standard effect size of 0.75 with 80% power using an independent, two-sample t test with equal variances assuming alpha=.05 and a 2:1 ratio between groups (n=44 for intervention, n=22 for control). This sample size will also have >95% probability of generating binomial CIs with half-widths ≤0.20. Therefore, we aim to enroll 82 (55 intervention, 27 control) participants to allow for a conservative 20% attrition rate.

Results

Enrollment began in July 2017 and data collection will continue through June 2018. Data cleaning and analysis will be conducted following the completion of data collection. We anticipate reporting results in late 2018 through professional presentations and publications.

Discussion

Parents' understandable and valid concerns about the consequences of chronic poor glycemic control can heighten their attention to nonadherence [54,55], making it difficult to recognize adolescents' positive self-management behaviors when they occur. The strengths-based Type 1 Doing Well intervention aims to focus parents' attention on specific positive behaviors that their adolescents are engaging in, teach strategies to recognize adolescents' strengths, and create frequent opportunities to offer reinforcement and praise. This explicit focus on identifying and reinforcing what adolescents are doing right has the potential to enhance supportiveness and collaboration in the parent-adolescent relationship around diabetes management, which are well-documented predictors of adherence and better glycemic control [7]. Training parents to consistently recognize and reinforce adolescents' strength behaviors may also increase these desired behaviors, which have demonstrated associations with key diabetes outcomes [21,22]. This pilot study will evaluate the feasibility of implementing the mHealth intervention to parents of adolescents, parents' and adolescents' satisfaction with the intervention, and its preliminary impact on key behavioral and clinical outcomes.

Potential limitations of this study are primarily related to the pilot nature of the study design. Because the emphasis is on evaluating the feasibility and satisfaction of the intervention to inform future research, the sample size may not be large enough to detect small to moderate effects. The sample size was based on an estimated standard effect size of 0.75. This is higher than reported effect sizes in other behavioral mHealth and eHealth research with youths with chronic health conditions (*d* range=0.13-0.35 for change in health behaviors or disease control outcomes [56,57]) or positive psychology interventions (*d* range=0.20-0.34 [58]). However, mobile phone-based behavioral interventions targeting adults report a wide range of effect sizes, including some that are large (*d*=0.09-1.38 [59]). Moreover, relatively higher effect sizes have been reported in mHealth and eHealth interventions delivered to caregivers of youths with chronic medical conditions compared with those delivered to the youths themselves [56], and among those that incorporate theory-based behavior change strategies [60], as is the case for this study. In light of these effect size ranges, basing our power analysis on *d*=0.75 was deemed appropriate for a pilot study with a sufficient sample to conduct preliminary analyses of impact on key outcomes and estimate a plausible effect size for a larger study [61].

The use of a convenience sample at a single children's hospital and the exclusion of non-English speaking participants may result in data that may not be representative of the population of families of adolescents with T1D. However, efforts are made to recruit a sample that includes parents and adolescents of both genders, adolescents spanning the eligible age range (12-17 years), and participants with diverse personal and clinical characteristics (eg, racial/ethnic background, insurance status, baseline HbA_{1c}) to maximize potential generalizability of findings. Because the eligibility criteria for the study are not dependent on baseline glycemic control, self-management behaviors, or family functioning, it is possible that changes will not be able to be detected because of floor or ceiling effects at baseline. Because the app is accessed via a mobile website, it is not accessible when the device is out of the range of mobile data, which may limit participants' use of the app in some situations. Conducting research in coordination with medical visits presents some challenges with scheduling and missed appointments. To minimize missing data at follow-up study visits, research staff remind all enrolled participants of upcoming scheduled clinic visits. However, some diabetes clinic visits do not occur at precise 3-month intervals. If a follow-up visit is not completed within 4 weeks of the 3-month follow-up window, a separate study visit is scheduled and glycemic data from the nearest clinic visit are used.

Promising results from this pilot study will inform the next phase of research to refine and further evaluate the effectiveness of this strengths-based mHealth intervention. The data gathered in this pilot study will comprise essential preliminary data to seek funding for evaluation in a larger, fully powered randomized controlled trial. In a larger trial, longer-term follow-up data will be collected to evaluate maintenance of improvements and/or additional improvements in outcomes over time. Ultimately, the goal is for this app to be used as a part of routine care of adolescents with T1D. Future research may include evaluation of this strengths-based app in combination with other mHealth technologies (eg, continuous glucose monitoring system platforms) or behavioral family interventions to enhance their impact on diabetes outcomes.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report.

[PDF File (Adobe PDF File), 155KB - resprot_v7i3e77_app1.pdf]

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Abbreviations

BG: blood glucose
HbA_{1c}: glycated hemoglobin
mHealth: mobile health
QOL: quality of life
SMS: short message service
T1D: type 1 diabetes
TIDW: Type 1 Doing Well

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Protocol

Evaluation of an Internet-Based Behavioral Intervention to Improve Psychosocial Health Outcomes in Children With Insomnia (Better Nights, Better Days): Protocol for a Randomized Controlled Trial

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Abstract

Background: Up to 25% of 1- to 10-year-old children experience insomnia (ie, resisting bedtime, trouble falling asleep, night awakenings, and waking too early in the morning). Insomnia can be associated with excessive daytime sleepiness and negative effects on daytime functioning across multiple domains (eg, behavior, mood, attention, and learning). Despite robust evidence supporting the effectiveness of behavioral treatments for insomnia in children, very few children with insomnia receive these treatments, primarily due to a shortage of available treatment resources.

Objective: The Better Nights, Better Days (BNBD) internet-based program provides a readily accessible electronic health (eHealth) intervention to support parents in providing evidence-based care for insomnia in typically developing children. The purpose of the randomized controlled trial (RCT) is to evaluate the effectiveness of BNBD in treating insomnia in children aged between 1 and 10 years.

Methods: BNBD is a fully automated program, developed based on evidence-based interventions previously tested by the investigators, as well as on the extant literature on this topic. We describe the 2-arm RCT in which participants (500 primary caregivers of children with insomnia residing in Canada) are assigned to intervention or usual care.

Results: The effects of this behavioral sleep eHealth intervention will be assessed at 4 and 8 months postrandomization. Assessment includes both sleep (actigraphy, sleep diary) and daytime functioning of the children and daytime functioning of their parents. Results will be reported using the standards set out in the Consolidated Standards of Reporting Trials statement.

Conclusions: If the intervention is supported by the results of the RCT, we plan to commercialize this program so that it is sustainable and available at a low cost to all families with internet access.

Trial Registration: ClinicalTrials.gov NCT02243501; https://clinicaltrials.gov/show/NCT02243501 (Archived by WebCite at http://www.webcitation.org/6x8Z5pBui)

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KEYWORDS

sleep; insomnia; children; randomized controlled trial; eHealth; Internet; treatment

Introduction

Pediatric Sleep Problems and Daytime Consequences

Sleep problems are highly prevalent among children [1,2]. Although there is a range of physiological causes for inadequate sleep (eg, sleep apnea, restless legs syndrome, and narcolepsy), by far the most common problem is *insomnia*. This condition is defined as "repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age appropriate time and opportunity for sleep, which results in some form of daytime functional impairment for the child and/or family" [3]. Insomnia affects approximately 10% to 25% of typically developing children in the general population. The higher estimates include children showing bedtime resistance; this is probably the most relevant rate, because this symptom is independently associated with functional impairment for the child and primary caregiver, henceforth referred to as parent. Sleep habits developed in childhood shape sleep habits in adulthood [4]; therefore, children with sleep problems often grow into adolescents and adults with sleep problems [5]. Early intervention therefore holds the promise of interrupting the cycle of insomnia that plagues many individuals throughout their lives.

Although there is less research on the effects of sleep problems in children than adults, there is evidence that poor sleep in children is associated with deficits in cognitive functioning (eg, attention) as well as with poor emotional regulation, lower academic achievement, and increases in negative mood and behavioral problems [6-11]. There is also preliminary evidence that short sleep in young children may be related to poorer physical health, such as increased obesity [12]. There is further evidence that sleep problems in children are associated with impaired parental sleep and daytime functioning, including increased parental stress, punitive parenting, and poorer psychological functioning in parents [13-17]. Most studies of the impact of children's poor sleep have been correlational in nature, rather than based on experimental manipulations. A national survey of 1273 members of the American Academy of Child and Adolescent Psychiatry outlining the prevalence of insomnia in pediatric populations in clinical practice speaks to the need for further experimental research to evaluate the impact of children's sleep problems and available treatment [18].

Treatment of Pediatric Insomnia

The most common treatment for insomnia in children (and adults) is medication. A chart review in outpatient health centers found that 81% of children presenting with a sleep disorder were prescribed medications [19]. This pattern of care is troubling because there are no approved medications for insomnia in children, and there are concerns about the safety and side effects of these medications [20,21]. Moreover, these medications are not effective in the long term, and their use remains unjustified in most children [22]. In contrast, behavioral interventions were recommended in only 22% of cases [19], despite overwhelming evidence of their safety, short- and long-term effectiveness [3,9,23-27], and acceptance by parents [28,29]. A systematic literature review of behavioral intervention studies reported that 94% of included studies (49/52) found that these interventions were effective in treating insomnia, and 80% of children treated demonstrated significantly improved sleep [3]. Behavioral interventions not only have a direct impact on children but also improve parents' sleep, and increase their sense of competence and control and ability to cope [30,31], as well as change their knowledge and perceptions about sleep problems [6]. The available evidence convincingly demonstrates that behavioral interventions should be the first line of treatment, but this is typically not the case.

Treatment Barriers

The primary reasons for the low rate of treatment are due to a shortage of available treatment resources and lack of knowledge among health professionals about sleep disorders and treatment [32]. Together, these issues result in sleep problems in children often being minimized or ignored [33,34], and being inadequately addressed even when acknowledged. Evidence-based behavioral intervention protocols are not readily available for clinical use, which is a classic case of a failure in knowledge translation. Even when effective treatments are available, they are usually provided in a traditional service delivery framework, involving weekly parent training sessions [35-38] or multiple clinic visits with health care professionals [39,40]. These traditional approaches may be difficult for parents because of scheduling conflicts, incidental costs, and travel

difficulties. Thus, a major challenge to the delivery of behavioral treatments is the inability of many families (especially those in rural or remote areas or those who are economically disadvantaged and lack insurance coverage for psychological services) to access the services they require [41].

Internet-Based Treatment Programs

A growing body of research supports the effectiveness of interventions delivered via the internet (eHealth, electronic health), with a number of randomized controlled trials (RCTs) demonstrating effectiveness for a range of chronic health and mental health disorders in adults and children [42-44]. There have been several studies evaluating internet-based treatment programs for adult insomnia [45-50]. A systematic review and meta-analysis published in 2016 on the effectiveness of internet-delivered treatment for insomnia in adults, which included 11 RCTs, reported that there was significant improvement in sleep parameters among the participants who received eHealth interventions [51]. A second systematic and meta-analysis published in 2016, which included 15 RCTs, also reported improved sleep in adults who received internet-based behavioral interventions [52]. Most recently, a systematic review examining mobile phone interventions for sleep disorders and quality published in 2017 identified 12 RCTs that determined that mobile interventions support the capability of attenuating sleep disorders and enhancing sleep quality [53]. Although internet-delivered interventions have proven effective for adults, to date, the effectiveness of eHealth interventions has not been established for typically developing children. To our knowledge, there are no published reports evaluating internet-based interventions for insomnia in preschool- and school-aged children. A recent study described the development of a mobile phone app to deliver cognitive behavioral therapy for insomnia in adolescents [54]. There are 2 studies that have reported on an internet-delivered intervention for infants and toddlers [55,56], both of which found significant improvement in children's sleep including decreased sleep onset latency, decreased frequency and duration of night awakening, and significant improvement in parental sleep and mood as well as increased parental confidence to manage children's sleep. Given that a survey of parents of young children found that all parents indicated an interest in internet-based treatment programs for sleep problems [57] and that 82% of North American parents with children ages 6 to 16 years old have internet access [58], the internet has the potential to be a powerful tool to overcome barriers to the delivery of treatment for pediatric insomnia.

Rationale

The Better Nights, Better Days (BNBD) program, which is an eHealth intervention for primary caregivers of children ages 1 to 10 years who present with insomnia, can bridge this knowledge to practice gap by providing a potential solution to one of the most common treatment barriers—access to care. BNBD is an innovative, bilingual (English and French) eHealth program for parents, which aims to provide accessible and evidence-informed care for insomnia in typically developing children.

This paper presents the protocol for a planned RCT to evaluate the effectiveness of the BNBD intervention for the treatment of insomnia in children. This is a 2-arm design, using an equal allocation ratio of 1:1, comparing participants assigned to the intervention group who receive the BNBD intervention (treatment) and those assigned to the usual care group who do not receive the BNBD intervention and are able to access other treatment resources (control). Assessments are conducted at 3 periods: baseline (pretreatment), 4 months postrandomization (end of treatment), and 8 months postrandomization (follow-up). To assess the impact of the intervention, the primary outcome measure of sleep efficiency is evaluated using data collected from actigraphs worn by children and sleep diaries completed by parents. Sleep efficiency is the ratio of total time spent asleep to the total amount of time spent in bed. In addition, secondary outcomes are captured by questionnaires that are collected to evaluate children's sleep and psychosocial health, as well as parental daytime functioning and psychosocial health outcomes.

Study Objectives

The purpose of the trial is to evaluate the effectiveness of BNBD, an eHealth intervention for insomnia in children 1 to 10 years of age.

Primary Objective and Hypothesis

The primary objective is to assess the *immediate impact* (baseline vs 4 months) of the intervention on children's sleep.

We hypothesize that at the end of the 4-month assessment period, children randomized to the intervention group will evidence improvement in their symptoms of insomnia compared with children in the usual care group. The outcome variables are sleep efficiency collected by both an objective measure (actigraphy) and a parent report measure (sleep diary).

There are 2 hypotheses for the primary outcome:

1. We hypothesize that children in the intervention group will show improvements in sleep efficiency calculated using *actigraphy* data compared with the usual care group.
2. We hypothesize that children in the intervention group will show improvements in sleep efficiency calculated using *sleep diary* data compared with the usual care group.

Note that sleep efficiency is a measure that captures both sleep quantity and quality and is defined as the amount of total sleep time divided by the amount of time spent in bed with the goal to be sleeping. For example, if a child went to bed at 8 PM and woke at 8 AM, but took 1 hour to fall asleep and was awake for 30 min throughout the night, the child's sleep efficiency would be 87.5% (ie, (630 min/720 min) × 100).

Secondary Objectives and Hypothesis

The secondary objectives are to (1) evaluate the longer-term impact (baseline vs 8 months) on children's sleep and psychosocial health and (2) examine the impact on parent daytime fatigue and psychosocial health outcomes.

1. We hypothesize that *children* in the intervention group will show improvement compared with children in the usual care group at the 8-month follow-up in their symptoms of insomnia, based on improvements in sleep efficiency calculated using actigraphy and sleep diary.

2. We hypothesize that *children* in the intervention group will show improvement compared with children in the usual care group at the 8-month follow-up in their symptoms of insomnia based on questionnaires that capture symptoms of insomnia.
3. We hypothesize that *children* in the intervention group will show improvement compared with children in the usual care group, in their psychosocial health at the 8-month follow-up, evaluated using a questionnaire that identifies internalizing and externalizing behaviors and quality of life of children.
4. We hypothesize that *parents* randomized to the intervention group, when compared with parents randomized to the usual care group, will show (1) decreased daytime fatigue, (2) increased psychosocial health, and (3) improved parenting strategies at the 8-month follow-up based on questionnaires.

Methods

Study Design

The study is a 2-arm RCT, using 1-to-1 allocation, comparing participants assigned to receive either the BNBD intervention (intervention group) or the control group (usual care group). The usual care group will receive the intervention at the end of the 8-month follow-up assessment. The Consolidated Standards of Reporting Trials (CONSORT) 2010 [59,60] guidelines and CONSORT eHealth guidelines [61] were used to design the trial and will be adhered to when reporting the results of the trial. The intervention is being delivered across Canada. The study is coordinated through Dr Corkum's research laboratory (Corkum LABS; Learning, Attention, Behaviour and Sleep) at Dalhousie University. Both the intervention group and usual care group are able to access any resources or programs and services while enrolled in the study, if they so choose.

Subject Population

We plan to enroll a total of 500 participants in the study. Participants are being recruited from across all Canadian provinces and territories.

Inclusion Criteria

Potential participants must meet the following criteria to be eligible to participate in the study:

- Primary caregiver of a child aged 1 to 10 years. (Note that children younger than 12 months are not targeted because sleep patterns are still being established; youth over 10 years of age may be entering puberty, during which time other sleep problems can arise. Moreover, children over 10 years of age may have more control over their own sleep patterns and as such should be included in an intervention. This intervention is only delivered to parents.)
- Live in any province or territory in Canada.
- Have regular access to high-speed internet connection and an email account.
- Comfortable communicating in English or French for day-to-day tasks (eg, listening to the news on the radio, watching TV, and reading books, magazines).
- Child has insomnia, defined as having sleep onset disturbance based on the criteria established by Anders and Dahl [62].

Exclusion Criteria

Potential participants who meet any of the following criteria are not eligible to participate in the study:

- Parent wishes to "bed-share" with their child [63].
- Child has a probable intrinsic sleep disorder (eg, sleep apnea) as assessed based on a questionnaire that screens for pediatric sleep-related breathing disorders [64].
- Child has a significant medical disorder that interferes with sleep (eg, asthma attacks during night, tube feeding, nonambulatory, and severe developmental disability affecting sensory systems such as vision), as determined by parent report and expert clinical review based on an author-made health-related questionnaire.
- Child has a mental health disorder that has required hospitalization or residential care or current use of psychotropic medications that are known to interfere with sleep (eg, stimulant medication for attention-deficit/hyperactivity disorder), as determined by parent report and expert clinical review based on an author-made health-related questionnaire.
- Parent does not have appropriate level of English or French language skill to engage in this intervention, assessed based on a questionnaire that captures proficiency in communication [65].

Recruitment

The recruitment strategy is a multiprong approach across Canada targeting 3 groups: (1) parents, (2) external stakeholders and organizations (ie, our partners including health care provider associations), and (3) the media.

The target audience of the BNBD intervention is parents with regular access to the internet; therefore, the recruitment strategy is primarily grounded on internet-based tools, notably the study website [66] and social media, including Facebook, Twitter, Instagram, and Pinterest. However, traditional recruitment methods are also employed, including media interviews and printed posters and conference presentations, to reach both potential participants and the health care community.

We plan to enroll 500 eligible participants in this study, with 80.0% (400/500) of the sample English speaking and 20.0% (100/500) of the sample French speaking, consistent with the Canadian demographics. The study sample is also stratified on the age group of the participant's child (toddler: 1-2 years; preschool: 3-5 years; and school-aged: 6-10 years), with equal numbers of participants enrolled from each of the 3 categories (target n=167).

Textbox 1. Biopsychosocial model of sleep.

Bio

- Opponent process model
- Physiological arousal

Psycho

- Classical conditioning
- Operant conditioning
- Psychological arousal
- Emotional regulation

Social

- Dyadic processes
- Family processes
- Environmental, cultural, socioeconomic influences

Recruitment is targeted to ensure that the study population includes representation from across Canada. Canada is divided into 4 geographical regions: Atlantic (New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island,), Central (Ontario, Quebec), Prairies and Northern Territories (Alberta, Manitoba, Saskatchewan, Northwest Territories, Nunavut, Yukon), and the West Coast (British Columbia).

Behavioral Change Model

The overarching model is based on Ritterband's eHealth behavioral change model [67]. This model states that an effective internet-based intervention produces and maintains behavior change and symptom improvement through the context (including user characteristics, environment, and website characteristics), which in turn impacts behavior change mechanisms, and ultimately impacts outcomes. In this situation, the behavior change mechanism is focused on changing the parents' cognitions, affective responses, and behavior responses, to change the child's insomnia symptoms. We used a biopsychosocial model to conceptualize the multiple predisposing, precipitating, and perpetuating factors related to the development and maintenance of, and the treatment of, insomnia in children. See Textbox 1 for further details.

Electronic Health (eHealth) Intervention

Participants randomized to the intervention group receive access to the BNBD intervention immediately, whereas participants randomized to the usual care condition receive access after they complete the 8-month follow-up assessment.

The BNBD intervention is fully self-guided (ie, there is no contact with coaches or clinicians), empowering parents to implement strategies independently. The program introduces evidence-based interventions, tailored content (ie, participants create personalized sleep routines, set individualized goals, and receive custom feedback on progress), and age-specific information delivered primarily through videos, supported by graphics, animations, and interactive elements to engage and encourage parents. Access to built-in tools and supports, such as sleep diaries and goal setting and tracking, provides feedback on participants' progress.

The intervention includes 5 sessions made available sequentially to participants. Table 1 summarizes the content of the intervention. The recommended completion time of the intervention ranges from 5 to 10 weeks. Participants receive an automated email reminder when a session becomes available, a prompt to complete each session, and 7 notices that the recommended completion time is approaching. The core content is delivered primarily via videos and interactive activities to support the parents' learning of these new skills.

Each session provides evidence-based information to parents, strategies for implementation of best practices to address sleep problems, and access to additional help and advice through a "Roadblock" question-and-answer style support detailing common obstacles to implementing the recommended interventional strategies and evidence-based methods to navigate these obstacles. There is also a "Reward Center" where parents can develop reward programs (eg, sticker charts) to help support the implementation of these sleep intervention strategies.

The program can be used at a time that is convenient for the participants, removing barriers to care and providing services in the comfort and privacy of their own homes. The intervention is hosted on the BeHealth Solution, LLC's proprietary technology platform [68] and can be accessed through participants' desktops, laptops, tablets, and mobile phones.

Before beginning each session, starting with Session 2, participants are asked whether they wish to continue the intervention program. If participants indicate they are not interested in participating further, they are asked to complete a questionnaire and provide the reason, in an open-ended question, regarding why they no longer wish to continue the program.

Table 1. Intervention sessions.

Session	Topic overview
Sleep information	Characteristics of sleep; types of sleep problems, sleep need; how sleep problems develop; impact and treatment of sleep problems
Healthy sleep practices	Daytime and bedtime routines; sleep hygiene/healthy sleep practices; sleep scheduling (including napping) and sleep routines
Independent settling at bedtime	Settling at bedtime; parents choose a sleep intervention that best fits their needs from 3 intervention strategies: controlled comforting, camping out, and bedtime fading
Night waking, napping, and early morning awakenings	Applying strategies to night waking; applying strategies to early morning awakenings; applying strategies to napping
Looking back and ahead	Relapse prevention; looking back at goals and progress; common pitfalls/roadblocks; what to expect at new developmental milestones; dealing with other sleep problems; making a plan

This allows participants the freedom to discontinue the program at any time and allows us to assess any issues that contributed to discontinuation. To allow for a process-level analysis, before starting each session, participants are also asked to complete the Insomnia Severity Index [69] scale and rate the sleep quality of their child to evaluate pediatric insomnia symptoms.

In addition, 2 measures are used to assess treatment fidelity. First, parents' implementation of the intervention is assessed using process measures administered at the beginning of each session of the program. In advance of each subsequent module, participants are asked to record how carefully they reviewed the material, what percentage of the recommended strategies they implemented, and how successful they were in implementing these strategies, as well as to provide an estimate of the overall percentage improvement of their child's sleep problems. Second, computer-generated user statistics captured by the intervention platform software are used to assess adherence, such as the number of times the site was accessed and the period of time taken to complete each module.

Usability and Quality Assurance

A usability study took place from September 2013 to January 2014 to evaluate user performance and satisfaction with the BNBD intervention. The study [70] was conducted with a prototype of the BNBD intervention, and both qualitative and quantitative data were collected. Qualitative data were analyzed using Ritterband's eHealth model [67] to better understand how any potential barriers to intervention use (eg, level of ease of accessing the internet) could be corrected and addressed (eg, increased social presence, increased interactivity and personalization). The results of this usability study were used to revise the BNBD intervention.

Quality assurance was also undertaken to evaluate the functionality of the intervention platform in the spring of 2016. Internal reviewers, including program developers with BeHealth Solutions, LLC, and research staff at Corkum LABS reviewed the intervention to identify technical problems. In addition to this, 6 parents of children aged 1 to 10 years old served as external reviewers for the program and completed 5 questionnaires to provide structured feedback on the technical operation of each session of the intervention. The goal of this step was to identify functional problems with the program (eg, broken links, incorrect routing) before conducting the RCT.

Measures

Primary Outcome Measures

The primary outcome variable is sleep efficiency based on both actigraphy and parent report sleep diary data. Actigraphs are couriered to the participants and sleep diary entries are completed on the internet by the parents. Participants are asked to fill out a sleep diary for 7 consecutive days, and the child is asked to wear an actigraph during the same time period. The dates of collection of actigraphy data should correspond to the sleep diary data collection dates. Sleep diary and actigraphy data are collected at each assessment point.

Actigraphy

An actigraph is a battery-operated device utilizing an accelerometer to detect motor activity. We use the Philips Respironics Actiwatch 2 (Koninklijke Philips N.V., Amsterdam, NL). When an actigraph is worn, a computer chip located inside the device records movement, which is used to determine a number of sleep variables, including but not limited to sleep efficiency (captured from lights out to awakening), sleep onset, total sleep time, and night waking [9,18].

Participants are asked to have their child wear the actigraph on their child's wrist of their less dominate hand. Children 1 to 2 years of age wear the actigraph on their ankle. Participants are instructed to record any instances in which the actigraph is removed from their child's body for any length of time. Participants are instructed to have their child wear the actigraph for 7 days, with a minimum requirement of 5 days.

Sleep Diary

An internet-based sleep diary was developed based on systematic reviews by Meltzer and Mindell [24] and Wu and colleagues [71]. Sleep diaries have been validated against actigraphy and polysomnography and have demonstrated good face validity and high internal consistency when used with child participants [72]. The sleep diary requires approximately 10 min to complete. The internet-based sleep diary is housed in the Research Electronic Data Capture (REDCap) platform (Vanderbilt University, Nashville, US), a secure, electronic, data capture system [73]. The internet-based sleep diary underwent technical and usability testing by research staff and external reviewers, as well as 6 parents of children aged 1 to 10 years, to ensure the proper functionality of the measure. Parents can either complete the sleep diary directly online or print a

copy and enter the information at a later point (within a 3-day time window). Data entered by participants into the internet-based sleep diary entry form are automatically populated into the REDCap database.

The sleep diary contains 25 items measuring the following variables: sleep duration, nighttime sleep duration, daytime sleep duration, sleep onset latency, bedtime, wake time, presence and frequency of night awakening, and the presence and frequency of bedtime resistance. The sleep diary also provides a measure of time spent in bed extracted from the time the light was turned off ("Down for the night") to the time light was turned on ("Up for the day"). Sleep efficiency is calculated from these variables.

Secondary Outcome Measures and Measures for Exploratory Analyses

Secondary outcomes and exploratory outcomes are assessed through the administration of internet-based questionnaires to assess children's sleep and psychosocial health, parental function, treatment barriers, and predictors to successful intervention adherence. Each participant answers 13 to 15 questionnaires based on the group assignment (intervention or usual care) and age of the child.

All measures are available in both English and French, based on whether the participant has enrolled in the English or French language trial. All secondary and exploratory outcome measures are administered on the internet via REDCap. All electronic questionnaires underwent technical and usability testing by research staff and external reviewers, as well as by 6 parents of children ages 1-10 years. All questionnaires are displayed in a sequential manner. Certain measures are age-dependent, and REDCap automatically delivers them accordingly. All measures, and the time points that each is administered, are indicated in Table 2.

Please see Multimedia Appendix 1 for a detailed description of all measures used throughout the study.

Study Procedures

Figure 1 displays the schematic overview of the study and each step is described below.

Prescreening

During the prescreening process, potential participants conduct a self-screening on the BNBD website [66]. Here, interested individuals read the inclusion and exclusion criteria in lay terms and self-assess to determine if they may be eligible. If parents feel they may meet eligibility criteria and are interested in the study, they click a link directing them to the REDCap database to continue with screening. A screening information and consent form to participate in the screening process is presented, and potential participants must consent to proceed. Participants are given an opportunity to contact research staff by email to have any questions answered and concerns addressed, if they so choose.

Screening and Consent

After completing the screening information and consent form, participants complete the screening questionnaire to assess whether they meet inclusion criteria [63]. Participant responses to the screening questionnaire are automatically assessed in REDCap using predefined eligibility criteria, and participants immediately receive an onscreen message stating whether they are eligible or ineligible to continue. Individuals who are eligible at screening are invited to consent to participate in the full study by completing the information and consent form. The information and consent form and study data are housed in different databases. Individuals who are ineligible are informed that they do not meet the study requirements. Participants are given an opportunity to contact research staff by email to have any questions answered and concerns addressed.

Eligibility

After completing the information and consent form, participants complete 4 eligibility questionnaires: behavioral insomnia questionnaire [62], pediatric sleep questionnaire [64], health-related questionnaire (HRQ; author made), and single item literacy scale [65]. REDCap automatically scores these questionnaires and determines if the participant is eligible or if further review is required. Further review is required if the participant responds "yes" to any of the questions on the HRQ.

The HRQ is reviewed within 72 hours post completion by a subcommittee comprised of 3 coinvestigators including at least 1 psychologist and 1 physician (also trained in sleep medicine) to evaluate if the child has any significant physical health disorders, mental health disorders, or sleep disorders that would make them ineligible to participate.

Participants are provided with the email address of the research staff whom they may contact in the event that they have concerns or questions about the decisions related to eligibility. Participants may also request a phone call to speak with research staff about these decisions.

Posteligibility

Eligible participants provide their mailing address and telephone number on the identifying information questionnaire, collected in a separate REDCap database (to ensure the privacy of participants' personal information). Research staff members contact participants by telephone to confirm their mailing address and answer questions regarding study procedures. Once contact with the participant is made, the study package, including the actigraph and sleep diary, is couriered to the participant's preferred address.

Baseline

Once participants receive their study package, an automated invitation email from REDCap is delivered to the participant to commence baseline measures. Participants complete 7 days of sleep diary entries and collect 7 days of actigraphy data. Participants also complete a series of questionnaires on REDCap before the end of the 7-day actigraphy and sleep diary data collection.

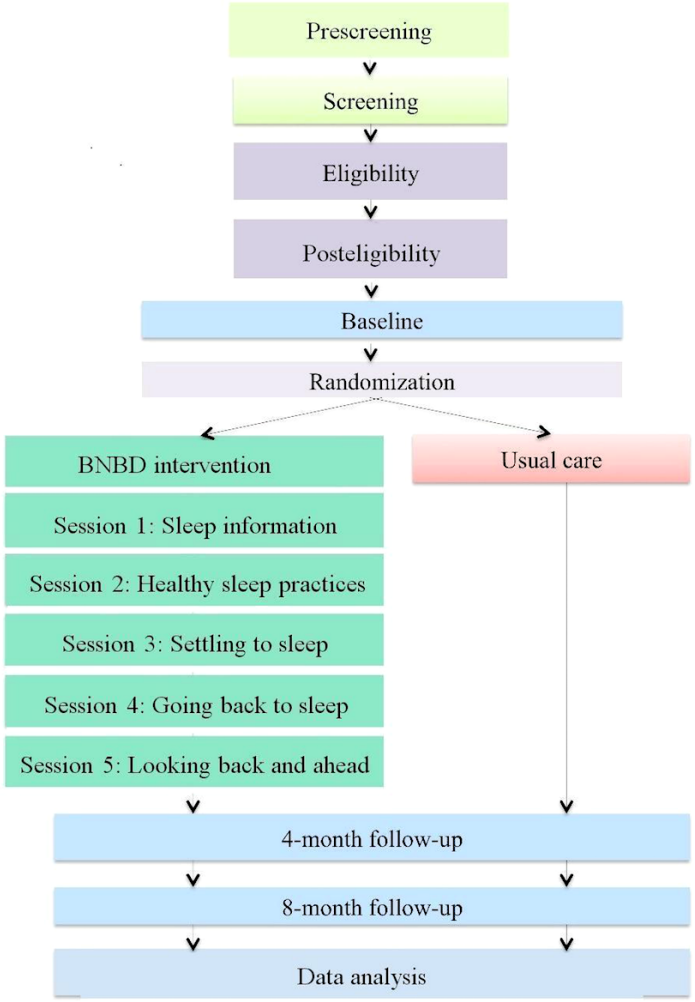
Table 2. Measures and collection schedule throughout the study period. The X symbol denotes at which assessment period(s) participants complete each measure.

Measures	Screening	Eligibility	Posteligibility	Baseline	Follow-up at 4 months	Follow-up at 8 months
Screening measures						
Screening questionnaire [63]	X					
Eligibility measures						
Behavioral insomnia questionnaire [62,74]		X		X[a]	X	X
Pediatric sleep questionnaire [64,74]		X				
Health-related questionnaire		X				
Single item literacy screen [65]		X				
Posteligibility measures						
Identifying information questionnaire			X			
Outcome measures						
Demographic questionnaire [75]				X		
Child sleep/insomnia						
Actigraphy				X	X	X
Sleep diary				X	X	X
Tayside children's sleep questionnaire/sleep disturbance scale for children [74,76,77]				X	X	X
Child daytime functioning—psychosocial/physical health						
Pediatric quality of life [78,79]				X	X	X
Child behavior checklist for ages 1½ to 5 years/child behavior checklist [80,81,82,83]				X	X	X
Caregiver-teacher report form/teacher report form [80,82,83]				X	X	X
Parent functioning/psychosocial health						
Single item fatigue impact scale [84,85]				X	X	X
Depression, anxiety and stress scales [86-89]				X	X	X
Parenting scale [90,91]				X	X	X
Measures for exploratory analyses						
Children's physical activity index [92]				X		X
Body mass index [93-95]				X		X
Parent's rating of clinically significant improvement [96]				X	X	X
Treatment utilization questionnaire [97]				X	X	X
Willingness to pay				X	X[b]	
Barriers to treatment participation scale [98,99]					X[b]	
Client satisfaction questionnaire [100,101]					X[b]	
Readiness for change [102-104]				X		
Bedtime routines questionnaire [105]				X	X	

[a]If baseline assessment is >30 days from eligibility assessment, the behavioral insomnia questionnaire is repeated at baseline.

[b]Intervention arm only.

Figure 1. Schematic overview of the study.



Randomization

After completion of baseline measures, participants are randomized. A blocked stratified randomization is used with 1-to-1 allocation for parents to either the intervention group or the usual care group. Participants are not blinded to their assignment group. Participants are stratified by age groups: toddler (1-2 years of age); preschool-aged (3-5 years of age); and school-aged (6-10 years of age). Blocks of 4 are used to randomize the participants for each stratum (ie, each age group).

The randomization table was created using the block random function in the R statistical software [106] and inputted into REDCap by a research staff member who is not associated with the management of participants. The only individuals who have access to the randomization table are not associated with participant management and include the research associate (EAB) who created the random allocation table based on the study design and a coinvestigator with extensive RCT design experience (RS) and the study statistician (PA), who reviewed the randomization table. The statistician conducting the primary analysis will be blinded to participant allocation to intervention or usual care groups (ie, the statistician will not be given the code for this variable).

Research staff members randomize participants using an automated REDCap procedure. The randomization table, created in Microsoft Excel, is uploaded into the REDCap database, where it cannot be modified or accessed. Only the research associate is able to view the randomization table. Once a participant completes baseline assessment, research staff members confirm all criteria are met and "trigger" the automated randomization by clicking a button within the program. An automated email is sent to participants to notify them of the randomization result.

Follow-Up at 4 Months and 8 Months

Primary outcome measures (sleep diary and actigraphy), secondary outcome measures (questionnaires), and measures to address exploratory questions are administered to all participants at baseline and at 4 and 8 months postrandomization. Participants receive an automated invitation email from REDCap to start their 4-month follow-up after 16 weeks postrandomization, and to start their 8-month follow-up 32 weeks postrandomization.

If participants do not begin follow-up assessment, research staff members make 12 attempts to contact participants by email and telephone at different times of day (eg, afternoon, evening) and various days of the week (eg, weekday, weekend), over the course 6 weeks (from 14 weeks postrandomization to 20 weeks postrandomization at 4-month follow-up, and 30 weeks to 36 weeks postrandomization at 8-month follow-up). This procedure

is designed to maintain communication with participants and ensure that outcome data are collected. Participants are deemed lost to follow-up for that assessment period if 4-month and 8-month assessments are incomplete by 20 weeks or 36 weeks postrandomization, respectively.

Compensation

To compensate participants for their time and to maximize adherence rates, participants receive an honorarium of $25 CAD for the completion of all measures at each of the 3 collection time points, as well as a completion stipend of $25 CAD at the end of the 8-month follow-up, if they completed all 3 assessments. Therefore, a maximum of $100 CAD per participant is given as an honorarium for study participation. At study completion, participants are entered into a draw to win a tablet; one entry is generated for each day that the participant completed the sleep diary and has corresponding actigraphy data.

Statistical Analysis

Sample Size Analysis

A total goal of 500 consented participants is expected. Using the assumption that 50.0% (250/500) of participants will be lost to follow-up, the target sample size at the end of the study is n=250 [107-109]. This gives us power of .80 to detect a significant group-by-time interaction with the effect size (*d*)=0.45 and alpha set to .025, for primary outcome measures calculated from actigraphy and sleep diary from baseline to 4-month follow-up. Given that 2 primary outcome variables are being used (sleep efficiency from actigraphy and sleep efficiency from sleep diaries), alpha was divided by 2 so that *P*=.025, rather than *P*=.05 would be accepted as indication of statistical significance. This is based on the assumption that an effect size of *d*=0.45 is clinically significant for sleep efficiency as measured by actigraphy and sleep diary [45].

Data Analysis

The primary outcome variables that will be used to evaluate the impact of the intervention program on insomnia symptoms are sleep efficiency from actigraphy and sleep efficiency from sleep diary data. Overall, 2 primary outcome measures are included to capture these variables of interest using both an objective measure of sleep (ie, actigraphy) and a parent report/subjective measure of sleep (ie, sleep diary), thus allowing us to compare our results with existing research in the field. In unblinded RCTs (ie, in which participants know their group assignment such as this study), there is evidence of bias toward significance of the active treatment; thus, an objective measure (eg, actigraphy) is used to mitigate this bias [110]. However, as parents are the primary decision makers with respect to seeking treatment for their child's health problems, it is also critical to obtain their perspective. Further, inclusion of patient-reported outcomes is recommended when testing interventions [111].

Secondary outcomes for this study examine the maintenance of changes in sleep, as well as the impact on the child's psychosocial health (behavioral, attentional, and emotional functioning) and on parents' psychosocial health (ie, psychological adjustment). Data analyses are overseen by the research team, including the statistician, using an intent-to-treat data analytic approach [112].

Conditional growth model methodology, also known as hierarchical models, a generalization of the standard linear model, which permits data to exhibit correlation and nonconstant variability, will be used to fit each outcome at baseline, 4 months, and 8 months [113] using PROC MIXED in the Statistical Analysis System. Model formulation is at 2 levels, with participants as level 1, and treatment group as level 2. The level 1 model is a linear individual growth model, and the level 2 model expresses variation in parameters from the growth model as random effects unrelated to any person-level covariates. For each parent, the actual time (in days) from baseline to when each follow-up assessment is completed is also entered, to account for variation in when parents actually complete assessments.

Primary Outcome

For the primary outcome (sleep efficiency based on actigraphy and sleep diary data), we will test for a significant interaction effect between time and group, which would indicate differential rate of change over time between groups. Differences in the estimated means between the intervention group and usual care group will also be compared at the 4-month post treatment time point (primary end point) to determine the magnitude of differences between groups [114].

Secondary Outcome

For the secondary outcomes, we will test differences between the 2 groups modeling changes in the outcome variables across the 3 points of measurement (baseline, 4 months, and 8 months postrandomization) to determine treatment effects at 8 months postrandomization. Again, a significant time × group interaction would indicate differential rate of change over time between groups. Differences in the estimated means at the 4-month and 8-month posttreatment time points will also be examined.

To examine the possibility of differential response to treatment across the 3 age groups, we will use a growth curve modeling of the 2 primary outcomes (sleep diary and actigraphy). Analysis is based on the methodology of the extension of the generalized linear model for longitudinal data, namely marginal and random effects modeling, which allows for varying intercepts and slopes across subjects, "G-side" random effects, and different within-person error variance covariance structure, "R-side" random effects [115,116]. An interaction of age group (toddler, preschool-aged, and school-aged) × time (3 assessments) × randomization group (intervention and usual care) would indicate differential response to treatment.

An intent-to-treat analysis will be conducted. Multiple imputation techniques will be used to deal with missing data. This method works well on longitudinal data and is robust to violations of non-normality of the variables used in the analysis.

Clinical Significance

The clinical significance of an improvement in outcomes in response to treatment for pediatric sleep problems has not been defined. Various methods have been used to examine clinical significance [117,118]. Minimal important difference (MID) is

an important metric of clinical significance. The MID refers to "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's (health care) management" [119]. The MID has not been determined for most pediatric health issues utilizing parent-reported outcomes [120]. We will examine clinical significance in 2 ways for both of the primary outcomes. First, the reliable change index (RCI) will be computed and the percentage of cases that exceeded RCI>1.96 will be determined [121]. The RCI is a distribution-based metric that informs the extent to which an observed change is reliable; it is often used in mental-health treatment studies [122,123]. Second, at baseline, all participants are asked to rate the "smallest amount of improvement" on their child's sleep problems that they would be satisfied with, using a 10 cm visual analog scale (not at all improved, 0%; completely improved, 100%). The average is used as a method of estimating the MID [124] and has been used in other pediatric sleep intervention trials [125]. The percentage of cases that achieve at least this level of improvement between baseline and either 4 months or 8 months postrandomization will be computed.

Results

The RCT for the English language population was launched in September 2016 and the expected date of completion is February 2018. The RCT of the French language population was launched in May 2017 and is expected to be completed in February 2018. Data analysis will be completed by 2019.

Discussion

Main Goals

Our primary purpose for this study is to provide a readily accessible, evidence-based eHealth intervention to increase access to care for insomnia in typically developing children aged 1 to 10 years. With the significant percentage of the Canadian population with internet access [126], eHealth delivery has the capacity to be a powerful tool to overcome traditional systemic barriers to treatment access. The internet-based BNBD program similarly has the potential to (1) be integrated within a stepped-care model of pediatric services, (2) improve parents' knowledge about behavioral treatments for insomnia, (3) improve accessibility of treatment interventions for children and their families, and (4) reduce service demands at the frontline of clinical practice.

Ethical Considerations

Informed Consent

Ethics approval was granted by IWK Health Centre Research Ethics Board. To ensure informed consent, participants must sign the internet-based screening information and consent form and the information and consent form after the nature of the study has been fully explained. Participants are not able to proceed to any study-related activity before electronically signing consent. These consent forms inform participants that participation is voluntary and that they may withdraw consent to participate at any time, and they are informed of the aims, methods, benefits, and risks of the study. All participants are given an opportunity to contact research staff by email or to request a phone call to have any questions answered and concerns addressed. A series of true and false questions to test participants' knowledge of their research rights are used to ensure informed consent. A copy of both the screening information and consent form and the information and consent form are available to be downloaded and saved by participants. Participants provide an electronic signature and date and click an "I Agree" button.

Privacy, Personal Health Information, and Study Data

The study is conducted in accordance with all applicable standards and procedures of the IWK Health Centre, as well as the Personal Health Information Act, Personal Information International Disclosure Protection Act, and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

Personal health information and study data that are collected, used, or disclosed are limited to those data that are necessary to fulfill the objectives of the study explained in this protocol, and all data are handled in a confidential manner. Study data are identified using a unique identifier code. A key file is used to link this identifier to participants' email addresses. Data are not affiliated with any personal health information, and all data are collected and stored on the Canadian-based secure servers, the REDCap electronic data capture system and the Dalhousie University server. Identifying information is accessible only to the study investigators, postdoctoral fellow, and data management and research staff. All study data will be kept in a secure and confidential location for at least 5 years post data publication and then destroyed according to IWK Health Centre's policy.

Safety Monitoring

This behavioral intervention involves minimal risk to the participants. Participants are provided with the email address of research staff whom they may contact in the event that they have concerns or questions related to the study. The study safety-monitoring plan involves communication between the research staff, who are in contact with participants, and the principal investigator (PVC), a registered psychologist. Any difficulties experienced by the participants that cannot be dealt with adequately by research staff are immediately communicated to the principal investigator or her delegate (coinvestigator) and follow-up with the participant is made to ensure their well-being. Data monitoring for adverse events or trends in outcome has not been undertaken given that this is a low-risk study. An adverse events committee, composed of the 3 members from Dalhousie University, not associated with the BNBD study, and having medical, psychology, and sleep expertise, will review adverse events if one becomes known during the course of the study.

Commercialization

If the BNBD intervention is found to be effective, to ensure its sustainability, the investigators anticipate commercialization of the BNBD intervention. The investigators will work to commercialize this program for a reasonable rate, so that all

parents of children with insomnia can have access to this intervention.

The BNBD intervention is protected by a trademark registered under the Canadian Intellectual Property Office. The Industry Liaison and Innovation Office with Research Services at Dalhousie University has executed an interinstitutional agreement for the BNBD study, which outlines and governs intellectual property (IP) rights, commercialization, and confidentiality and publication agreements between Dalhousie University and the partnering institutions: the Hôpital Rivière-des-Prairies, the Hospital for Sick Children, McGill University, University of Alberta, University of British Columbia, Université de Montreal, University of Toronto, and Western University. The IP relating to the session content remain with Dalhousie University and are licensed for use to the industry partner. The IP relating to the proprietary platform used to host the internet-based BNBD Intervention remains the property of the industry partner. Any IP that is jointly developed throughout the commercialization process has shared ownership.

Conclusions and Significance

This research addresses significant public health issues through knowledge creation and translation to achieve direct benefits for the health and well-being of Canadian children and parents. This study aligns with the recognized need to more rapidly transfer new scientific knowledge to improve patient care and population health and targets the validation of new treatment delivery models to increase availability of effective treatment resources. This research is novel for Canadian and international pediatric health services and has the potential to have a direct and significant impact both in Canada and abroad.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Description of Measures.

[PDF File (Adobe PDF File), 78KB - resprot_v7i3e76_app1.pdf]

Multimedia Appendix 2

CONSORT-EHEALTH checklist (V 1.6.1).

[PDF File (Adobe PDF File), 694KB - resprot_v7i3e76_app2.pdf]

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Abbreviations

BNBD: Better Nights, Better Days
CONSORT: Consolidated Standards of Reporting Trials
eHealth: electronic health
HRQ: health-related questionnaire
IP: intellectual property
MID: minimal important difference
RCI: reliable change index
RCT: randomized controlled trial

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Protocol

Therapist-Assisted Progressive Resistance Training, Protein Supplements, and Testosterone Injections in Frail Older Men with Testosterone Deficiency: Protocol for a Randomized Placebo-Controlled Trial

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Abstract

Background: Fall accidents are a major cause of mortality among the elderly and the leading cause of traumatic brain injury. After a fall, many elderly people never completely recover and need help in coping with everyday life. Due to the increasing older population in the world, injuries, disabilities, and deaths caused by falls are a growing worldwide problem. Muscle weakness leads to greatly increased risk of falling, decreased quality of life, and decline in functional capacity. Muscle mass and muscle power decrease about 40% from age 20 to 80 years, and the level of testosterone decreases with age and leads to impaired muscle mass. In addition, 20% of men older than 60 years—and 50% older than 80 years—have low levels of testosterone. Treatments after a fall are significant financial burdens on health and social care, and it is important to find treatments that can enhance function in the elderly people.

Objective: The purpose of this study is to investigate whether testosterone and progressive resistance training alone or combined can improve muscle strength and reduce the risk of falls in older men. Additionally, we will examine whether such treatments can improve quality of life, functional capacity, including sexual function, and counteract depression.

Methods: This is a randomized placebo-controlled, double-blind trial in which frail older men with testosterone deficiency are treated with testosterone supplemental therapy and therapist-assisted progressive resistance training for 20 weeks, with the possibility to continue treatment for 1 year. Four study arms of 48 participants each are provided based on factorial assignment to testosterone supplemental therapy and progressive resistance training. The 4 groups are as follows: controls given placebo injections without physical exercise for 20 weeks, testosterone-alone group given testosterone injections without physical exercise for 20 weeks, training-alone group given placebo injections for 20 weeks combined with 16 weeks of progressive strength training, and combination group given testosterone injections for 20 weeks combined with 16 weeks of progressive strength training. Performance in the 30-second chair stand test to measure improvement of general strength, balance, and power in lower extremities is the primary endpoint. Secondary endpoints comprising tests of cognition, muscle strength, and quality of life are applied before and after the training.

Results: Funding was provided in October 2016. Results are expected to be available in 2020. Sample size was calculated to 152 participants divided into 4 equal-sized groups. Due to age, difficulty in transport, and the time-consuming intervention, up to 25% dropouts are expected; thus, we aim to include at least 192 participants.

Conclusions: This investigation will evaluate the efficacy of testosterone supplemental therapy alone or combined with progressive resistance training. Additionally, improvements in quality of life and cognition are explored.

Trial Registration: Clinicaltrials.gov NCT02873559; https://clinicaltrials.gov/ct2/show/NCT02873559 (Archived by WebCite at http://www.webcitation.org/6x0BhU2p3)

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KEYWORDS

accidental falls; aged; exercise; testosterone; therapeutics; men

Introduction

Among the elderly, invalidity and mortality after falling constitute a major health problem. Every year, about 40% of all people aged 65 years or older experience a fall, and approximately 10% of these falls lead to serious injury and increased mortality and invalidity [1-3]. Invalidity after fall accidents increases the need for support and is associated with extensive social costs expected to rise significantly in the future [4-6].

Accidental Falls in the Elderly: Causes and Injuries

The cause of serious falls is because of several factors: primarily reduced muscle strength in the elderly, especially in the thigh muscles [7]. Muscle mass decreases by about 40% from age 20 to 80 years [7].

Specifically, the loss of muscle power (muscle strength × contraction rate) associated with sarcopenia is related to increased risk of falling and decreases by approximately 3.5% annually from the age of 65 years [8]. In addition, 1 week of immobilization may result in a reduction of muscle strength of up to 20%, and a loss of bone of up to 1% of the maximum bone mass corresponding to the normal annual reduction [9]. Especially among weak elderly persons, extended bed rest can cause muscle strength to decline below a critical threshold because of which basic daily activities can no longer be performed. However, significant gains in both muscle strength and muscle power can be achieved through strength training in the elderly. In a 2009 Cochrane review of 121 studies, investigators found that 8 to 12 weeks of progressive strength training significantly increased muscle strength by 10% to 45% in persons aged 60 years and older [7].

Male testosterone levels decrease with age. Furthermore, 20% of men older than 60 years and 50% older than 80 years are hypogonadal with serum testosterone below 10 nmol/L or 300 ng/dL [10,11]. The normal average is approximately 22 nmol/L (650 ng/dL) with an upper limit of 35 nmol/L (1000 ng/dL) [11].

Hypogonadism

Hypogonadism is associated with impaired muscle mass, muscle strength, and bone mass [10,12]. In a meta-analysis of 17 studies, 3 to 36 months of testosterone supplement induced a significant increase of 2.7% in lean body mass (corresponding to increased muscle mass) [12]. Despite significant increases in muscle mass, only tendencies toward increases in muscle strength were observed in two meta-analyses of, respectively, 10 and 11 studies investigating 1 to 39 months of testosterone supplementation [12,13]. Thus, it could be speculated that a training stimulus may be needed to translate the increased muscle mass into a measurable increase in muscle strength. In older men with verified hypogonadism, positive effects on bone mass have been found after 24 to 36 months of testosterone supplementation [14,15]. In a randomized controlled trial, it was shown that the growth in muscle mass, strength, and power induced by testosterone supplementation was dose dependent [16]. Testosterone supplemental therapy for hypogonadal men has resulted in a significant improvement in balance [17], and in a recent study, investigators found a direct correlation between testosterone deficiency and increased risk of fall [18].

The effect of strength training is increased when supplemented with protein intake immediately after exercise [19-22]. For many elderly persons, malnutrition is a barrier to improvements achieved by strength training [10]. Vitamin D deficiency can lead to loss of bone mass and adversely affect the neuromuscular function [23], and vitamin D supplements may reduce the risk of fall in the elderly [24]. A study of 100 resident elderly showed that 19% had moderate (12-25 nmol/L) and 12% had severe (<12 nmol/L) vitamin D deficiency [23].

Unlike previous studies, participants in this study will be older and have verified hypogonadism. By continuous regulation of protein and vitamin D supplementation, participants will be ensured optimal conditions for strength training. Testosterone supplementation has been shown to prevent impaired bone and muscle mass, and improved body composition, quality of life, and physical ability in a controlled study of the effect of testosterone without concurrent training for elderly men with low and slightly reduced testosterone levels [25]. Additional studies are needed to verify the above-mentioned results.

Hypogonadism is a risk factor for obesity, type 2 diabetes, atherosclerosis, myocardial infarction, chronic heart failure, and erectile dysfunction [26-28]. Furthermore, it has been found that testosterone supplements for hypogonadal men may reduce depression and improve cognition [29-31]. Testosterone supplements for men with testosterone deficiency significantly counteract erectile dysfunction, that is, impotence [32].

Dosage of approximately 100 mg testosterone weekly was associated with the best cognitive results, compared with significantly higher or lower doses [33]. Experiments with particularly positive effects of testosterone supplements used weekly intramuscular injections with approximately 100 mg slow-acting testosterone esters, although the effect of transdermal applications was not equivalently positive [34]. Intramuscular injections have been associated with improved

bone mass, although transdermal testosterone did not induce a similar effect [35].

Study Aim and Hypotheses

The aim of this study was to investigate the effect of intramuscular injections of testosterone and progressive resistance training either alone or in combination in older men. Our hypotheses are that both interventions can improve muscle strength and potentially reduce the risk of falls, and that an additive effect of a combined intervention will be present. Additionally, we will examine the effect on quality of life, functional capacity, sexual function, and depression. The findings of this trial may have fundamental importance for future recommendations for the elderly male population and for efforts to improve quality of life by reducing muscle weakness, loss of function, bone loss, falls, and fractures.

Methods

Study Design

This trial is designed as a double-blind, randomized, placebo-controlled intervention trial using a 2×2 factorial design.

Recruitment of Study Participants

Eligible patients are consecutively recruited primarily by newspaper advertising and then included from several departments at Herlev University Hospital, including the Medical and Geriatric Departments, the Injury Center, and the Emergency Medical Reception Section. Thus, this is a single-center trial. Permission to use newspaper advertising was granted by the ethical committee. A screening log is kept. In addition, medical records from the outpatient fall clinic and the geriatric department are retrospectively screened up to 2 years before the start of the project, and potentially eligible patients are invited for eligibility screening. Anonymous information from medical records may be disclosed. Participation is optional, and participants must provide a written consent.

The first contact to an eligible trial participant is made when a participant contacts an investigator according to the instruction provided through newspaper advertising or in connection with a hospitalization at Herlev University Hospital. The contact will be made to the primary investigator, who at the hospital provides eligible participants with written trial information and oral information about the trial. The conversation takes place undisturbed, either in the single room or an office. Eligible patients will be informed of their rights, and if necessary, relatives will also be informed. Persons with pronounced dementia or severe cognitive impairment will not be included, in accordance to the exclusion criteria mentioned below. Each participant is allowed up to 1 week to provide written consent.

Participants

The trial is intended to enroll 192 hypogonadal older men with physical impairment causing reduced walking ability and increased risk of falls. Criteria for inclusion and exclusion of participants follow the national treatment guide for male testosterone deficiency prepared by the Danish Endocrinological Society.

Randomization and Blinding

Participants are randomized to 4 groups, each with 48 participants by opening sealed consecutive numbered envelopes, each containing a computer-generated treatment group assignment of the patient. To ensure evenly age distribution, 50% of the envelopes are for participants aged 70 to 84 years and 50% are for participants aged 85 years or older. Thus, the following 4 groups are established:

- A control group is given placebo injections without physical exercise for 20 weeks.
- A testosterone group is given testosterone injections without physical exercise for 20 weeks.
- A training group is given placebo injections for 20 weeks combined with 16 weeks of progressive strength training and supplementation of vitamin D, calcium, and protein commencing 4 weeks after the first injection.
- A combination group is given testosterone injections for 20 weeks combined with 16 weeks of progressive strength training and supplementation of vitamin D, calcium, and protein commencing 4 weeks after the first injection.

Participants are randomized into 4 arms so that the effects of training supplemented with vitamin D and protein, testosterone supplementation, or the combination of exercise and testosterone supplementation can be evaluated against placebo. Furthermore, the effect of combination treatment can be evaluated against the two individual treatments. Note that only participants in the 2 groups receiving progressive strength training are receiving supplements of vitamin D, calcium, and protein. Vitamin D, calcium, and protein are only given on days where participants receive progressive strength training corresponding to 3 times weekly.

The treatment with testosterone is made double blind, whereas exercise with training must be single blind, because it is not possible to blind the patients for exercise. We will ensure that investigators testing participants or performing statistical analyses are blind to treatment arms. A flowchart is given in Figure 1, showing the basic trial setup where treatments are discontinued in week 20.

During week 12, participants are asked if they are willing to continue the trial for a total of 52 weeks including injections in weeks 28 and 40 to investigate longitudinal treatment results. After week 20, such participants are asked to continue treatments according to their initial treatment arm, and participants receiving progressive resistance training are asked to continue similar training on their own. In week 52, all participants receiving extended treatment are retested using the same test battery as they completed at baseline and in week 20.

Eligibility

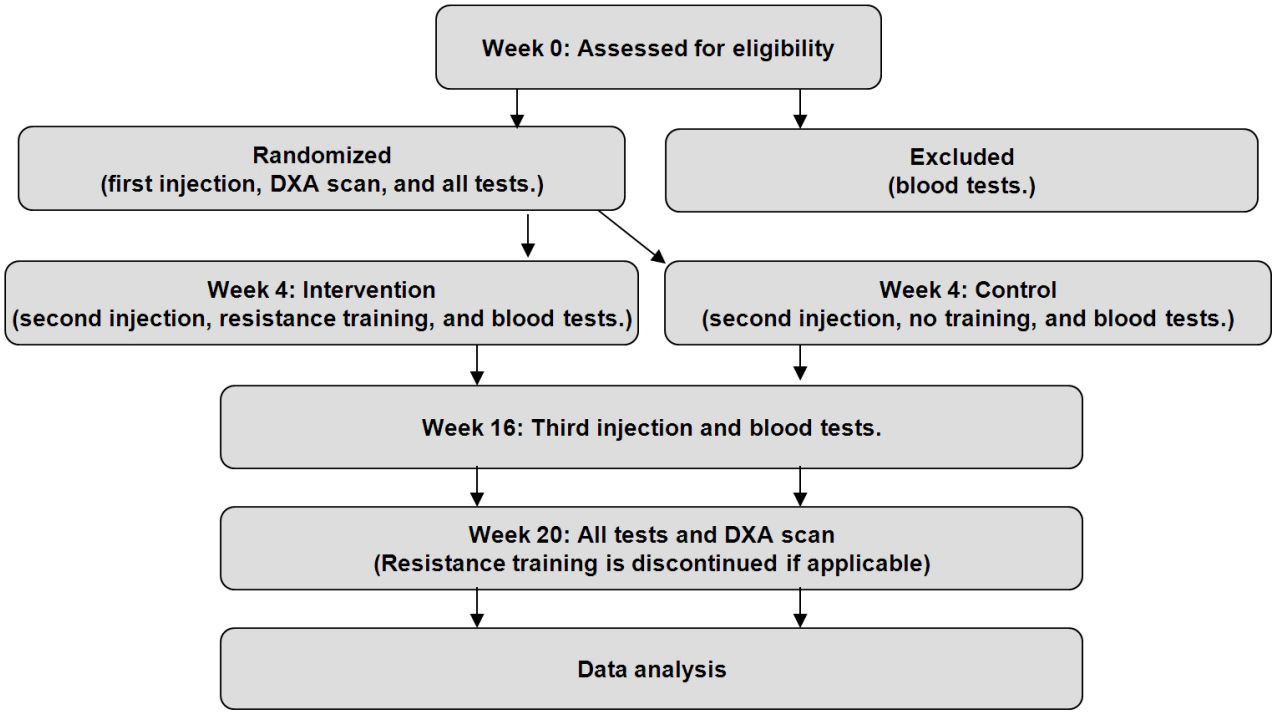
Inclusion and exclusion criteria are given in Textbox 1. Note that serum testosterone level was based on a previous study [16].

Supplements

Testosterone supplementation is given intramuscularly using 1000 mg testosterone undecanoate, which has a lasting effect of about 12 weeks [36-39], but which can be repeated more

frequently between first and second administration. Therefore, the injection is repeated in week 4. A total of 3 injections are expected per subject in weeks 0, 4, and 16. Experiments have shown that injections of 1000 mg testosterone undecanoate resulted in normalization of testosterone levels in hypogonadal men without significant fluctuations. The placebo group is treated with a similar solution just without testosterone undecanoate.

Figure 1. Flowchart.



Textbox 1. Inclusion and exclusion criteria for this study.

Inclusion criteria

- Men aged 70 years and older experiencing loss of physical function, but who are able to walk independently with or without the use of assistive devices
- A 30-second chair stand test performance ≤12, a timed up and go performance ≥14 seconds, or walking difficulties must be present with significantly reduced walking ability and balance problems at least during the last month
- Serum testosterone level ≤13 nmol/L

Exclusion criteria

- Patients in active medical treatment for prostate cancer, or prostatic specific antigen>5 ng/mL if a urologist subsequently diagnoses a treatment-requiring prostate cancer
- Severe cardiovascular disease
- Liver aspartate transaminase (AST) >2× upper normal limit) or renal insufficiency (serum creatinine >200 micromol/L)
- Severe epilepsy with frequent tonic-clonic (grand mal) seizures
- Insulin treatment (type 1 diabetes)
- Active cancer disease requiring chemotherapy or radiation therapy
- Severe chronic disease (eg, cirrhosis and AIDS)
- Primary testosterone deficiency in the form of testicular dysgenesis, Klinefelter syndrome (47, XXY), 46, XX male, luteinizing hormone resistance, Y chromosome deletions, and other sex chromosomal abnormalities
- Severe mental retardation, dementia, or physical disabilities leading to inability to participate in the exercise intervention and the physical tests, or to give informed consent
- Contraindications for testosterone undecanoate treatment such as presence of liver tumors and breast carcinoma

Participants receiving resistance training also receive a total of 34 g of protein supplement immediately after each completed training session. Protein supplement has shown beneficial effect in participants aged 70 years [40], and participants are instructed to note this in a project diary. Additionally, participants are given a daily vitamin D supplement of 38 mg in combination with 800 mg calcium.

Training Intervention

Four weeks after the first injection, participants in the training groups will receive progressive resistance training 3 times weekly (Monday, Wednesday, and Friday) for 16 weeks led by 1 or 2 physiotherapists in groups of up to 10 participants. Group size may vary depending on rate of inclusion and the random allocation of participants to training. Groups of up to 5 participants will be supervised by 1 physiotherapist, and an extra physiotherapist will be assigned to larger groups. A group of 5 physiotherapists with varying experience (2-17 years) led and instructed by a physiotherapist with extensive experience with progressive resistance training of patients with different diagnoses including older men with prostate cancer [41] will supervise the training sessions. The training takes place in the rehabilitation facilities at the hospital, where appropriate strength training equipment (Technogym, Gambettola, Italy) and stationary bikes (Monark model 828E and 927E, Vansbro, Sweden) are used.

Motivation and Compliance

The supervising physiotherapists will continuously motivate the participants to perform the exercises with the intended intensity and try to facilitate an inspiring training environment and a sense of team spirit. Time and place for social interaction between participants before and after each training session are provided, and the participants are encouraged to engage.

A log book of attendance to training sessions is kept by the physiotherapists. The number of sets and repetitions performed for each exercise at every training session is noted by the participants and physiotherapists in collaboration, and close supervision of execution of the exercises is provided by the physiotherapists to ensure compliance with the planned program.

Progressive Resistance Training Program

Participants start with a 10-min self-paced warm-up on a stationary bike. Patients with comorbidities that compromise stationary cycling, warm up on a rowing ergometer (Concept2 model D, Concept2, Morrisville, VT, USA). The warm up is followed by approximately 45 min of progressive resistance training on machines (Technogym, Element series) including the following specific machines: leg press, leg curl (hamstrings), leg extension (quadriceps), abdominal crunch, lower back, low row, and chest press. Adjustment of the machines is done by the supervising physiotherapist at the initial training session and followed up throughout the training period. The machines are adjusted to fit the individual participants aiming for full range of motion while accommodating any individual needs of the participants. The order of the exercises may vary from session to session. To induce adequate muscular fatigue and thus an adequate training stimulus, all sets of one exercise are completed with a 1- to 2-min rest in between sets before moving on to the next exercise. The intensity of the exercises is progressed by increasing the weight lifted and the number of sets performed while decreasing the number of repetitions in each set during the 16-week training period. The American College of Sports Medicine (ACSM) guidelines for progression are used for guidance [42] while carefully accommodating participant feedback and special needs and challenges of the individual participants. A slow progression beginning with 2×15 repetitions of each exercise with low load for the first 2 sessions is used to give the often relatively frail patients time to get familiarized with the machines, learn the correct execution of each exercise, and adapt to the training without experiencing excessive muscle soreness. The initial loading of each exercise is decided by the supervising physiotherapist in close cooperation with each individual participant. The targeted progression over the 48 planned training sessions is illustrated in Table 1. To ensure a proper progression in the training load in accordance with the program, the weight lifted in each exercise is continuously adjusted throughout the training period by the supervising physiotherapist. If a participant can perform significantly more (2-3 repetitions) than the planned number of repetitions in each set of a particular exercise, the loading is increased to reach the desired repetition maximum (RM)— that is, the number of repetitions that can be performed with proper technique before repetition failure. If one or more training sessions are missed, the loading will be adjusted by the supervising physiotherapist aiming for the number of repetitions in each set and the corresponding RM for the session when the participant returns in accordance with the progression plan in Table 1.

Table 1. Progression of resistance training over the 48 planned training sessions.

Sessions	Sets × repetitions	Intensity
1-2	2 × 15	20-25 RM[a]
3-6	2 × 12	12-15 RM
7-13	3 × 12	12-15 RM
14-48	3 × 10	10-12 RM

[a]RM: repetition maximum; the number of repetitions that can be performed with proper technique.

Data Collection

A data collection procedure and a database are prepared for registration and data processing. Information regarding demographic and physical characteristics collected at baseline includes the following: age, single or cohabiting, help at home, mobility aids, social network, height, weight, waist-hip ratio, smoking habits, and alcohol consumption. Baseline testing as described below is performed before participants are randomized to one of the training groups, starting training on day 30. Patients are retested after 20 weeks, when training is discontinued. Participants receiving no training are tested in the same way and at the same time points as those who receive progressive resistance training.

Primary Endpoint

The 30-second chair stand test is used to measure improvement of general strength, power, and endurance in lower extremities. The number of times the participant can rise from a chair in 30 seconds with arms crossed over the chest and returning to a sitting position between each repetition is counted by a test leader. Repetitions are only counted as successful if full extension of the hips and knees is achieved for each rise. The back does not need to touch the backrest of the chair when returning to a sitting position, but contact with the seat must be made. This test has a satisfactory correlation (r=.78) with leg press exercise abilities [43], and an acceptable test retest reliability (interclass correlation [ICC]=.86) has been found [44]. The 30-second chair stand test provides a reasonably reliable and valid measurement of lower body strength of older adults, and easily separates low-active participants from high-active participants [45]. For men aged 70 to 74 years, a 30-second chair stand test performance between 12 (25th percentile) and 17 (75th percentile) is considered normal; thus, we chose to only include older men in this trial with a performance of 12 or less [46]. It has recently been scientifically proven that the ability of elderly persons to perform a slightly different version (timing of 5 chair-stands) of this simple test correlates with the risk of serious fall injuries [47].

Secondary Endpoints

Frequency and Severity of Adverse Events

This is recorded using a questionnaire for each subject and is included in the monitoring of adverse events.

The Mobility Scale of Avlund

The mobility scale of Avlund include questions about experienced fatigue and support needs in activities of daily living. The mobility scale of Avlund is correlated with isometric muscle strength, simple functions [48], increased risk of hospitalization [49], and mortality [50]. Inter-rater reliability values of kappa .72 to 1.00 have been shown [51].

Major Depression Inventory

This questionnaire will be used to estimate depression severity and mental well-being [52].

Montreal Cognitive Assessment

Montreal Cognitive Assessment is a cognitive screening test used to provide an estimate of the cognitive functions. This test is sensitive to mild cognitive problems and dementia [53].

Quality of Life EuroQol-5 Domain

This questionnaire is used to estimate experienced quality of life in participants [54].

Fatigue Severity Scale

This questionnaire is used to estimate fatigue among participants [55].

Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire-12

This questionnaire is used for evaluation of sexual function before and after treatment, including assessment of sexual ability and sexual desire. Improved sexual function, mood, muscle power, and body composition have been found in hypogonadal men treated with testosterone supplement [32].

Graded Cycling Test with Talk Test

This is a submaximal aerobic exercise test that will be used to measure potential changes in aerobic capacity [56,57].

Arm Flexion Test

This test measures general strength in upper extremities. The number of times in 30 seconds a participant can flex the elbow with a 3 kg weight in the hand is counted. The test has a satisfactory correlation (r=.81) with muscle strength of the biceps, chest, and upper back muscles and an acceptable test retest reliability (ICC=.81) [44].

Timed Up and Go Test

This test measures basic mobility in the elderly. The time taken to rise from a chair, walk 3 m away, and return to a sitting position in the chair is measured. A moderate to good correlation has been shown between this test and Berg's Balance Scale (r=.81), velocity (r=.61), and Barthel Index (r=.78) [38], and good test retest reliability has been observed (ICC=.98) [43]. The best of three attempts is recorded [58].

Dual-Energy X-ray Absorptiometry Scanning and Bioimpedance Measurement of Body Composition

Dual-energy x-ray absorptiometry (DXA) scanning is used to measure lean body mass corresponding to measurements of fat and fat-free mass as well as total bone mass. DXA is performed as whole-body scan at baseline and at the end of the study.

Bone mineral density in the columnar, bilateral distal forearm, total hip bilaterally, and overall skeleton is measured. If osteoporosis is detected, treatment will be initiated according to the department's usual guidelines after the participant has finished trial participation.

These measurements are performed as fasting morning measurements. If fasting is impossible or extremely difficult, a standardized breakfast will be used. It is expected that the fat-free mass will increase and that the fat percentage will be reduced from baseline to the end of training. In addition, a further improvement of the aforementioned variable in the active

treatment group is expected, thus documenting an additive effect of the combination of exercise, protein supplements, and testosterone substitution. The two methods for estimating body compositions over time will be compared. Importantly, each test result at the end of the trial is compared with the similar test result obtained at baseline, so that changes over time can be measured for each participant. This approach has been used in several publications [59,60].

Safety Parameters Measured Before Every Injection of Placebo or Testosterone Undecanoate

Blood pressure is checked, and blood tests are performed for the following: serum testosterone, hemoglobin, hematocrit, lipid profile, potassium, sodium, creatinine, C-reactive protein, aspartate aminotransferase, bilirubin, alkaline phosphatases, thyroid-stimulating hormone, ionized calcium, parathyroid hormone, Ca^{2+}, and 25-OH vitamin D. Before and during treatment with testosterone undecanoate, prostate palpation is performed to examine for prostate cancer. Subjects with enlarged prostate or irregular prostate surface are examined by a urologist and may be considered for prophylactic treatment against benign prostatic hyperplasia with Finasteride, which suppresses prostate hyperplasia with testosterone supplementation without side effects [34]. In addition, adverse reactions and adverse events are recorded very carefully, for example, in the form of falls and fall severity, ischemic episodes, and the like.

Blood samples are not stored for more than 1 week and are not included in a research biobank. The biological material is analyzed immediately and destroyed afterward. No part of the blood samples will be used in personally identifiable ways.

Sample Size Estimation

The primary endpoint is to improve 30-second chair stand test performance [35]. According to normative scores, a performance of 15 is considered normal (50th percentile) for older men aged 70 to 74 years, whereas a performance of 11 or less is considered abnormal [46]. Our main hypothesis is that controls will achieve a performance in the 30-second chair stand test performance of 11 (64% of the 75th percentile), whereas the combination group will achieve a performance of 15 (88% of the 75th percentile). If an alpha value of .05 and a beta value of .2 are used; the needed sample size is 38 participants in each group. Due to the high age and time-consuming intervention, up to 25% dropouts are expected, and we therefore need to include 48 participants in each group.

Statistical Analysis

The results will be analyzed by intent-to-treat and per protocol for participants who have followed 60% of testosterone treatment and exercise. Regarding statistical data processing, data will be ranked and group comparisons will be performed by nonparametric tests (Kruskal-Wallis and Mann-Whitney). Comparisons of ranks at baseline and at the end of the study period are performed using Wilcoxon nonparametric test and optionally categorically variable with chi-square test. Nonlinear correlations will be evaluated using the Spearman rank correlation coefficient. Untrusted or unused data are not included in the statistical evaluation and will be treated as missing data, that is, no calculations are made using such data. Lack of data is acceptable as long as an assessment of the primary endpoint is still possible. Thus, data from subjects that make it possible to assess the primary endpoint will be used as a minimum; however, we hope that data from all randomized patients can be used to evaluate secondary effect variables. *P* values of less than .05 will be considered significant.

Ethics

The project complies with the Helsinki Declaration. The trial is approved by the Danish Data Protection Agency, and the trial protocol has been approved by the relevant scientific ethics committee, protocol number: H-16020521, and can be initiated. ClinicalTrials.gov Identifier: NCT02873559.

In the trial, only patients with testosterone deficiency are treated; thus, testosterone undecanoate is used according to indication and in compliance with recommendations by the Danish Medicines Agency. The following section describes possible side effects and risks. We do not expect significant adverse reactions from participants; treatments may primarily result in improved motor skills, reduced fall risk, improved cognitive skills, reduced risk of cardiovascular disease, improved quality of life, better sexual function, and lower risk of developing depression. The project is focused on normalizing and increasing both health and quality of life. We are convinced that the benefits of the treatments in this trial by far outweigh the risks of adverse events.

Adverse Events and Risks

Strength training can cause delayed onset muscle soreness following the first training session. The mild soreness is temporary and diminishes as the muscles quickly adapt to the training. There are no serious side effects related to strength training. There are no side effects to protein supplements [19] and vitamin D [23]. Common (1-10%) adverse reactions to testosterone undecanoate include discomfort at the injection site, weight gain, elevated hematocrit, elevated hemoglobin, polycythemia, hot flushes, acne, elevated prostate-specific antigen, and prostate hypertrophy. Uncommon (0.1%-1%) adverse reactions include pain, dyspnea, hypertension, cardiovascular events, gynecomastia, hypercholesterolemia, hypertriglyceridemia, arthralgia, depression, mood disorders, dizziness, tremor, alopecia, erythema, hypersensitivity, lower respiratory tract infections, and urinary retention. Rare (0.01%-0.1%) adverse reactions include priapism. Very rare (<0.01%) adverse reactions include liver changes.

Cases of increased libido will be registered and will be addressed by the primary investigator who has many years of experience working with geriatric populations.

DXA Scan

The participant must be able to lie supine for 15 min and will be in constant contact with personnel. No contrast materials are used. The scanner emits X-rays, which are harmful when exposed to larger doses. In this study, participants receive a small amount of radiation, corresponding to approximately 6 days of background radiation. In one scan, the risk of developing a life-threatening cancer increases from 25% (because of the background radiation) to 25.00025% — and to 25.00050% for

two scans. Dropouts in both groups are noted with cause. Adverse events are recorded.

Results

Funding was provided in October 2016. Enrollment was initiated in November 2016, and the first patient was included in January 2017. In January 2018, about 50 participants were included. Results are expected to be available in 2020.

Discussion

Overview

To the best of the authors' knowledge, this is the first time an investigation will evaluate the effects of testosterone supplemental therapy and progressive resistance training on cognition, physical well-being, and quality of life. We have received all necessary funding. Our broad spectrum of secondary endpoints ensures a thorough examination of therapeutic benefits, beyond previous investigations. Furthermore, unlike previous studies, participants in this study will be older and have verified hypogonadism.

High-quality, randomized trials are lacking in older men, and therefore in this trial, a diagnosis of hypogonadism is based on the presence of both clinical symptoms and low serum testosterone levels similar to diagnosing hypogonadism in younger or middle-aged men [61]. To complicate hypogonadism diagnosis further, other symptoms caused by aging may overlap with symptoms of hypogonadism. We are aware that using serum testosterone levels ≤13 nmol/L may cause an overdiagnosis of hypogonadism, because many older men with low testosterone are asymptomatic. To avoid treating potentially asymptomatic older men, in this trial, we only include older men with low testosterone experiencing reduced physical abilities. It may be noted that this trial does not primarily focus on improving serum testosterone, but focuses on improving overall physical and mental abilities of older men, where serum testosterone is one of the several potential key components.

Testosterone supplements have previously been suspected of contributing to cardiovascular disorders, but a recent investigation based on 7245 men did not find any correlation between testosterone supplements and cardiovascular disorders [62]. Furthermore, investigators performing a major meta-analysis based on 122,889 participants supported these findings [63]. It should be noted that the mean age of the study with 7245 men was 54 years; thus, most men were not among the elderly, and few octogenarians if any may have been included. The study of 122,889 men currently has been published as an abstract without any description of the mean age of participants. Thus, it is not known if results obtained from such huge materials are relevant for older men.

Previously, it has also been found that testosterone deficiency is a risk factor for atherosclerosis, myocardial infarction, and chronic heart failure [26-28]; thus, we believe that the overall health of participants receiving testosterone supplemental therapy combined with physical resistance therapy will be significantly improved through this trial.

Limitations

Finding eligible patients may be difficult, and our inclusion and exclusion criteria limit our investigation to frail older men still able to walk unassisted. Our results will not include patients with a more profound need of rehabilitation and treatment.

Conclusions

This trial will evaluate the effects of testosterone supplemental therapy alone or combined with progressive resistance training. By using a broad spectrum of tests, we aim to provide a clear answer to whether or not such intervention may benefit frail older men.

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Authors' Contributions

KO and RSR designed the study. All authors helped providing methodological considerations and English editing of the manuscript. RSR and KO provided statistics, whereas AMR and AV described training interventions and compliance. RSR wrote the first draft and the final version of the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DXA: dual-energy x-ray absorptiometry
ICC: interclass correlation
RM: repetition maximum

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Protocol

Impacts of Urban Agriculture on the Determinants of Health: Scoping Review Protocol

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Abstract

Background: Since the 1990s, urban agriculture (UA) has contributed to improving food security in low- and middle- income countries. Now, it is implemented as a multifunctional intervention that can influence various determinants of health (eg, food security, social relationships). Studies of interest stem from several research disciplines, use a wide range of methods, and show results that are sometimes inconsistent. Current studies have not summarized the overall effects of UA on health and its determinants.

Objective: The objective of this protocol is to develop a research strategy for a scoping review that characterizes studies of beneficial and adverse impacts of UA on health and its determinants in a wide range of disciplines.

Methods: Initially, with the help of a library specialist, a list of publications will be obtained through a systematic search of seven electronic bibliographic databases: PubMed, Embase, MEDLINE (Embase), CINAHL Plus with full text, Academic Search Premier (EBSCO host), CAB Abstract (Ovid), and Web of Science. Secondly, a three-step screening by two independent reviewers will lead to a list of relevant publications that meet eligibility and inclusion criteria. Finally, data on the bibliography, type of participants, type of study, results of study, and countries will be extracted from included articles and analyzed to be presented in a peer-reviewed article.

Results: The findings are expected to identify research gaps that will inform needs for UA research in specific fields (eg, mental health), among certain population groups (eg, adults) or within different economic contexts (eg, low-, middle-, or high-income countries). Furthermore, the findings are expected to identify knowledge gaps and direct future research needs.

Conclusions: This is an original study that seeks to integrate beneficial and adverse effects of UA on health at different level of influence (individuals, households, and community) in order to facilitate a better understanding of UA impacts. This protocol is a first of its kind and is expected to lead to a characterization of UA impacts based on sociodemographic profiles of participants and income levels of the studied countries. This will be relevant for policy makers and UA practitioners.

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KEYWORDS

urban agriculture; health; determinants of health; scoping review

Introduction

Background

Since the 1990s, urban agriculture (UA) has been a strategy contributing to improving income and food security for individuals and households in low- and middle- income countries, particularly in Africa [1-5]. In cities such as Dar-es-Salaam, Tanzania and Bamako, Mali, UA provides more than 30% of the city's vegetable needs and generates wages equivalent or higher than civil servants or unskilled construction workers [5]. In high-income countries, UA has contributed to food security in times of emergency or economic crisis [6-8]. For example, it is documented that countries in North America and Europe have encouraged their citizens to engage in UA activities during the first and second World Wars in response to pressures on the food supply [9,10]. Beyond its traditional purposes (food security and income improvement), UA is now considered as a multifunctional intervention [11,12]. It is part of health promotion strategies [13,14], urban planning [12], and/or global policies to develop sustainable city food systems [15,16]. It can also play an important role in the availability of green infrastructure and biodiversity in the urban environments [17]. Its function in the recycling of urban organic waste is also recognized [18]. In some contexts, it is perceived and practiced by urban dwellers to reduce the ecological footprint of the food industry [12]. It is supported by a range of actors including health professionals [19], government agencies, community groups, and researchers [20]. In general, it can be viewed as small areas used in cities for agricultural production or to raise animals for domestic consumption or local sales [21].

UA as an intervention can have social and economic impacts on individuals, households, and/or an entire community by directly influencing health or its determinants. It can influence food security, mental or physical health, or social relationships at different population levels. A significant number of studies have already attempted to demonstrate the contribution of UA to food security [22,23] by assuming an association between UA and access to food [24] or its association with improved household nutrition through consumption of fresh fruits and vegetables [25]. In addition, engagement in UA may improve physical activity and contribute to well-being and health by reducing stress [26,27]. However, the effects of UA on health and its determinants remain inconsistent. Many of these studies have been criticized for their lack of empirical evidence. For example, among studies that have shown UA contribution to food security at individual or household levels, some are often criticized because of poor data quality or lack of methodological rigor [28,29].

Other studies have focused on the negative effects of UA. For example, several studies highlight the potential public health risks associated with UA [19] by addressing concerns related to urban soil and water contamination. Some have raised concerns about the presence of heavy metals in UA soils or harvested crops [30-33] that may have implications for food safety. In fact, traces of heavy metals can be found in vegetables and fruit grown in urban areas, representing a health risk for individuals who consume such products [33,34]. On the other hand, the potential effects of UA products from contaminated soils on humans are unclear. The concentration of heavy metals in soil does not necessarily reflect heavy metal concentrations in harvested crops and the utilization of these crops does not inevitably represent a risk to human health [35,36]. Nevertheless, it is important to note that UA has potential public health risks, which need to be documented.

Although some systematic reviews have been conducted on UA and health, specifically food security and wellbeing [27], there are no reviews that refer to the adverse effects of UA. To our knowledge, most of these types of studies have not considered a holistic approach that includes beneficial and adverse impacts of UA. Three systemic reviews [28,37,38] have examined the contribution of UA to one type of determinant of health in a specific context; food outcomes in low- or middle-income countries. Two of them: Warren et al [28] and Poulsen et al [37] recommended new research due to poor quality and heterogeneity of the primary studies included. Although both studies have considered food security as an analytical framework, they only had four included studies in common. Poulsen et al [37] only included studies conducted in Africa, even though "region" was not part of the inclusion criteria. In contrast, Warren et al [28] included studies from other geographic locations. The differences may be due to a lack of consistency in research strategy or differences in their selection criteria. Korth et al [38] targeted studies in countries with similar characteristics, low- and middle-income countries, and failed to identify any studies. This reinforces our argument about a lack of consistency in UA contribution to food security in the systematic review processes. One of the common points between the three reviews was the absence of high-income countries in their analysis.

The consideration of high-income countries in literature reviews of interventions similar to UA is not new. Other systematic studies have already evaluated gardening or school gardening, which to some extent are similar interventions to UA. These studies do not allow to draw conclusions about the impacts of UA on health. For example, Ohly et al [39] used a mixed methods approach to measure the impacts of school gardens on health and well-being in high-income countries. However, the assessed studies were qualified as low or moderate quality based on the authors' criteria. While methodological weaknesses were also reported for the included quantitative studies, the qualitative studies were described as ideological aspirations. Nicklett et al [40] used the same concept of gardening to demonstrate its association with physical health in high-income countries. Yet, like Ohly et al [39], the review identified methodological weaknesses in the primary studies included, which limit conclusions on a possible impact of gardening activities on physical health.

At this time, current studies have not been able to draw definite conclusions on the effects of UA on specific determinants of health or health in general. Given that UA is a multidisciplinary topic (eg, nutrition, agriculture, urban planning), it may be better to address it first in a more general systematic process such a scoping review and consider a broader impact outcome like health prior to engaging future systematic reviews.

With this scoping review we seek to identify evidence from peer reviewed literature that demonstrates beneficial and adverse impacts of UA on the determinants of health according to countries' income level as defined by the World Bank [41]. The determinants of health are defined as socioeconomic factors that influence health [42]. We aim to identify knowledge gaps and facilitate a better understanding of the global impact of UA on health and its determinants by considering the following two research questions:

1. What are the impacts of UA on health and its determinants?
2. How do these impacts differ according to countries' income level or sociodemographic characteristics of studied participants?

Conceptually, by answering these questions, we will have a better understanding of how UA as an intervention can affect different health outcomes such as food security, nutrition, social relationships, physical or mental health. Furthermore, we are interested in categorizing these outcomes according to level of influence (individual, household, and community) and countries' income level (high-, middle-, and low-income). The findings will allow us to draw a global picture of the potential impacts of UA on health present in the existing literature. Identifying research gaps will also allow researchers and policy makers to make informed decisions about future UA research needs and implications for public policy.

Objective

The specific objectives of this study are:

1. To identify UA impacts on health and its main determinants
2. To characterize the results according to population and country income levels

Methods

This scoping review will follow the five steps described by Arksey and O'Malley [43] for similar studies with improvements suggested by Levac et al [44]:

1. Identification of the research questions (listed above)
2. Identification of relevant studies
3. Selection of relevant and reliable studies
4. Data extraction from included studies
5. Collating, summarizing, and reporting the findings

Identification of Relevant Studies:

This scoping review will use the method suggested by Aromataris and Riitano [45] to construct a strategy that can help us target relevant publications on UA impacts on health and its determinants. First, we will identify keywords that are related to our main research questions. To identify keywords, elements of a modified PICOS framework (participants, intervention or concept, context, outcomes, study design) [46] will be specified to establish eligibility criteria defined according to the following:

- Types of participants: This study considers all human participant groups (eg, children, youth, and adults) at different level of influence (eg, individual, household, or community) who have been implicated by UA.
- Intervention or concept: For the purpose of this review, UA is defined as food growing initiatives that include the production of edible plants and livestock in urban areas. The review will seek studies that assess UA in all its forms when it is used as an intervention consisting to grow food or raise animals for domestic consumption, local sales, or as a leisure activity.
- Outcomes: The targeted outcomes are a set of determinants of health inspired from Dahlgren and Whitehead [42]. For example, food security, income, social relations, and factors that influence mental or physical health (listed in Table 1).
- Context: To be included, studies must have been conducted in urban settings of a high-, middle-, or low-income country according to the World Bank's income-based country classification [41].
- Type of study: Peer reviewed quantitative or qualitative studies demonstrating one or more effects of UA on health or its determinants will be included. Narratives, essays, gray literature and theses will be excluded. Other systematic studies will not be included in the analysis but the list of their references will be examined to identify relevant studies.

Search Strategy

The search strategy has been designed with the help of a library specialist and searches will be performed in the following seven electronic bibliographic databases: PubMed, Embase, MEDLINE (Embase), CINAHL Plus with full text, Academic Search Premier (EBSCO host), CAB Abstract (Ovid), and Web of Science. The outlined keywords in Table 1 and their alternative terms will be searched in the index terms, title, and abstract (tiab) of each database. In case a keyword is not found in the index terms, it will be substituted by its alternative term or a synonym in the index search and will be searched in titles and abstracts only. For example, in PubMed, the index is the medical subject heading (MeSH). The word *food security* does not appear as a MeSH, so in the search for MesH, we will use *food supply* as an alternative but the keyword *food security* will also be searched as it is written in the titles and abstracts. Boolean operators *OR* will also be used to combine individual keywords while the Boolean operator *AND* will be used to combine sets of keywords (eg, the words urban agriculture/urban farm or city agriculture/city farm, are searched as following: (urban *OR* city) *AND* (agriculture *OR* farm). An example of the complete search strategy used on PubMed is described in Table 1. This strategy will then be adapted to the other databases using the according syntax and proximity operators.

Table 1. Example of search strategy used on PubMed and adapted to other bibliographic databases

Category, number, and keywords		Index terms or search-field descriptors
Outcome measures		
1	Food supply	Mesh
2	Food security	Tiab
3	Food insecurity	Tiab
4	Food access	Tiab
5	Food availability	Tiab
6	Food quality	Mesh:NoExp, tiab
7	Food safety	Mesh:NoExp, tiab
8	Food contamination	Mesh:NoExp, tiab
9	Food	Mesh:NoExp
10	Health* food	Tiab
11	Income	Mesh:NoExp, tiab
12	Cost savings	Mesh:NoExp, tiab
13	Poverty alleviation	Tiab
14	Nutritional status	Mesh:NoExp, tiab
15	Nutrient deficiency	Tiab
16	Fruit and vegetable intake	Tiab
17	Fruit and vegetable consumption	Tiab
18	Fruits and vegetables	Tiab
19	Vegetables	Mesh:NoExp
20	Fruit	Mesh:NoExp
21	Fruit? Intake	Tiab
22	Vegetable? Intake	Tiab
23	Diet	Mesh:NoExp, tiab
24	Dietary diversity	Tiab
25	Malnutrition	Mesh:NoExp, tiab
26	Undernutrition	Tiab
27	Overweight	Mesh:NoExp, tiab
28	Obesity	Mesh:NoExp, tiab
29	Quality of life	Mesh:NoExp, tiab
30	Healthy lifestyle	Mesh:NoExp, tiab
31	Exercise	Mesh:NoExp
32	Physical activity	Tiab
33	Leisure activity	Mesh:NoExp
34	Leisure	Tiab
35	Well-being	Tiab
36	Interpersonal relations	Mesh:NoExp, tiab
37	Social capital	Tiab
38	Personal development	Tiab
39	Empowerment	Tiab
40	Education	Mesh:NoExp
41	Nutrition education	Tiab

Category, number, and keywords		Index terms or search-field descriptors
42	Civic engagement	Tiab
43	Community engagement	Tiab
44	Horticultural therapy	Mesh
45	Therapeutic garden	Tiab
46	Mental health	Mesh:NoExp, tiab
47	Dementia	Mesh:NoExp, tiab
48	Stress psychological	Mesh:NoExp
49	Stress	Tiab
50	Perceptions of life	Tiab
51	Cultural connection	Tiab
52	Violence	Mesh:NoExp
53	Depression	Mesh:NoExp
54	Security perception	Tiab
55	Health risk	Tiab
56	Resilience	Tiab
57	Pain	Mesh:NoExp, tiab
Intervention/Concept		
58	Agriculture	Mesh:NoExp, tiab
59	Food production	Tiab
60	Gardening	[Mesh]
61	Community garden*	Tiab
62	Farm*	Mesh, tiab
63	Allotment$	Tiab
64	Horticultur*	Tiab
65	Rooftop$	Tiab
66	Home garden*	Tiab
67	School garden*	Tiab
Context		
68	Cities	Mesh:NoExp
69	City	Tiab
70	Urban	Tiab
71	Metropol*	Tiab
72	Suburban	Tiab
73	Town	Tiab

Textbox 1. Data extraction for analysis (type of data and variables)

Reference

- Author
- Year

Study location

- City, country
- Country income level

Population

- Type of participants (individual, household, community)
- Characteristics of participants (age; sex; children, youth, adults)

Type of study

- Study purpose
- Study design
- Outcomes measured

Results

- Type of impacts (beneficial, adverse)
- Results of study

Selection of Relevant and Reliable Studies

Due to a limited accessibility of UA scientific papers prior the 1980s, the search will be restricted to articles published between 1980 and 2017. Titles in languages other than English, French and Spanish will be excluded in the selection phase. All identified publications will be transferred to EndNote (X8, Thomson Reuters) and articles whose publication dates and languages do not meet our requirements will be removed. All remaining publications will be transferred to an online systematic review software (DistillerSR, Evidence Partners, Ottawa, Canada), to remove duplicates and for title and abstract screening by two independent reviewers. The full text of eligible articles will be screened by two independent reviewers according to the following inclusion criteria:

- Relevance: The study must be relevant to the question and objectives of our research. It will be considered relevant if it demonstrates one or more beneficial or adverse impacts of UA on human health or its determinants.
- Study design: To be included into the scoping review, the study must also present data collected from human participants. Furthermore, the design of the study must be appropriate to answer the studied research questions. Studies that report environmental impacts will be considered only if they report effects on humans (eg, study on soil contamination will not be included unless it reports the effects of soil contamination on human health).

A list of all excluded articles at this stage will be provided with the reasons for exclusion. The reference lists of included studies will also be reviewed to identify relevant studies. The identified studies will be assessed with the same eligibility criteria to validate their inclusion or exclusion. Final inclusion of the publications will be discussed by the two reviewers and any disagreement on the inclusion or exclusion will be resolved by consensus.

Study Quality Assessment

The quality of the included studies will be evaluated using the criteria of the Effective Public Health Practice Project (EPHPP) guide for quantitative studies, and the qualitative study evaluation criteria of Wallace et al [47] used by Ohly et al [39] for the assessment of the quality of qualitative studies. The evaluation of the quality of the studies, in both cases, will take into account the risks of bias in the methodologies of the studies. Thus, any evaluated study with a high risk of bias will be reported in the results section.

Collating, Summarizing and Reporting the Results

Data as described in Textbox 1 will be extracted from the included articles and the results will be presented in a way to identify the main areas of interest and gaps in the literature on UA impacts.

Once this information is extracted, the results will then be presented in two forms to make a narrative account of the literature [43]. As a first step, a numerical analysis will be presented in the form of a diagram [48] that will highlight the measured outcomes—determinants of health according to number, the nature, and the geographical distribution of the included studies. In a second step, the studies will be grouped according to the category and characteristics of studied participants (individuals, households, and communities; age and sex) to make comparisons, identify contradictions in evidence, methodology, and find research gaps.

Results

The findings are expected to identify research gaps that will inform needs for UA research in specific fields (eg, mental health), among certain population groups (eg, adults) or within different economic contexts (eg, low-, middle- or high-income countries). Furthermore, the findings are expected to identify knowledge gaps and direct future research needs.

Discussion

To our knowledge, this scoping study is the first of its kind to explore both beneficial and adverse impacts of UA on health determinants. Other systematic studies have already provided valuable information on specific benefits of UA. However, in the current context of urbanization and climate change where health and environmental challenges are related to food production in cities, it is obvious that the adverse impacts of UA are a concern [49]. Therefore, the identification of evidence that only include beneficial impacts of UA, does not allow an objective analysis to draw conclusions on its impacts. With our findings, we hope to bring a set of elements that allow a better understanding when defining the advantages and disadvantages of the UA as an intervention.

This study will highlight the state of research on the association between UA and health. A holistic approach that considers beneficial and adverse effects of UA, may inform better public policies and target intervention populations. The scoping review will allow for a better understanding of the contributions or consequences of UA on specific determinants of health. It may also be used by policy makers to target indicators that can help better evaluate UA as an intervention that directly impacts individuals, households, or communities. Such approach will also serve to inform urban planning decisions where the role of agricultural production has not always been evident [50].

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Authors' Contributions

PPA and AL conceptualized the scoping review protocol. PPA developed search strategy with guidance from the library specialist and inputs from the entire team (PPA, MAF, GC, AL). PPA and MAF wrote the manuscript of the scoping review protocol with critical inputs and appraisal from GC and AL. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

MeSH: medical subject headings
PICOS: participants, intervention or concept, context, outcomes, study design
UA: urban agriculture

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Protocol

Oncologic Therapy Support Via Means of a Dedicated Mobile App (OPTIMISE-1): Protocol for a Prospective Pilot Trial

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Abstract

Background: The increasing role of consumer electronics and Web-enabled mobile devices in the medical sector opens up promising possibilities for integrating novel technical solutions into therapy and patient support for oncologic illnesses. A recent survey carried out at Heidelberg University Hospital suggested a high acceptance among patients for an additional approach to patient care during radiotherapy based on patient-reported outcomes by a dedicated mobile app.

Objective: The aim of this trial (OPTIMISE-1: Oncologic Therapy Support Via Means of a Dedicated Mobile App – A Prospective Feasibility Evaluation) is to prospectively evaluate the feasibility of employing a mobile app for the systematic support of radiooncological patients throughout the course of their radiotherapy by monitoring symptoms and patient performance, and facilitating the background-exchange of relevant information between patient and physician.

Methods: The present single-center, prospective, exploratory trial, conducted at Heidelberg University Hospital, assesses the feasibility of integrating an app-based approach into patient-care during radiotherapy. Patients undergoing curative radiotherapy for thoracic or pelvic tumors will be surveyed regarding general performance, treatment-related quality of life (QoL) and symptoms, and their need to personally consult a physician by means of a mobile app during treatment. The primary endpoint of feasibility will be reached when 80% of the patients have successfully answered 80% of their respective questions scheduled for each treatment day. Furthermore, treatment-related patient satisfaction and health-related QoL is assessed by the Patient Satisfaction Questionnaire Short Form (PSQ-18) and the European Organization for Research and Treatment of Cancer (EORTC) questionnaires at the beginning (baseline) and end of radiotherapy, and at the first follow-up.

Results: This trial will recruit 50 patients over a period of 12 months. Follow-up will be completed after 18 months, and publication of results is planned at 24 months after trial initiation.

Conclusions: This study will serve as a basis for future studies aiming to exploit the constant innovation in mobile medical appliances and integrate novel patient-centered concepts into patient care in the context of radiotherapy.

Trial Registration: ClinicalTrials.gov NCT03168048; https://clinicaltrials.gov/ct2/show/NCT03168048 (Archived at WebCite http://www.webcitation.org/6wtWGgi0X)

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KEYWORDS

mHealth; radiotherapy; mobile application; quality of life; cancer; mhealth; Patient-Reported Outcome Measures (PROMs)

Introduction

The role of consumer electronics and Web-enabled mobile devices in the medical sector is ever increasing, broadening the scope for mobile health apps [1]. The availability and market share of such appliances, summarized by the World Health Organization under the term "mobile health" (mHealth), has steadily grown over the past years [2]. Areas of use include assistance in appointment-making, the monitoring of certain parameters in patients with chronic illnesses or the regular documentation of pain or other symptoms [3-5]. Initial experience for the use of mobile apps in the area of oncology has shown promising results: A prospective pilot trial was able to demonstrate significantly improved overall survival for lung cancer patients, who were systematically telemonitored with the help of a mobile phone app based on patient-reported data and using the dynamics of patients' clinical symptoms for risk-stratification and individualized follow-up [6]. This study showed that the use of an app-based identification of high-risk patients may help to initiate earlier treatment, contributing to improved patient outcomes. Furthermore, the patient compliance within the scope of a systematic follow-up regimen proved superior to the control group whose follow-up only consisted of regular computed tomography scans and no additional supervision by a mobile phone–based app [7].

On the other hand, a survey among German health care providers showed a high readiness to incorporate the use of mobile health apps into oncologic treatment regimens, thereby utilizing the obvious advantages of mobile devices in patient care [8]. In this survey, the ability to monitor patient performance more closely even over longer geographical distances, the possibility to overcome language barriers or selectively address special needs of patient subgroups, such as ethnic minorities or children, were reported among the main advantages of mHealth in the field of oncology [9,10].

At present, the spectrum of apps available in the oncologic field is still rather limited and lacks validation by larger systematic analyses, so that the relevance of mobile apps for patient care and therapy support during prolonged oncologic treatments, such as radiotherapy or chemotherapy, remains largely unclear [11].

Based on the promising preliminary results of a systematic survey being conducted at Heidelberg University Hospital among a large number of cancer patients demonstrating a high acceptance of mobile app–based measures of therapy support, the present OPTIMISE-1 trial (which stands for **O**ncologic Thera**p**y Suppor**t** V**i**a **M**eans of a Ded**i**cated Mobile App – A Pro**s**pective F**e**asibility Evaluation) aims to assess the feasibility of introducing a mobile app to the treatment schedule of patients undergoing radiotherapy, as well as measuring its impact on patient satisfaction and health-related quality of life (QoL).

Methods

Study Design

The present study is designed as a prospective, single-center pilot study and will be conducted at Heidelberg University Hospital's Department of Radiation Oncology. Cancer patients undergoing radiotherapy are offered a novel model of therapy support during the course of treatment, where a mobile app will be used to monitor patient-reported outcomes concerning general performance and therapy-related symptoms, and enable patients to express the need to see a physician when clinical symptoms occur. The length and frequency of consultations with a physician will be analyzed to assess the economic aspect of the model. Furthermore, the necessity of admitting a patient to inpatient care during the course of therapy will be documented together with the timepoint of admission. Since routine bloodwork is independently conducted at regular intervals for all patients undergoing radiotherapy, the data from this bloodwork together with the clinical parameters documented in this study (eg, symptoms, toxicity, etc) will be screened for predictive factors for the necessity of inpatient admission by means of correlation. This is done as part of an exploratory side analysis unrelated to the primary objective of this study.

Recruitment

Patients are screened for eligibility during their first consultation at our department prior to radiotherapy by a study nurse. The consulting radiation oncologist presents each eligible patient with information about the trial and answers any questions about its nature, course, benefits and risks. If radiotherapy is medically indicated and the patient provides informed consent, the patient is included in the trial. Relying on logistic considerations based on the expected annual recruitment of patients fulfilling the inclusion criteria, the recruitment period has been set at 12 months. Roughly 1000 patients are available for screening yearly, based on intrainstitutional patient statistics. This means that the likelihood of fulfilling the inclusion criteria is highly probable. On the basis of a conservative assumed consent ratio of 5%-10%, meeting the recruitment target within 12 months is realistic.

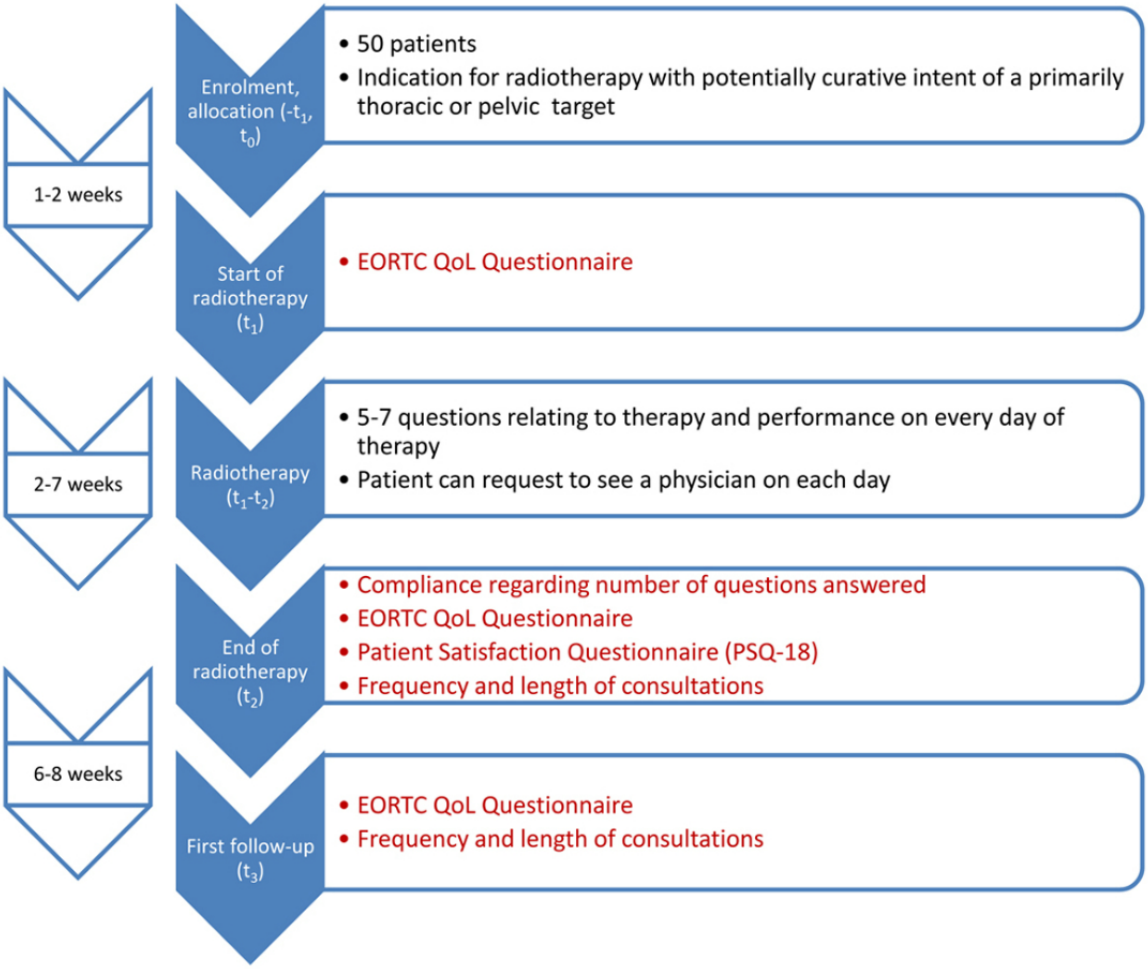
The study duration for each individual subject depends on the duration of radiotherapy, which differs with diagnosis. Typically, the period from the start of radiotherapy until the first follow-up will be between 10 and 14 weeks. A detailed timeline with interventions and assessments is illustrated in Figure 1.

Target Population

The study population includes patients receiving radiotherapy of a primarily thoracic or pelvic target and with a curative intent. This applies to a range of malignancies and depending on diagnosis to a range of tumor stages. This approach is intended to diversify the sample on which the mobile app is tested. Examples for thoracic targets are cancers of breast and lung,

whereas pelvic targets include malignancies of uterus, vagina and vulva, prostate, and rectum.

Figure 1. Time-line for trial subjects. Endpoints are marked in red. EORTC QoL questionnaire: European Organisation for Research and Treatment of Cancer quality of life questionnaire.



Patients receiving a regime of chemoradiation that prospectively requires them to be treated as inpatients for a substantial portion of the duration of radiotherapy are not eligible to participate in this trial. According to standard operating procedures (SOP) at our institution, this would exclude most patients with cancers of the cervix, esophagus, anus and rectum. Exceptions from this rule are possible in individual cases (eg, patients with rectal cancer, very good clinical performance and oral chemotherapy), if the screening physician deems it feasible to conduct the treatment on an outpatient basis.

Inclusion and Exclusion Criteria

Patients enrolled in this pilot trial must fulfill the following inclusion criteria:

- Indication for radiotherapy with potentially curative intent of a primarily thoracic or pelvic target
- Karnofsky performance score ≥70%
- Prospective ability to receive treatment as an outpatient
- ≥18 years of age

Patients with the inability to give informed consent will be excluded from the study.

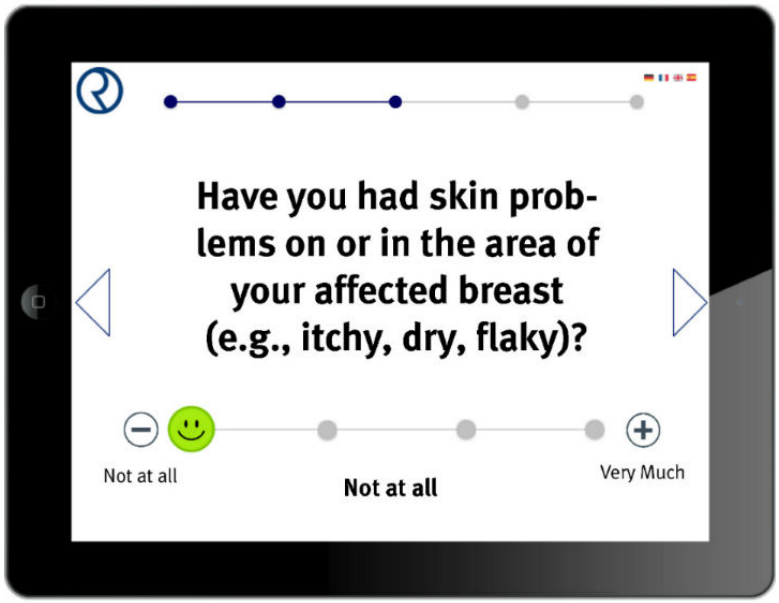
App-Based Therapy Support

Patients will be given a mobile tablet device and will be asked to answer 5-7 differing questions. The respective answers will be collected as patient-reported outcome. This type of digital survey is conducted during clinic hours on each day prior to radiotherapy. A sample screenshot is displayed in Figure 2.

To assess the patient's general and specific wellbeing during radiotherapy, a system of rotating questions based on the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ) has been developed. Since the wording of the questions is extracted directly from the EORTC questionnaires, which are available in multiple languages, the OPTIMISE-1 survey app will be multilingual. Depending on individual diagnosis, the patient is presented with questions extracted from the respective EORTC module (eg, BR23 for breast cancer, PR25 for prostate cancer, LC13 for lung cancer; all modules available on the EORTC website) that cover the patient's therapy-related wellbeing, symptoms for expected toxicities and general performance. Questions are automatically rotated by the application so that by posing 5-7 questions daily, the complete module is covered within one week of therapy. A diagnosis-dependent questionnaire rotation schedule is assigned to each patient prior

to the beginning of radiotherapy with the help of a Web-based backend interface. In addition to the aforementioned rotating questions, unchanging questions are posed every day at the beginning and end of the survey.

Figure 2. Sample screenshot of the mobile application for patient support during radiotherapy.



For example, patients are asked to describe their general health/QoL subjectively on a 7-point scale covering a range from "excellent" to "very poor" (adapted from EORTC QLQ-C30). Furthermore, patients are asked to state whether or not they feel the need to personally consult a physician on that respective treatment day. If they do, upon completing the survey, an automatic notification is triggered at the medical-technical assistants' management terminal, prompting them to schedule a visit with the supervising physician on that day. The information provided via the survey application is presented regularly to a supervising physician via the Web-based backend interface used for monitoring treatment and toxicity and preparing for regular patient visits. Routine check-up visits are conducted once weekly, and additional visits are arranged as requested by the patients via the app. The number and length of all visits are documented. The app-based therapy support is continued daily as long as the patient is in outpatient care.

The standard of care outside this trial at our institution for patients undergoing outpatient radiotherapy consists of weekly scheduled visits with a supervising physician and bloodwork at an interval depending on diagnosis (usually once weekly or less). The therapy support provided within this trial represents an additional, more close-knit and individualized form of care during radiotherapy.

Assessment of Primary and Secondary Endpoints

The primary aim of this study is to assess the feasibility of an app-based therapy support. It will be assessed by the primary endpoint—the proportion of patients who answered at least 80% of the app-based questions during their radiotherapy as outpatients. For every study subject, the number of answered questions is documented on each day of radiotherapy for the assessment of the primary endpoint. This definition of feasibility was derived mainly from clinical and logistical considerations. Due to logistical difficulties unrelated to the trial (eg, personnel change, transfer of patients to different radiation units due to technical maintenance), a certain portion of treatment days is to be expected where some patients fail to receive the survey tablet device. Since there is no previous systematic data on this specific issue, we estimate the portion of those expected irregularities at a realistic 20% based on clinical experience.

The following secondary endpoints are considered:

- Patient satisfaction
- Number of medical consultations
- Duration of medical consultations (in min)
- Need for toxicity-caused hospitalization
- Health-related QoL

Patient satisfaction is measured by the PSQ-18, which includes 18 items in 7 subscales: general satisfaction, technical quality, interpersonal manner, communication, early reaction to treatment side effects, time spent with doctor, accessibility and convenience. Responses to each item are given on a 5-point scale, and based on the questionnaire, a total sum score will be calculated and transformed to a scale ranging from 1 to 5.

Health-related QoL is assessed by the EORTC QLQ-C30 questionnaire in addition to the diagnosis-specific questionnaire module (eg, BR23 for breast cancer or PR25 for prostate cancer). Patients are prompted to fill out these questionnaires prior to the initiation of radiotherapy, at the time of treatment completion and at the first follow-up visit, which is routinely scheduled at 6-8 weeks after the completion of therapy. The duration and number of all visits during radiotherapy is documented to estimate the average cost of this form of therapy support. Per our SOP, the beginning and end of every consultation for all patients is documented by the physician by setting status flags within the Radiation Oncology Clinic Information System

(ROKIS). The duration of every consultation can then be extracted by querying the ROKIS database. The software solutions in use for those purposes at our institution are MOSAIQ (ELEKTA, Stockholm, Sweden) for ROKIS and Crystal Reports (SAP, Walldorf, Germany) for generating database reports.

Table 1 shows the intervention and assessment schedule for the trial. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist [12] on different protocol items related to this trial is included in Multimedia Appendix 1.

Statistical Analysis

The calculation of the sample size was done with respect to the primary endpoint and the primary analysis. Using the exact binomial test, we aim to show that the primary endpoint is reached at values of ≥80% of all study subjects answering ≥80% of the app-based questions during their radiotherapy as outpatients. With a sample size of 50 patients in this pilot study and an assumed percentage of 92% for the primary endpoint, a power of 1-β=80% is reached with a one-sided significance level of α=5%. Considerations regarding sample size and power were done using the *PROC POWER* procedure in SAS (version 9.4). The primary endpoint will be evaluated using the exact binomial test, which is the primary analysis. The one-sided significance level for this feasibility study is set to 5%.

Methods of descriptive data analysis will be used to describe patient characteristics and secondary outcomes, including calculation of appropriate summary measures of the empirical distribution, such as mean and standard deviation, median and interquartile range for continous variables, as well as absolute and relative numbers for categorical variables. Additionally, according to tumor type, subgroup analyses will be performed as a sensitivity analysis. Additionally, multivariable regression models will be used to analyze the relationship between patient characteristics and the primary endpoint. However, we will consider the primary variable on the original scale without any cut-off value (ie, the relative number of app-based answered questions) as the outcome variable and, thus, linear regression models will be applied. Age, gender and the need of toxicity-caused hospitalization will be included as predictors. The same model will be applied for the secondary endpoints. In addition, correlations will be considered. Graphical methods will be applied to visualize the results.

Ethics Approval and Informed Consent

The Heidelberg Ethics Committee approved this study on June 26, 2017 (S-216/2017). Inclusion of a patient into this trial requires meeting the above-mentioned inclusion and exclusion criteria as well as the patient's written informed consent. Continuous information will be supplied to the committee about all changes to the study that may influence patient safety, as well as about the conclusion or discontinuation of the study. Participation in the clinical trial is voluntary for subjects. Before inclusion in the study, a potential subject will be thoroughly and in detail informed about the nature, aims, risks and benefits of the study before informed consent can be given. Detailed information will be provided in a fashion and language understood by the patient.

An informational handout as well as an informed consent form—both documents conforming to the standards of the International Conference on Harmonization-Good Clinical Practice—will be provided to the patient before inclusion. Informed consent must be given only after an appropriate amount of time for consideration and then must be in writing and complemented with information about date and time of signature in the patient's own handwriting. Informed consent must be countersigned by the treating physician. If a patient is incapable of signing the informed consent form, oral informed consent must be confirmed by the signature of a witness.

Clinical subjects are free to refuse to participate in the study or to withdraw from it at any time for any reason without incurring any penalty or withholding of treatment on the part of the investigator. This study includes no additional invasive or otherwise harmful or burdening procedures.

Table 1. Intervention and assessment schedule for the OPTIMISE-1 trial.

Steps	Enrolment	Allocation	Start of RT[a]	End of RT	First follow-up
Enrolment					
Eligibility screen	✓				
Informed consent	✓				
Allocation		✓			
Interventions					
RT			✓	✓	
Patient support with help of a mobile app			✓	✓	
Assessments					
EORTC QLQ[b]			✓	✓	✓
# of app-based questions answered				✓	
Patient satisfaction (PSQ-18[c])				✓	
Frequency and length of consultations				✓	✓

[a]RT: radiotherapy.

[b]EORTC QLQ: European Organisation for Research and Treatment of Cancer quality of life questionnaires.

[c]PSQ-18: Patient Satisfaction Questionnaire Short Form.

Results

The results of this trial will be published in a peer-reviewed journal within 24 months of trial initiation, independently of the outcome of the trial. Publication will be prepared under the lead of the principal investigator of the study. The first and last authorship will be assigned by the principal investigator.

Discussion

Study Rationale

As consumer electronics become increasingly employed in the medical sector, their use for the support of oncologic patients opens up a range of possibilities from the gathering of information on patient health and symptoms to patient notification about appointments or test results. The present single-center prospective pilot trial conducted at the Department of Radiation Oncology of Heidelberg University Hospital explores the possibility of employing a mobile app for the systematic support of radiooncological patients throughout the course of their radiotherapy by monitoring symptoms and patient performance, and facilitating the exchange of relevant information between patient and physician. We aim to assess the feasibility and patient acceptance of incorporating such a mobile app into active patient care. Furthermore, we aim to estimate the economic and financial aspects of this novel approach to therapy support.

Limitations and Future Perspectives

In the current study, the survey app is not deployed using the patient's own mobile device but is installed on a tablet computer belonging to the investigator and integrated into the institution's information technology infrastructure according to data protection regulations. For future trials, it is planned (after establishing feasibility and usefulness) to expand the scope of the app so that patients can use their own devices for survey completion outside the clinic.

On the other side, the aforementioned approach may contribute to addressing a possible selection bias. By presenting the application to patients on an institution-owned tablet device, we do not exclude patients who do not themselves own a mobile device, thus testing the application on patients regardless of their technical abilities and/or affinity.

The definition of feasibility in this trial is largely derived from intrainstitutional clinical experience and logistical considerations. There is, however, to date no systematic data from which a more general definition of feasibility can be derived in this context. A systematic survey conducted at our institution on oncologic patients' use of and affinity towards mobile devices is in accordance with previously published data [13] in suggesting that roughly three quarters of patients would be inclined to use a mobile app in the context of radiotherapy. This further suggests that expecting a patient compliance of 80% to demonstrate feasibility is realistic.

Conclusions

The findings of this study will play an important role in clinically validating the mobile app we have developed for the collection of patient-reported outcome measures from patients undergoing radiotherapy. By proving the usefulness and feasibility of an app-based approach to radio-oncologic patient supportive care, the present exploratory study prepares the ground for the larger-scale evaluations we are planning to perform on this promising subject.

Acknowledgments

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Authors' Contributions

RAES and NHN developed and planned this trial. TM, NB, DO and JD are responsible for developing and maintaining the mobile app used in this study, as well as for electronic data management. DW is responsible for the statistical considerations/basis of the analysis. TS is responsible for the comparative calculation of treatment costs. All authors read and approved the final manuscript.

Conflicts of Interest

TM holds shares in OPASCA GmbH (Mannheim, Germany). All other authors declare that they have no competing interests.

Multimedia Appendix 1

SPIRIT checklist of different protocol items related to this trial.

[PDF File (Adobe PDF File), 180KB - resprot_v7i3e70_app1.pdf]

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Abbreviations

EORTC: European Organisation for Research and Treatment of Cancer
mHealth: mobile health
OPTIMISE-1: Oncologic Therapy Support Via Means of a Dedicated Mobile App – A Prospective Feasibility Evaluation
PSQ-18: Patient Satisfaction Questionnaire Short Form
QLQ: quality of life questionnaire
QoL: quality of life
ROKIS: Radiation Oncology Clinic Information System
SOP: standard operating procedures
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Robotic Versus Open Renal Transplantation in Obese Patients: Protocol for a Cost-Benefit Markov Model Analysis

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Abstract

Background: Recent studies have reported a significant decrease in wound problems and hospital stay in obese patients undergoing renal transplantation by robotic-assisted minimally invasive techniques with no difference in graft function.

Objective: Due to the lack of cost-benefit studies on the use of robotic-assisted renal transplantation versus open surgical procedure, the primary aim of our study is to develop a Markov model to analyze the cost-benefit of robotic surgery versus open traditional surgery in obese patients in need of a renal transplant.

Methods: Electronic searches will be conducted to identify studies comparing open renal transplantation versus robotic-assisted renal transplantation. Costs associated with the two surgical techniques will incorporate the expenses of the resources used for the operations. A decision analysis model will be developed to simulate a randomized controlled trial comparing three interventional arms: (1) continuation of renal replacement therapy for patients who are considered non-suitable candidates for renal transplantation due to obesity, (2) transplant recipients undergoing open transplant surgery, and (3) transplant patients undergoing robotic-assisted renal transplantation. TreeAge Pro 2017 R1 TreeAge Software, Williamstown, MA, USA) will be used to create a Markov model and microsimulation will be used to compare costs and benefits for the two competing surgical interventions.

Results: The model will simulate a randomized controlled trial of adult obese patients affected by end-stage renal disease undergoing renal transplantation. The absorbing state of the model will be patients' death from any cause. By choosing death as the absorbing state, we will be able simulate the population of renal transplant recipients from the day of their randomization to transplant surgery or continuation on renal replacement therapy to their death and perform sensitivity analysis around patients' age at the time of randomization to determine if age is a critical variable for cost-benefit analysis or cost-effectiveness analysis comparing renal replacement therapy, robotic-assisted surgery or open renal transplant surgery. After running the model, one of the three competing strategies will result as the most cost-beneficial or cost-effective under common circumstances. To assess the robustness of the results of the model, a multivariable probabilistic sensitivity analysis will be performed by modifying the mean values and confidence intervals of key parameters with the main intent of assessing if the winning strategy is sensitive to rigorous and plausible variations of those values.

Conclusions: After running the model, one of the three competing strategies will result as the most cost-beneficial or cost-effective under common circumstances. To assess the robustness of the results of the model, a multivariable probabilistic sensitivity analysis will be performed by modifying the mean values and confidence intervals of key parameters with the main intent of assessing if the winning strategy is sensitive to rigorous and plausible variations of those values.

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KEYWORDS

renal transplantation; obesity; cost benefit analysis; markov model

Introduction

Kidney transplantation (KT) is the best treatment strategy for patients with end-stage renal disease (ESRD). KT allows patients to return to a normal lifestyle with relatively few side effects from modern immunosuppression medications [1]. Several investigators have shown that from a societal point of view, KT is cost-effective [2-4]. However, these findings have been challenged by the increasing proportion of patients affected by obesity and renal failure and the introduction of costlier surgical technologies, such as robotic-assisted surgery. The constraints on health-care resources raise the question of the cost-benefit ratio of new medical or surgical therapies that are expensive or that provide a marginal benefit in comparison to already established therapies. Due to the lack of cost-benefit studies on the use of robotic-assisted renal transplantation versus open surgical procedure, the primary aim of our study is to develop a Markov model to analyze the cost-benefit of robotic surgery versus open traditional surgery for the treatment of obese patients undergoing renal transplantation. The secondary aim is to perform a cost-benefit analysis between the two competing surgical techniques.

Innovation

The insufficient degree of freedom provided by non-articulating laparoscopic instruments and the two-dimensional view of conventional laparoscopic cameras have represented significant barriers preventing the widespread use of minimally invasive techniques for renal transplantation. However, most of those obstacles have been overcome by the introduction of robotic technologies such as the da Vinci surgical system (DVSS) (Intuitive Surgical, Mountain View, CA, USA). Robotic surgery allows intracorporal maneuvers that mirror the natural dexterity of surgeons' hands with the additional advantages of eliminating the natural hand tremor [5-7]. Other significant benefits of using the robotic surgical system is the three-dimensional stereoscopic images and improved ergonomics for the primary surgeons in addition to the reduced discomfort for the patients who benefit from the minimally invasive approach and can return to their full functional capacity faster than open surgery [8].

Limitations of Current Knowledge and Primary Aim of the Study

Due to the lack of cost-benefit studies on the use of robotic-assisted renal transplantation versus open surgical procedure, we aim to develop a mathematical model designed to analyze the cost-benefit of robotic surgery versus open surgery for the treatment of obese patients undergoing renal transplantation. Our primary aim is to assess the cost-benefit ratio for the health care payer's perspective. The selection of obese recipients for this study is based on the current evidence indicating that, for this group of patients, robotic assisted renal transplantation is associated with a significant lower risk of wound complications, and therefore, lower costs for wound care and other expensive interventions such as repair of incisional hernias or use of open negative pressure wound dressings.

Significance

The number of patients affected by renal insufficiency and obesity is growing, especially in North America where obesity has reached epidemic proportions [9]. Recent epidemiological data indicate that 20-50% of patients on dialysis are obese [10]. Obesity is associated with an increased risk of wound complications [9]. Wound infections are the most common nosocomial adverse events in patients who undergo complex surgical procedures or who are immunosuppressed or diabetic [11-13]. Most obese patients who undergo renal transplantation are diabetic and their risk of developing wound complications (infections, seromas, dehiscence, hernias) is increased further using immunosuppression medications that predispose to the development of infections and dehiscence or hernias. In obese recipients, wound complications have been estimated to range from 20-30% to 40% when body mass index (BMI) > 40 kg/m^2 [11-15].

The Economic and Clinical Burden of Wound Infections

Wound infections, incisional hematomas, and seromas are predisposing factors for incisional hernias that, most of the times, will require surgical repair to prevent intestinal incarceration or strangulation, causing abdominal or back pain due to the disruption of balance between the anterior abdominal wall muscles and the paraspinal posterior musculature.

In theory, all wound complications are preventable. Yet, they still represent a significant clinical and economic burden to the health care system [16-20]. Wound infections are responsible for longer hospitalizations, increased costs for antibiotic therapy and topical wound care during the same admission and after discharge. In addition, patients who develop wound complications have decreased functional capacity and rely on the assistance of family members or other providers who need to take time off work to drive patients to their frequent clinic appointments [21]. More importantly, in obese renal transplant recipients, surgical site infections (SSIs) have been associated with lower graft survival [14].

Wound Complications in Obese Patients

The higher incidence of wound complications in obese patients is multifactorial. Obese patients have a higher prevalence of diabetes that is a predisposing factor for delayed wound healing and to bacterial infections [22-25]. In addition, due to the extra-adipose tissue in the subcuticular space, obese patiens are prone to develop seromas that often become infected because of the suboptimal vascularization of the adipose tissue [26-29]. Furthermore, obese patients require longer incisions and their surgeries are, most of the time, longer with subsequent increased risk of tissue dissication and intraoperative contamination [30] that are predisposing factors for incisional hernias [31].

Outcomes of Robotic Surgery in Renal Transplantation

During the period between June 2009 to December 2011, a prospective cohort of 39 obese patients underwent robotic kidney transplantation at the University of Illinois Hospital and Health Sciences System [30]. This cohort was compared to a similar group of patients who had open transplant surgery prior to June 2009. The two groups were matched for many clinical and sociodemographic characteristics [30]. Delayed graft function was observed in one patient (3.6%) who had robotic renal transplant compared to none in the open surgery group. Wound complications occurred in one patient (3.6%) who underwent robotic renal transplantation versus 8 (28.6%) who underwent open surgery (*P*=.004). There were no patient or graft losses within the first six months after transplantation and the two groups had comparable graft function with similar serum creatinine levels (1.5 mg/dL for robotic recipients versus 1.6 mg/dL for open surgery recipients) [30]. The authors analyzed possible differences in resource utilization between the two groups. Comparisons between robotic surgery and open surgery showed similar hospital stay (8.2 days versus 8.1 days respectively; *P*=.98), number of hospital days during the first 6 months after transplantation (14.3 days versus 15.8 days; *P*=.69), mean number of readmissions (1.6 versus 1.5; *P*=.82), percentage of reoperations during the first six months after surgery (0% versus 3.6%; *P*=.99), hospital costs for transplantation ($75,148 versus $60,552; *P*=.02) and total hospital costs over six months ($86,272 versus $66,487; *P*=.04) [30]. Oberholzer et al. suggested that the lower rate of SSIs observed with the minimally invasive approach was due to the fact that the classical suprainguinal incision located in a highly colonized skin area was replaced with a 7 cm periumbilical incision that was much smaller and located in a more favorable area of the abdominal wall. In their experience, only one patient with BMI of 54.5 kg/m^2 and who underwent robotic assisted renal transplant developed an incisional hernia that required surgical repair.

Costs and Benefits of Competing Therapies

In recent years, there has been a trend to move health services towards value-based organizations and to improve the cost-effectiveness of interventions by reducing costs and increasing the value of care [32-34]. Porter, one of the initiators of value-based care, defines value as the desired level of "health outcome achieved per dollar spent" [32]. By this definition, value-based care represents health services that create added value by optimizing how services are organized, delivered, and paid for in relation to the outcomes achieved [35]. The introduction of operative techniques that use more sophisticated and expensive equipment seems to work against the principle of cost-effective care and reduction of costs. However, this might not be the case if the initial higher costs are associated with better quality of life, shorter hospital stay, and reduced adverse outcomes. Wound infections are responsible for longer hospitalizations and decreased functional capacity of renal transplant recipients who require extramural nursing for the management of their wound-vacuum devices and local debridement and packing of their incisions. On the other hand, DVSS and other robotic surgical systems are associated with higher costs due to the initial acquisition of the primary robotic equipment in addition to the ongoing maintenance and buying of disposables that are needed for each surgery. Until the uncertainty on possible benefits of robotic surgery for patients undergoing renal transplantation is resolved by a randomized controlled trial, the development of a cost-benefit decision analysis models remain the best method to investigate whether robotic renal transplant surgery is cost-effective for patients at high risk of wound complications. We hypothesize that the increased intra-operative costs of using robotic surgery might be mitigated by the shorter hospital stay and decreased costs of wound care.

Rationale for Cost-effectiveness and Cost-benefit Analysis

Cost-benefit analysis (CBA) in health care focuses on the analysis of the use of resources relative to expected medical benefits [36]. CBA plays an important role in selecting priorities or treatment strategies to be made in the presence of limited resources. CBA measures the correlation between costs and benefits using an equal unit of measure, usually monetary. It can be used to answer both technical and efficiency questions and can be applied to many sectors of the economy including health care. CBA and cost-effectiveness analysis (CEA) play an increasingly important role in the evaluation of interventions in modern health care systems [4]. With the advancement of treatment options available to treat common conditions, policy-makers and healthcare professionals are often required to choose among several competing therapies or surgical interventions that might be equally safe and effective but have different costs [37]. The purpose of CEA is comparison of alternative health interventions to make the most productive use of limited resources [36]. This has been made possible by modern computers able to handle multiple variables that populate probabilistic mathematical models.

Methods

Systematic Review of Clinical Effectiveness

With assistance of a librarian, electronic searches will be conducted to identify published studies on comparisons between open renal transplantation versus robotic assisted renal transplantation. Highly sensitive search strategies will include appropriate subject headings and text word terms, interventions under consideration, and specific study designs. No language restriction will be used but searches will be restricted from year 2000 onwards, reflecting the time of introduction of robotic assisted surgery. MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, BIOSIS, Science Citation Index, and Cochrane Central Register of Controlled Trials will be searched for primary studies, while the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database will be searched for reports of evidence syntheses. Reference lists of all included studies will be scanned to identify additional potentially relevant reports. Conference abstracts from meetings of the European, American, and British Urological Associations will be searched. Ongoing studies will be identified through searching Current Controlled Trials, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry

and the National Institutes of Health Research Portfolio Online Reporting Tools Expenditures and Results. Websites of manufacturers, professional organizations, regulatory bodies, and the Health Technology Assessment will be checked to identify unpublished reports.

Data Extraction Strategy

Two reviewers will independently screen titles and abstracts of all potentially relevant manuscripts. Full-text copies will be obtained whenever possible. Necessary variables found in the literature will be used to populate the mathematical model. Central tendency values and their variances will be used to create distributions used in the model. Probabilistic sensitivity analysis will be performed to assess the critical variables that influence the results of the model. For variables for which values are still unknown, we will elicit expert opinions to create plausible distributions. Alternatively, we will extract values reported in scientific publications that did not include transplant recipients but that used comparable surgical techniques or interventions. For example, variables associated with the costs of using robots in renal transplantation are unavailable. However, there are several observational studies and systematic reviews that analyzed the costs of robotic-assisted prostatectomies or partial nephrectomies that can be used for our model [38,39]. Similarly, costs of treatment of surgical site infections [19], repair of incisional hernias [40], and utility of patients undergoing incisional hernia repair [20] will be extracted from non-transplant scientific literature as we will assume that these values are applicable to our study population.

Identification of Costs and Benefits

In this part of the study, transplant surgeons, robotic surgeons, and transplant nephrologists will create a list all the possible costs that might be associated with open and robotic assisted renal transplant surgery. After reaching a state of saturation where no further costs are identified, investigators and a representative sample of individuals who require renal replacement therapy will list all the potential benefits for the two competing surgical interventions. Costs and benefits of the two interventions will be captured for the perioperative period. Since the costs of immunosuppression medications and follow-up appointments occurring after renal transplantation are similar for both groups of patients, these costs will not be included in our final analysis. On the other hand, due to the expected differences in the incidence of wound complications leading to incisional hernias between robotic versus open renal transplantation, the added costs for the care of the repair of incisional hernias will be included and added to the operative costs of transplant surgery. We will assume that the costs for the care of wound complications and repair of incisional hernias between the two groups of patients will be the equivalent.

Assignment of Monetary Value to the Costs

Costs associated with the two surgical techniques will incorporate the expenses of the resources used for the operations (eg, operative equipment, operative room time, and disposables). Training cost for surgeons will not be included as it depends on many variables including the overall level of experience of the surgeons, the number of hours spent for training on the robotic platform by the surgeons, and the maintenance costs for the training robotic system. Also, we will not include the costs to train operative nurses and technicians, anesthesia, and other health care providers working in the operating room to reach adequate proficiency in robotic assisted surgery. Similarly, because the preoperative workup is comparable for both groups, these costs will not be considered in our analysis.

Assignment of Monetary Value to the Benefits

Monetary values associated to the benefits of each surgical technique will be obtained from studies already published in peer-reviewed scientific journals. We will include the costs of obese patients who might remain on renal replacement therapy since some transplant programs will not consider them candidates for renal transplantation unless their BMI is lower than 40. To obtain pertinent costs, a systematic search of the scientific literature will be performed with the assistance of one of the librarians at the University of Pittsburgh or University of Pittsburgh Medical Center. When unavailable, monetary values will be obtained using unpublished data from the University of Pittsburgh Medical Center or from suitable hospital accounting services. Additionally, there will be intangible, or soft, benefits associated to overall patients' satisfaction, different levels and duration of perioperative discomfort, cosmetic results, time to full recovery, potential publicity, and marketing value associated with robotic surgery for either the hospital or the surgical team. To address how these intangible benefits should be measured and whether they should be included in the computerized model, all the members of our research team and a representative sample of patients requiring renal replacement therapy will be invited to a Delphi session to stimulate ideas and solutions based on sound clinical and methodological decisions. The Delphi Technique is a method used to estimate the likelihood and outcome of future events or to estimate probabilities or values that are unknown or not measurable [41,42]. A group of experts exchange views, and each independently gives estimates and assumptions to a facilitator who reviews the data and issues a summary report. The group members discuss and review the summary report and give updated forecasts to the facilitator, who again reviews the material and issues a second report. This process continues until all participants reach a consensus. In case consensus among the members of the research team is not reached, we will consult with other stakeholders and experts in decision analysis within the school of medicine at the University of Pittsburgh.

Creation of Decision Analysis Tree

A decision analysis model will be developed to simulate a randomized controlled trial comparing three interventional arms: A) continuation of renal replacement therapy for patients who are considered non-suitable candidates for renal transplantation due to obesity; B) transplant recipients undergoing open transplant surgery; and C) transplant patients undergoing robotic-assisted renal transplantation. TreeAge Pro 2017 R1 (TreeAge Software, Williamstown, MA, USA) will be used to create a Markov model and microsimulation will be used to compare costs and benefits for the two competing surgical interventions (Multimedia Appendix 1).

Patient Population, Model, and Variables

The model will simulate a randomized controlled trial of adult (age ≥ 18) obese patients affected by end-stage renal disease undergoing renal transplantation. The absorbing state (final state) of the model will be patients' death from any cause. By choosing death as the absorbing state, we will be able simulate the population of renal transplant recipients from the day of their randomization to transplant surgery or continuation on renal replacement therapy to their death and perform sensitivity analysis around patients' age at the time of randomization to determine if age is a critical variable for CBA or CEA comparing renal replacement therapy, robotic-assisted surgery, or open renal transplant surgery.

Obesity will be defined as patients' BMI higher than 30 according to the World Health Organization classification [43,44]. For simplicity, the model will not simulate the possibility of patients assigned to the robotic surgery to cross arm and be converted to open surgery. Variables of the model will include: costs for robotic and open surgery, costs of remaining on renal replacement therapy, cost associated with the development of wound infections and hernia repair, probabilities of developing surgical site infections for both groups, probabilities of developing incisional hernias after uncomplicated robotic and uncomplicated open renal transplantation, and probability of developing incisional hernias after developing surgical site infections after robotic and open renal transplantation. A summary of some of the variables and ranges that will be used in the model are reported in Multimedia Appendix 2. The model will simulate the entire life span of patients included in the study until their death. For simplicity, the probability of developing incisional hernia requiring surgical repair after renal transplantation will be limited to two events only. Expected survival of each patient will be estimated from survival tables of individuals living in North America adjusted for their age at the time of inclusion.

Sensitivity Analysis

After running the model, one of the three competing strategies will result as the most cost-beneficial or cost-effective under common circumstances. To assess the robustness of the results of the model, a multivariable probabilistic sensitivity analysis will be performed by modifying the mean values and confidence intervals of key parameters with the main intent of assessing if the winning strategy is sensitive to rigorous and plausible variations of those values. The rationale of sensitivity analysis in decision analysis is summarized in Textbox 1.

Textbox 1. Uses and contribution of sensitivity analysis for cost-benefit and cost-effectiveness analysis.

Primary aims

- Testing the robustness of an optimal solution.
- Identifying critical values, thresholds or break-even values where the optimal strategy changes.
- Identifying sensitive or important variables.
- Investigating sub-optimal solutions.
- Developing flexible recommendations which depend on circumstances.
- Comparing the values of simple and complex decision strategies.
- Assessing the "riskiness" of a strategy or scenario.

Communication

- Making recommendations more credible, understandable, compelling or persuasive.
- Allowing decision makers to select assumptions.
- Conveying lack of commitment to any single strategy.

Increased Understanding or Quantification of the System

- Estimating relationships between input and output variables.
- Understanding relationships between input and output variables.
- Developing hypotheses for testing

Model Development

- Testing the model for validity or accuracy.
- Searching for errors in the model.
- Simplifying the model.
- Calibrating the model.
- Coping with poor or missing data.
- Prioritizing acquisition of information

Results

The model will simulate a randomized controlled trial of adult obese patients affected by end-stage renal disease undergoing renal transplantation. The absorbing state of the model will be patients' death from any cause. By choosing death as the absorbing state, we will be able simulate the population of renal transplant recipients from the day of their randomization to transplant surgery or continuation on renal replacement therapy to their death, and perform sensitivity analysis around patients' age at the time of randomization to determine if age is a critical variable for CBA or CEA comparing renal replacement therapy, robotic-assisted surgery, or open renal transplant surgery. After running the model, one of the three competing strategies will result as the most cost-beneficial or cost-effective under common circumstances. In the discussion, we will summarize the results of our study and put them in the contest of the current knowledge on the value of robotic-assisted minimally invasive renal transplantation. We expect that, for some groups of patients, robotic surgery will be the most cost-effective treatment. The strength and limitations of our study will be presented and we will assess if our study could lead to the development of future research projects.

Discussion

After running the model, one of the three competing strategies will result as the most cost-beneficial or cost-effective under common circumstances. To assess the robustness of the results of the model, a multivariable probabilistic sensitivity analysis will be performed by modifying the mean values and confidence intervals of key parameters with the main intent of assessing if the winning strategy is sensitive to rigorous and plausible variations of those values.

Data Sharing

Sharing of data generated by our study is an essential part of our proposal. We would wish to make our results available to the community of scientists interested in robotic surgery, minimally invasive surgery, and transplantation to avoid unintentional duplication of research. We would welcome collaboration with other researchers within the University of Pittsburgh and from other institutions interested in CBA and CEA of new technologies in surgery. From this project, we expect that approximately two presentations will be delivered at national or international meetings. In addition, it is our explicit intention that the results of our study will be made readily accessible to the scientific community after the final analysis of the data generated by our mathematical model through publications in peer-reviewed journals.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Graphical representation of the decision analysis tree that will be used to perform a cost-benefit analysis between remaining on renal replacement therapy, robotic-assisted minimally invasive renal transplantation, and open surgery renal transplantation for obese patients affected by end-stage renal disease.

[PNG File, 423KB - resprot_v7i3e74_app1.png]

Multimedia Appendix 2

Summary of all variables that will be used in the mathematical model to perform a cost-benefit analysis between robotic-assisted minimally-invasive renal transplantation versus open surgery. All the variables were extracted from the most recent scientific literature.

[PDF File (Adobe PDF File), 349KB - resprot_v7i3e74_app2.pdf]

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Abbreviations

BMI: body mass index
CBA: cost-benefit analysis
CEA: cost-effectiveness analysis
DVSS: da Vinci surgical system
ESRD: end-stage renal disease
KT: kidney transplantation
SSI: surgical site infection

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Protocol

Impact of Medication Adherence on Mortality and Cardiovascular Morbidity: Protocol for a Population-Based Cohort Study

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Abstract

Background: Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels, such as coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease. CVD is the leading threat to global health, whether measured by mortality, morbidity, or economic cost. Long-term administration of aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers improves survival in patients with stablished coronary heart disease. Nevertheless, adherence to prescribed medication is poor for long-term drug treatment.

Objective: We aim to assess the relationship between adherences to the four pharmacological groups recommended for secondary prevention and the clinical outcomes of cardiovascular morbidity and mortality in patients with established CHD according to the level of adherence to these drugs in a population of incident cases of acute coronary syndrome (ACS).

Methods: Population-based cohort study of patients with a first episode of ACS during 2006-2015 in the Information System for Research in Primary Care (SIDIAP) database. We will estimate adherence to these drugs. The primary endpoint is a composite of all-cause mortality, ACS, and ischaemic stroke. Bivariate analyses will be performed estimating odds ratios for categorical variables and mean differences for continuous variables. Hazard ratios for adherences will be calculated for outcome events using Cox proportional hazard regression models, and proportionality of hazards assumption will be tested.

Results: We expect to estimate adherence to all four study treatments, the incidence of MACE, and to analyze if this incidence is associated with the level of drug adherence.

Conclusions: We expect to find that adherent patients have a lower risk of the primary endpoints compared with nonadherent patients.

Trial Registration: This study protocol was classified as EPA-OD by the AEMPS (IJG-EST-2017-01-2017-01, 07/04/2017) and registered in the EU PAS register (EUPAS19017, 09/05/2017).

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KEYWORDS

cardiovascular diseases; coronary heart disease; acute coronary syndrome; adherence; aspirin; statins; beta-blockers; angiotensin-converting enzyme inhibitors; angiotensin-receptor blockers

Introduction

Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels, such as coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease. CVD is the leading threat to global health, whether measured by mortality, morbidity, or economic cost [1]. In 2012, it was the leading cause of mortality worldwide, accounting for 31% of an estimated 56 million deaths from all causes. Also, CVD was responsible for the largest proportion of deaths for noncommunicable diseases under the age of 70 years, 37% of 16 million deaths [2].

Despite these numbers, the incidence of CVD death has decreased dramatically over the last four decades due to both population-level lifestyle changes in diet, smoking, and physical activity, and the development of effective interventions to treat individuals. The latter includes invasive procedures and effective drugs to tackle modifiable CVD risk factors [3].

A number of randomized clinical trials, meta-analyses and cohort studies have demonstrated that long-term administration of aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB) improve survival in high-risk patients, particularly those with established CVD. Nevertheless, adherence to prescribed medication is poor for long-term drug treatment in CVD [1,4-6]. Different factors have been described to be related with long-term nonadherence [1,5-7].

In a recent cohort study conducted by Bansilal et al [4], 4015 patients who had suffered an acute myocardial infarction (AMI) were categorized according to their drug adherence to statin and ACEI into three categories: fully adherent (≥80% proportion of days covered [PDC]), partially adherent (40-79% PDC) or nonadherent (<40% PDC). Fully adherents had lower rates of major cardiovascular events (MACE) than partially adherents, 18.9% vs 24.7% (adjusted hazard ratio [HR] 0.81, 95% CI 0.69-0.94) and nonadherents, 18.9% vs 26.3% (HR 0.72, 95% CI 0.62-0.85).

In the cohort study conducted by Lafeber et al [8], 2706 CHD patients were included. Of them, 67% were treated with a combination of aspirin, statin, and at least one blood pressure (BP)-lowering agent for secondary prevention. After a median follow-up period of five years, the combination therapy compared with no combination showed lower rates for all events: AMI, HR 0.68 (95% CI 0.49-0.96); ischaemic stroke, HR 0.37 (95% CI 0.16-0.84); vascular mortality, HR 0.53 (95% CI 0.33-0.85); composite endpoint of the previous events, HR 0.66 (95% CI 0.49-0.88); and all-cause mortality, HR 0.69 (95% CI 0.49-0.96).

A population-based cohort study performed in Spain assessed adherence to secondary prevention drugs in a cohort of 7462 patients who survived an acute coronary syndrome (ACS) [6]. Medication adherence was evaluated by determining the PDC for each therapeutic group (antiplatelet agents, beta-blockers, ACEI or ARB, and statins) in the nine months following hospital discharge. Full adherence was defined as PDC75, at least 75% of days of the follow-up period covered by treatments dispensed. PDC75 for antiplatelet agents was reached by 5216 (69.9%) patients, for beta-blockers by 3231 (43.3%) patients, for ACEI/ARB by 3388 (45.4%) patients, and for statins by 4388 (58.8%). Only 3552 (47.6%) patients reached PDC75 for three or more therapeutic groups, whereas 1343 (18%) of patients did not reach PDC75 with any treatment. Some factors found to be related with nonadherence were older age, female sex, or copayment of drugs dispensed.

In a meta-analysis of 20 studies [9] in 376,162 patients assessing adherence to drugs for the primary or secondary prevention of a CHD event using prescription refill frequency, the estimated overall adherence to cardiovascular medications was only 57% (95% CI 50–64) after a median of 24 months, although it was superior in secondary prevention 66% (95% CI 56–75) than in primary prevention users (50%, 95% CI 45–56).

A large epidemiological study enrolled 7519 participants with established CVD from urban and rural communities in countries at various stages of economic development [10]. Use of antiplatelet drugs, beta-blockers, ACEI or ARB, and statins was assessed. Overall, 4421 (58.5%) individuals were not taking any of the four proven effective drugs, whereas 233 (3.1%) were taking all four drug types. Individuals recruited in high-income countries had had a CHD event or stroke a median of 6.0 years (interquartile range [IQR] 3.0–10.0) before inclusion. Although medication use increased in line with increase of country economic status, adherence rates in high-income countries were sparse too: 62.0% for antiplatelet drugs, 40.0% for beta-blockers, 49.8% for ACEI or ARB and 66.5% for statins.

A meta-analysis of randomised clinical trials assessed adherence to therapy comparing different dosing regimens in patients with chronic CVD.[11] The study showed that dosing regimens with once-daily administration, compared with two or more daily administrations, were associated with a significant 56% risk reduction of nonadherence to drug therapy (relative risk 0.44, 95% CI 0.35–0.54).

Due to the improvement of morbidity and mortality found with the quadruple drug therapy with antiplatelet, beta-blocker, ACEI or ARB, and statin in patients with established CVD, it is necessary to assess the long-term adherence to these drugs in the Catalan population and its relationship with cardiovascular events and mortality. Our hypothesis is patients with established CHD who adhere to drug therapy with the four recommended pharmacological groups have a lower risk of MACE and all-cause mortality compared with patients who do not adhere to drug therapy.

The main objective of our study is to assess the relationship between adherences to the four pharmacological groups recommended for secondary prevention and the clinical

outcomes of cardiovascular morbidity and mortality in patients with established CHD. The outcomes which are included as components of the composite endpoint are all-cause mortality, ACS, and ischaemic stroke. The secondary objectives are: 1) to assess the incidence of the composite endpoint in patients who are adherent to treatment with all four drugs compared with patients who are adherent to any combination of three, two or one drug, or no drug; 2) to assess the relationship between baseline sociodemographic and clinical characteristics and adherence to drug therapy; 3) to compare the number of days on sickness leave due to any cause according to adherence to drug therapy; 4) to estimate prevalence of use of the four drug treatments; and 5) to describe the posology prescribed for the four drug treatments.

Methods

Study design

The study is a population-based retrospective cohort study.

Study Period

Inclusion period was between 2006-2015. The follow-up period was up to 2016.

Study Population

The study population includes individuals ≥18 years with an incident diagnosis of ACS during the study period 2006-2015, with at least two months of follow-up in the Information System for Research in Primary Care (SIDIAP) [12] after the index date. The next patients will be excluded: pregnant women on the index date; patients with a recorded diagnosis of ischaemic stroke in the six months prior to index date; patients living in a nursing home on the index date; and patients with Alzheimer's disease or other dementias.

Case definition: patient with an incident diagnosis of ACS registered in CMBD-HA (dataset of diagnoses at hospital discharge) [13] of the Catalan Health Institute (ICS) within the period from 2006-2015. Index date definition: date of ACS episode.

Data Collection and Data Sources

Diagnoses for study inclusion and endpoints will be obtained from CMBD-HA, which contains diagnoses at hospital discharge from all ICS hospitals, coded with International Classification of Diseases, Nineth Revision (ICD-9) [14]; see Table 1.

The rest of the variables will be captured from SIDIAP, which contains anonymized clinical information of all 279 PHC centres managed by the ICS in Catalonia (North-East Spain), covering a population of more than 5.8 million patients (about 80% of the total of 7.5 million population in Catalonia). The information contained in SIDIAP is registered by PHC general practitioners (GP), nurses and administrative staff in ECAP (electronic health records in ICS): comprehensive sociodemographic information, health conditions registered as ICD10 codes [15], specialist referrals, clinical parameters, toxic habits, PHC laboratory test results, GPs prescriptions and their corresponding pharmacy invoice data registered as Anatomical, therapeutic, chemical classification system (ATC) codes [16], date of sickness leave due to any cause, and date of death. Several reports have shown that SIDIAP data is useful for epidemiological research [17-25]. SIDIAP is listed under the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database [26].

Sample Size

The sample will be all patients with a first episode of ACS registered in CMBD-HA of ICS hospitals who meet all inclusion criteria and none of the exclusion criteria during the study period. In a previous study on patients with ACS conducted with SIDIAP database (publication pending) during the period 2009-2011, there were 3415 cases of ACS for all hospitals in Catalonia. Data from CMBD-HA of ICS hospitals corresponds approximately to 30% of all hospitals. Taking into account that our study period is 2006-2015 (10 years), we estimate to find approximately 3400 cases of ACS meeting inclusion criteria for our study.

Variables

Exposure Definition

Patients will be classified as "exposed" to the study drugs (antiplatelet agents, beta-blockers, ACEI or ARB, statins) if they are prescribed any of them after the episode of ACS (up to two months after the event). The dose prescribed in ECAP will be considered the daily dose used for the patient, and the number of tablets contained in each package will cover the same number of days (see drugs of study in Table 2).

Table 1. International Classification of Diseases, Nineth Revision (ICD-9) codes for endpoints of study and procedures.

ICD-9 code	Description
411*	Unstable angina and other forms of acute coronary heart disease
410*	Acute myocardial infarction
433*, 434*, 435*, 436*, 437*	Ischaemic stroke
00.66, 36.03, 36.09, 39.50	Coronary angioplasty

Table 2. Anatomical, therapeutic, chemical classification system (ATC) codes for drugs of interest.

ATC code	Description of therapeutic group
Study drugs	
B01AC	Platelet-aggregation inhibitors
C07	Beta-blockers
C09A, C09B	Angiotensin-converting enzyme inhibitors
C09C, C09D	Angiotensin-receptor blockers
C10AA, C10B	Statins
Concomitant drugs	
C03	Diuretics
C02	Antihypertensive drugs
C08CA, C08D	Calcium-channel blockers (dihydropyridines/verapamil, diltiazem)
B01AA, B01AB, B01AD, B01AE, B01AF, B01AX	Anticoagulants
A10	Drugs used in diabetes mellitus
C10AB, C10AC, C10AD, C10AX	Other lipid-lowering drugs
C01A, C01B	Digoxin and antiarrhythmic drugs
C01DA	Nitrates
N05A	Antipsychotics
M01A, N02BA, N02BB	Non-steroidal anti-inflammatory drugs

Adherence Definition

To estimate medication adherence, we will calculate the PDC for all four study treatments during eight months of follow-up after the index date. The PDC calculation is based on the packages dispensed and days of supply for each package, considering that the number of tablets contained in one package covers the treatment necessary for 28 or 30 days, depending on the drug. The information will be obtained from the pharmacy invoice data. For the PDC calculation, the numerator is the number of packages dispensed (invoice register) during the first 8 months of follow-up, and the denominator is the period of 8 months, which is the period for the adherence measure. Based on the PDC, patient adherence to each study drug is usually classified into one of two categories using the standard threshold of 75% (≥75%: adherent, <75%: nonadherent) [6,9]. PDC=75% accounts for six packages (each one including one month of drug treatment) dispensed during eight months. We define adherent patients as those who have received at least six packages during the first eight months after the event. Finally, according to adherence to all four study drugs, patients will be classified as adherent if they get the refill for all study drugs: PDC antiplatelet ≥75% + PDC beta-blockers ≥75% + PDC ACEI/ARB ≥75% + PDC statin ≥75%.

Study Endpoints

ICD-9 codes for primary and secondary endpoints can be seen in Table 1. They will be captured from CMBD-HA database.

Primary Endpoint

The primary endpoint will be a composite endpoint of all-cause mortality, ACS and ischaemic stroke. From the index date (first episode of ACS), patients will be followed up to the end of follow-up or until a new diagnosis of any of the endpoints stated above. Patients who experience more than one endpoint during the study follow-up will be censored upon the first event of interest. Patients who do not experience any of the clinical events included in the composite endpoint during the follow-up will be censored at the last date of follow-up.

Secondary Endpoints

The secondary endpoints will be AMI, unstable angina, ischaemic stroke, all-cause mortality, overall number of days on sickness leave due to any cause and due to CVD events, prevalence of use of the four pharmacological groups of interest, posology of the four pharmacological groups of interest.

Other Variables

All the following variables will be considered as potential confounders or effect modifiers in the association between adherence to the drug therapy and risk of the composite endpoint. They will be captured from SIDIAP database:

Patient Baseline Characteristics

All sociodemographic characteristics will be measured on the index date: index year, number of visits to PHC, age, sex, MEDEA index (socioeconomic deprivation index) [27], smoking status, alcohol intake, height, weight, Body Mass Index (BMI); the information comes primarily from a codified variable. If the patient has no information, it is calculated from height and weight and physical activity.

Table 3. ICD-10 codes for comorbidities of interest or diseases for exclusion

ICD-10 code	Description
I24*, I25*	Coronary heart disease
I63*, I65*, I66*, I67.2, I67.8	Ischaemic stroke
G45	Transient cerebral ischaemic attack
I70*, I73*, I74*	Peripheral vascular disease
E78*	Dyslipidaemia
I10*, I15*	Hypertension
E10*, E11*	Diabetes mellitus
I48	Atrial fibrillation
I50*	Heart failure
C00*-C97*	Malignancies
J40*-J44*	Chronic obstructive pulmonary disease
F30*-F39*	Depression
M05*, M06*, M15*-M19*	Arthritis (osteoarthritis or rheumatoid arthritis)
M80*, M81*	Osteoporosis
N18*	Chronic kidney disease
B20*-B24*	HIV
G30*, G31*	Alzheimer's disease, other dementias

Comorbidities and Clinical Parameters

They will be measured closest to the index date: type of cardiovascular event at index date (AMI and unstable angina and other forms of ACS captured from CMBD-HA), presence of coronary angioplasty implant after the event (data source CMBD-HA), cholesterol and other lipid parameters (low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, total-cholesterol, and triglycerides), blood pressure measured (systolic and diastolic blood pressure), glycated hemoglobin, glomerular filtration rate, serum creatinine, specific comorbid conditions (see ICD-10 codes in Table 3), Charlson comorbidity index [28,29].

Concomitant Drug Use

For all patients, baseline information on other medications for CVD prescribed throughout follow-up will be captured from the pharmacy invoice (see ATC codes for drugs in Table 2).

Statistical analysis

Demographic and baseline characteristics of the participants will be described using frequencies and percentages for categorical variables and mean, standard deviation or median and interquartile range for continuous variables, as appropriate. Bivariate analyses will be performed estimating odds ratios for categorical variables and mean differences for continuous variables as well as their respective 95% CI. Multiple imputations by chained equations will be used to replace baseline missing values. Case-complete and imputed data results will be compared as a sensitivity analysis. The raw and adjusted HRs for adherences will be calculated for outcome events using Cox proportional hazard regression models, and proportionality of hazards assumption will be tested. Association analyses between adherence to study drugs, incidence of the endpoints or sick leave, and drug therapy (objectives 1, 2 and 3) will be analysed by means of generalized linear models. Objectives 4 and 5 are descriptive and they will be described using frequencies and percentages as appropriate.

Ethical Aspects and Data Confidentiality

The present study follows national and international regulations: Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and Good Research Practice principles and guidelines. The study protocol has been approved by Institut Universitari d'Investigació en Atenció Primària (IDIAP) Jordi Gol Clinical Research Ethics Committee, the reference institution for research in PHC of the ICS, at May 3, 2017. Regarding the data contained in the databases and according to Spanish legislation about confidentiality and data protection (Ley Orgánica 15/1999 de 13 de diciembre de Protección de Datos de Carácter Personal), data included in SIDIAP are always anonymized. Thus, it is not necessary to ask for informed consent from the participants.

Results

We expect to estimate adherence to all four study treatments, the incidence of MACE, and to analyze if this incidence is associated with the level of drug adherence. Adherence to drug treatment has shown better results in terms of risk reduction of MACE, so we expect to find that adherent patients have a lower risk of the primary endpoints in comparison with nonadherent patients.

Discussion

We expect to find that adherent patients have a lower risk of the primary endpoints in comparison with nonadherent patients.

Selection bias is a common limitation in observational studies. In order to avoid this bias, where the population with missing data differs from those with complete data, missing values for continuous variables will be imputed instead of excluding records with missing data.

Another limitation is the presence of potential confounders. To minimize confounders' effects, Cox regression models adjusted for sociodemographic characteristics and for possible confounders and predictive factors will be used.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

ACEI: angiotensin-converting enzyme inhibitors
ACS: acute coronary syndrome
AEMPS: agencia Española de medicamentos y productos sanitarios
AMI: acute myocardial infarction
ARB: angiotensin-receptor blockers
ATC: anatomical, therapeutic, chemical classification system
BMI: body mass index
BP: blood pressure
CHD: coronary heart disease
CMBD-HA: conjunt mínim bàsic de dades a d'hospitalització d'aguts (minimum dataset of
CVD: cardiovascular disease
ECAP: electronic health records in PHC
ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GP: general practitioner

HR: hazard ratio
ICD: International classification of diseases
ICS: Catalan Health Institute (Institut Català de la Salut)
IDIAP: Institut Universitari d'Investigació en Atenció Primària
IQR: interquartile range
MACE: major cardiovascular events
PDC: proportion of days covered
PHC: primary healthcare
SIDIAP: Information System for the Improvement of Research in Primary Care

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Protocol

Epidemiology of Surgical Site Infections With Staphylococcus aureus in Europe: Protocol for a Retrospective, Multicenter Study

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This is a corrected version. See correction statement: http://www.researchprotocols.org/2019/1/e10712/

Abstract

Background: Surgical site infections (SSIs) are among the most common hospital acquired infections. While the incidence of SSI in certain indicator procedures is the subject of ongoing surveillance efforts in hospitals and health care systems around the world, SSI rates vary markedly within surgical categories and are poorly represented by routinely monitored indicator procedures (eg, mastectomy or hernia surgery). Therefore, relying on indicator procedures to estimate the burden of SSI is imprecise and introduces bias as hospitals may take special precautions to achieve lower SSI rates. The most common cause of SSI is *Staphylococcus aureus* (*S. aureus*), as recently confirmed by a Europe-wide point-prevalence study conducted by the European Centre for Disease Prevention and Control (ECDC).

Objective: The primary objective of this study is to determine the overall and procedure-specific incidence of *S. aureus* SSI in Europe. Secondary objectives are the overall and procedure-specific outcomes as well as the economic burden of *S. aureus* SSI in Europe. Explorative objectives are to characterize the composition of the surgical patient population and to estimate the number of patients at risk for *S. aureus* SSI.

Methods: A retrospective, multinational, multicenter cohort study (*Staphylococcus aureus* Surgical Site Infection Multinational Epidemiology in Europe [SALT] study) with a nested case-control part will be conducted. The study will include all surgical procedures at a participating center in order to prevent selection bias and strengthen the understanding of SSI risk by determining the incidence for all common surgical procedures. Data will be assessed in the cohort population, including 150,000 adult patients who underwent any surgical procedure in 2016, and the case-control population. We will match patients establishing *S. aureus* SSI 1:1 with controls from the same center. Data on demographics, surgery, and microbiology will be exported from electronic files. More detailed data will be captured from the case-control population. The SALT study will include 13 major or academic surgical centers in Europe, comprising 3 in France, 4 in Germany, 2 in Italy, 3 in Spain, and 1 in the United Kingdom. Sites were selected using a feasibility questionnaire.

Results: The SALT study is currently recruiting patients. The aim is to complete recruitment in February 2018 and to close the database in September 2018. The final results are expected by the end of 2018.

Conclusions: Results of the SALT study will help to better understand the precise risk of certain procedures. They will also provide insight into the overall and procedure-specific incidence and outcome as well as the economic burden of *S. aureus* SSI in Europe. Findings of the study may help guide the design of clinical trials for *S. aureus* vaccines.

Trial Registration: ClinicalTrials.gov NCT03353532; https://clinicaltrials.gov/ct2/show/NCT03353532 (Archived by WebCite at http://www.webcitation.org/6xAK3gVmO)

(JMIR Res Protoc 2018;7(3):e63) doi:10.2196/resprot.8177

KEYWORDS

surgical site infection; Staphylococcus aureus; cohort study; nested case-control

Introduction

Background

Surgical site infections (SSIs) are among the most common hospital acquired infections and constitute an important quality criterion in health research [1,2]. The incidence of SSIs in certain indicator procedures is the subject of ongoing surveillance efforts in hospitals and health care systems around the world [1,3,4]. However, SSI rates vary markedly within surgical categories and are poorly represented by routinely monitored indicator procedures such as mastectomy, upper limb amputation, or inguinal hernia surgery [4]. Therefore, relying on indicator procedures to estimate the overall burden of SSIs is imprecise and introduces bias as hospitals may take special precautions to achieve lower SSI rates in indicator procedures. *Staphylococcus aureus* (*S. aureus*) is the most common cause of SSIs, as recently confirmed by a Europe-wide point-prevalence study conducted by the European Centre for Disease Prevention and Control (ECDC) [5].

Treatment of *S. aureus* infections is challenging due to the emergence of multi-drug resistant strains such as methicillin-resistant *S. aureus* (MRSA). To better plan future trials on new treatment strategies, knowledge on incidence and risk factors is of utmost importance.

Currently available data suggest that while the overall SSI rate and the proportion of SSIs caused by *S. aureus* vary, the absolute *S. aureus* SSI rate is similar for different procedures. Focusing on *S. aureus* SSIs, we aim to demonstrate that the *S. aureus* SSI rate is independent of the procedure performed and rather a consequence of cutaneous incisions. Such a demonstration would amount to a paradigm shift and allow future prevention studies to proceed differently.

SSIs are associated with poor outcome, prolonged hospitalization, and increased treatment costs [6]. Estimated excess treatment costs range between US $ 1000 to $20,000 [6-10]. Treatment costs depend, among other factors, on the depth of SSI (superficial, deep, or organ space) and the prior surgical procedure. However, the exact treatment costs remain unknown, as previous estimates are based on limited data from single institutions [9], provider networks [11], or highly aggregated data from surveillance programs [7]. Due to this heterogeneous data source, prior cost estimates for Europe show a wide range of results [12].

Rationale

Active, prospective SSI surveillance lowers SSI rates [13]; therefore, unbiased SSI rates should be determined by retrospective, non-interventional studies. This cohort study will sample a large percentage of the surgical population and thereby generate representative data. For the selection process and documentation of the overall cohort, we will limit data items to those that are generally available in electronic form, thus facilitating the sampling of an adequately sized and complete cohort with comparably low effort. Feasibility analysis of candidate study centers will assess center capability for electronic data provision. If needed, single data items may be waivered during the selection process. In this case, these data items would instead be documented as part of the nested case-control study.

The nested case-control part of this study is necessary to generate data required for outcomes and cost analyses, as most centers will not have electronic records sufficiently detailed to allow this analysis for the whole cohort. The approach avoids bias that has been introduced, for example by relying on reimbursement data to estimate costs [14], and thus describing the SSI price rather than its cost. Therefore, the best possible approach to an accurate, precise cost analysis is manual documentation by on-site medical personnel (eg, study nurses). Documentation must comprise relevant cost drivers of SSI cases and well-matched controls to allow analyses of incremental costs caused by SSI. On-site medical personnel would receive appropriate electronic case report form (eCRF) training prior to commencing documentation. In addition, manual data capturing allows concomitant plausibility checking.

Nesting the case-control study within a cohort ensures generalizability of the case-control results to the respective center as well as the cohort and, by means of a representative cohort, to the overall surgical population in Europe.

Objectives

Primary Objectives

The primary objectives of this study are (1) to determine the overall incidence of *S. aureus* SSIs in Europe; and (2) to determine procedure-specific incidence of *S. aureus* SSIs in Europe.

Secondary Objectives

The secondary objectives of this study are (1) to determine the overall outcomes of *S. aureus* surgical SSIs in Europe; (2) to determine the procedure-specific outcomes of *S. aureus* SSIs

in Europe; (3) to determine the overall economic burden of *S. aureus* SSIs in Europe; and (4) to determine the procedure-specific economic burden of *S. aureus* SSIs in Europe.

Exploratory Objectives

The exploratory objectives of the study are (1) to characterize the composition of the surgical patient population in Europe; (2) to estimate the number of patients at risk for *S. aureus* SSIs; and (3) to estimate the economic burden, including direct treatment and indirect costs, imposed by *S. aureus* SSIs in Europe.

Methods

Study Design

This is a retrospective, multinational, multicenter cohort study with a nested case-control. The study includes all surgical procedures at a participating center in order to prevent selection bias and strengthen the understanding of SSI risk by determining incidence for all common surgical procedures. Furthermore, the study will analyze the risk composition of the surgical patient population to enable the calculation of the number of patients at risk in the overall surgical population in Europe.

Retrospective Record

Data from all patients undergoing any surgical procedure—minimal invasive biopsies and eye surgery excluded—will be collected retrospectively. Collection will be performed by surveying electronic health records (EHRs) and databases from all participating sites (Figure 1).

Administrative and microbiological data will be accumulated to identify the target population.

Nested Case-Control Design

The nested case-control study generates data for analyzing costs and outcomes. Participants acquiring *S. aureus* SSIs will be documented in an electronic database and matched 1:1 to controls within each center. Criteria for matching are similar epidemiological data and procedure type, but without SSI and are specified in the Data Collection section.

Study Procedure

Populations

Data will be assessed in the cohort and the nested case-control population (Textbox 1).

The following are the matching criteria for the nested case-control population: (1) type of procedure, (2) age, (3) BMI, (4) duration of procedure (as a percentile for this procedure), (5) diabetes, and (6) sex.

Study Sites

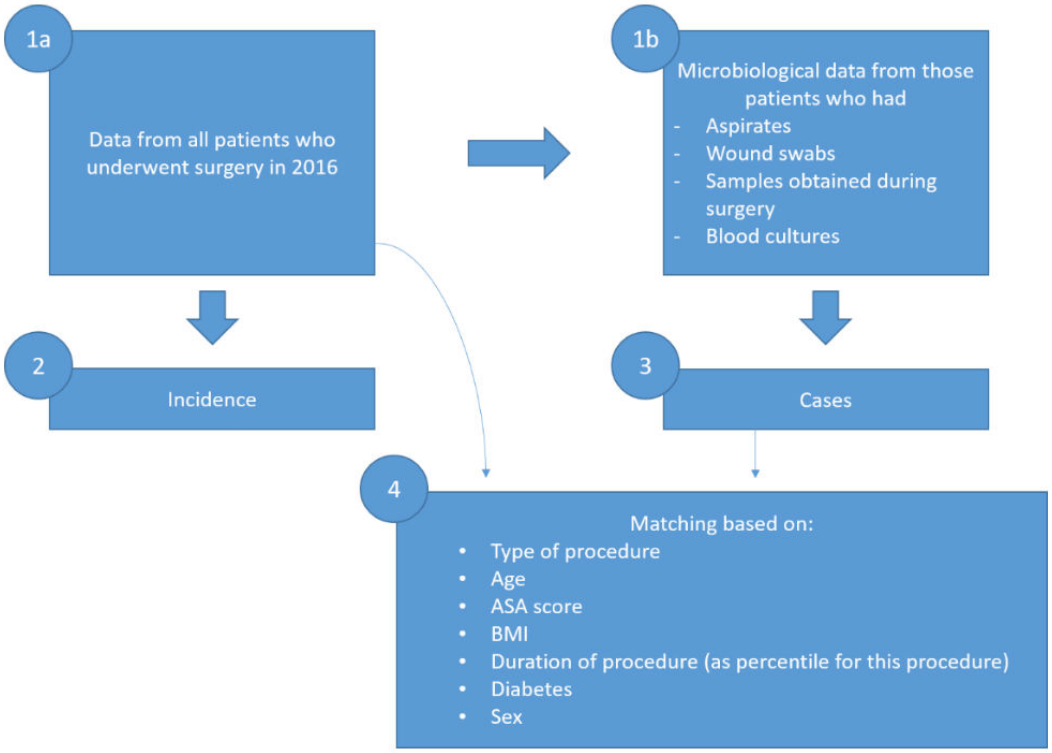
Approximately 13 surgical centers in Europe will be included in this study. To ensure adequate representation of each type of surgery, only centers with more than 10,000 surgeries will be considered. The distinction between academic and non-academic centers was chosen to ensure broad coverage and prevent selection bias.

Sites interested in participating will be identified through prior publications on SSI, prior SSI study participation, and membership in appropriate European scientific societies, including surgical, microbiological, and infectious diseases societies. Sites will be contacted and selected using a feasibility questionnaire (Multimedia Appendix 1) and procedure.

Target Population and Eligibility

All adult patients with a SSI after any surgical procedure—minimal invasive biopsies and eye surgery excluded—in 2016 will be part of our target population. Data from 2015 to 2017 will be collected if not enough data are available in 2015. The inclusion and exclusion criteria are shown in Textbox 2.

Figure 1. Data assessment and matching procedure. ASA: American Society of Anesthesiologists; BMI: body mass index.



Textbox 1. Data assessed in the cohort and nested case-control population.

- Cohort population
  - Export of electronic file data on demographics
  - Surgical procedure code
  - Duration of procedure
  - American Society of Anesthesiologists score
  - Body mass index
  - Comorbidity International Statistical Classification of Diseases and Related Health Problems codes
  - Wound class of all patients undergoing surgery
- Nested case-control: for patients establishing *S. aureus* surgical site infections (SSI) and 1:1 matched controls from the same center
  - Length of hospitalization
  - Length of intensive care unit (ICU) stay
  - Reason and attribution to SSI
  - Survival at 30 and at 90 days
  - Antibiotic treatments including duration, functional status at admission and at final discharge, necessity for surgical revision, and death attributed to SSI
  - If readmission is necessary, the following will be recorded:
    - Reason and attribution to SSI
    - Length of hospitalization
    - Length of ICU stay
    - Antibiotic treatments and their duration

Textbox 2. Inclusion and exclusion criteria.

- Inclusion
  - Age 18 years or greater at the time of surgery
- Exclusion
  - Patients undergoing minimal invasive biopsies and eye surgery
  - SSI at the time of surgery
  - Cases with missing data defined as missing completely at random

Time Schedule

The time schedule for the study is shown in Figure 2.

Sample Size

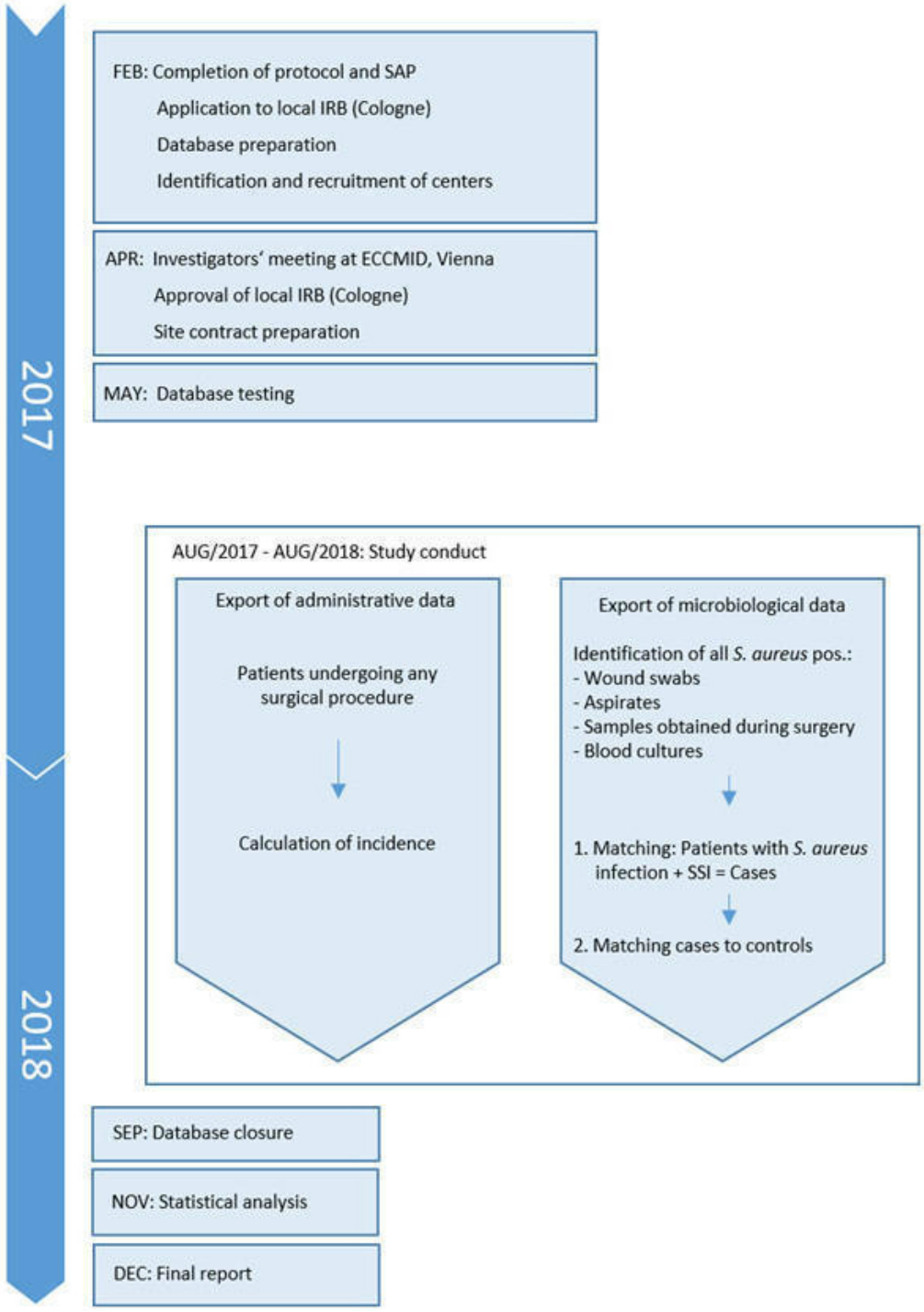
We assume a 1.5% incidence rate of *S. aureus* SSI. Incidence rates can be determined with a 95% CI of plus or minus 0.5% by observing 1500 surgical procedures, assuming a mean *S. aureus* SSI rate of 1%. Lower incidence rates would result in smaller 95% CIs with a similar sample size or similar CIs with a smaller sample size. Therefore, at least 15 centers should be included in the analysis, resulting in 90,000 to 150,000 patients observed patients. This will allow us to calculate incidence rates with meaningful precision for all surgical procedures performed on at least 1% to 1.5% of respective patients. To further broaden the scope of this study, 1 or 2 centers per country will be included specializing in types of surgery not traditionally performed at academic surgical centers but highly relevant to the prevention of SSI in otherwise healthy patients (eg, plastic surgery). Assuming a 1.5% incidence rate of *S. aureus* SSI, in a population of 150,000, 2250 cases will be matched to 2250 controls.

Data Collection

Cohort

The following variables will be collected from EHRs for descriptive purpose only: (1) age by category; (2) sex; (3) BMI; (4) comorbidities (International Statistical Classification of Diseases and Related Health Problems [ICD-10] codes); (5) diabetes; (6) type of procedure; (7) duration of procedure; (8) occurrence of SSI related to observed procedure within 90 days, including date of diagnosis; (9) wound class.

Figure 2. Study timelines. SAP: Statistical Analysis Plan; IRB: institutional review board; ECCMID:European Congress of Clinical Microbiology and Infectious Diseases; SSI: surgical site infections.



Surgical Site Infection Cases

SSI cases will be identified through EHR review in conjunction with microbiological data. The data recorded is shown in Textbox 3.

Detection of *S. aureus* Surgical Site Infection

As a first step, we will export the data listed in the Data Collection Cohort section from all patients who underwent surgery in each center in 2016. We expect a minimum of 100,000 cases to be included in the cohort. *S. aureus* SSI that occurred in 2016 will be detected using microbiological data.

To ensure feasibility, only centers with the capability of electronic microbiologic data export will participate. All patients presenting a *S. aureus* infection from the following will be identified: (1) wound swabs, (2) aspirates, (3) samples obtained during surgery, and (4) blood cultures.

Subsequently, electronic matching with clinical data will be performed in order to determine those patients who underwent a surgical procedure and had an *S. aureus* infection. This approach provides a sensitivity of 100% for identification of proven *S. aureus* SSI cases.

Textbox 3. Data collected for surgical site infection cases.

- Length of hospitalization
- Length of intensive care unit (ICU) stay
  - Reason for ICU stay; attribution to surgical site infections (SSI)
  - Hours of mechanical ventilation
  - Hemodialysis
- Survival at 30 and 90 days

  In case of death, attribution to SSI
- Necessity for revision surgery

  In case of SSI, attribution to SSI
- Necessity for readmission

  In case of readmission:
  - Reason
  - Attribution to SSI
  - Length of hospitalization
  - Length of ICU stay
    - Hours of mechanical ventilation
    - All antibiotic treatments, including duration and dosage
- All antibiotic treatments, including duration
- Functional status at admission and at final discharge
- Causative pathogens including resistance patterns
- Type of SSI according to European Centre for Disease Prevention and Control criteria

All patients identified will be documented manually. Occurrences of SSI will be verified on a case-by-case following the criteria of the Hospital Acquired (HAI) SSI protocol [1].

Superficial Incisional

Infection occurs within 30 days after the operation and involves only skin and subcutaneous tissue of the incision and at least 1 of the following: (1) purulent drainage with or without laboratory confirmation, from the superficial incision; (2) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision; (3) at least 1 sign or symptom of infection (pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative); and (4) diagnosis of superficial incisional SSI made by a surgeon or attending physician.

Deep Incisional

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if the implant is in place and the infection appears to be related to the operation and infection involves deep soft tissue (eg, fascia, muscle) of the incision and at least 1 of the following: (1) purulent drainage from the deep incision but not from the organ/space component of the surgical site; (2) a deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least 1 sign or symptom (fever greater than 38° C, localized pain or tenderness, unless incision is culture-negative); (3) an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination; or (4) diagnosis of deep incisional SSI made by a surgeon or attending physician.

Organ Space

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if the implant is in place and the infection appears to be related to the operation and infection involves any part of the anatomy (eg, organs and spaces) other than the incision that was opened or manipulated during an operation and at least 1 of the following: (1) purulent drainage from a drain that is placed through a stab wound into the organ/space; (2) organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space; (3) an abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination; or (4) diagnosis of organ/space SSI made by a surgeon or attending physician.

Controls

Cases will be matched to controls that received the same procedure but did not develop a SSI. Further variables to be included are (1) age; (2) sex; (3) American Society of

Anesthesiologists (ASA) score; (4) BMI; (5) duration of operation (as a percentile); and (6) diabetes. If available, comorbidities other than diabetes and underweight or overweight as well as the Charlson comorbidity index [15] and its components will be included.

Limitations

As this project is performed at different surgical centers in 5 countries across Europe, procedure and documentation characteristics may vary. Thus, the data set has to be limited to a common set of data frequently reported by all sites.

Statistical Analysis

Assuming a mean *S. aureus* SSI rate of 1% [5], incidence rates can be determined with a 95% CI of plus or minus 0.5% by observing 1500 surgical procedures. Therefore, at least 15 centers will be included in the analysis, resulting in 90,000 to 150,000 observed patients. Assuming an incidence rate of *S. aureus* SSI of 1.5% in a population of 150,000, 2250 cases will be matched to 2250 controls.

Data will first be analyzed for missing values. We will perform a qualified evaluation of missingness mechanisms for each variable with more than 1% missing values. In case data are missing completely at random, patients with the missing value will be excluded from that respective analysis step (complete record analysis). For values not missing at random, multiple imputation using chained equations will be performed and compared to a complete record analysis for improved robustness of results. We will perform in-depth descriptive statistics of all parameters observed. Country-based and institution-based incidence rates will be determined for each procedure (eg, ventral hernia repair) and each category (eg, vascular surgery). For each incidence rate, the 95% CIs for a binominal proportion will be calculated. Costs will be calculated for both procedures and categories. Accounting for the usually non-normal distribution of costs in medical settings, statistical analyses (eg, CI construction) will be carried out using non-parametric bootstrap procedures. Reported SSI rates and cost will be further stratified by depth of SSI (eg, superficial, deep). Association between major cost drivers and SSI occurrence, as well as overall costs and SSI occurrence, will be determined using bootstrapped t tests.

Multivariable regression analysis will be used to confirm significance of SSI occurrence for overall treatment costs.

Primary Analysis

The primary objective of this study is to determine the overall and procedure-specific incidence of *S. aureus* SSI in Europe. The primary analysis will consist of calculating the incidence using 95% CIs.

Secondary Analysis

The secondary analysis will consist of determining the overall and procedure-specific outcomes of *S. aureus* surgical site infections in Europe as well as the overall and procedure-specific economic burden of *S. aureus* SSI in Europe. Therefore, patients having established *S. aureus* SSI will be matched 1:1 to controls from the same center based on a propensity score and optimal matching with the following covariates: (1) type of procedure, (2) age, (3) ASA score, (4) BMI, (5) duration of procedure (as percentile for this procedure), (6) diabetes, and (7) sex.

Exploratory Analysis

Based on case-control matching, the composition of the surgical patient population in Europe will be characterized and the number of patients at risk for *S. aureus* SSI estimated.

The economic burden, including direct treatment and indirect costs, imposed by *S. aureus* SSI in Europe will be calculated by multiplication of the per-unit price for major cost drivers with the number of units used. The following variables will be included in the cost analysis as major cost drivers: (1) length of hospitalization, (2) length of ICU stay, (3) hours of mechanical ventilation, and (4) number and type of revision surgeries.

Further Statistical Evaluation

Distribution of data within groups will be described using count, percentage, or valid n, mean, standard deviation and percentiles (0, 25, 50, 75, and 100) as appropriate. CIs (level 95%) will be calculated to aid interpretation. Sensitivity analyses will include further multiple regression approaches (eg, Poisson regression for rates).

Data Management

Data will be recorded securely and electronically. The data are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized sponsor's representatives or appropriate regulatory authorities, without written permission from the sponsor.

The investigator will ensure that all data are entered legibly, completely, accurately, and conform to source documents.

The investigator will review and approve the data; the investigator's validation serving as attestation of the investigator's responsibility for ensuring that all data are complete, accurate, and authentic.

All data will be submitted to an automatic control in order to detect missing data, data out of limits, or inconsistent data. The obvious corrections, as spelling mistakes, will be done by the data manager, in accordance with the sponsor, and will be recorded.

All information obtained during the study will be recorded digitally in conformity with the applicable laws and regulations.

Ethical Standards

The study will be performed in accordance with the all applicable laws and regulations, including the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.

GCP requires that prior to the study onset, the protocol and any other written information regarding this study to be provided to the participant must be approved by an institutional review board (IRB) and/or an independent ethics committee (IEC).

The investigator agrees to allow the IEC/IRB direct access to all relevant documents.

The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. All approvals should be signed by the IEC/IRB chairman or designee and must identify the IEC/IRB name and address, the clinical protocol by title and/or protocol number, the documents received and their version number, and the date approval and/or positive opinion was granted.

The sponsor will provide the investigator with relevant documents that are needed for IEC/IRB review and approval of the study. The sponsor must receive copies of the IEC/IRB approval and any other information that the IEC/IRB has approved for presentation to potential participants.

If the protocol, or any other information that the IEC/IRB has approved is amended during the study, the investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. Copies of the IEC/IRB approval of the amended documents and these amended documents must be forwarded to the sponsor.

Data Confidentiality

The study protocol, documentation, data, and all other information generated by this study will be maintained in a secure manner and will be kept confidential as required by law.

The sponsor will affirm and uphold the principle of the participant's right to protection against the invasion of privacy. Throughout this study and any subsequent data analyses, all data will be assessed anonymously. No identifiable data (eg, patients name or date of birth) will be assessed. There will also be no use of pseudonyms, which would make a retrospective re-identification of the patient possible. Data collected refers to common treatment modalities in medical care, such that no re-identification of the individual case based on these data will be possible.

The investigator will respect and protect the confidentiality of the subject in all possible ways.

Data access will be limited to study personnel and data will be entered at each site by local study personnel. All information regarding the study, including conduct and results is confidential. No information can be divulged without written consent from the sponsor.

Data Handling and Record Keeping

The investigator will be provided with a study file, which should be used to file the protocol, correspondence with the sponsor, and other study-related documents. The investigator must retain the study file for a period of 15 years after the end or premature termination of the study.

The sponsor should inform the center as to when these documents no longer need to be retained. The center should contact the sponsor prior to disposing of any such records.

The study file will be archived according to the procedures applicable in the center. The sponsor should be notified if the Investigator relocates, retires, or for any reason withdraws from the study. The trial records must be transferred to an acceptable designee, such as another investigator, another institution, or to the sponsor.

All documentation pertaining to the study will be kept by the sponsor for at least 15 years after the end or premature termination of the study.

Confidentiality, Ownership of Data, and Publication Policy

All information disclosed or provided by the sponsor (or any company/institution acting on their behalf), or produced during the study, including, but not limited to the protocol, the case report forms (CRF), and the results obtained during the course of the study, is confidential prior to the publication of results.

The investigator, and any person under his/her authority, agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the sponsor. The investigator's collaborators shall be bound by the same obligation as the investigator. The investigator shall inform collaborators of the confidential nature of the study. The investigator and collaborators shall use the information solely for the purposes of the study, to the exclusion of any use for their own or for a third party's account.

The submission of this protocol and other necessary documentation to the IEC/IRB and the regulatory authority is expressly permitted, their members having the same obligation of confidentiality.

Statistical analysis and the final report will result in several original articles published in high impact journals.

Results

The *Staphylococcus aureus* Surgical Site Infection Multinational Epidemiology in Europe (SALT) study is currently recruiting patients. Thirteen surgical centers across Europe have completed the feasibility process and are actively enrolling patients at present. The aim is to complete recruitment in February 2018 and to close the database in September 2018. An investigator meeting is planned for April 2018. The final results are expected by the end of 2018.

Discussion

Principal Findings

The SALT study is a cohort study and will sample a large percentage of the surgical population and thereby generate representative data. Use of non-aggregated (ie, patient level) data will allow a precise and differential assessment of SSI burden on health care systems. This study will include all surgical procedures to prevent bias and strengthen the understanding of SSI risk by determining incidence for all common surgical procedures. Furthermore, the study will analyze the risk composition of the surgical patient population to enable calculation of the number of patients at risk in the overall surgical population in Europe. Currently, about 850 million people reside in Europe (depending on the definition of Europe). To improve feasibility, the study is restricted to France,

Germany, Great Britain, Italy, and Spain, thus covering about 300 million Europeans from northern, central, and southern European countries for best possible representativeness.

For the selection process and documentation of the overall cohort, data items were limited to those that are generally available in electronic form, thus facilitating the sampling of an adequately sized and complete cohort with comparably low effort. Feasibility analysis of candidate study centers assessed center capability for electronic data provision.

The nested case-control part of this study is necessary to generate data required for outcomes and cost analyses, as most centers do not have electronic records sufficiently detailed to allow this analysis for the entire cohort. The approach prevents bias that has been introduced, for example by relying on reimbursement data to estimate costs [14], and thus describing the SSI price rather than its cost. Therefore, the best possible approach to an accurate precise cost analysis is manual documentation, by on-site medical personnel (eg, study nurses). Documentation must comprise relevant cost drivers of SSI cases and well-matched controls to allow analysis of incremental costs caused by SSI. On-site medical personnel receives appropriate eCRF training prior to commencing documentation. In addition, manual data capturing allows plausibility checking.

Nesting the case-control study within a cohort ensures generalizability of the case-control results to the respective center as well as the cohort and, by means of a representative cohort, to the overall surgical population in Europe.

With SSI rates being the primary endpoint, SSI detection methodology is crucial in this study. Prior studies and surveillance effort, if specifying detection methodology at all, are usually limited to the analysis of administrative code data [14,15]. However, a recent publication demonstrated that using bacteriological data is superior and combining both—administrative and bacteriological data—could be even more advantageous [16]. In this very study, the detection by means of bacteriologic data will result in high sensitivity, specificity, and negative predictive values (96.4%, 91.4%, and 99.9%, respectively) for deep SSI with no significant difference to the use of both types of data.

Cases are matched 1:1 to controls within each center by software provided by the coordinating center. Matching cases and controls within centers addresses the need for risk-adjustment to institutional characteristics and practices. Cases are matched to controls that received the same type of procedure. Individual pair-wise matching will be used, utilizing optimal matching to ensure the overall smallest possible Euclidean distance between cases and controls. Acknowledging the limited utility of using the National Healthcare Safety Network (NHSN) risk index, which only accounts for the existence of certain risk factors but not their composition, a propensity score is determined by logistic regression.

Costs are calculated by multiplication of the per-unit price for major cost drivers with the number of units used. Minor cost drivers, such as drug use, will be disregarded, as length of stay has been repeatedly shown to account for 90% of excess SSI costs [11].

Limitations

A limitation of this study is the inability to detect late infections occurring post discharge by only analyzing in-patient laboratory data for SSI case identification. Depending on the procedure in question, infections occurring after discharge constitute a notable percentage of SSI. A post discharge surveillance approach will be subject of a future sub study.

Conclusion

Results of the SALT study will help to better understand the risk of certain procedures. It will allow conclusions on the overall and the procedure-specific outcomes as well as the economic burden of *S. aureus* SSI in Europe. Furthermore, the composition of the surgical patient population in Europe will be characterized and the number of patients at risk for *S. aureus* SSI will be estimated. Findings of the study may help designing clinical trials for *S. aureus* vaccines.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Feasibility questionnaire.

[PDF File (Adobe PDF File), 1MB - resprot_v7i3e63_app1.pdf]

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Abbreviations

ASA: American Society of Anesthesiologists
BMI: body mass index
CRF: case report form
ECDC: European Centre for Disease Prevention and Control
eCRF: electronic case report form
EHR: electronic health record
GCP: good clinical practice
ICD: International Statistical Classification of Diseases and Related Health Problems
ICU: intensive care unit
IEC: independent ethics committee
IRB: institutional review board
***S. aureus*:** *Staphylococcus aureus*
SSI: surgical site infections

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Original Paper

Assessing the Feasibility of a Social Media to Promote Weight Management Engagement in Adolescents with Severe Obesity: Pilot Study

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Abstract

Background: Severe obesity in adolescents has deleterious physical and psychological complications necessitating frequent multi-disciplinary clinic visits. Greater treatment engagement has been equated with weight-loss. However, traditional medical weight-loss programs for adolescents have high attrition rates. Social media is widely used by adolescents and may enhance medical weight management engagement and success.

Objective: The first objective was to examine the acceptability and feasibility of using a private social media group as an adjunct to medical weight management in youth ages 14 to 20 years with severe obesity [body mass index (BMI) ≥ 35 kg/m2]. The second objective was to pilot test the use of social media to improve treatment engagement and decrease attrition rates.

Methods: In this single arm, 12 week pre-post study, participants attended individual clinic visits and participated in a moderated private social media group that received nutrition, exercise, and behavior change social media communications or "posts" 3 to 4 times/week. Youth commented and/or liked posts from the moderator and each other. Social media engagement was measured with the number of likes and comments on social media. Clinic attrition was compared, measuring clinic visit attendance 12 weeks prior, during, and after the intervention with mixed linear regression models. Correlations of social media engagement with changes from baseline for BMI, BMI-z score, and psychosocial measures were fit.

Results: All 13 enrolled youth completed the study and reported that the group was enjoyable, helpful, reinforced their weight management program, and would recommend using social media to support other youth. The pilot trial was acceptable and feasible. Youth mean weekly engagement (likes + comments) in social media was greater than once a day (8.6 ±3.6). Compared to 12 weeks prior to the intervention, there was no significant decrease in clinic visit attendance at the end of the intervention (M=.231, *P*=.69) or 12 weeks at the conclusion of the intervention (M=.589, *P*=.28). Increased social media comments correlated with weight change (*r*=–.633, *P*=.04).

Conclusions: This pilot trial demonstrated that the use of social media as an adjunct to medical weight management was feasible and acceptable to adolescents with severe obesity. Based upon these preliminary findings, social media may be an effective way to mitigate attrition from obesity treatment programs, and improve health outcomes in this high-risk population.

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KEYWORDS

e-medicine; adolescents; social media; obesity; intervention; nutrition; internet

Introduction

Over 3 million youth in the United States (9%) ages 10 to 19 have severe obesity, defined as a body mass index (BMI) ≥ 120% above the 95th percentile or BMI ≥ 35 kg/m^2 [1,2]. Severe obesity and its associated physical impairments such as type 2 diabetes, obstructive sleep apnea and hypertension require treatment involving frequent follow-up with a multidisciplinary team (ie, dietitian, physical activity specialist, psychologist, physician and nurse) [3-5]. The United States Preventive Services Task Force recommends weekly contact with the weight management team over six months [5]. Challenges such as missing school or work, lack of social support, and frustration with weight-loss success contribute to observed attrition rates up to 82% in pediatric weight management programs [6-10]. Social media may provide an avenue to keep youth motivated and engaged in treatment.

The use of social media as an adjunct to traditional weight management allows for both peer-based and professional support. Social media can provide tailored and immediate feedback as well as practical, informational and peer support, which may be beneficial in childhood obesity treatment [11]. Traditional adolescent obesity treatment programs include parents and families, but generally do not include peers. Adolescent peers influence health-related behavior through modeling, imitation, and social learning [12,13]. Social media is readily accessible with 87% of youth ages 12 to 17 using social media and having internet access [14]. Further, 73% of all teens and 64% of teens with household incomes of ≤ $50,000, have smartphones [14]. Yet there is a paucity of studies examining the use of social media in weight management of children or adolescents with obesity [15]. This pilot study examined the feasibility of using private social media groups in conjunction with traditional weight management to promote obesity treatment engagement and to decrease attrition rates in adolescents with severe obesity. We hypothesized that the peer support social media intervention would improve clinic visit attendance.

Methods

Study Design

This single-arm feasibility study employed a pre-post design. We piloted a social media intervention among youth ages 14 to 20 years enrolled in a multi-disciplinary weight management clinic. To assess change in clinic attrition with and without the social media intervention, adolescents were enrolled in social media after they had completed 12 weeks of weight management in a tertiary care center.

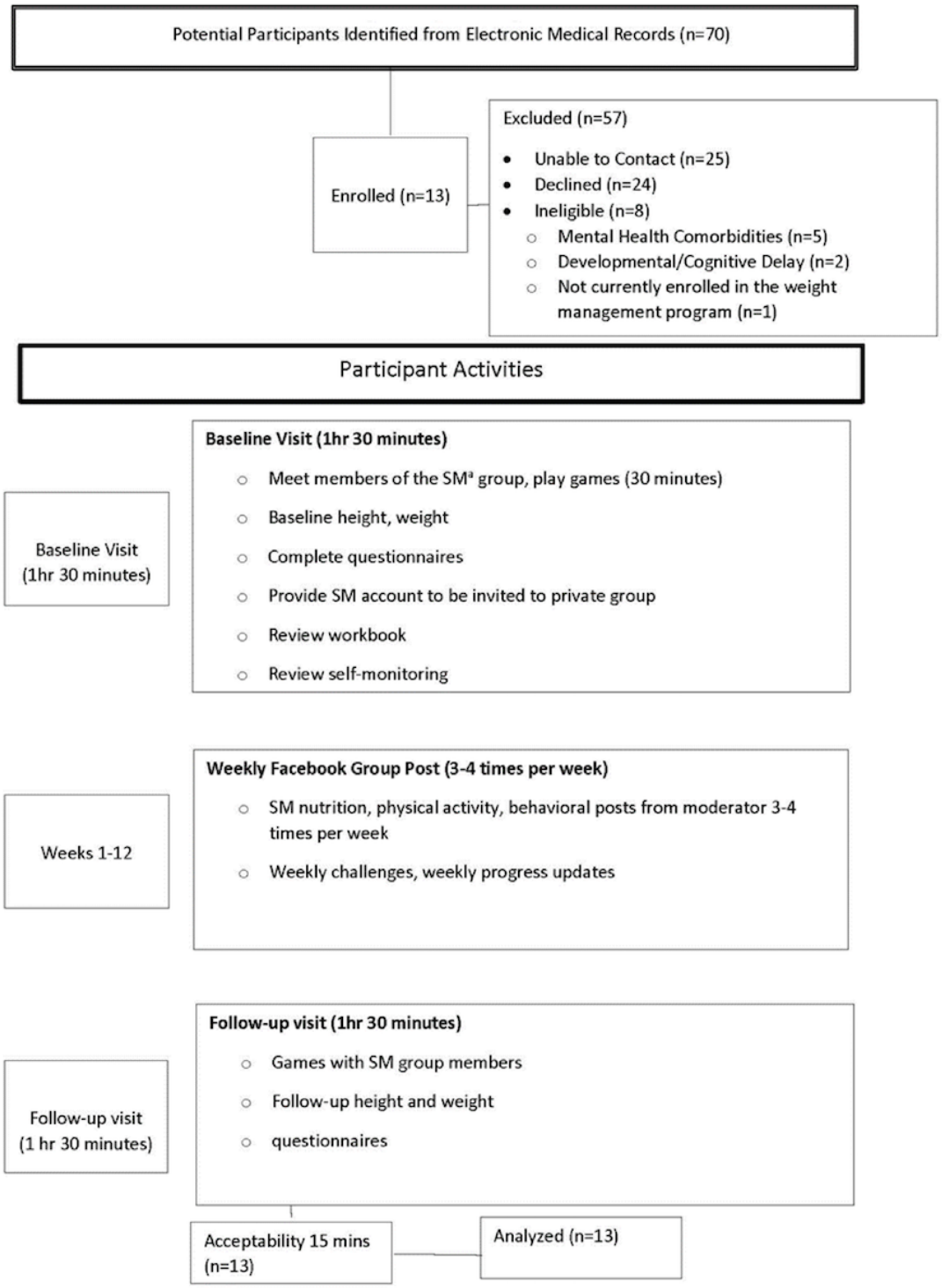
Recruitment

Participants were recruited from two urban tertiary care centers that treated adolescent obesity. Rosters were generated from the electronic health record of potentially eligible participants. Letters describing the study were sent to the home and participants were contacted and screened by telephone. Additionally, study flyers were placed in clinics. Eligible youth (n=13) were currently enrolled in an outpatient medical weight management program, had a BMI ≥ 35 kg/m^2, spoke English and had access to either a computer, tablet or a smartphone with a data and text plan. Youth with syndromic or secondary obesity, developmental delay, active substance abuse, untreated depression, psychosis, or an eating disorder other than binge eating disorder were excluded. Secondary to issues of social maturity, youth were divided into two groups based upon age: Group 1 (14 to 16 years) and Group 2 (17 to 20 years). Informed consent was obtained for experimentation with human subjects. The study flow is outlined in Figure 1.

Enrollment Visit

Youth were encouraged to attend monthly clinic visits with 1 or 2 medical weight management team members (dietitian, exercise physiologist, physician and psychologist) for 45 minutes and to follow their recommendations. At the enrollment visit, youth met the members of their age-based group and the group moderator, played icebreaker games, were invited to the private social media Facebook group, as well as MyFitnessPal. Acceptance of the invitation to the group was confirmed at the visit. Youth were given an age appropriate treatment manual based upon national guidelines that has previously been tested in adolescents to complement the in-person clinic visits [16,17]. They were advised to consume 1300-1500 kcal/day, to increase daily physical activity to 60 minutes, and to self-monitor these goals daily. Participants completed surveys in person at the enrollment and 12-week follow-up visits.

Figure 1. Study Flow diagram. SM=social media.



Intervention

This 12-week pilot intervention utilized the private social media group moderated by a clinical psychologist. The moderator posted challenges and requests for updates on progress of participants' goal setting weekly, and posted videos three times each week. Videos featured both youth and "experts" (dieticians, exercise physiologist, physicians, and the psychologist from their weight management team). Video content complemented the treatment manual and included: nutrition, physical activity, behavioral modification topics, cooking, and exercise demonstrations, and youth describing successes and challenges with adopting healthier behaviors (Figures 2 and 3). Youth were encouraged to share their own videos of behaviors and to comment on the moderator and peer posts. The moderator logged in twice a day to check and respond to posts.

As the study involved participants using their personal mobile phones to access the group, each received a US $25 monthly stipend for 3 months to offset the cost of their phone data plan. Youth were informed that in order to be eligible for the stipend, they needed to post, like, or comment in Facebook at least 3 times per week. Beyond those basic guidelines, they were told

that they could participate in the group as much or as little as desired. Participants who did not access the group for over 1 week received a private Facebook message with a reminder from the group moderator. Youth were also compensated for two in-person study visits to collect questionnaires and measure height and weight ($25/each). Facebook was chosen as the social media platform because of prior work, and because it was the most popular with youth in our age demographic at the time [14]. A generic name was given to the group "FACE" (Figure 2) that was not health or obesity related. Youth were counselled about the privacy settings. The Children's Hospital of Philadelphia Internal Review Board was an active participant in insuring participant privacy and protection. Only participants who were invited by the study team could view or post to the group. Participants were able to receive individualized tailored feedback weekly in their social media inbox from the moderator and during their regular clinic appointments. Participants were encouraged to set individual goals, and to post them to the group based upon the weekly challenges and video posts. Participants were encouraged to share feedback on the progress of their goals with the group and to also provide feedback to their peers. They also had the option to inbox the moderator with the progress of their goals, to receive feedback.

Measures

Acceptability and Clinic Attrition

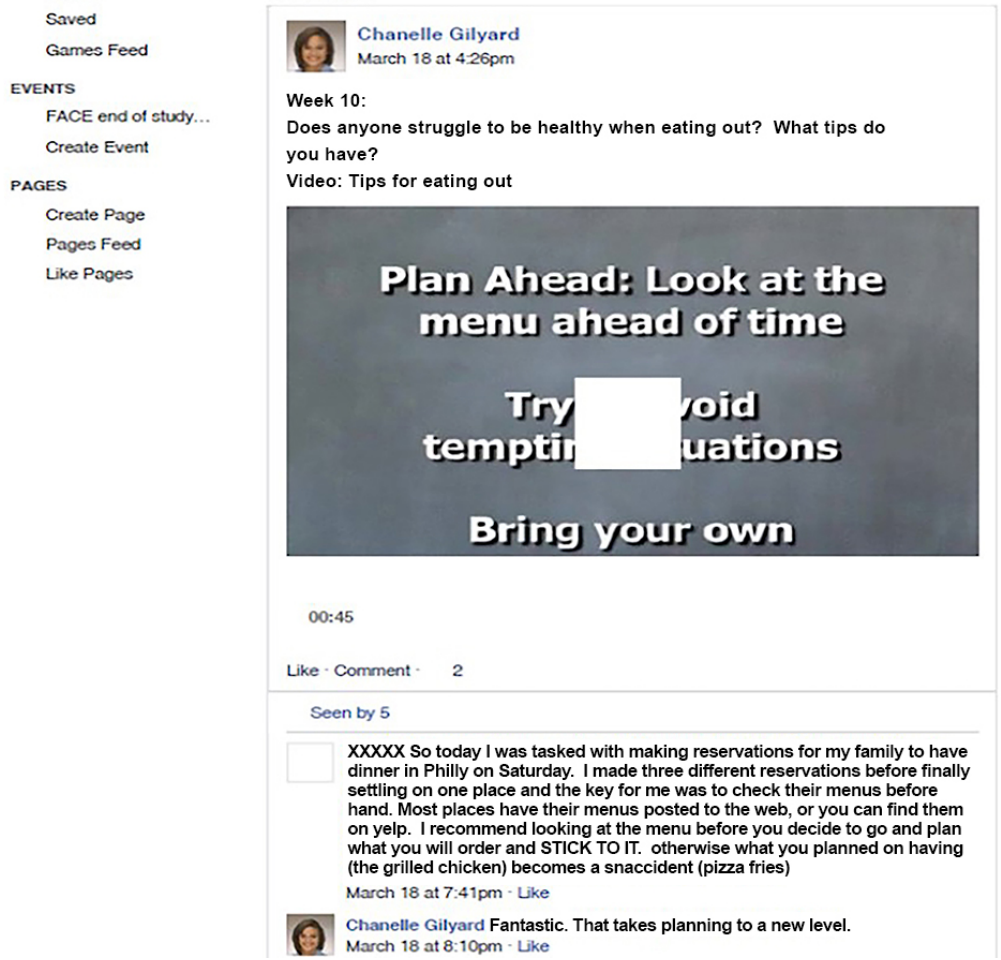
Acceptability of the social media group was assessed using a 28-item questionnaire which consisted of 14 Likert-scale questions and 14 open-response questions adapted from a previously used questionnaire [15]. Families were advised (by their medical team) to come to clinic once a month. Clinic attendances 12 weeks prior, during, and after the intervention were compared. The total clinic visits attended over a 12-week period were calculated to determine attrition. [8].

Social Media Engagement

Social media engagement was assessed by compiling the total number of "likes" plus comments [18]. "Likes" and comments were each also examined separately. Participants were incentivized to engage a minimum of 3 times per week in order to watch the 3 video postings. Participants were not considered to be engaged in social media if total engagement was less than or equal to 3 times per week. In exploratory analysis, the effect of social media engagement on BMI, BMI-z-score, depression, quality of life and perceived social support was examined.

Figure 2. This is the Facebook support page video introduction.

Figure 3. This is a FACE page with prompt and participant response leading to the video.



Anthropometrics

BMI (kg/m^2) and BMI-z-score were calculated from mean weight (to 0.1 kg) and height (0.1cm), which were measured on a digital electronic scale and wall-mounted stadiometer in triplicate at the enrollment visit and at the end of 12 weeks. Youth changed into scrubs at each measurement visit.

Psychosocial measures

Psychosocial outcomes included depression, quality of life and perceived social support, which were measured by self-report measures. Depression was measured by using the Beck Depression Inventory II (BDI-II), a 21-item inventory that measures mood with a higher score indicating greater depression [19]. Quality of life was measured with the Impact of Weight on Quality of Life Kids (IWQOL-kids), a 27-item inventory designed to assess the impact of weight status on quality of life, with a higher score indicating a better quality of life [20]. Perceived social support was assessed with the Multidimensional Scale of Perceived Social Support (MSPSS), a 12-item inventory assessing the social support of family, friends, and significant others, with a higher score indicating increased perceived social support [21]. The BDI-II, the IWQOL-kids and the MSPSS items report a test retest reliability of ≥ .78 and a validity score of ≥ .80 in obese adolescents [19,21,22].

Statistical Analysis

Descriptive analyses were described using calculated means and standard deviations. For the exploratory analysis of secondary outcomes, Wilcoxon rank sum was used to test changes at 12 weeks. Models were fit correlating mean total engagement (likes + comments), total likes and total comments, and total weekly engagement as a binary variable ≤ or > three times per week and total engagement ≤ or > 36 times total with BMI, BMI-z, depression, quality of life and perceived social support. To test our hypothesis and to assess changes in clinic visit, attendance over time mixed effects analysis were used. Mixed-model analyses allow for the incorporation of proper time trends (eg, nonlinear) and a variance-covariance structure that accounts for the correlation between repeated measures. The mixed-model included the group variable and time. Results are summarized with mean and by time. Analyses were conducted utilizing SAS statistical software (version 9.4; SAS Institute, Cary, NC). For all analyses, an α level of 0.05 was considered statistically significant.

Results

Participant Characteristics

Secondary to the limited sample size, results for the combined groups are presented. The majority of youth were female, with private insurance, and had an average BMI of 45 kg/m^2, which

is adult class III extreme obesity, or pediatric severe obesity. There was an almost even racial distribution. The mean age of participants was 16 years of age (Table 1).

Social Media Usage

Overall, youth remained engaged in social media weekly (likes/comments > 4 times per week), mean 8.6 (SD 3.6). Youth "liked" more than they "commented" (Table 2). The number of times that posts were viewed by participants was unknown.

Intervention Acceptability

Overall, youth found the social media support group to be enjoyable (100% [13/13]), helpful (100% [13/13]), a source of motivation (100% [13/13]), and would recommend the social media group to other youth with severe obesity (100 [13/13]). Participants felt the group was helpful for peer support (85% [11/13]), advice on nutrition (100% [13/13]), exercise (85% [11/13]), and helpful to reinforce the goals for their weight management program (100% [13/13]). From the open responses, youth identified the group as helping them to be "accountable and feel that they were not alone" and "to receive positive reinforcement." Youth reported that it was important to have an in-person weight management program along with the social media support group (92% [12/13]). Although adolescents could participate in social media at whatever time was convenient to them, they listed "time constraints of schoolwork and extracurricular activities" as preventing more frequent logins.

Intervention Feasibility

There were a total of 105 social media contacts from the moderator. Posts from the moderator included videos (63), challenges (6), requests for updates from participants (12), polls (2), pictures and links (9) and other information relevant to the intervention (13). Youth also uploaded videos and pictures (12). The moderator spent approximately 5 hours per week posting material and moderating comments for a total of 60 hours over the course of the 12-week intervention. All participants (n=13) completed the intervention and based upon insurance information included socioeconomically diverse background with 38% (5/13) using Medicaid.

Table 1. Participant baseline characteristics (N=13). BMI: body mass index.

Characteristic	Value
Age (years), mean (SD)	16.0 (1.30)
Age (years), range	14-20
Sex (male), n	4
Weight (kg), mean (SD)	127.0 (20.00)
BMI (kg/m^2), mean (SD)	45.5 (7.30)
BMI-z-score, mean (SD)	2.52 (0.2)
Clinic attendance, mean (SD)	5.85 (4.08)
Race (African American), n	6
Medicaid coverage, n	5
Depression, mean (SD)	7.62 (7.85)
Quality of life, mean (SD)	
Total score	79.64 (12.79)
Body Esteem subscale score	33.30 (6.94)
Social Life subscore	27.50 (3.06)
Perceived social support, mean (SD)	74.31 (9.01)

Table 2. Descriptive results of social media engagement over the course of 12 weeks (total) and weekly (N=13). Engagement = likes + comments.

Total and weekly engagement	Mean (SD)	Range
Total likes	43.1 (23.5)	9-82
Total comments	12.9 (3-43)	3-18
Total engagement	56 (24.3)	14-85
Weekly engagement	8.6 (3.6)	14-85

Table 3. Spearman Correlation of social media engagement with change in secondary outcomes in all subjects (N=13). BMI: body mass index.

Secondary outcomes	Total likes		Total comments		Total likes + comments	
	r	*P* value	*r*	*P* value	*r*	*P* value
Weight (kg)	.463	.11	–.724	.005	.138	.65
BMI (kg/m^2)	.275	.36	–.550	.05	.008	.98
BMI z-score	.252	.43	–.532	.08	–.053	.87
Depression[a]	.277	.36	–.084	.78	.064	.84
Quality of life[b]	–.119	.71	383	.22	–.077	.81
Perceived social support[c]	.204	.50	.198	.51	.044	.97

[a]Depression measured by the Beck Depression Inventory II (higher=worse depression).

[b]Quality of life measured by the Impact of Weight on Quality of Life—Kids (higher=better quality of life).

[c]Perceived social support measured by Multidimensional Scale of Perceived Social (higher=better social support)

Clinic Attrition

In mixed effects analysis, we included all subjects controlling for group to evaluate change in clinic attendance with time. The number of visits prior to the start of the intervention (baseline) were compared at 12 weeks (the end of the intervention) mean (M) =.231, *P*=.69, and 6 months (3 months at the conclusion of the intervention) (M=.589, *P*=.28). There was no significant change in clinic visit attendance across time points. This indicates there was not an increase in clinic attrition. Given high attrition rates from adolescent obesity treatment programs, this preliminary finding of continued engagement in treatment is encouraging [9].

Social Media Engagement

All analyses were exploratory and conducted in the combined sample controlling for group effect, secondary to the sample size. Mean changes were observed at 12 weeks for all participants for weight in kilograms (odds ratio [OR] –1.01 [95% CI –6.1, 4.08]), BMI (OR –1.25 [CI –2.99, 0.49]), BMI-z-score (OR –0.03 [CI –0.1, 0.03]), depression (OR –1.69 [CI –4.96, 1.57]), quality of life (OR 3.84 [CI –2.63, 10.31]) and perceived social support (OR 3.46 [CI –1.06, 7.99]). Greater numbers of comments correlated with weight-loss at 12 weeks (*r*=–.633, *P*=.04) (Table 3).

Discussion

Principal Findings

All enrolled adolescents (n=13) completed this social media intervention and found the use as an adjunct to medical weight management feasible and acceptable. Adolescents enjoyed the social media group, found it that it kept them motivated, encouraged, accountable, and informed. More than half of the group wanted to have more in-person groups as part of an intervention. Participants remained engaged in the social media group and within the in-person clinic. Clinic attrition decreased during the intervention. Youth remained engaged in the social media group overall with more likes than comments. Increased engagement with comments was correlated with weight-loss and increased perceived social support. We developed a privacy and safety plan that met the requirements of the institutional review board, which included the use of a private/secret group and monitoring/screening of posts.

Comparison with Prior Work

Compared with prior studies, our pilot demonstrated lower clinic visit attrition rates (27%) vs 42-82% [6-8]. The addition of a social media support group addressed key factors identified by adolescents for attrition from obesity treatment: a lack of peer support, logistical challenges, poor expectations, and a lack of tailoring of treatment for adolescents [7,23]. Participants confirmed the role of social media on clinic attendance in our acceptability survey in which they indicated that the social media group influenced their clinic participation, motivation and compliance with behavior changes.

Despite the small size of our pilot group, the overall engagement in social media was high at 71% compared with studies using social media alone in older adolescents (41%) [11,18]. In order to achieve higher rates of engagement, we incorporated successful strategies from prior studies such as having an in-person group session for participants to meet one another at the beginning of the intervention, the use of a facilitator who provided constant reinforcement of participation according to Social Learning Theory, and utilized a “secret” group for privacy [15,24]. While polls were the most popular type of post in a study examining types of posts in adults, videos were the most popular post in this study [18]. Videos also included other adolescents, which may have encouraged participation. [25] Also similar to prior work we provided a US $25 monthly incentive to assist with the cost of mobile data for active participants [15]. Participants were incentivized for 3 posts and did not receive any additional incentives. Participant engagement was more than twice the incentivized amount (weekly mean=8.6 compared with requested 3 times per week). Additionally, youth were not incentivized to attend clinic visits.

To our knowledge, this is the first study to examine the influence of a social media support group on medical weight management engagement/attrition. Attrition from in-person clinic visits did not increase in our study compared to rates of 50% or more normally seen in this population. Our use of age-based adolescent peer groups may address attrition by providing adolescent tailored interventions and increasing perceived peer

support [26]. On the acceptability survey, participants indicated that the social media group influenced their clinic participation and reinforced what they learned in their medical weight management (100% [13/13]).

Inclusion of Parents/Family Members

Finding ways to incorporate parents/caregivers into the social media component will be important in next steps. Parents purchase the food for the home, provide transportation and financial support for physical activity, serve as role models of behavior and provide encouragement and support for behavioral modification [27-29]. In this study, parents attended clinic sessions with adolescents where goal setting was made at both the family and individual levels. During baseline and 12-week follow-up visits, parents of participants remained in a separate room to get to know one another. Parents expressed interest in a parent social media group. As parents are key agents of change, providing peer support on the parent level may also increase adolescent clinic attendance and should be explored in next steps.

Limitations and Strengths

Our study has both strengths and limitations. This single arm pilot study had a small sample size to determine feasibility. All enrolled participants completed this pre-post study. Although our sample size was small, it was racially and socioeconomically diverse. Heights and weights were objectively measured. Both quantitative and qualitative assessments of acceptability were used. Despite the small sample size, some significant associations were detected.

However, as this is a cross-sectional study, the associations found do not necessarily reflect causality. Furthermore, it is possible that participants in this sample had a higher level of intrinsic motivation which kept them engaged. The data from this pilot trial will inform the conduct of a larger randomized controlled clinical trial. Adolescents were incentivized to like or comment which could have increased social media engagement. Incentives did not increase for liking vs commenting, or for engagement above the required 3 times per week. Engagement was above the minimum requirement for incentivization. While the majority of peer support came from social media, we acknowledge that the two in-person visits (for measurements and to meet other group members) could have also influenced perceived social support. That being said, adolescents were not incentivized to attend clinic visits. Our findings cannot be extrapolated to other forms of social media. Facebook was the most popular form of social media in youth at the time of our study [13]. Although, not as popular with youth today, Facebook is still one of the most popular social media platforms used by adolescents [14]. That being said, other platforms should also be tested.

Other studies have found that social media engagement decreases over time [18,30]. It will be important to test the effects of a social media group longer term on attrition. Similar to prior studies, we measured engagement as a combination of likes and comments [18]. We acknowledge that commenting most likely reflects a higher level of engagement than liking as it requires reflection. This is also reflective of increased commenting as opposed to liking being associated with weight-loss. Finding ways to assist youth with interacting through comments is important for future interventions.

Conclusions

In summary, youth with severe obesity found social media support acceptable and useful as an adjunct to clinical care, and perceived it as helpful to remain motivated to attend medical weight management. Pilot results suggest social media groups may assist with decreasing clinic attrition rates and potentially contribute to successful weight management in this high-risk population.

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Authors' Contributions

EPP and CTB conceptualized and designed the study. DLH assisted with developing videos, other intervention materials, and moderating the group. EPP, CTB, and AG implemented the pilot group intervention. EPP, and ARG acquired the data. EPP, RHM, ZL analyzed data. EPP, CTB, ZL, and DBS interpreted the data. EPP drafted the initial manuscript. All authors critically reviewed the final manuscript for submission. The contents of this manuscript were presented in 2015 at the ObesityWeek annual meeting in Boston, MA.

Conflicts of Interest

None declared

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Abbreviations

BDI-II: Beck Depression Inventory II
BMI: body mass index
IWQOL-kids: Impact of Weight on Quality of Life Kids
MSPSS: Multidimensional Scale of Perceived Social Support
OR: odds ratio
CHOP: The Children's Hospital of Philadelphia

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Protocol

Improving Health-Related Quality of Life of Patients With an Ostomy Using a Novel Digital Wearable Device: Protocol for a Pilot Study

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Abstract

Background: Ostomy surgeries involving the placement of an ostomy bag (eg, colostomy, ileostomy, urostomy, etc) have been shown to have a negative impact on health-related quality of life. To date, no studies have been conducted examining what impact, if any, wearable biosensors have on the health-related quality of life of ostomy patients.

Objective: In the present study, we plan to assess the quality of life of ostomy patients using the Ostom-i alert sensor, a portable, wearable, Bluetooth-linked biosensor that facilitates easier ostomy bag output measurements. We hypothesize that using the Ostom-i alert sensor will result in an improved, ostomy-specific, health-related quality of life as compared to baseline measurement before the use of the sensor.

Methods: A total of 20 ostomy patients will be screened and recruited to participate in this prospective, observational, cross-over pilot study using an Ostom-i alert sensor for one month. The primary outcome of this study will compare ostomy-specific, health-related quality of life at baseline (prior to Ostom-i alert sensor use) to ostomy-specific, health-related quality of life after 2 and 4 weeks of Ostom-i use by utilizing the City of Hope Quality of Life Questionnaire for Patients with an Ostomy. Secondary outcomes of general health-related quality of life and adjustment to ostomy will be evaluated using the Medical Outcomes Study 36-item short form health survey and the Olbrisch Ostomy Adjustment Scale Short Form 2.

Results: The project was funded by the Department of Anesthesiology, Perioperative and Pain Medicine at Stanford University School of Medicine. Enrollment is currently underway and data analysis is expected to be completed in 2018.

Conclusions: Proposed benefits of mobile, internet-linked personal health monitors, such as the Ostom-i, include a reduction in the cost of care by reducing resource utilization and infection rates, improving patient-provider communication, reducing time spent as an inpatient as well as improved quality of life. Prior studies have demonstrated decreased health-related quality of life in patients with an ostomy bag. We aim to examine the extent to which the Ostom-i alert sensor affects the health-related quality of life of its users. The Ostom-i alert sensor has the potential to improve quality of life of users by giving them the freedom and confidence to partake in daily activities with the knowledge that they can check how full their ostomy bag is in a private, discrete manner.

Trial Registration: ClinicalTrials.gov NCT02319434; https://clinicaltrials.gov/ct2/show/NCT02319434 (Archived at WebCite at http://www.webcitation.org/6xhFDThmq)

(JMIR Res Protoc 2018;7(3):e82) doi:10.2196/resprot.7470

KEYWORDS

ostomy; quality of life; eHealth

Introduction

Background and Rationale

Ostomy surgeries such as colostomy (large bowel), ileostomy (small bowel), and urostomy (bladder), which require the use of an ostomy bag either temporarily or permanently, may result in a change in health-related quality of life as patients adjust to life with their ostomy [1-4]. While the average wear time of an ostomy bag in the United States has been reported to be 4.8 days, up to 40%-60% of stoma will never be reversed and many patients with severe inflammatory bowel disease or advanced colorectal cancer may wear an ostomy bag long-term [5-7]. Colostomies requiring an ostomy bag are common in patients with colorectal cancer, which as of 2016 was the second most commonly diagnosed cancer in men and the third most commonly diagnosed cancer in women in the United States [8]. In 2016, the number of newly diagnosed cases of colorectal cancer was 724,690 and 727,350 in men and women, respectively. Estimates suggest that there will be 910,190 newly diagnosed cases of colorectal cancer in men and 885,940 new cases in women in 2026. It has been reported that colostomy surgery is more common in patients with rectal cancer (29%) than for patients with colon cancer (12%) [8].

While ostomy surgery may improve health-related quality of life by reducing disease burden, it can often decrease general quality of life in other ways. Common themes in health-related quality of life for ostomy patients include factors such as social adjustment, fatigue, pain, leakage, physical functioning, changes in clothing, and diet [9]. A significant concern of patients with an ostomy bag is return to work, work efficiency, and worries about social and personal life due to the presence of the ostomy bag [10]. While factors such as coping, acceptance, and availability of ostomy specialist to patients have been identified as methods to improve health-related quality of life of ostomy patients, there have been few technological advancements geared towards improving health-related quality of life of individuals with an ostomy bag [11,12]. Existing portable technologies are primarily focused on the cleaning of the ostomy bag, such as a 2004 patent allowing the user to clean the bag more completely and with greater ease; however, no mobile health (mHealth) technologies currently exist to alert the wearer as to the fullness of their ostomy bag [13].

We are conducting a prospective trial to evaluate the impact of the Ostom-i alert sensor on short-term, health-related quality of life of ostomy patients. The Ostom-i alert sensor is a wearable device intended to make life easier for patients with ostomy bags by allowing for easier output measurements and anticipation of bag changes via a Bluetooth connection to their mobile smart phone. Using the City of Hope Quality of Life Questionnaire for a Patient with an Ostomy (CoH-QOL-Ostomy), we determine to what extent, if any, the Ostom-i sensor affects health-related quality of life of the user [14].

Objective

We hypothesize that using the Ostom-i alert sensor will result in an improved ostomy-specific, health-related quality of life as compared to baseline measurement before the use of the sensor. We intend to assess the change in ostomy-specific health-related quality of life, with the Ostom-i alert sensor. We will use the City of Hope Quality of Life Questionnaire for Patients with an Ostomy. Secondarily, we aim to measure the change in general health-related quality of life and ostomy adjustment using the Medical Outcomes Study 36-item short form health survey (SF-36) and the Olbrisch Ostomy Adjustment Scale Short Form 2 (OAS-SF2), respectively [15,16].

Methods

Participants, Interventions, and Outcomes

Study Setting

Patient recruitment will occur at the Stanford University Medical Center. Data analysis and all other matters related to manuscript drafting will occur at the Stanford University School of Medicine. Both settings are located in Palo Alto, California within Santa Clara County.

Eligibility Criteria

Recruited patients will be required to meet the eligibility criteria outlined in Textbox 1. Any participants who do not meet our inclusion criteria will be excluded from the study. Our decision to exclude participants who have had an ostomy for less than 6 months was based off the work of Husain and Cataldo [6], who determined that 93% of ostomy-related complications occur within the first six months after ostomy surgery. Furthermore, they determined that psychological adjustment to the ostomy occurs 6 to 10 weeks after surgery, implying that participants in our population will be fully psychologically adjusted to their ostomy [6]. We are limiting our study to patients with colostomy, ileostomy or urostomy. Large urostomy bags will not work with the Ostom-i sensor and thus individuals with large urostomy bags (>9 cm) will be excluded from the study (see Textbox 1 for a complete list of patient inclusion and exclusion criteria).

Recruitment

Participants will be recruited from the Stanford University Medical Center via word of mouth, online advertisements, flyers posted in the hospital as well as referrals from ostomy physicians and nursing staff. Patient recruitment will be facilitated with the help of a number of ostomy nurses at Stanford. Persons interested in the study will be directed to a Web page which includes information about the study sensor, what study participation involves, and a link to a complete online eligibility survey. Participants will not receive monetary compensation for participating in this study, but will be able to keep the Ostom-i sensor which retails for US $125.

Textbox 1. Study eligibility inclusion and exclusion criteria.

Inclusion Criteria

- Ability to read and understand English
- 18-80 years of age
- Current use of an ostomy bag
- Use of an ostomy bag for 6 months or more
- Use of an ostomy bag for the duration of the study
- Access to and ability to use an iOS or Android smartphone, iPod Touch or tablet

Exclusion Criteria

- Ostomy bag other than colostomy, ileostomy or urostomy
- Urostomy bag larger than 9 cm

Screening

Participant screening will occur either online via the Web page, in person, or over the phone. The online screening survey will use Stanford Medicine Qualtrics to collect and analyze data on eligible persons [17].

Randomization

Patients will serve in both the control and interventional arms of this cross-over pilot study. A cross-over design is advantageous for this pilot study as it allows patients to serve as their own control, therefore variances attributable to confounding factors [18,19]. Once eligibility is confirmed, consent will be obtained and the baseline survey will be given (CoH-QOL-Ostomy, SF-36 and OAS-SF2). After completion of the baseline survey, the participant will be given their Ostom-i alert sensor along with a video tutorial which explains how to use the device.

Intervention

Once completing the baseline survey, patients will enter the intervention arm of the study where they will receive an Ostom-i sensor which they will use over the course of 4 weeks. Two and 4 weeks after receiving the sensor, primary and secondary outcome measures will be assessed. The Ostom-i is a flexible, Bluetooth-linked sensor that attaches to the patient's ostomy bag. The sensor portion of the Ostom-i device is a flexible potentiometer produced by Spectra Symbol [20]. The sensor determines the level of the ostomy bag based on the angle of flex it experiences and automatically adjusts when the user is laying down or standing up. The sensor can be adjusted in size from 7 cm to 9 cm to fit a variety of ostomy bag sizes. Data collected by the sensor is sent via Bluetooth to the user's iOS or Android device and provides alerts informing the wearer of the level of their ostomy bag (Figure 1 and 2).

Participant Timeline

Participants will retake all 3 surveys after 2 and 4 weeks of device use as previous validation studies of these surveys have used 2-4 week intervals [16,21]. Following completion of the week 4, survey participant involvement in the study will end (see Figure 3 for the study flowchart). Participants will have the option to take the week 2 and week 4 surveys either in person at the hospital or at home, using a paper-based or online format.

Primary Outcome Measures

The modified CoH-QOL-Ostomy is an ostomy-specific, health-related quality of life instrument with four dimensions. The four dimensions—physical, psychological, social, and spiritual well-being are defined in Table 1. Ostomy-specific, health-related quality of life is calculated by summing scores for each question then dividing by the total number of questions (ie, 43 questions). Total scores for each of the four dimensions are calculated by adding scores on all dimension items and dividing by total number of dimension items. Ostomy-specific, health-related quality of life will be measured at baseline prior to receiving the Ostom-i device, then again after 2 and 4 weeks of device use.

Secondary Outcome Measures

Two secondary outcome measures will be utilized including the SF-36 and the OAS-SF2. The SF-36 is a commonly used general health-related quality of life instrument. In this study, it will be used to compare ostomy-specific, health related quality of life to general (nonostomy-specific) health-related quality of life. The OAS-SF2 is used to examine subjective response to ostomy as well as psychological adjustment to the ostomy.

Null Hypothesis and Sample Size

Our null hypothesis states that there will be no improvement in ostomy-specific, health-related quality of life as measured by the CoH-QOL-Ostomy, compared to baseline measurements prior to sensor use. To calculate the desired sample size to test our null hypothesis, the following paired *t*-test formula was used:

$$n=[\sigma_d^2(Z_{power}+Z_{\alpha/2})^2]/\mu_d^2$$

where our mean and variance is based on the work of Gemmill et al [22], who examined 307 ostomy patients and reported a mean of 8.0 (SD 1.7) for the social well-being dimension within the CoH-QOL-Ostomy, with 80% power and 95% confidence [22]. Our sample size calculation (n=16 for a 15% difference in the dimension of social well-being) was again based on Gemmill et al [22], who reported social well-being to have a higher mean (8.0) than overall quality of life (mean 7.7).

Figure 1. Screenshots from the Ostom-i patient app showing status, hydration, and graph.

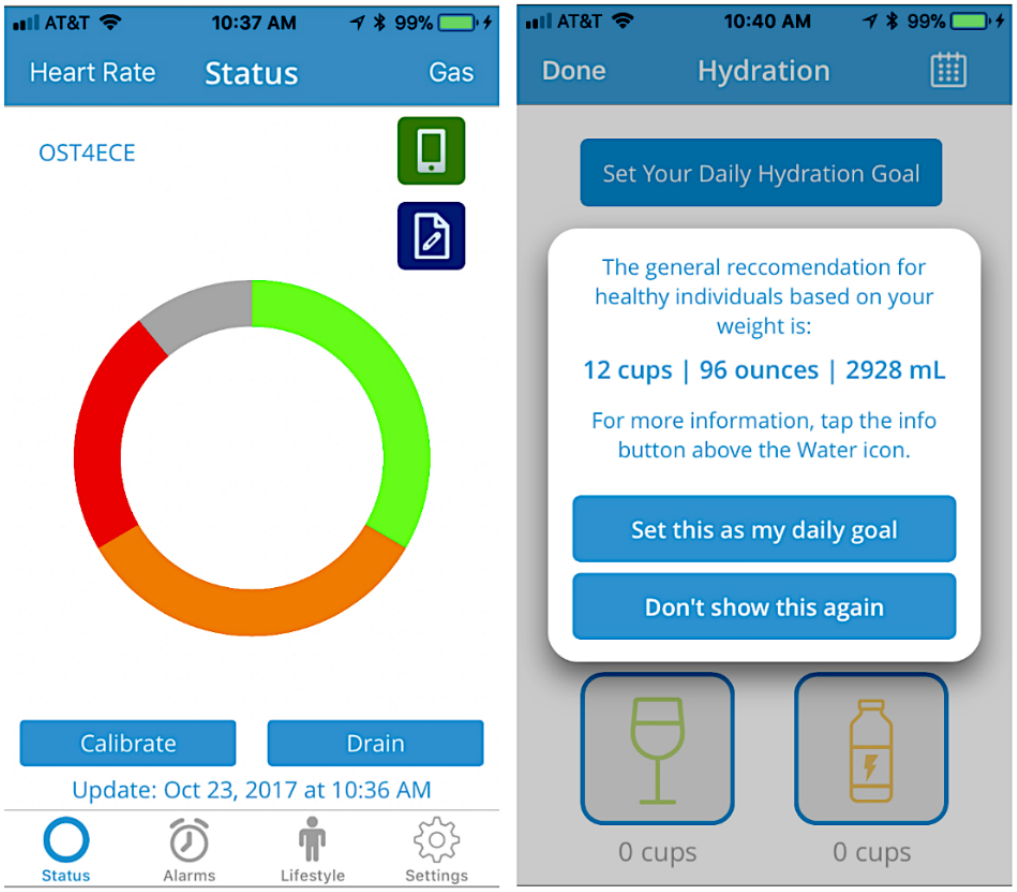

Figure 2. Screenshot from the Ostom-i patient app showing user interface, status, hydration, and graph.

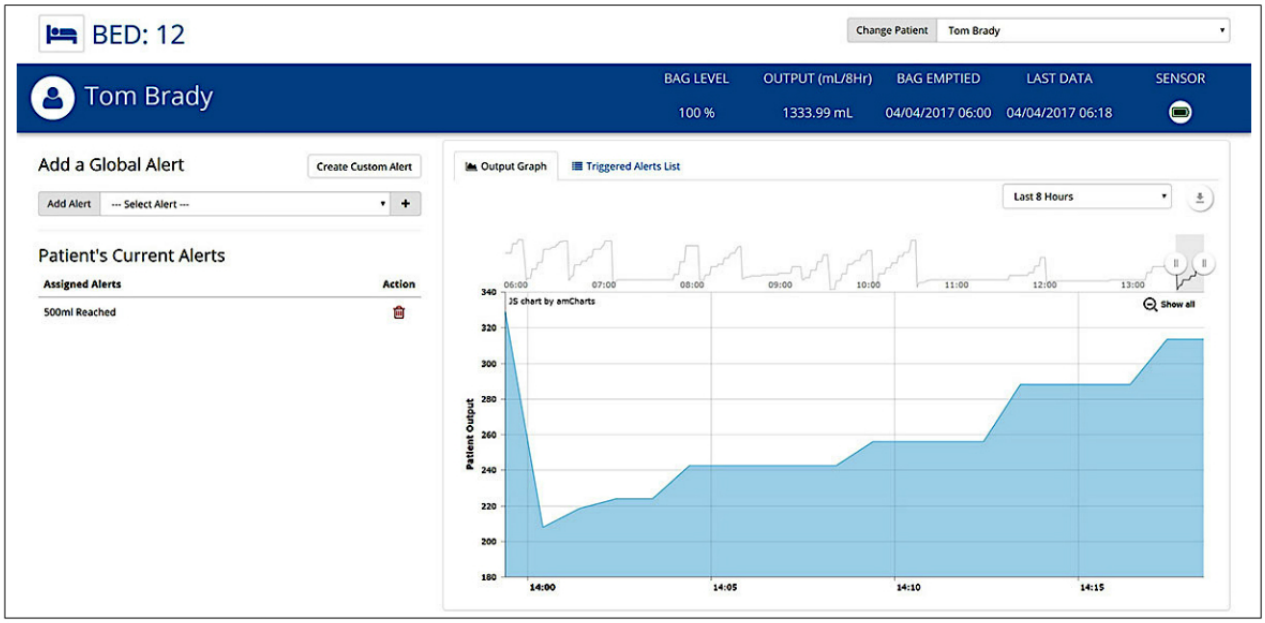

Figure 3. Participant flowchart. QOL-Ostomy: Quality of Life Questionnaire for a Patient with an Ostomy.

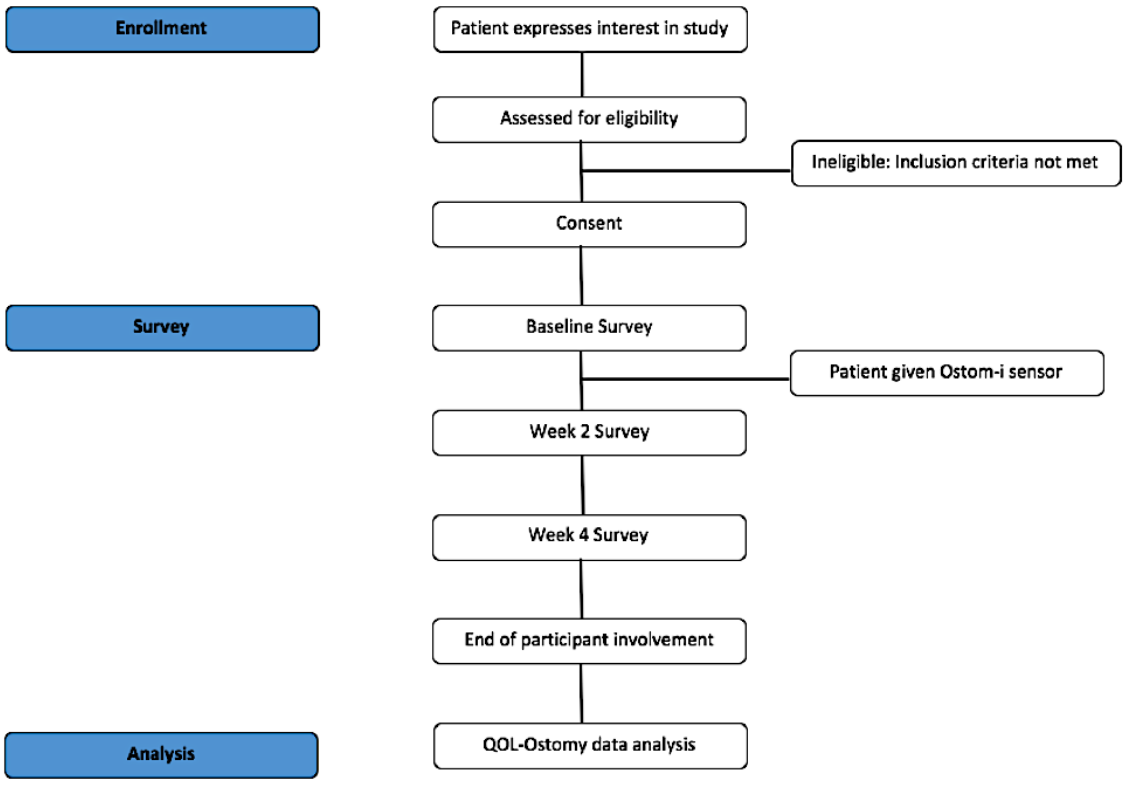

Table 1. City of Hope quality of life dimension definitions obtained from Gemmill et al [22].

Dimension	Definition
Physical well-being	Physical symptoms and functional ability
Psychological well-being	Emotional components of the illness including positive as well as negative aspects
Social well-being	Role of the patient with the family and society including occupational, sexual, and personal relationships
Spiritual well-being	Religious aspects and existential concerns

Table 2. Desired sample size number (N) based on % difference.

% Difference	Absolute change in dimension of well-being (μd)	Sample size (N)
10	0.8	35
15	1.2	16
30	2.4	4
40	3.2	2

Furthermore, Gemmill et al [22] report a lower SD for the dimension of social well-being (SD 1.7) as compared to physical well-being (SD 1.8), psychological well-being (SD 1.9), and spiritual well-being (SD 2.3). Thus, we chose to base our sample size calculation on the dimension of social well-being. With a sample size calculation of n=4 for 30% difference, we are concerned that our results would lack generalizability. Therefore, by increasing our sample size to 20, we hope that our results will be more generalizable and may help account for a potential 20% attrition rate during recruitment (Table 2).

Trial Design

The design of our pilot study is a prospective, single group, observational, prepost cross-over trial. Ethical approval was obtained from the Institutional Review Board at Stanford University (Protocol #32211). This study is registered at ClinicalTrials.gov (NCT02319434).

Data Collection, Management, and Analysis

Primary Outcome Data Collection Methods

Our primary outcome, change in ostomy-specific, health-related quality of life from baseline, will be measured using the modified CoH-QOL-Ostomy. This survey was designed and studied for reliability and validity by Grant et al [14] with an overall questionnaire alpha of .95, suggesting strong consistency. The survey can be divided into 6 sections: 1) social adjustment to ostomy (coefficient alpha=.90, correlation to single quality

of life item: *r*=.44, *P*>.001); 2) general quality of psychological well-being (coefficient alpha=.83, correlation to single quality of life item: *r*=.76, *P*>.001); 3) general quality of physical well-being (coefficient alpha=.88, correlation to single quality of life item: *r*=.39, *P*>.001); 4) disease-specific effects on physical well-being (coefficient alpha=.77, correlation to single quality of life item: *r*=.24, *P*>.001); 5) general quality of spiritual well-being (coefficient alpha=.81, correlation to single quality of life item: *r*=.51, *P*>.001); and 6) disease specific effects on psychological well-being (coefficient alpha=.82, correlation to single quality of life item: *r*=.38, *P*>.001) [14]. This validated survey has successfully been used by number of studies examining ostomy-related quality of life [22-27].

Secondary Outcome Data Collection Methods

Our secondary outcomes, general health-related quality of life and psychological adjustment to the ostomy, will be measured using the SF-36 and the OAS-SF2. The SF-36 involves a scale which measures 8 health profiles including physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). The SF-36 also yields physical and mental health summary measures and is scored using a Likert scale [28]. Furthermore, the SF-36 has been validated and was found to be reliable across a diverse group of patients with various physical and psychological issues [28,29]. Each of the 8 dimensions of the SF-36 have been found to have a Cronbach alpha statistic greater than the minimum standard of .70; PF (alpha=.90), SF (alpha=.76), RP (alpha=.88), RE alpha=.80), MH (alpha=.83), VT (alpha=.85), GH (alpha=.78), and BP (alpha=.82) suggesting strong internal-consistency and reliability [28,30,31].

Adjustment to ostomy will be evaluated using OAS-SF2 [16]. The OAS is a subjective scale specific to persons with an ostomy, and examines social, psychological, and sexual functioning adjustment to living with an ostomy. The OAS is measured on a 6-point Likert scale and contains 34 items. Cronbach's alpha for the scale was calculated at alpha=.85 with a test-retest reliability at *r*=.72 and later confirmed in studies of Swedish, Norwegian, and Chinese patients with an ostomy [32-34]. Two, 17-question short forms (short form 1 and short form 2) were created by Olbrisch based on the original 34 questions. It was determined that each short form could be used independently without compromising reliability or validity of the 34-question-long form (*r*=.96). Furthermore, short form test-retest consistency and reliability was determined to be *r*=.69 [21].

Data Management

Survey assessments will be collected via Stanford Qualtrics (Qualtrics, Provo, UT) survey or pen-and-paper [17]. Data will be entered into the Stanford Research Electronic Data Capture (REDCap) databases (Vanderbilt, Nashville, TN) [35]. All data will be entered and de-identified by trained staff and undergo data quality and accuracy checks.

Statistical Analysis

Data will be presented as mean (SD). Changes between pre- and postintervention quality of life will be assessed using a dependent participant's paired *t*-test with 95% confidence interval. Depending on participant retention throughout the course of the study, we may choose to use mixed model regression analysis which would allow us to incorporate incomplete data sets from participants who might not complete the study. Furthermore, we also may choose to use repeated measures analysis of variance to examine differences in population mean scores over the 3 study sessions.

Monitoring

Data Monitoring

A data monitoring committee (DMC) will not be used in this study. In accordance with the United States Food and Drug Administration Title 21 (21 Code of Federal Regulation 812) and the Stanford University Institutional Review Board (IRB), the Ostom-i alert sensor was not deemed to pose a significant risk to study participants [36]. Furthermore, there is an overall low level of concern for patient safety with the Ostom-i alert sensor. Given the short timeframe of the study, a DMC may not be practical and it is not likely that a DMC will aid in improving the scientific validity of this study [37]. This study is in full compliance with the guidelines outlined by ClinicalTrials.gov.

Risk and Side Effects

Due to the minimal intervention in this study, participants are at very low risk for adverse events. Should any adverse events occur, they will be systematically logged and reported to ClinicalTrials.gov. Adverse events involving the ostomy site or the ostomy bag, which are not related to the Ostom-i alert sensor, will be directed to the study participant's gastroenterologist.

Auditing

This study is being conducted independently from the Ostom-i alert sensor parent company, 11 Health and Technologies, LLC. 11 Health and Technologies, LLC will not audit any aspect of the study. Due to the short duration of this study (12 months), auditing is not deemed a necessary component of our protocol.

Ethics and Dissemination

Research Ethics Approval and Protocol Amendments

Ethical approval was obtained from the IRB at Stanford University (Protocol #32211). Any amendments made to the study protocol will be immediately reported to the IRB at Stanford University as well as to ClinicalTrials.gov.

Consent or Assent and Confidentiality

Informed consent will be obtained from study participants by study research personnel prior to in-person baseline evaluation. Phone conversations and in-person visits will take place in a private room to protect patient privacy. Data collected by the Ostom-i alert sensor will remain on the participant's personal device (iPhone, Android, tablet etc) for the duration of the study. Meetings and phone calls will not be recorded and will only involve necessary study staff.

Data collected from participants will include demographic information such as names, telephone numbers, addresses, birthdates, email addresses, illness/diagnosis, gender, age, height, weight, ethnicity, marital status, records of waste output as measured by the Ostom-i alert sensor as well as results from the CoH-QOL-Ostomy, SF-36, and Olbrisch's Ostomy Adjustment Scale. Demographic and survey data will be collected and stored in a secure database on an encrypted computer.

Participants will be assigned a random, 2-digit numerical identifier which will be stored in a locked safe in the laboratory. Collected data will also be stored in the secure REDCap database and necessary data transfer will occur using secure methods (eg, emails marked as secure). All aspects of data security in this study are in full compliance with the Stanford University Office of Audit, Compliance, Risk and Privacy.

Access to Data

Final trial data will only be available to study research personnel. All necessary demographic and results data will be uploaded to ClinicalTrials.gov in accordance with their rules and regulations.

Ancillary and Posttrial Care

Should study staff identify health issues in participants over the course of the study, they will be immediately referred to their primary care physician or gastroenterologist. Furthermore, study physicians will be available to answer study participant questions. No poststudy follow-up of participants will occur.

Dissemination Policy

The study authors plan to publish collected data in a peer-reviewed journal (to be determined at a later date). Furthermore, this study is fully compliant with the guidelines set forth by ClinicalTrials.gov and as such all necessary information will be made available in a timely manner. All listed authors and/or contributors are compliant with guidelines outlined by the International Committee of Medical Journal Editors for author inclusion in a published work. Public access to the study protocol and other necessary aspects will be made available through our ClinicalTrials.gov identifier (NCT02319434).

Results

The project was funded by the Department of Anesthesiology, Perioperative and Pain Medicine at Stanford University School of Medicine. Enrollment is currently underway and data analysis is expected to be completed in 2018.

Discussion

The Ostom-i alert sensor is a novel, wearable sensor that allows for easier output measurements and anticipation of ostomy bag changes via Bluetooth connection to a mobile phone. The Ostom-i alert sensor has the potential to improve quality of life of users by giving them freedom and confidence to partake in daily activities with the knowledge that they can check how full their ostomy bag is in a private, discrete manner. To examine the extent to which the Ostom-i alert sensor affects quality of life, 20 participants will be recruited to wear the Ostom-i alert sensor for 1 month. Health-related quality of life will be determined by using the CoH-QOL-Ostomy. This survey will be given at baseline to individuals who have had an ostomy bag for 6 months or longer, then again 2 and 4 weeks after beginning with the Ostom-i sensor. Ultimately, we anticipate that the Ostom-i alert sensor may improve health-related quality of life as measured by the CoH-QOL-Ostomy.

Proposed benefits of mHealth technologies, such as the Ostom-i, include a reduction in the cost of care by lowering resource utilization and infection rates, improving patient-provider communication, and reducing time spent as an inpatient [38-40].

A number of mHealth technologies, such as the Ostom-i alert sensor have recently been released including devices, such as the Withings Blood Pressure Monitor, the Sanofi iBGStar Blood Glucose Meter, and the AliveCor Mobile ECG. While these devices have all been validated in the peer-reviewed literature, few studies have examined to what extent, if any, they reduce burden on health care systems [41-43].

A 2006 study by Leijdekkers and Gay [44] analyzed a novel, cell phone–linked heart monitor and suggest that by visualizing their personal cardiac data in real time, users are less likely to visit the hospital, which in turn reduces hospital staff workload, reduces costs of patient-provider communication, and improves patient self-care [44]. Free et al [45] examined the literature and found 42 controlled trials of mobile technology–based systems aimed at improving health care service delivery [45]. They report only a modest benefit towards clinical management and diagnosis with the use of mobile technologies.

Bloss et al [46] examined the extent to which the Withings Blood Pressure Monitor, the Sanofi iBGStar Blood Glucose Monitor, and the AliveCor Mobile ECG affected health care resource utilization measured by both health insurance claims and hospital visits. In their study, participants were split into control and intervention arms where those in the intervention arms utilized one of the 3 aforementioned technologies based on their health care needs. No difference between groups was observed for office visits (P=.46), inpatient stay (P=.82), emergency room visits (P=.06), or pharmacy claims (P=.60). Furthermore, no difference in self-efficacy change was observed between control and intervention group (P=0.85), and no difference in filed insurance claims between the 2 groups was observed (P=0.62) [46].

While future studies may examine whether mHealth technologies, such as the Ostom-i alert sensor, influence cost of care or duration of hospital stay, the purpose of the present study is to examine the extent to which the Ostom-i alert sensor affects the health-related quality of life of its users. To our knowledge, no such studies have been conducted, making this a unique undertaking.

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Conflicts of Interest

The authors have no conflicts of interest to report and will not be rewarded in any way, either financially or other by 11 Health Technologies, LLC. Ostom-i alert sensors will be donated by 11 Health Technologies, LLC for use by enrolled study participants only.

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Abbreviations

BP: bodily pain
CoH-QOL-Ostomy: City of Hope Quality of Life Questionnaire for a Patient with an Ostomy
DMC: data monitoring committee
GH: general health perceptions
MH: mental health
OAS-SF2: Ostomy Adjustment Scale Short Form 2
PF: physical functioning
RE: role limitations due to emotional problems
REDCap: Research Electronic Data Capture
RP: role limitations due to physical health problems
SF: social functioning
SF-36: Medical Outcomes Study 36-item short form health survey
VT: vitality

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Protocol

Safety, Quality, and Acceptability of Contraceptive Subdermal Implant Provision by Community Health Extension Workers Versus Nurses and Midwives in Nigeria: Protocol for a Quasi-Experimental, Noninferiority Study

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Abstract

Background: As part of its Family Planning 2020 commitment, the Nigerian government is aiming for a contraceptive prevalence rate of 36% by 2018, and in 2014, approved a policy to allow community health extension workers (CHEWs), in addition to doctors, nurses, and midwives, to provide contraceptive subdermal implants. There is a lack of rigorous evidence on the safety of long-acting reversible contraceptive provision, such as implants, among lower cadres of health providers.

Objective: This study aimed to compare implant provision by CHEWs versus nurses and midwives up to 14 days post insertion.

Methods: The quasi-experimental, noninferiority study will take place in public sector facilities in Kaduna and Ondo States. In each state, we will select 60 facilities, and from these, we will select a total of 30 nurses and midwives and 30 CHEWs to participate. Selected providers will be trained to provide implant services. Once trained, providers will recruit a minimum of 8125 women aged between 18 and 49 years who request and are eligible for an implant, following comprehensive family planning counseling. During implant insertion, providers will record data about the process and any adverse events, and 14 days post insertion, providers will ask 4410 clients about adverse events arising from the implant. Supervisors will observe 792 implant insertions to assess service provision quality and ask clients about their satisfaction with the procedure. We will conclude noninferiority if the CI for the difference in the proportion of adverse events between CHEWs and nurses and midwives on the day of insertion or 14 days post insertion lies to the right of −2%.

Results: In September and October 2015, we trained 60 CHEWs and a total of 60 nurses and midwives from 12 local government areas (LGAs) in Kaduna and 23 LGAs in Ondo. Recruitment took place between November 2015 and December 2016. Data analysis is being finalized, and results are expected in March 2018.

Conclusions: The strength of this study is having a standard care (nurse and midwife provision) group with which CHEW provision can be compared. The intervention builds on existing training and supervision procedures, which increases the sustainability and scalability of CHEW implant provision. Important limitations include the lack of randomization due to nurses and midwives in Nigeria working in separate types of health care facilities compared with CHEWs, and that providers self-assess their own practices. It is unfeasible to observe all procedures independently, and observation may change practice. Although providers will be trained to conduct implant removals, the study time will be too short to reach the sample size required to make noninferiority comparisons for removals.

Trial Registration: ClinicalTrials.gov NCT03088722; https://clinicaltrials.gov/ct2/show/NCT03088722 (Archived by WebCite at http://www.webcitation.org/6xIHImWvu)

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KEYWORDS

drug implants; contraceptive prevalence; contraception; delivery of health care; family planning services; task shifting, Nigeria; community health workers; long-acting reversible contraception

Introduction

In 2012, an estimated 222 million women had an unmet need for modern contraception [1]. Meeting this need would avert an estimated 218 million unintended pregnancies and 118,000 maternal deaths [1]. Nigeria has a large (191 million in 2017) and rapidly increasing population [2] and a high maternal mortality ratio, estimated to be 576 per 100,000 live births in 2013 [3]. In 2013, 15% of currently married women aged between 15 and 49 years were using some method of contraception, a figure considerably lower than the global (63%) and sub-Saharan Africa (27%) estimates for the same year, and 16% had an unmet need for contraception [3].

There are many inequities in contraceptive access, with lower levels of use among women in rural and remote areas, and among those who are poorer, less educated, and younger [4]. In Nigeria, contraceptive prevalence is just 9% in rural areas versus 27% in urban areas [3]. In addition, the most effective contraceptive methods are often the most difficult to access [5]. Long-acting reversible contraceptives (LARCs), such as intrauterine devices (IUD) and implants, are the most effective reversible methods of contraception, with failure rates of between 0.05% and 0.8% in the first year of use (contraceptive pills have a failure rate of 8%) [6]. LARCs also have lower discontinuation rates than short-term methods (such as the pill, injectable, and condom) [5] and generally have high user satisfaction [7]. In sub-Saharan Africa, unlike Asia and North America, short-term contraceptive methods dominate [8]. In Nigeria in 2013, 9.8% of currently married women were using a modern method of contraception, and most (7.1%) were using short-term methods; just 1.1% were using an IUD and 0.4% an implant [3].Contraceptive implants consist of flexible matchstick-sized rods, inserted below the skin on the nondominant upper arm. They release small amounts of progestin hormone to prevent pregnancy for 3 to 5 years [9]. Insertion is quick and does not require pelvic examinations or laboratory tests. Complications are rare (although may include infection at the insertion site, expulsion, or difficult removal), and once inserted, implants require no regular action by the user or health system [6].

Key barriers to LARC use include lack of availability (of method or skilled providers), perceived cost, and misperceptions about risks and benefits [5,10,11]. Low LARC availability has been driven by lack of trained providers and, in the case of implants, high commodity costs [12]. In recent years, costs have fallen [13] but low provider numbers remain: the African continent faced an estimated shortage of 4.2 million health care workers in 2013 [14]. Shortages are more acute in rural areas: whereas the national average number of doctors per 100,000 population in Nigeria was estimated to be 12 in 2007, in the more rural northwest and northeast, the ratio was only 4 [15]. Task-shifting or task-sharing is a strategy recommended by the World Health Organization (WHO) to address health worker shortages [16]. This involves expanding specific tasks, where appropriate, from highly qualified health workers to those with shorter training and fewer qualifications [17]. Task-sharing of implant services has been implemented in several African countries [12]. After a policy change allowed nurses, as well as physicians, to provide implants in Tanzania, insertion rates increased from around 10,000 per quarter in 2007 to more than 20,000 in 2009 [18], and in Ethiopia, 15,000 rural community health extension workers (CHEWs) have been trained to insert implants (removals are still handled by higher-level cadres) [12].

In 2012, Nigeria's Honorable Minister of Health announced a goal to increase contraceptive prevalence to 36% by 2018 [19]. The priority activities are to train more health care workers to provide injectables, implants, and IUDs [19] and to change national policy to permit CHEW provision of implants [20]. CHEWs are health care staff who undergo a 36-month course in a training institution approved by the Community Health Practitioners Registration Board of Nigeria [20]. CHEWs may be located in larger urban health centers, with nurses and midwives, or at smaller health centers, working alone or with another CHEW. In a pre- and posttest pilot study conducted in Sokoto and Bauchi States in Nigeria to assess the feasibility of training CHEWs to provide implants [21], 166 CHEWs were trained for 2 to 3 weeks, and they inserted 3588 implants in 151 health facilities over 6 months. Most CHEWs achieved competency in implant insertions after insertions with 4 to 5 clients. Clinical observations revealed that CHEWs performed implant insertion tasks correctly at least 90% of the time for 16 out of 19 checklist items. The amount of information that CHEWs provided clients increased between baseline and end

line, and over 99% of surveyed clients reported being satisfied with CHEWs' services.

Making implants more widely available could reduce the unmet need and contribute toward achieving the ambitious 2020 contraceptive prevalence rate goals (the percentage of women of reproductive age who are married or in union and are currently using or whose sexual partner is currently using a modern method of contraception) set by many countries in Africa and elsewhere at the family planning (FP) summit in 2012 [22]. A systematic review of the effectiveness and safety of task-sharing for the delivery of injectable contraceptives, contraceptive implants, IUDs, tubal ligation, and vasectomy in low- and middle-income countries found little or no difference between cadres, but admitted that only limited conclusions could be drawn from the small number of eligible studies [23]. The conclusion of this review and the recent policy change in Nigeria mean that there is opportunity and need to evaluate the safety, quality, and acceptability of implant services provided by CHEWs in Nigeria.

Methods

Study Design, Aim, and Objectives

The aim of this quasi-experimental, noninferiority study was to compare insertion of contraceptive implants (Implanon Classic and Jadelle; Table 1) by CHEWs with nurses and midwives in Nigeria.

The primary objective was to compare the safety of implant insertions by CHEWs with that of midwives and nurses on the day of the procedure and up to 14 days post insertion. Secondary objectives were to: (1) compare the quality of implant insertions by CHEWs with that of midwives and nurses; (2) compare client acceptability of implant insertions by CHEWs with that of midwives and nurses; and (3) assess acceptability of CHEW provision of implants to other health staff, clinic managers, and other key individuals such as policy makers.

For the purpose of this study, *safety* refers to implant insertions that minimize risk and harm to service users. We hypothesize that implant provision by CHEWs will be as safe and of high quality as provision by existing cadres of implant providers. Safety will be assessed by comparing rates of any adverse events (ie, those with a minor, moderate, or severe impact on a woman's health) at the time of the procedure, or up to 14 days post insertion (Table 2). As the study is evaluating the provider and not the method itself, method-related adverse events such as hormone-related changes to menstruation pattern, headaches, and nausea will not be recorded; neither will the study examine the effectiveness of the method.

We define *quality* as the degree to which a provider or facility meets certain objective and subjective levels of health care delivery standards. The term covers all aspects of clinical service provision such as correct insertion, infection prevention, and disposal procedures, as well as pre- and post counseling and taking a client-centered approach. We define *acceptability* as the level of satisfaction experienced with the service received (in the case of the client) and the level of satisfaction with this aspect of the job (in the case of the provider).

Study Implementation

This study is a partnership between Marie Stopes International (MSI); Marie Stopes International Organisation Nigeria (MSION); the Federal Ministry of Health of Nigeria (FMOH); Kaduna and Ondo State Ministries of Health, Nigeria; the WHO's Department of Reproductive Health and Research Geneva; and the University of Ibadan, Nigeria. Clinical training and research components will be conducted by MSI and MSION. MSION established its first clinic in Abuja in 2009 and now serves women in 25 states. Its mission is to provide reliable information to women about their FP options and to improve their access to FP methods. MSION is one of the only providers of LARCs in Nigeria. Services are delivered through clinics, mobile outreach teams, a social franchise network of private providers, and partnerships with government providers.

Site and Provider Selection

The study will take place in public sector facilities in 2 Nigerian states, 1 in the north (Kaduna) and 1 in the south (Ondo). The north and south of Nigeria differ in religious beliefs, contraceptive prevalence rate, and availability of health care providers, making it necessary to generate evidence in each context. We will purposively select local government areas (LGAs) in Kaduna and Ondo States for study participation by excluding LGAs with overlapping interventions and, given the extensive supervision needs of the study, hard-to-reach LGAs.

Facilities will be eligible if they provide referral services on site or are located within 20 km of a referral facility, in case of adverse events resulting in the need to refer clients; if there is a provider interested in participating in the study who expects to be in the facility for the 12-month period of client recruitment; and if the facility has been providing FP in the previous 3 years and does not currently provide implants. Larger urban centers staffed by nurses, midwives, and CHEWs and smaller rural health centers staffed by a nurse or midwife only will be eligible for inclusion.

A total of 60 facilities will be selected in each state from eligible facilities, yielding a total of 120 facilities. Where there are more than the required number of eligible facilities, simple random sampling will be used to select facilities for inclusion. At least 30 nurse or midwife-led facilities will be selected in each state to allow inclusion of 30 nurses and midwives in the study. The remaining 30 facilities will include as many CHEW-led facilities as possible. From each CHEW-led facility, 1 CHEW will be trained, and 1 nurse or midwife or 1 CHEW will be trained from each nurse or midwife-led facility. The providers trained will be the individuals responsible for providing FP services at their facility.

Table 1. Details of implant brands to be included in the study.

Product	Composition	Labeled duration of use	Format
Jadelle	150 mg levonorgestrel, 2 rods	5 years	2 rods, separate disposable trocar
Implanon Classic	68 mg etonorgestrel, 1 rod	3 years	1 rod preloaded in trocar

Table 2. Implant insertion adverse events to be recorded.

Description of adverse reaction	Day recorded relative to procedure
Anaphylactic reaction to the implant	0
Implant insertion unsuccessful on first or second attempt	0
Implant breaks	0
Palpitations resulting from the local anesthetic	0
Expulsion of implant	14
Paresthesia due to neural damage (numbness, tingling, tickling, pricking, or burning sensation at implant site)	14
Pain post procedure for >1 week and requires further outpatient observation and medical intervention	14
Infection	0
Local redness swelling	14
Discharge	14
Fever	14
Scarring	14
Hematoma or bruising requiring medical intervention	0 and 14
Bleeding around the injection area	0 and 14
Other adverse reaction requiring medical treatment or resulting in long-term incapacity or fatality	0 and 14

Intervention Implementation

The intervention will have 4 phases, which are discussed below.

Clinical Supervisor Training

A total of 12 clinical supervisors (qualified nurses or midwives with extensive experience of implant service provision) will be trained over 3 days. Training will cover how to train study providers to provide implants, clinical supervision of study providers, and the research study and data collection procedures.

Provider Training in Implant Provision and the Research

Clinical supervisors will train providers on counseling and on insertion and removal of Implanon Classic and Jadelle. Training will comprise classroom and clinic components and include a written test. Training will be based on the FMOH's competency-based training package for LARCs. This involves working with providers at different levels to bring them up to the same level, and so the number of days of training can vary [24]. The implant clinical training materials, previously only used to train nurses and midwives, will be reviewed and adapted if necessary for CHEWs. Training will be free for providers.

All providers will be trained on the study protocol for managing adverse events, which is based on MSI's adverse event standard operating procedures. The protocol details when to refer clients to a higher-level provider, particularly important for CHEWs who may be working in clinics without a higher-level provider, and adverse event support and reporting mechanisms. Any major adverse event must be reported immediately to the MSION clinical services manager, who will inform the study manager and the MSI medical development team in London within 24 hours. For this study, moderate adverse events will also be reported to the clinical services manager who will inform the study manager. Reportable adverse events are shown in Textbox 1. Other conditions are to be reported if the level of adversity is judged to be persistent or difficult to manage. The clinical services manager will be responsible for ensuring any adverse event reported is managed effectively.

MSION research staff will train providers on the research study, including participant recruitment and consent, data collection, and data storage. Full training (implant provision and research) is expected to take approximately 8 days.

Supervised Provision

After training, the trainee can provide implants to clients at their clinic only in the presence of a MSION clinical supervisor.

The trainee will encourage FP clients to attend on scheduled days when the supervisor is present. Clients will be counseled on the available methods, and if they choose an implant, they will be given the option of Jadelle or Implanon Classic. Supervision visits will take place every 2 weeks but exact timings will depend on the volume of implant clients. After 5 successful supervised insertions of each brand of implant, the trainee is accredited to insert implants without clinical supervision.

Textbox 1. Moderate and major adverse outcomes to be reported to ensure participant safety.

Moderate level of adverse event

- Partial expulsion of implant, putting the woman at risk of pregnancy
- Pain at insertion site continues for more than 1 week and requires further outpatient observation and medical intervention
- Bleeding that does not stop and requires a transfer to receive medical care
- Infection that persists after 7 days of antibiotic treatment (may require implant removal)

Major level of adverse event

- Complete expulsion of the implant resulting in pregnancy
- Palpitations from the local anesthetic
- Bleeding that requires hospital care or results in long-term health impacts
- Infection that requires hospital care or results in long-term health impacts
- Paresthesia that requires hospital care or results in long-term health impacts
- Scarring that requires hospital care or results in long-term health impacts
- Anaphylactic response to the implant

MSION staff will conduct demand-generation activities in the local area to increase awareness of the range of contraceptive methods available, including implants, to ensure that trainees have sufficient clients. Activities may include in-facility awareness raising on special days such as antenatal care, immunization, and child welfare days, and recruiting designated locals to encourage potential clients in their communities to attend the nearest study facility for FP.

On the basis of MSION's previous experience of conducting training and supervision of midwives, nurses, and doctors, it is expected that most providers will have been accredited for insertion by the end of their first supervision visit. Additional visits will be undertaken in cases where accreditation of insertion is not achieved within the prescheduled supervision visit.

Unsupervised Provision

After accreditation, participating providers will start to offer unsupervised implant services in their clinics and to recruit clients to the study. Participating providers will be invited to attend a monthly study meeting at the state level where they will receive study updates and tools and, if necessary, additional training. Providers will receive lunch and travel costs. Supervision visits will still occur but they will be less often following provider accreditation.

Participant Recruitment and Eligibility

Women requesting an implant from a participating facility will be eligible to participate if they are aged between 18 and 49 years and are eligible to have the implant. On presenting at a participating clinic, each client will be provided with comprehensive FP counseling and offered all available FP methods (balanced counseling technique) [25]. Participating providers will invite all clients who request an implant, and meet the inclusion criteria, to participate in the study, using a study information sheet and consent form. If the client chooses an implant, she will be offered Jadelle or Implanon Classic, and the same service provider will do the insertion. Clients who want an implant but do not want to participate in the study will be advised of the nearest available facility providing this service.

Clients will be recruited until the sample size is reached (anticipated to be approximately 7 months). Participants who are asked to return for a 2-week follow-up visit will be reimbursed for their travel costs. Women who do not return after 14 days will be contacted by telephone (if they gave consent to be contacted and a phone number). In total, 3 attempts will be made to contact women by telephone before they are considered lost to follow-up. Those who are contacted by phone will be asked to attend the facility for the 14-day follow-up visit or, if unable, to answer questions over the telephone.

The number of clients who refuse to take part and who withdraw will be documented, along with the reason for refusal or withdrawal where given. If they agree, very basic sociodemographic data and the reason for refusal will be recorded.

All health care staff at participating facilities will be eligible for participation in semistructured in-depth interviews to assess acceptability of CHEW implant provision. A range of staff types (doctors, nurses, midwives, and CHEWs) will be approached by a senior research staff member and asked for their willingness to participate. Policy makers involved in FP will be contacted individually by researchers and asked to participate in an interview. All participants will be asked for their informed consent before the interview.

Sample Size

Day of Insertion

Calculation of the number of participants required for the study is based on the primary outcome—the frequency of adverse events associated with insertion on the day of the procedure.

Studies documenting adverse events of implant insertion on the day of procedure have found them to be rare. For example, a randomized clinical trial of 2008 women found that 0.2% clients

using Jadelle and 0.8% clients using Implanon Classic experienced complications at insertion [26].

To detect a difference in proportion of adverse events between the 2 study arms with a noninferiority limit of 0.5%, 80% power, and 95% confidence level on the day of implant insertion, we would require a sample size of 2462 in each study arm, giving a total sample size of 4924. To account for possible clustering, we will include a design effect of 1.5, increasing the sample size to 7386. To allow for incomplete records, we will increase this by 10% to a total sample size of 8125.

We estimate that each provider will receive approximately 10 insertion clients per month and that we may see a refusal rate of 20%. With a total of 120 providers, we expect to recruit 1200 clients per month. We would therefore need to recruit clients for approximately 7 months to achieve the required sample size for insertions.

By Day 14

We expect the number of adverse events observed by day 14 to be higher than that at day 0 as we may start to see infections. This reduces the required sample size needed to detect a difference between health care provider types. To detect a difference in proportion of adverse events between the 2 study arms with a noninferiority limit of 1%, 80% power, and 95% confidence level 14 days after implant insertion, we would require a sample size of 1225 in each study arm, giving a total sample size of 2450. To account for possible clustering, we will include a design effect of 1.5, making the size 3675. Assuming 20% loss to follow-up makes a total sample size of 4410. If we expect to recruit 1200 clients per month, it will take around 4 months to recruit the sample size we require.

All recruited clients will be asked to return to the inserting provider for a follow-up visit at 14 days post insertion until the sample size of 4410 is reached.

Quality and Acceptability of Implant Provision

To detect a difference in the quality and acceptability of implant provision between the 2 study arms, assuming that each group would score an average of 80% of quality and acceptability indicators being met, with a noninferiority limit of 10%, 80% power, and a significance level of 5%, we will need 198 observations in each group. Adjusting for 10% incompleteness, we need 220 in each group (440 total). Assuming a design effect of 1.8 requires a minimum of a total of 792 observed implant insertions. There will be approximately 10 providers per supervisor. So, assuming approximately 10% of insertions can be observed (and client acceptability measured through exit interviews), this equals 812 insertions, which is sufficient according to the sample size calculation.

Acceptability of Community Health Extension Worker Implant Provision to Health Staff, Facility Managers, and Policy Makers

Approximately 3 to 5 interviews with providers from each cadre will be conducted, until no new information or opinion is yielded from each subsequent interview. Views from the north and south, urban and more remote locations, and different ethnic and wealth contexts will be included; if views are already known, a mix of supporters and opponents of CHEW implant provision will be interviewed.

Data Collection

Safety—Days 0 and 14

At the time of insertion, the provider will record baseline data about the implant insertion, the occurrence of adverse events, and the client's background (including demographics, socioeconomic information, reproductive history, and reasons for getting an implant). At day 14 post insertion, the provider will ask the client about side effects or complications arising from the procedure.

To assess the ongoing safety of the study, any participant coming to the facility with complaints about her implant up to 30 days after the procedure will be asked a few questions by the provider about what the participant has experienced and her responses will be documented. Responses will be reviewed by project staff.

Quality of Implant Provision

Each provider will be visited by her clinical supervisor at 0 (accreditation), 1, 2, 3, and 6 months post training. During these 1 to 2 day long visits, all implant insertions will be observed, and data on quality recorded. Visits will be scheduled in advance and previsit FP demand-generation activities will be conducted by MSION and health care workers. The quality assessment tool includes clinical and nonclinical dimensions, including cleanliness, infection control, taking a client-focused approach, and being responsive to client needs. The tool comprises a checklist of 28 items, observed by the clinical supervisor. For each item, the supervisor will assess provider competence (ie, the provider knows the steps for the skills and can perform them correctly or needs further follow-up) and support to achieve competency (ie, the provider does not know the steps for the skills and does not perform them correctly). The number of items marked "competent" will be totaled to give the provider a score.

Acceptability of Implant Provision—Client Exit Interviews

During supervisor visits, clients participating in the study will be interviewed by the supervisor in private, before leaving the clinic. They will be asked to rate 7 aspects of service provision on a 5-point scale, with responses being totaled to give a satisfaction score. They will be asked if they would recommend the service to a friend.

Data collection points are summarized in Table 3.

Table 3. Summary of data collection procedures.

Timing of data collection	Who collects data, and how	Data to be collected	Sample size
At the time of procedure	Supervisor (if present), observes procedure	Quality of service provision	792
Immediately post implant procedure	Community health extension worker (CHEW), nurse or midwife who conducted procedure, observes client and asks her questions at clinic	Client background, record of procedure including complications at the time	8125
	Supervisor (if present), conducts exit interview with client	Client satisfaction, completeness of counseling information, critical information provision	792
2 weeks post procedure	CHEW, nurse or midwife who conducted procedure, asks client questions at clinic or by telephone	Complications following procedure	4410
Within 30 days of procedure	CHEW, nurse or midwife who conducted procedure, records client's problems at clinic	Complications following procedure	All cases reported spontaneously at the facility

Acceptability of Community Health Extension Worker Implant Provision to Health Care Staff and Policy Makers

Interviews with staff members and policy makers will cover themes such as perception of confidence and competence in CHEW provision of insertions, support for policy change, perceptions of effectiveness of demand-generation activities, supervision levels, supply chain, and cost-effectiveness. Responses will be recorded on paper using shorthand notes with verbatim quotes as far as possible, and audio-recorded as a backup.

Data Management

Client identifiers, such as name or phone number, will be recorded in a client register and will not be included on client data collection forms. The 2 forms will be stored separately and linked using a client identification number. Study documents will remain in locked cabinets in the provider's office, if available, or in a secure location where medical records are secured.

Providers will keep the anonymized data collection forms for 30 days after insertion and will record any spontaneous client reports of adverse events over this 30-day period. After 30 days, the anonymized forms will be sent to MSION head office in Abuja. The client register will be kept at the clinic for the duration of the study. At the end of the study, client registers will be sent to MSION head office in Abuja and will be kept in a locked cabinet separate from data collection forms. Completed and anonymized exit surveys will be kept on the person of the clinical supervisor or researcher conducting the interview until the end of the visit, after which they will be sent to MSION in Abuja.

Data entry will be conducted by an independent consultant engaged by MSION. Paper forms will be checked for completeness and obvious errors by the data entry clerk when they arrive in Abuja, and queries will be checked by telephone with the provider, clinical supervisor, or researcher. The data entry clerk will double-enter all data into a password-protected electronic database, verify any discrepancies between the 2 data entries, and clean the data in preparation for safety monitoring analysis every 3 months. When all complication data have been collected, entered, and cleaned, the full dataset will be transmitted to the research team in MSI London for analysis.

The cleaned, anonymized electronic dataset will be kept by MSI London for a minimum of 5 years and will be made publicly available by request to Marie Stopes [27]. Paper forms will be kept securely by MSION in Abuja until 1 year after publication and then destroyed.

Audio recordings will be transcribed verbatim. The recordings will be stored in locked cabinets until they have been transferred to a computer, after which they will be destroyed.

Data Analysis

Quantitative data will be analyzed using statistical software Stata, version 13 (Stata Corp. College Station, Texas). Complete case analysis will be conducted. For safety monitoring, complication rates by provider will be generated by the study manager in Abuja every 3 months, to identify any providers with unusually high complication rates. These data will be checked and response activities will be agreed at the 3 monthly technical advisory committee meetings to be held in Abuja, which will be attended by staff from MSION and MSI, and ministry of health officials.

Training and supervision data will be presented using descriptive statistics. Insertion adverse events of CHEWs will be compared for noninferiority against the complication rates of nurses and midwives. To assess the equivalence between the nurses and midwives and the CHEWs, the risk difference between the 2 provider types together with their 95% CI will be derived by use of a generalized estimating equation model to adjust for clustering. If the CI of the risk difference between the 2 groups falls within the predetermined margin of equivalence (–2% to 2%, which is equivalent of lower bound of one side 97.5% CI), the 2 types of service providers can be considered equivalent.

Sensitivity analysis will be designed to control for group assignment bias among the 2 states. They will be analyzed both separately and together to identify any differences in performance between CHEWs in the northern state compared with the southern state.

All quality and acceptability indicators will be weighted equally, except for those most critical (infection prevention, correct clinical technique, and advice on where to go in case of

problems), which will be given a higher weight. The difference in mean quality and acceptability scores between CHEWs and midwives will be compared using a *t* test.

Analysis of qualitative data will be undertaken manually or using a qualitative analysis software such as N-Vivo. Quotations will be labeled by cadre of speaker, and a thematic analysis will be carried out. Transcripts will be read and reread. Extracts will be coded according to themes and subthemes that emerge from the data or that have been identified before the analysis such as those included in the in-depth interview guide. A selection of quotes representing different cadres and views will be used to write a report structured around these themes.

Dissemination Policy

Findings will be shared with stakeholders through formal reports and presentations at local and national levels, and more broadly through peer-reviewed publications and international conference presentations. Authorship eligibility will be dependent on substantial contributions to planning, implementing, analyzing, or drafting of findings. The deidentified dataset will be made publicly available following the publication of study results.

Results

In total, 12 LGAs were selected in Kaduna State and 23 in Ondo State. We trained 60 CHEWs and a total of 60 nurses and midwives (30 of each from each state) in September and October 2015, and recruitment took place between November 2015 and December 2016. Data cleaning is complete and analysis is being finalized. Results are expected in March 2018.

Discussion

Besides resulting in 120 more health care staff qualified to provide contraceptive implants, this study will provide robust evidence on the safety, quality, and acceptability of contraceptive implant provision by CHEWs compared with nurses and midwives in Nigeria. This evidence may also serve to support future decision making about task-sharing implant services to community health workers in other countries. Strengths of the study include being able to compare CHEW provision with an existing standard of care (nurse and midwife provision). The study builds on existing training and supervision procedures, which will increase the sustainability and scalability of CHEW implant provision if the results are promising.

The main limitations of the study are the lack of randomization and that that providers will be assessing their own practices. Clients cannot be randomized because they usually access their local area clinic, and providers cannot be randomized because they work at either CHEW-led or at nurse- or midwife-led public clinics. Where both cadres work together, the national policy is to train 1 provider in each clinic. This could result in bias due to nonequivalence of the intervention and control groups (ie, if participating CHEWs tend to work in more remote clinics with poorer supply chain for infection prevention supplies than participating nurse and midwives). It is not feasible to arrange independent observation of all procedures; furthermore, observation itself may change practice. Bias will be assessed by comparing adverse event rates recorded by supervisors with those documented by providers themselves. Providers will be informed that this checking will take place.

Although both CHEWs and the nurses and midwives will be trained in and will conduct implant removals, there will be insufficient time during the study period to collect enough information on removals to make any noninferiority comparisons.

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Authors' Contributions

The study was designed by TN, MA, KR, KH, KO, and EM. KH and KR wrote the study protocol, and KR and OE submitted the protocol for ethical review. TN, MA, AU, SPT or, EM, and OA critically reviewed the protocol, and KR addressed the feedback from reviewers and from the ethics committees. SP drafted the manuscript from the study protocol, and all authors critically reviewed it.

Conflicts of Interest

KR, SPT, OA, KH, TN, KO, MD, OE, EE, and EM are or have been employed by Marie Stopes International or Marie Stopes Nigeria. Marie Stopes Nigeria delivers implant training to providers in Nigeria. MA and UU have no competing interests to declare.

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Abbreviations

CHEW: community health extension worker
FMOH: Federal Ministry of Health of Nigeria
FP: family planning
IUD: intrauterine device
LARC: long-acting reversible contraceptive
LGA: local government area
MSI: Marie Stopes International
MSION: Marie Stopes International Organisation Nigeria
WHO: World Health Organization

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Protocol

Building Yol u Skills, Knowledge, and Priorities into Early Childhood Assessment and Support: Protocol for a Qualitative Study

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Abstract

Background: Yolngu or Yolŋu are a group of indigenous Australian people inhabiting north-eastern Arnhem Land in the Northern Territory of Australia. Recent government policy addressing disparities in outcomes between Indigenous and other children in Australia has resulted in the rapid introduction of early childhood interventions in remote Aboriginal communities. This is despite minimal research into their appropriateness or effectiveness for these contexts.

Objective: This research aims to privilege Aboriginal early childhood knowledge, priorities and practices and to strengthen the evidence base for culturally responsive and relevant assessment processes and support that distinguishes “difference” from “deficit” to facilitate optimal child development.

Methods: This collaborative qualitative research employs video ethnography, participant observation and in-depth interviews, involving Aboriginal families and researchers in design, implementation, interpretation and dissemination using a locally developed, culturally responsive research approach. Longitudinal case studies are being conducted with 6 families over 5 years and emerging findings are being explored with a further 50 families and key community informants. Data from all sources are analyzed inductively using a collaborative and iterative process. The study findings, grounded in an in-depth understanding of the cultural context of the study but with relevance to policy and practice more widely, are informing the development of a Web-based educational resource and targeted knowledge exchange activities.

Results: This paper focuses only on the research approach used in this project. The findings will be reported in detail in future publications. In response to community concerns about lack of recognition of Aboriginal early childhood strengths, priorities and knowledge, this collaborative community-driven project strengthens the evidence base for developing culturally responsive and relevant early childhood services and assessment processes to support optimal child development. The study findings are guiding the development of a Web-based educational resource for staff working with Aboriginal communities and families in the field of early child development. This website will also function as a community-developed tool for strengthening and maintaining Aboriginal knowledge and practice related to child development and child rearing. It will be widely accessible to community members through a range of platforms (eg, mobile phones and tablets) and will provide a model for other cultural contexts.

Conclusions: This project will facilitate wider recognition and reflection of cultural knowledge and practice in early childhood programs and policies and will support strengthening and maintenance of cultural knowledge. The culturally responsive and

highly collaborative approach to community-based research on which this project is based will also inform future research through sharing knowledge about the research process as well as research findings.

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KEYWORDS

early child development; Aboriginal; culture; internet-based resources

Introduction

Access to high quality experiences in the early years is widely acknowledged to lead to improved health, education, and social outcomes for young children [1]. However, potential positive outcomes provided by participation in early childhood programs/services are lost when families do not use them [2,3]. The under representation of Aboriginal children in early childhood services in the Northern Territory (NT) of Australia is widely reported [4-6]. Although there is scant research on the reasons for this under representation, particularly for remote Aboriginal families, one reason for resistance may be fear regarding the dominance of Western approaches [7]. Programs that prioritise Western perspectives are criticised for failing to consider local values, goals, domains, languages, learning styles, and learning-teaching paradigms when applied cross-culturally [8-11]. Indeed, recent work in the USA [12], Canada [13,14] and New Zealand [15,16] demonstrates the value of culturally relevant strategies for early child development.

In Australia, there is a growing body of research that points to the need for policies and interventions responsive to distinctive remote Aboriginal cultures and contexts, and the interrelationship of health, wellbeing, and culture [17-19]. Although there has been considerable investigation of Aboriginal parenting practices, few empirical studies of Aboriginal child development have been conducted in Australia. Most of the research related to both child development and parenting has been based on observation by non-Aboriginal researchers [20] or indirect methods such as surveys or questionnaires [1]. Australian research also tends to focus on Aboriginal children in urban areas, and especially on participation rates of Indigenous families in early childhood education [17-19,21]. There continues to be a dearth of research regarding assessment frameworks and outcome measures appropriate to remote Aboriginal populations in Australia [22,23] although there has been recent work to adapt an existing child development assessment tool for remote Aboriginal contexts [23].

The evidence base on which to make decisions about appropriate early childhood interventions (ie, those that are effective for addressing disparities in outcomes between Aboriginal children and other Australian children over the long term) is not strong [24]. While research has demonstrated the promise of some well-known "evidence-based" programs, few have been tested or evaluated over the longer term in an Australian (or Indigenous) context [6,24]. A review of early childhood interventions identified significant gaps in knowledge that create "impediments to implementing interventions more widely and reaping the benefits they promise" [25]. Robinson et al [19] recommend examination of the "cultural logic" and appropriateness of assumptions about child development embedded in such programs and practices.

There are risks in adopting "evidence-based" interventions designed and developed for people in different countries and circumstances, who speak another language and who hold different cultural values. Aboriginal families may reject or not utilise such programs, as noted already in the Northern Territory [26]. Byers et al [27] point out that where world views underpinning an intervention are very different to those of the target group considerable scope exists for misunderstanding, miscommunication of important information and a devaluing of Aboriginal ways of knowing that can reinforce "systematic discrimination and racism" [27]. For example, a recent review of literature on transition to school indicates that where Aboriginal children are assessed using standards and tools developed for mainstream populations their strengths may be overlooked [28].

Early childhood research and education has been critiqued for its reliance on Western methodologies and use of limited epistemological and ontological frameworks [11,29,30]. For example:

> *Limited experience and knowledge outside the dominant culture has led many well-meaning researchers, policy makers, and local and international government agents to assume that practices within their own highly schooled community define norms for all children's development, learning and social interaction. This makes it easy to misinterpret the ways of people from many other backgrounds according to a deficit model—to assume that the others have something wrong with them.* [11]

Findings from the Longitudinal Study of Indigenous Children [31] highlight the importance of using a strengths-based rather than deficit framework. Taylor [32] notes that Aboriginal children's strengths, such as superior visual-spatial and motor skills as well as ability to assess risk, "rarely appear on ECE checklists or school reports as strengths to be encouraged" [32]. Evans and Myers [33] recommend "interweaving practices that "scientific" evidence would suggest a child needs with effective traditional childrearing practices and beliefs" [33]. Quality early childhood programs that meet the needs of remote Aboriginal children and their families must be informed by local cultural perspectives [24]. Key features of successful early childhood programs and practices consistently recommended by Aboriginal authors and organisations [2,34,35] include that they are responsive, holistic and culturally safe.

The "Growing up children in two worlds" project is being conducted in a remote coastal community in northern Australia with local Indigenous (Yolŋu) community members. The project

draws on in depth and situated child development and child-rearing knowledge and practice, providing an evidence base from which early childhood programs, assessment practices and interventions can draw and benefit. It reinforces the value of local cultural knowledges and practice that can foster community ownership and ongoing genuine community engagement, not only supporting local agency but enabling community-controlled decision making [36]. The strengths-based research approach adopts an ethically sound and culturally valid methodology that engages concerned and invested community members in generating and analyzing the knowledge upon which to build a more culturally competent [28] approach to early childhood education and care for Aboriginal children. The project has been funded for a period of three years by Lowitja Institute (2016-18) and extends an initial exploratory project conducted between 2013-15. In summary, this project aims to:

- Privilege Yolŋu (Aboriginal) voices in generating child development and child rearing knowledge
- Identify skills and knowledge (both Aboriginal and Western domains) that Yolŋu families want their children to develop and the strategies they use to foster this development
- Strengthen the evidence base for culturally responsive and relevant assessment processes and support that distinguishes difference from deficit to facilitate optimal child development

The study has received ethical approval from the Charles Darwin University Human Research Ethics Committee.

Methods

Study Design

This collaborative qualitative research project draws on culturally responsive methods developed through previous studies of child development and learning, including language socialisation, as well as intercultural communication in Aboriginal health care [37-39]. This approach is closely aligned with elements of constructivist grounded theory [40] in which data collection and analysis occurs simultaneously in an iterative process emphasising theory construction rather than description or application of current theories. The project is a direct response to concerns expressed by community members regarding:

1. Dominance of Western values and practices in early childhood policy and programs
2. Lack of respect and recognition for Yolŋu knowledges, priorities and practices on how best to raise young children and what is important for their development
3. Assessment processes that do not accurately differentiate between “difference” and “deficit”

This project is also a response to the lack of diverse Indigenous perspectives in the early childhood research literature that could inform and improve programs, practices and materials. The research will address these issues and lead to action through providing health and education policy makers and program implementers with new knowledge resources to inform and improve early childhood development assessments and practices.

Research Team and Governance

The project has been developed in collaboration with senior community members and is a direct response to their concerns. One of the Project Leaders is a senior Yolŋu researcher who has primary control of the research process in collaboration with the two other Project Leaders. As well, emerging Yolŋu researchers participate as members of the research team in data collection, analysis and dissemination activities. All consultation and consent processes as well as research activities are conducted in the preferred language of participants to ensure optimal communication is consistently achieved. Community members and researchers are involved in developing the knowledge-sharing website that is a key component of this project. The strong collaborative approach on which this project is based also engages participants (family members and other key community informants) in interpretation of the data as well as decisions about dissemination. The Aboriginal Project Leader and Partner researchers play a key role in all dissemination activities including authorship of publications and conference presentations.

The project is being conducted in partnership with the Yalu Marŋgithinaraw (an Indigenous community education and research organization). The Balanda (non-Aboriginal) researchers have a long history of collaboration with the community and previous projects have been successfully conducted in partnership with the Yalu to ensure genuine community leadership and engagement is achieved. This collaborative approach and high level of community participation in the project ensures that the research process and specific methods are guided by the Yolŋu researchers and are responsive to community needs and preferences. Collaboration with Secretariat of National Aboriginal and Islander Child Care (SNAICC): National Voice for Our Children (the national nongovernmental peak body representing the interests of Aboriginal and Torres Strait Islander children) is also a critical element of the project to explore broader relevance beyond the study setting and to ensure optimal research translation into policy and practice. SNAICC is providing independent review and advice on the research methodology and findings for the purposes of supporting validation of its robustness and integrity. Importantly, SNAICC review and advice does not seek to impose upon or compromise local Indigenous research methodologies which are integral to the quality of the research process. Rather, SNAICC staff observe the research processes and continuously test research findings with wider audiences for feedback into the project. Through this partnership, SNAICC is in a position at the end of the project to provide strong endorsement of research findings in its role to communicate findings to broader research, community and policy development audiences. The research is supported by two additional groups:

1. *Community Backbone Committee* (Advisory Group) of key community members—this culturally responsive approach developed over many years by the Yolŋu researchers ensures the research process is informed and guided by appropriate Elders and others through continual (often informal) engagement and consultation.
2. *National Backbone Committee* established by SNAICC and comprised of interested groups and individuals who are

positioned to facilitate the wider application and dissemination of the project findings and outputs.

Setting and Participants

The study is being conducted in a large remote community in Northern Australia where Yolŋu (Aboriginal people of Northeast Arnhemland) make up more than 90% of the population [41]. In this region traditional languages as well as cultural knowledge and practice remain strong. English is learned as an additional language at school but is used for limited purposes in the community in interactions with Balanda (non-Yolŋu), for example, in the shop, school and health services. The community is located on an island and accessible only by limited air services or boat and the nearest major town is 500 kilometers away. Participants include children, parents, grandparents and other extended family members involved in six in-depth case studies commenced during an earlier stage of the project (2013-15) that will continue until late 2018. Ages of the six focus children at commencement of the initial project ranged from 1 month to 2 years and all are continuing their participation in the current study. Families from a range of clan groups and key community informants with particular interest and / or expertise in early childhood and identified as appropriate by Yolŋu researchers are being invited to participate in in-depth interviews to further explore the emerging findings from the case studies (approximately 50 participants).

Data Collection and Analysis

Multiple methods are being used to enable triangulation of data, comparing and contrasting data from a range of sources and perspectives, thus enhancing the trustworthiness and authenticity of findings. These include:

1. Case studies: extensive video recording of six children and their extended families engaging in every day interactions was conducted over two years at 2-3 month intervals as family circumstances allowed. This is continuing at approximately 6 monthly intervals for the duration of this project (providing longitudinal data over 5 years) in response to the participating families' strong desire to continue this process until their children commence school and beyond. Ongoing interpretation of the video data by family members and Yolŋu researchers, as well as in-depth interviews with participants, identify salient features of child development and child rearing in their specific cultural context as well as relevant strategies to address their needs and priorities. This provides rich empirical data as a basis for the expanded research process and research translation activities that are the focus of this project.
2. Cross-sectional data: the emerging findings from the six case studies are being further explored and expanded through in-depth interviews with interested families from a range of clan groups as well as key community informants identified as appropriate by Yolŋu researchers and the Backbone Committee (Community Advisory Group).

Data from all sources are translated into English and transcribed. An inductive and collaborative approach is used in which categories of analysis are derived from the data to reflect participants' perspectives and to avoid filtering of the data through a set of restricted and predetermined codes. A qualitative data management program (QSR NVivo 10) is being used to enhance rigor and support the collaborative process of analysis and interpretation implemented with the Yolŋu researchers. Data collection and analysis occurs simultaneously in an iterative process that includes theoretical sampling to elaborate and refine emerging findings [40].

A provisional framework of key features of child development and child rearing, to inform developmental assessment processes and support relevant to the needs and priorities of participants, is under development based on the findings of (1) and (2) and then will be further explored and refined in collaboration with Yolŋu researchers, other key informants, and the Backbone Committees.

Dissemination and Research Translation

A Web-based multimedia resource integrating the findings is under development by the project team to facilitate transfer of the findings into policy and practice. Elements of the framework based on the findings will be illustrated by salient examples from the video data (selected by participants and used with their informed consent). The website is a mechanism for enabling wide and continued access to Yolŋu perspectives on key aspects of child development and child rearing. This website will provide a training resource to strengthen the cultural competence of staff working in the early childhood field. It will also facilitate cultural maintenance and strengthening of cultural knowledge and practice for Yolŋu across the region with potential wider relevance beyond this specific cultural context. Research dissemination and knowledge exchange will also be achieved with support from the Project Partners (Yalu Marŋgithinaraw and SNAICC), through dissemination of user friendly research reports (written and oral), publications targeting discipline specific journals (ie, health, education, social policy), conference presentations, through the National Backbone Committee (see above) as well as through the project website.

Results

This article focuses on the research approach used in this project and, therefore, findings will be reported in detail in further publications. However, some initial emerging themes are summarised here. They include: a strong focus from birth on developing children's Yolŋu identity through understanding of connections to people, place and other elements of the natural world; intensive interaction with, and nurturing by, a wide range of both female and male extended family members; robust stimulation of verbal and nonverbal communication development and recognition of the child as actively engaged in communication from conception. Many aspects of children's development are closely monitored and regularly purposefully "assessed" by adults in ways that are very specific to the cultural context. Developmental expectations are not age-related and developmental differences are recognised but accepted and valued as individual attributes rather than as deficits. A deeper understanding of diverse cultural strengths and priorities in early child development is crucial to ensure these are recognised, valued and supported. Such evidence may be overlooked or deemed irrelevant through the use of standardised assessment

tools but is essential to address the continuing domination of Western values and practices in early childhood policy and practice in remote communities and to ensure "difference" is not confused with "deficit."

Discussion

Principal Findings

The "Growing up children in two worlds" project is a direct response to concerns expressed by community members about the lack of recognition of Yolŋu skills, knowledge and priorities in early child development (see Multimedia Appendix 1). The project provides the opportunity for Yolŋu to influence the ways in which the development of their children is assessed and supported and opportunities for employment are provided to Yolŋu researchers which supports further development of their research expertise. The project will contribute to a deeper understanding of early child development from the perspectives of community members in this cultural context thus enabling more culturally responsive and relevant action to facilitate optimal child development. The collaboration with SNAICC as a project partner will help to share these learnings where they can benefit Aboriginal and Torres Strait Islander children around the country.

The health and wellbeing of Aboriginal people is linked to the degree of control they experience over their lives. Lack of control can lead to high levels of stress which then contributes to other health and social problems [42]. The opportunities offered through participation in this project, to share one's knowledge and influence policy and practice to be more responsive to one's needs and preferences, may begin to ameliorate the chronic lack of control experienced by participants and provide a model for others to follow.

Consultations by Guilfoyle et al [43] found Aboriginal families prefer early childhood programs that reflect and incorporate "the culturally based beliefs, values and practices, including child-rearing practices, of individuals, families and communities using that service." Families, and thus their children, are more likely to use and benefit from such "culturally competent" programs [42]. These can only be developed through strong engagement with the community, such as this project seeks to do.

Aboriginal children are regularly assessed using frameworks that foreground needs and deficiencies over strengths [31]. This "deficit" discourse impacts negatively on their self-esteem and wellbeing. Culturally relevant assessment processes, of the sort this project seeks to facilitate, can more accurately identify their strengths as well as their support needs leading to optimal development and wellbeing.

This project aims to increase understanding of both strengths and challenges related to early childhood in this context, identifying and responding to opportunities to advocate for appropriate action at both policy and practice levels. The findings of this research will provide health and education policy makers and service providers with new knowledge resources to inform and improve early childhood development assessments and support practices. Knowledge exchange activities will be tailored to each target group (eg, teachers, child care workers, health workers, policy makers and governments). As the project progresses the most effective ways to share information will be identified through consultation with each potential user and stakeholder group. Ongoing engagement of Yolŋu researchers and participants in the knowledge production and dissemination processes is a key element of the project.

Conclusions

Enhanced wellbeing for children is related to their connections to cultural knowledge and practice [44]. Keeping Aboriginal children connected to their culture is seen as a protective factor in their wellbeing and development [45]. This project provides information and a mechanism to enable cultural knowledge and practices to be recognised and reflected more widely in early childhood programs and policies and supports strengthening and maintenance of cultural knowledge. The culturally responsive and highly collaborative approach to community-based research on which this project is based will also inform future research through sharing knowledge about the research process as well as research findings.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Yolŋu perspectives on early childhood.

[MP4 File (MP4 Video), 194MB - resprot_v7i3e50_app1.mp4]

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Abbreviations

NT: Northern Territory
SNAICC: Secretariat of National Aboriginal and Islander Child Care

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Protocol

The Physiological Bases of Hidden Noise-Induced Hearing Loss: Protocol for a Functional Neuroimaging Study

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Abstract

Background: Rodent studies indicate that noise exposure can cause permanent damage to synapses between inner hair cells and high-threshold auditory nerve fibers, without permanently altering threshold sensitivity. These demonstrations of what is commonly known as hidden hearing loss have been confirmed in several rodent species, but the implications for human hearing are unclear.

Objective: Our Medical Research Council–funded program aims to address this unanswered question, by investigating functional consequences of the damage to the human peripheral and central auditory nervous system that results from cumulative lifetime noise exposure. Behavioral and neuroimaging techniques are being used in a series of parallel studies aimed at detecting hidden hearing loss in humans. The planned neuroimaging study aims to (1) identify central auditory biomarkers associated with hidden hearing loss; (2) investigate whether there are any additive contributions from tinnitus or diminished sound tolerance, which are often comorbid with hearing problems; and (3) explore the relation between subcortical functional magnetic resonance imaging (fMRI) measures and the auditory brainstem response (ABR).

Methods: Individuals aged 25 to 40 years with pure tone hearing thresholds ≤20 dB hearing level over the range 500 Hz to 8 kHz and no contraindications for MRI or signs of ear disease will be recruited into the study. Lifetime noise exposure will be estimated using an in-depth structured interview. Auditory responses throughout the central auditory system will be recorded using ABR and fMRI. Analyses will focus predominantly on correlations between lifetime noise exposure and auditory response characteristics.

Results: This paper reports the study protocol. The funding was awarded in July 2013. Enrollment for the study described in this protocol commenced in February 2017 and was completed in December 2017. Results are expected in 2018.

Conclusions: This challenging and comprehensive study will have the potential to impact diagnostic procedures for hidden hearing loss, enabling early identification of noise-induced auditory damage via the detection of changes in central auditory processing. Consequently, this will generate the opportunity to give personalized advice regarding provision of ear defense and monitoring of further damage, thus reducing the incidence of noise-induced hearing loss.

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KEYWORDS

functional magnetic resonance imaging; auditory pathways; auditory brain stem response

Introduction

Background and Rationale

Noise exposure is the main cause of preventable hearing loss worldwide, as identified by the World Health Organization [1]. Noise exposure can occur environmentally [2], occupationally in the workplace [3], and recreationally during personal leisure time [4]. Damage from noise exposure can manifest at many points along the auditory pathway, including the sensory hair cells in the cochlea, and the connections between hair cells and nerve cells (synaptopathy, [5]). Damage to the auditory nerve can also lead to tinnitus (perception of sound in the absence of external sound) and hyperacusis (diminished tolerance of moderate- to high-level sounds) [6].

Controlled experiments on the effects of noise exposure on the cochlea use an animal model of acute noise trauma. A striking discovery showed that noise exposure can cause substantial neural damage without a reduction in threshold sensitivity. Mice exposed to a 100 decibel sound pressure level (dB SPL) stimulus for just 2 hours permanently lost up to half of their hair-cell or auditory-nerve synapses in certain frequency regions (cochlear synaptopathy), despite a complete recovery of thresholds for sounds in quiet [7]. Several weeks after exposure, auditory-nerve activity (as measured by electrophysiological auditory evoked potentials; AEPs) was normal at low sound levels but reduced at suprathreshold levels. This suggests that the damage affects auditory nerve fibers with high thresholds, which are also thought to be the fibers that encode acoustic information at medium to high levels and in background noise [8]. These findings have been replicated in the guinea pig [9] and chinchilla [10], suggesting a general mammalian effect. These studies suggest that even moderate noise exposure can cause substantial damage to the auditory nerve, while leaving hair cells macroscopically intact. Particularly troubling is that neuropathy has also been reported in mice exposed to a stimulus of just 84 dB SPL (a level of noise exposure that is below the Health and Safety Executive action point for health surveillance) for 168 hours per 1 week [3,11]. However, confidence in this finding is reduced by the observation that synaptic counts in the exposed mice were similar to those of control mice in previous studies [12]. Nevertheless, the prediction from these acute noise trauma models is that human noise exposures, accumulated over a lifetime, exert a similar causative effect by damaging the synapses between the inner hair cells and the auditory nerve fibers leading to nerve fiber degeneration.

Hearing ability is typically assessed using pure tone audiometry, which measures the ability to detect quiet sounds by determining the threshold for single-frequency tones up to 8 kHz [13]. Until recently, it had been assumed that hearing loss results mainly from damage to the sensory hair cells in the cochlea [14]. However, the literature cited here suggests that primary damage to neural structures may precede hair cell loss and may not be detectable by pure tone audiometry. Hence, cochlear synaptopathy with perceptual effects is sometimes referred to as hidden hearing loss [15].

The auditory brainstem response (ABR) is the AEP of the brainstem and vestibulocochlear nerve. The amplitude of each peak of the ABR reflects the number and synchronicity of neurons firing, and the latencies represent the speed of transmission of the AEP [16]. The amplitudes of waves I and V of the ABR, and often the wave I/V amplitude ratio are reported, and either a reduction in the amplitude or the ratio between these amplitudes has been related to tinnitus [16,17]. Conversely, other studies have failed to replicate these findings [18,19].

Noise exposure leads to sensorineural damage, which degrades the information carried by the nerve from the ear to the brain [14]. Studies [20,21] suggest that people with a history of noise exposure, but with normal pure tone audiometric thresholds, experience problems with sound discrimination, particularly understanding speech in noisy environments. For example, noise-exposed workers demonstrated worse speech recognition in the presence of multitalker babble at −5 dB signal-to-noise ratio compared with controls [20], and high-risk college students scored lower on word recognition in noise than did their low-risk counterparts [21]. However, contradictory to this, some studies find no evidence of any link between noise exposure and speech perception deficits [22-24]. In addition to the immediate perceptual deficits that may result from damage to auditory nerve fibers and/or hair cells, it is known that noise damage earlier in life exacerbates hearing problems associated with old age [25]. From this, it is possible to infer that cumulative lifetime noise exposure may be predictive of hidden hearing loss due to the effect of exposure on hair cell or auditory nerve fiber aging. Furthermore, cumulative lifetime noise exposure may be predictive of tinnitus [19] and/or reduced sound-level tolerance.

The link between the physiological results and the perceptual deficits is as yet unclear, although some studies have small, but significant, associations between synaptopathy and deficits in auditory perception [26]. To date, however, we have found no discernible relation between any property of the electrophysiological ABR or frequency following response and either (1) noise exposure or (2) tinnitus in young adult humans. This has been determined from electrophysiological measures and lifetime noise exposure reports in (1) a group of 126 participants (aged 18-36 years) with matched audiometric thresholds up to 8 kHz [18] and (2) a group of 20 participants exhibiting tinnitus, when compared with controls matched for age and audiometry up to 14 kHz [19]. It is important to consider the literature when planning study design, and our protocol specifically addresses the following aspects. First, the study will collect cumulative lifetime measures of noise exposure, as opposed to recent short-term noise exposure measures [27]. Second, the study will recruit a large sample of 90 individuals spanning a range of ages. Third, care will be taken to ensure closely matched audiometric thresholds over the range of 500 Hz to 8 kHz, in contrast to the previous studies [17], and to

assess high-frequency audiometric thresholds at 12 and 16 kHz which may influence ABR amplitudes [16,19]. The key extension compared with studies reported to date [18,19] includes assessment of functional magnetic resonance imaging (fMRI) measures from the brainstem, analogous to electrophysiological brainstem measures described above, and to perform this in a slightly older cohort aged 25 to 40 years, while still maintaining control on audiometric matching. From this study, we hope to achieve greater sensitivity to detect a relation between lifetime noise exposure and neurophysiology.

Previous fMRI studies have shown increased responses to auditory stimuli in the ascending auditory pathway and auditory cortex of individuals perceiving tinnitus and reduced sound-level tolerance [28-30]. This can be taken as evidence that physiological correlates of tinnitus perception and sound-level tolerance can be detected using fMRI. Additionally, this provides evidence for an association between central gain in the ascending auditory pathway and tinnitus or reduced sound-level tolerance. The overall aim of our 5-year research program is to understand the damage to the human auditory system that results from environmental noise, focusing on hidden hearing loss that is not detected by standard hearing tests. Our initial hypotheses are that noise exposure is associated with abnormal gain in the ascending auditory pathway and also with tinnitus, reduced sound-level tolerance, and impaired speech perception.

Objectives

The primary objective of this neuroimaging experiment is to identify any central auditory biomarkers associated with hidden hearing loss. Specifically, we will determine whether fMRI techniques can detect physiological changes in the central auditory system of individuals with normal audiometric thresholds that are statistically associated with the degree of cumulative lifetime noise exposure. These changes are hypothesized to be detected in structures of the ascending auditory pathway, comprising the cochlear nucleus (CN), inferior colliculus (IC), medial geniculate body (MGB), and primary auditory cortex. We hypothesize that lifetime noise exposure will be associated with abnormal gain in the ascending auditory pathway, that is, increased fMRI response to auditory stimuli. To test this, we will first determine whether there are any differences between low and high noise exposure groups in the fMRI responses to broadband noise in the above key anatomically defined regions. Thereafter, we will assess whether there is any correlation between lifetime units of noise exposure and fMRI responses in the same regions.

A secondary objective is to investigate whether there are any additive contributions to these physiological changes attributable to tinnitus or diminished sound-level tolerance, conditions which are often comorbid with hearing problems.

A further secondary objective is to test the hypothesis that noise exposure is associated with a reduction of the ABR wave I and/or a reduction of the wave I/V amplitude ratio across low and high noise exposure groups, closely matched for audiometric thresholds.

Finally, this study will provide an opportunity to explore the relationship between ABR and fMRI measures in the ascending auditory pathway.

Study Design

This study is designed to assess differences in individual fMRI responses in hypothesized, anatomically defined regions that may relate to units of lifetime noise exposure while controlling for age and audiometric threshold. Sound-related fMRI responses will be examined for differences that correlate with noise exposure using an analysis of variance (ANOVA). Presence of tinnitus and reduced sound-level tolerance will also be considered as factors of interest. Participants will be grouped in a factorial analysis, where the factors are noise exposure, tinnitus, and reduced sound-level tolerance.

The Organization for Human Brain Mapping Committee on Best Practice in Data Analysis and Sharing [31] states that reproducibility of fMRI studies can be improved by the process of preregistration [32]. Furthermore, there is a growing precedent for publishing fMRI protocols before completion [33]. In light of this, the methods here are reported in sufficient detail that they may be fully replicated and that any future publications resulting from this study can be cross-referenced to this paper.

Methods

Participants, Interventions, and Outcomes

Study Setting

The study protocol has been approved by the University of Nottingham School of Medicine Research Ethics Committee and will be conducted in accordance with these ethically approved procedures (reference: B/1207/2016). The study is part of a 5-year program that has been funded by the Medical Research Council (MRC) (grant number: MR/L003589/1 awarded to the University of Manchester). Progress is reported and monitored at annual Advisory Panel meetings attended by researchers at both universities, as well as a representative from the charity Action on Hearing Loss.

The magnetic resonance imaging (MRI) scanning will be conducted at the Sir Peter Mansfield Imaging Centre (SPMIC), a translational imaging center at the University of Nottingham. The data analysis will be conducted at the SPMIC and National Institute for Health Research Nottingham Biomedical Research Centre. All procedures will be performed by a member of research staff at the University of Nottingham. All study participants will give written informed consent.

Eligibility Criteria

Healthy adult volunteers aged 25 to 40 years will be included in the study. Participants will have clinically normal hearing thresholds as per BSA guidance on pure tone audiometry [13], that is, 20 dB hearing level or below from 500 Hz to 8 kHz. Exclusion criteria are contraindications for undergoing MRI, and signs of conductive hearing loss or ear disease identified by otoscopy and tympanometry [34]. Furthermore, any participants reporting exposure to explosions (large infantry weapons, light artillery or antiaircraft guns, large artillery

weapons or naval guns, explosions) will be excluded from the study.

Participant Timeline

Table 1 shows a schematic diagram of the time schedule of enrollment and assessments for participants based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines for reporting protocols of clinical trials [35].

Sample Size

In total, up to 90 individuals will be recruited into the study to one of two groups, depending on the noise exposure of the individuals recruited. Statistical power in fMRI research is influenced by 10 parameters, including study design and temporal autocorrelation [36,37], and we estimate that 30 individuals per group will provide acceptable reliability to differentiate between the groups with 80% power.

Recruitment

Recruitment will be stratified to ensure a balanced distribution of age and gender in each of the noise exposure groups. For example, we will aim for equal numbers of individuals reporting high and low noise exposure in the age ranges of 25 to 27, 28 to 30, 31 to 33, 34 to 36, and 37 to 40 years. Recruitment is expected to close in December 2017.

Participants will be recruited through advertisements displayed in public areas of University buildings (eg, library noticeboards, departmental noticeboards allocated to recruitment leaflets), on noticeboards in other public and private buildings (with the owners' consent), Internet message boards, departmental websites, social media, local radio, and community magazines. We will specifically target buildings associated with activities that incur noise exposure, for example, music technology departments and live music venues.

Potential participants will be given an electronic copy of the information sheet, informed consent form, and MRI safety-screening questionnaire at least 24 hours before participating in the study to ensure that they have adequate opportunity to consider what is involved in the study. On arrival at the SPMIC, participants will be given paper copies of all study materials.

Data Collection, Management, and Analysis

Screening Procedure

Suitability to undergo MRI will be determined by completion of a 19-item self-report screening questionnaire including questions about surgical history, implants and foreign bodies, epilepsy or blackouts, claustrophobia and tinnitus, tattoos, and willingness to remove all metal (eg, body-piercing jewelry, false teeth, hearing aid). Participants who do not meet the safety requirements and data-quality requirements for scanning will not be included in any part of the study.

The participant will undergo audiometry to determine hearing thresholds. Audiometry will be performed in a soundproof environment, free from distractions. Stimuli will be presented using an M-Audio M-Track Quad external sound card (M-Audio, Cumberland, Rhode Island, USA) over Sennheiser HDA300 audiometric headphones suitable for high-frequency audiometry (Sennheiser electronic GmbH & Co KG, Wedemark, Germany). Stimuli will be generated using in-house software written in Matlab (version 2016a, The MathWorks Inc., Natick, Massachusetts). Audiometry will be performed using a two-interval, two-alternative forced choice visually cued adaptive paradigm with a two-down one-up rule and a step size of 2 dB. The adaptive procedure will be stopped after 12 reversals, and the geometric mean of the signal level at the last eight reversals will be computed.

Table 1. Time schedule of enrollment and assessments for participants based on the SPIRIT guidelines. Questionnaires address biographical data, tinnitus and intrusiveness of tinnitus, hearing, and reduced sound-level tolerance.

Interaction	Email exchange	Study period	
	Pre-enrollment (timepoint t_{-1})	Enrollment (timepoint t_1)	Assessment (timepoint t_2)
Enrollment			
Screen for age and MRI[a] contraindications	X		
Informed consent		X	
Otoscopy and tympanometry		X	
Audiometry		X	
Assessments			
Questionnaires		X	
Structured interview for lifetime noise exposure		X	
ABR[b]		X	
fMRI[c]			X

[a]MRI: magnetic resonance imaging.

[b]ABR: auditory brainstem response.

[c]fMRI: functional magnetic resonance imaging.

This paradigm will be used to establish monaural thresholds, in the left ear, followed by the right ear, at frequencies of 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, and 16.0 kHz. Stimuli used at frequencies 250 Hz to 8 kHz will be sinusoidal pure tones. Stimuli used at frequencies 12 and 16 kHz will be half-octave narrowband noise, to minimize the influence of ear canal resonances and threshold microstructure on measured thresholds.

Data Collection Methods: Lifetime Noise Exposure

Total noise exposure units will be estimated using a structured interview informed by the Noise Exposure and Rating Questionnaire [3]. Cumulative noise exposure over the lifetime will be assessed by a methodical and systematic approach, including noise exposure accrued in the settings of (1) occupational and educational, (2) social, and (3) gunshot and explosive noises.

For each setting, the participant will be asked to identify activities they engage in, in environments estimated to exceed 80 dB(A). For each activity, the participant will then be asked to estimate the level of exposure using a vocal effort scale comprising six different levels of vocal effort ranging from “raised voice” (87 dB(A)) to “shouting close to listener’s ear” (110 dB(A)). The participant will then be asked to estimate the duration for which they were in that environment/engaging in that activity, breaking this down into number of years, number of weeks per year, number of days per week, and number of hours per day. Finally, the participant will be asked to recall whether or not ear protection was used, what type of protection it was, and the proportion of time for which that ear protection was effective.

Data Collection Methods: Questionnaires

Participants will complete 3 questionnaires on (1) biographical data, including handedness, ethnicity, employment status and education; (2) tinnitus and hearing, including reduced sound-level tolerance, using the Tinnitus and Hearing Survey [38]; and (3) tinnitus intrusiveness, using the intrusiveness subscale of the Tinnitus Functional Index [39].

Data Collection Methods: Auditory Brainstem Response

Electrical activity will be recorded from all participants using the BioSemi ActiveTwo multichannel electroencephalography (EEG) system with active electrodes (BioSemi BV, Amsterdam, Netherlands). Three channels will be used; electrodes will be attached to the (1) vertex/Cz, (2) right mastoid, and (3) left mastoid with 10/20 electrode paste. Additional electrodes will be attached to the forehead, less than 3 inches apart, to form the ground (Common Mode Sense and Driven Right Leg).

Stimuli will be generated using in-house software written in Matlab and the same external sound card as for audiometry. Stimuli will be transmitted via shielded Etymotic ER3A transducers with disposable insert foam ear tips. ABR stimuli will consist of single-polarity high-pass filtered clicks (using a first-order Butterworth filter with high-pass cut-off=1.4 kHz) presented at 102 dB peak equivalent SPL. Click presentation will alternate between ears, at a rate of 22 s^{-1}(11 s^{-1} per ear) for a total of 7000 clicks per ear. The recording will last approximately 10 min.

Recording will be performed in an electrically shielded, darkened, soundproof room. Participants will be lying flat or near-flat and covered with a blanket. Participants will be instructed to close their eyes, relax as much as possible, and told that they should feel free to fall asleep if they are able. Stimuli will be presented near-continuously throughout the relaxation and recording period. Recording will only commence when the EEG trace has stabilized and motion artifacts have subsided.

Data Collection Methods: Magnetic Resonance Imaging

fMRI will assess auditory responses from changes associated with cerebral blood flow, volume, and oxygenation using Blood-Oxygen-Level Dependent (BOLD) contrast. BOLD responses in hypothesized cortical and subcortical regions of interest (namely the primary auditory cortex and subcortical regions of CN, IC, and MGB) will be assessed on a subject-by-subject basis.

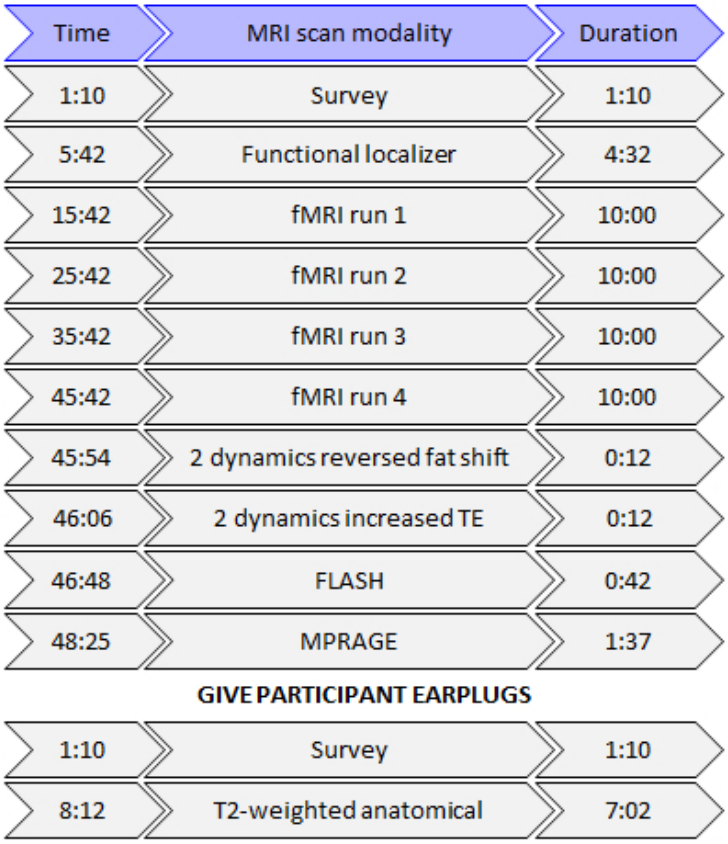
Scanning

All MRI measures for this study will be performed on a Philips 3.0 T Ingenia MR scanner (Philips Healthcare, Best, Netherlands) using a 32-element sensitivity encoding (SENSE) head coil. Subjects will wear noise-canceling headphones for the fMRI acquisition (see *Stimulus Presentation* below). A schematic of the MRI protocol is shown in Figure 1. Physiological data will be acquired throughout the scan session using respiratory bellows and a peripheral pulse unit for the purpose of performing RETROICOR (retrospective image-based correction; [40]) on the functional images to correct for physiological artifacts.

Functional MRI will be collected using a gradient echo (GE) echo-planar imaging (EPI) acquisition with high 1.5-mm isotropic spatial resolution and an echo time, TE, of 35 ms; flip angle of 90°; parallel imaging with SENSE factor of 2.5; field of view of 34.5 × 34.5 mm and a repetition time, TR, of 2 s. In total, 23 contiguous slices will be acquired with equidistant temporal slice spacing and descending slice scan order. Slices will be planned in a coronal oblique orientation to provide coverage of the brainstem and Heschl’s gyrus. Four fMRI runs will be collected in the scan session.

Before the main study fMRI runs, a functional localizer will be performed to confirm that the placement of the imaging slab includes the primary auditory areas. Responses will be elicited in these areas using a 10-Hz amplitude-modulated broadband noise stimulus of duration 24 s with a 40-s rest period, for a total of four repeats. To maximize statistical power of the functional localizer scan to detect activity in the primary auditory cortex, images will be acquired at a coarser spatial resolution of 2 mm isotropic and with a sparse repetition time, TR, of 8 s to ensure that auditory activation induced by the scanner noise has minimal influence [41].

Figure 1. Schematic of the magnetic resonance imaging (MRI) protocol used in the study. fMRI: functional magnetic resonance imaging; TE: echo time; FLASH: fast low angle shot; MPRAGE: magnetization prepared rapid acquisition gradient echo.



Following the fMRI acquisition, additional images will be acquired for image distortion correction in the preprocessing stage, particularly important for studying group responses in the brain stem. This requires the acquisition of additional EPI image volumes with each of the following modifications: (1) reversal of the fat-shift direction, that is, right as opposed to left and (2) TE increase of 2 ms, that is, 37 ms as opposed to 35 ms. Figure 2 shows uncorrected EPI distortion side by side with an image that has been distortion corrected. To assist with linear coregistration of images between image types or contrasts, and for nonlinear coregistration to standard anatomical Montreal Neurological Institute (MNI) space (MNI, Template; Montreal Neurological Institute, Montreal, Canada), a distortion-free three-dimensional (3D) fast low angle shot (FLASH; [42]) image will be acquired with the same spatial resolution and geometry as the fMRI GE-EPI scans with a TE of 20 ms, TR of 880 ms, and flip angle of 18°. In addition, a whole-brain 3D anatomical magnetization prepared rapid acquisition gradient echo (MPRAGE) acquisition also with the same resolution and angulation as the GE-EPI data will be collected.

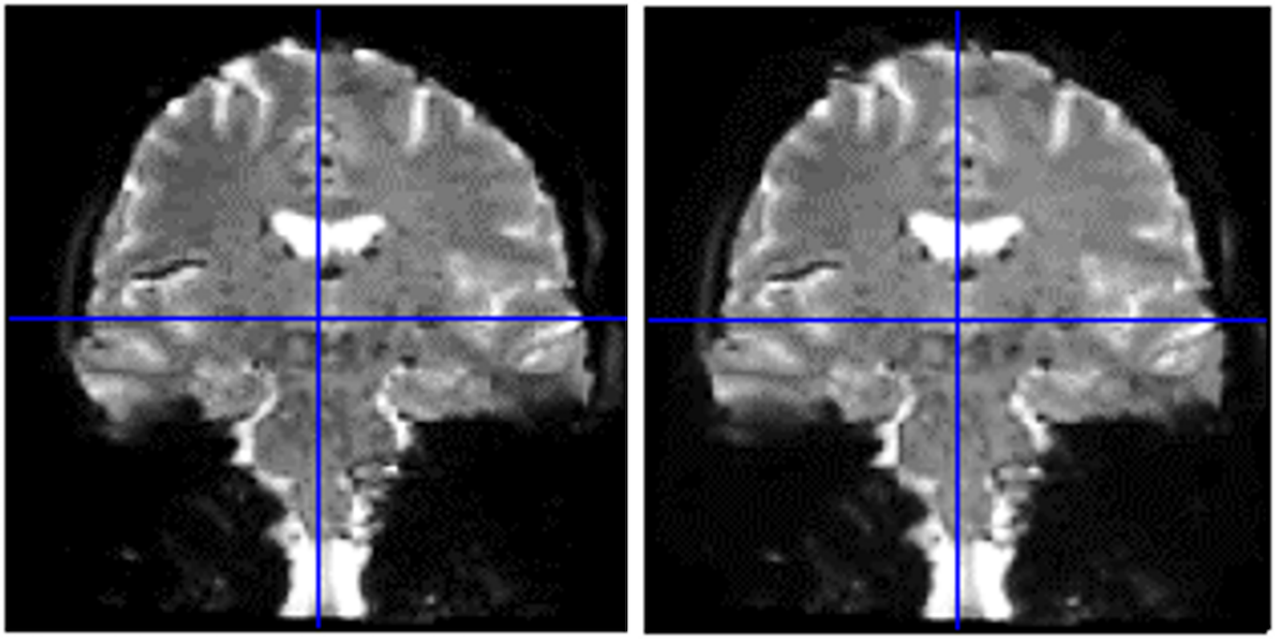
Following this session, the participants will be withdrawn from the MR scanner, and allowed to sit up and walk around if desired. They will then be given earplugs for insertion to ensure participant comfort before commencing a further scan to collect a high-resolution anatomical image. This will be a 3D T_2-weighted turbo spin echo, TSE with TE of 278 ms, a TR of 2000 ms, and flip angle of 90°; with a field of view of 249 × 249 × 72 mm and reconstructed voxel size of 0.576 mm^3.

Stimulus Presentation

The level of acoustic scanner noise during the high-resolution fMRI scans is reported by the scanner software to be 111.1 dB SPL. Auditory stimuli will be presented using the OptoActive Active Noise Cancellation Headphones system (Optoacoustics Ltd., Moshav Mazor, Israel). This provides MR-compatible delivery of high-quality sounds through circumaural headphones combined with 24-dB ear-defenders for passive attenuation of the scanner sound. Following an initial 16-s learning period, the active noise cancellation reduces the effective scanner sound to approximately 70 dB (accounting for both passive and active attenuation). Stimuli will consist of broadband noise, filtered (using a first-order Butterworth filter) between 1.4 and 4.1 kHz, and presented at 85 dB SPL.

Following an initial rest period (which includes the learning period for active noise cancellation), broadband noise will be presented for 24 s followed by a 42-s rest period. The task is passive listening and the stimulus will be presented for 8 repeats per run of 296 dynamics (10 min). A total of four 10-min fMRI runs will be performed, interspersed with a period of rest in which the researcher can communicate with the participant, and comfort can be ensured.

Figure 2. The effect of echo-planar imaging (EPI) distortion correction on the image. An uncorrected, distorted EPI (left) and corrected image (right).



A fixation cross will be presented using a 32" BOLDscreen with a 1920x1080 widescreen LCD display (Cambridge Research Systems Ltd., Rochester, UK); subjects will view the screen using a mirror attached to the head coil placed approximately 10 cm from the face, will be instructed to maintain fixation on the cross throughout the functional scans, and will be reminded to do so at the beginning of each functional run.

Data Management

All data will be anonymized at source. All electronic data will be stored on a secure remote data storage drive maintained and backed up by the University of Nottingham.

Data Preprocessing and Analysis

Lifetime Noise Exposure Data

Total noise exposure units will be calculated for each activity using the equation shown in Figure 3 [3], where *Y* is the number of years of exposure, *W* the number of weeks per year of exposure, *D* the number of days per week of exposure, *H* the number of hours per day of exposure, *L* the level of exposure, in dB (*A*), as estimated by the participant, *A* the attenuation of hearing protective equipment (dB), and *P* the proportion of time protective equipment was worn, between 0 and 1. Units for all activities will be calculated and then summed to give a participant's total lifetime noise exposure, a measure linearly related to total energy of exposure above 80 dB(A).

Auditory Brainstem Response Data Preprocessing and Analysis

ABR data will be processed using software coded in Matlab, using a procedure informed by Guest et al [19]. For each ear, the time-course of the potential difference between Cz and the ipsilateral mastoid will be filtered (using a fourth-order Butterworth filter between 30 Hz and 1.5 kHz) and divided into epochs extending from 10 ms prestimulus to 13 ms post stimulus, after correcting for the 0.91 ms acoustic delay introduced by the tube connecting the transducer to the ear. Epochs with a root-mean-square amplitude of more than 2 standard deviations above the mean will be rejected. Data will then be averaged and the resulting waveform linearly detrended. An automatic peak-picking algorithm will then identify waves I and V of the ABR for each ear based on the time windows given in Table 2.

A secondary hypothesis focuses on differences in ABR wave I amplitude and in wave I/V amplitude ratio across low and high noise exposure groups. To answer this research question, individual ABR waveforms will be obtained for each ear separately. We will explore effects of the laterality of click presentation. To do this, we will perform a mixed ANOVA of derived measures (amplitude, latency) from each ear, with left and right ears as a within-subject factor and noise exposure as a between-subjects factor.

Magnetic Resonance Image Preprocessing

Image preprocessing will be performed using FSL version 5 brain-mapping software (Functional Magnetic Resonance Imaging of the Brain, FMRIB, Analysis Group, Oxford University, UK), SPM12 (Statistical Parametric Mapping version 12, Wellcome Trust Centre for Neuroimaging, University College London, UK), and in-house software toolboxes coded in Matlab. For individual participants, the fMRI timeseries will first undergo motion correction in SPM12. Data will then be distortion corrected using FSL's TOPUP algorithm [43,44]. Data will then undergo physiological artifact correction for respiratory and cardiac effects using RETROICOR [40]. Following this, data will be spatially smoothed using a Gaussian kernel of full-width half-maximum 2 mm. Binarized masks of white matter and cerebrospinal fluid will be formed from the MPRAGE image using the segmentation tool in SPM12 and threshold at a level of 0.99999. These masks will be used to calculate mean time courses of white matter and cerebrospinal fluid (CSF) for use as nuisance covariates in the general linear model (GLM).

Figure 3. Calculation of total noise exposure units, where Y is the number of years of exposure, W the number of weeks per year of exposure, D the number of days per week of exposure, H the number of hours per day of exposure, L the level of exposure, in dB (A), as estimated by the participant, A the attenuation of hearing protective equipment (dB), and P the proportion of time protective equipment was worn, between 0 and 1.

$$total\ units = \frac{Y \times W \times D \times H}{2080} \times \left[P \times 10^{\frac{L-A-90}{10}} + (1-P) \times 10^{\frac{L-90}{10}}\right]$$

Table 2. Time windows used to constrain auditory brainstem response peak-picking algorithm.

ABR feature	Time window
Wave I peak	1.55-2.05 ms after stimulus peak
Wave I trough	0.3-1.0 ms after wave I peak
Wave V peak	5.1-6.6 ms after stimulus peak
Wave V trough	Baseline–see explanation in [19]

Individual subject data coregistration between the fMRI timeseries and the standard anatomical template will first be performed using the distortion-free MPRAGE/FLASH images, generating a matrix transform. This transform will then be applied to individual statistical parametric maps (SPMs) for region-of-interest (ROI) analyses in group or MNI space. This will allow the use of prespecified anatomically defined binary image masks of ROIs in the CN, IC, and MGB of the ascending auditory pathway, and additionally primary auditory cortex.

For interrogation of the sound-related activity at an individual level, ROIs can additionally be defined on high-resolution anatomical images. Coregistration between individuals' anatomical scan and the fMRI timeseries will be performed using the distortion-free MPRAGE image, generating a matrix transform. This transform will then be applied to the hand-drawn ROI volumes for use on the fMRI timeseries. This may be preferable for analyses involving subcortical anatomical regions, as it will take into account the intersubject anatomical differences in the brainstem.

Functional Magnetic Resonance Imaging (fMRI) Data Analysis

Statistical analyses will be performed in SPM12 using a GLM which specifies the onset, offset, and duration of the auditory stimulus as predictor variables of interest, and the 6 motion-correction parameters and mean time courses of both white matter and CSF as nuisance covariates. Three predictor variables are required to optimally describe the shape of the fMRI response, which is known to change at different stages of the auditory pathway from a response that is sustained over the stimulus duration (eg, in the CN, IC) to one that is phasic with peaks just after stimulus onset and offset (eg, in the MGB, cortex) [45].

The fit of the individual fMRI timeseries to this GLM will be calculated and SPMs corresponding to the stimulus onset, offset, and duration will be generated for each participant. These SPMs contain information about the parameter estimates in the form of voxel-wise beta estimates for each predictor variable.

The primary objective is to identify any central auditory biomarkers associated with the estimate of cumulative lifetime noise exposure. This question will be addressed using 2 analysis strategies, each using a quantification of the sound-related fMRI responses in the predesignated ROIs. First, the individual SPM outputs will form the input to a second-level GLM that will account for intersubject variability across the sample. The model will again specify the onset, offset, and duration of the auditory stimulus as within-subject factors and with low- and high-risk noise exposure as a between-subject factor. This GLM will test the question of whether there are group differences in sound-related activity. The statistical significance of the findings generated by this model will be interpreted after applying a small volume correction using the group-level ROIs. Second, the individual SPMs will be interrogated to quantify the average parameter estimate (beta value) within the individual-level ROIs, separately for the 3 predictor variables of interest. Simple linear regression analyses will be performed using units of noise exposure as a continuous regressor, and age as a regressor of no interest, to explain the variance in sound-related activity.

A secondary objective is to investigate whether there are any additive contributions to these physiological changes attributable to tinnitus or diminished sound-level tolerance, conditions which are often comorbid with hearing problems. The linear regression model will be expanded to a stepwise multiple regression modeling to examine the relative additional contributions of tinnitus and reduced sound-level tolerance to the total variance explained.

Missing Data

Any participants that have contraindications for MRI will be excluded as stated in the protocol. Analyses will be based on all observed data, but the study team will be particularly vigilant to reduce missing data. The number of these participants excluded, and those with missing data, will be reported in subsequent publications.

Incidental Findings

As the individuals this study aims to recruit are healthy, it is extremely unlikely that any MRI scan will show an abnormality. Furthermore, MRI scans will not be routinely inspected by a neuroradiologist. However, if a researcher working on the study did suspect that there was something abnormal on a scan, then

the images will be sent to a neuroradiologist who will contact the participant's GP if they decide that the scan needs further investigation.

Likewise, as the study aims to recruit individuals with normal hearing, it is not anticipated that any hearing losses measured will be severe enough to warrant concern or further investigation. If any individual is concerned by the outcome of investigation by audiometry, tympanometry, or otoscopy, the participant will be recommended that they should see their GP or visit an audiologist.

Results

The MRC-funded program was awarded in July 2013. Enrollment for the study described in this protocol commenced in February 2017 and was completed in December 2017. Results are expected in 2018.

Discussion

Dissemination Plan

To ensure maximum reach of results throughout the clinical and research communities, all work will be presented at the annual conferences of the British Society of Audiology, the Association for Research in Otolaryngology, the Tinnitus Research Initiative, and the International Society of Magnetic Resonance in Medicine, and published in peer-reviewed otolaryngology and neuroimaging journals, with Open Access. Additionally, plain language descriptions of the key findings and clinical implications will be summarized in newsletters and social media channels published by patient-facing organizations such as American Tinnitus Association, Action on Hearing Loss, British Tinnitus Association, and TinnitusHub. Anonymized raw or processed data can be made available to interested parties through communication with the corresponding author.

Conclusions

The imaging study described in this protocol seeks to provide the first comprehensive characterization of the physiological effects of noise exposure on the brains of audiometrically normal humans within major structures of the ascending auditory pathway. Our findings have the potential to inform diagnosis and prevention of hearing problems due to noise exposure. In this final section, we speculate on what those future gains might be. With respect to diagnosis, the results of this study have the potential to lead to patient benefit through early identification of cochlear damage not yet measurable by pure tone audiometry. Depending on our findings, it may be that in the future, such MRI and ABR procedures should always be used in conjunction with other available objective clinical diagnostics, such as otoacoustic emission testing, which can be important for determining subclinical dysfunctions at the level of the outer hair cells, efferent feedback control system, and the olivocochlear nucleus [18]. As such, individuals presenting with symptoms characteristic of hidden hearing loss or early signs of noise-induced cochlear synaptopathy may be offered a more informative investigation with the potential of a more specific diagnosis. With respect to prevention, identification of at-risk individuals through early detection will enable improved and personalized health care advice, promoting behaviors that improve long-term hearing health, such as increased use of ear protection. Additionally, evidence from this research can be used to determine exposure levels that are safe for the majority of individuals. This may lead to an alteration (lowering) of the current occupational noise exposure guidelines or regulations, and increased monitoring of individuals who approach unsafe exposure levels, with the advantage of greater diagnostic power afforded by the techniques outlined in this report. These latter two mechanisms in turn will lead to prevention of noise-induced hearing loss, thereby reducing the demands on health care resources.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

ABR: auditory brainstem response
AEP: auditory evoked potential
BOLD: Blood-Oxygen-Level Dependent
CN: cochlear nucleus
CSF: cerebrospinal fluid
EEG: electroencephalography
EPI: echo-planar imaging
FLASH: fast low angle shot
fMRI: functional magnetic resonance imaging

GE: gradient echo
IC: inferior colliculus
MGB: medial geniculate body
MNI: Montreal Neurological Institute
MPRAGE: magnetization prepared rapid acquisition gradient echo
MRI: magnetic resonance imaging
SENSE: sensitivity encoding
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
(SPMIC: Sir Peter Mansfield Imaging Centre
SPL: sound pressure level
TE: echo time
TR: repetition time
TSE: turbo spin echo

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Protocol

Physical Trauma Patients with Symptoms of an Acute and Posttraumatic Stress Disorder: Protocol for an Observational Prospective Cohort Study

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Abstract

Background: Injury, medical treatment, and rehabilitation can have major impacts on patients' wellbeing. About 25-33% of the patients experience an acute stress disorder (ASD) or a posttraumatic stress disorder (PTSD) after injury. ASD is a relatively new diagnosis. Therefore, knowledge about patients' experiences, the course of ASD and PTSD, and who is at risk for developing ASD or PTSD is lacking.

Objective: The aims of this multi-method study are to explore patients' experiences with injury (and their care) using a focus group study. Then, in the observational study, different courses of ASD, PTSD, and quality of life will be examined. In addition, this study will examine if these courses could be characterized by socio-demographic, clinical, and psychological variables. Consequently, a risk profile will be developed to determine which patients are at risk for developing ASD or PTSD during the 12 months after injury.

Methods: Trauma patients treated in the shock room (in 2015) of the Elisabeth-TweeSteden Hospital will share their experiences with injury in the focus group study. Open, axial, and selective coding will be used to analyze the data. Concerning the observational study, patients treated in the shock room (during 2016 and 2017, Elisabeth-TweeSteden Hospital and Erasmus Medical Centre) will be asked to participate. The inclusion period is 12 months. Participants will complete the Impact of Event Scale-Revised, MINI-plus, the Hospital Anxiety and Depression Scale, and the World Health Organization Quality of Life-BREF after inclusion and at 3, 6, 9, and 12 months after injury. The NEO-Five Factor Inventory and the State-Trait Anxiety Inventory-Trait are completed after inclusion only. Repeated measures of latent class analysis and linear mixed models will be used to examine the research aims.

Results: This project was funded in August 2015 by ZonMw. The results of the focus group study are expected in the first trimester of 2018. With regard to the observational study, recruitment is currently underway. Data collection will be completed in November 2018. The first results will be expected in the first trimester of 2019.

Conclusions: This is the first multi-method study in trauma patients that examines patients' experiences (qualitative design) as well as psychological disorders (observational prospective). This study will contribute to necessary information on psychological consequences after injury. Moreover, it provides knowledge about which patients to include in future psychological intervention research. Finally, awareness in clinicians about the psychological consequences can be created, so they are able to act more effectively to provide patient-oriented care.

Trial Registration: Netherlands Trial Registry NTR6258; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6258 (Archived by WebCite at http://www.webcitation.org/6xSCiO1bS)

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KEYWORDS

acute stress disorder; posttraumatic stress disorder; PTSD; ASD; trauma; injury; observational study; qualitative study; focus groups

Introduction

Due to registration and implementation of specialized trauma care, the quality of medical treatment has been improved and survivorship has been increased [1-6]. Trauma is related to physical disabilities (eg, pain, fatigue and impaired wound healing), acute stress disorder (ASD), posttraumatic stress disorder (PTSD), and psychological distress [7-13]. Moreover, trauma patients experience an impaired quality of life (QOL) compared to the general population [14-20].

About 25% of trauma patients have subsyndromal ASD during hospitalization and about 30% had PTSD one month after injury [8,21]. Six months after injury, 49% showed a delayed onset of PTSD. This percentage decreased to 20% at 24 months after injury. A recent systematic review showed that patients diagnosed with ASD had a higher risk of developing PTSD [8]. However, the prevalence rate of patients with ASD who develop PTSD is unknown. Diagnostic criteria for ASD and PTSD are similar; however, dissociative symptoms (eg, depersonalization, derealization, and dissociative amnesia) are only emphasized in ASD and not in PTSD. Moreover, ASD can only be diagnosed within the first month after trauma and last for less than a month, while PTSD symptoms persist for at least one month after injury [22]. PTSD symptoms may begin either after trauma or months or years afterwards [23].

In addition to QOL, PTSD, anxiety, and depression are most frequently examined after injury [15-20]. However, information about ASD is scarce. The existing studies of ASD and PTSD are often cross-sectional. Moreover, in the case of an observational prospective design, examination of PTSD is limited to only several months after trauma. One or several measurements are needed to examine patients' psychological recovery shortly after injury. Important information about the courses of ASD and PTSD (ie, main scores of onset and development, such as the stability of symptom severity over time) and patients' characteristics is lacking [8,24,25]. More specifically, it is unknown if and in what way patients' experiences with injury and treatment, for instance, in the shock room, contribute to psychological consequences. Moreover, factors related to communication between medical staff and patient, treatment of injury, and environment are not known. Gaining information about the development of ASD and PTSD and their sustaining risk factors will increase the quality of care because patients at risk can be offered psychological treatment, thereby preventing the development of psychological disorders, such as ASD and PTSD. Health care providers with the knowledge of medical and psychological consequences after trauma can better anticipate patients' needs so that patient-centered care can be provided.

This multi-method study consists of a focus group study and an observational prospective study. The ultimate goal of this multi-method study is to provide valuable insight into the severity of psychological consequences, including ASD and PTSD, and the need for a psychological intervention study to prevent PTSD. First, focus groups are held to examine patients' experiences with injury (and their care). In this way, potential factors related to the development of psychological problems (eg, depressive symptoms) and disorders (eg, anxiety, ASD, and PTSD) can be obtained and taken into account for the observational study (aim 1). Subsequently, an aim of the observational study is to examine the courses of ASD and PTSD (aim 2). In addition, it will be examined which socio-demographic (ie, sex, age, marital status, and education level), clinical (ie, type of trauma, Injury Severity Score (ISS), Glasgow Coma Score, being hospitalized, being treated on the intensive care unit, complications during treatment, and treatment by a medical psychologist or psychiatrist), and psychological variables (eg, anxiety, depressive symptoms, and personality) characterize the courses of ASD and PTSD. Subsequently, a risk profile will be developed to determine which patients are at risk for ASD and/or PTSD (aim 3). Finally, to study the effect(s) of the natural course of ASD symptoms on the development of PTSD, anxiety and depressive symptoms, and QOL across time will be analyzed (aim 4).

Methods

Design

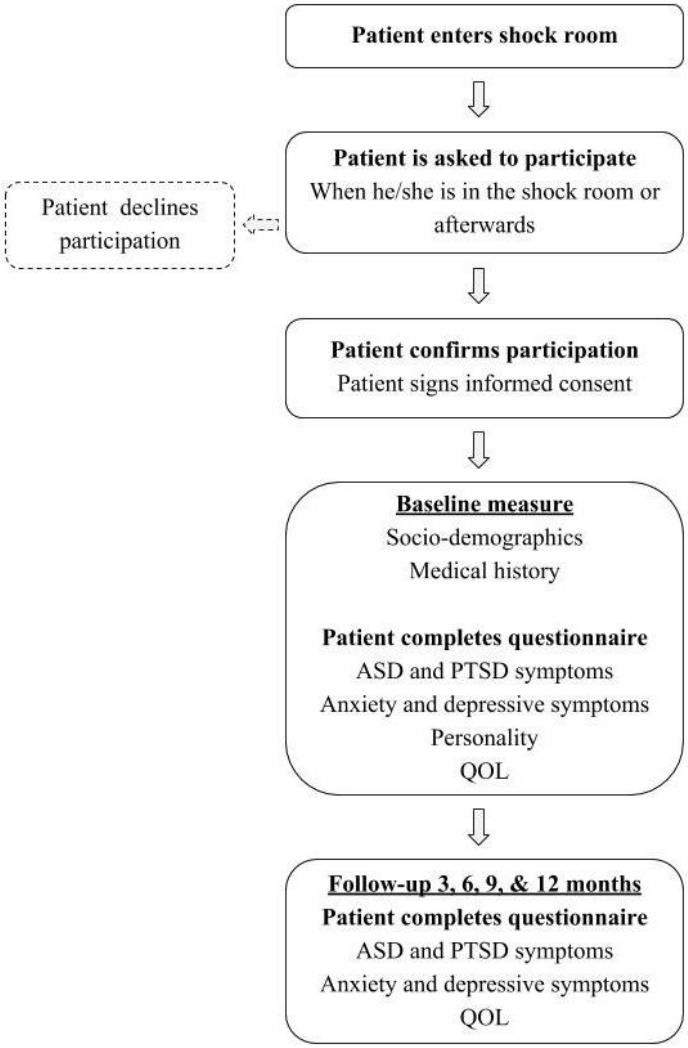
First, using a qualitative focus group study design, patients' perspectives on the injury, treatment in the shock room and hospital, and rehabilitation are explored. A focus group is a commonly used method of qualitative research as it is a valid and reliable technique. Moreover, focus groups facilitate the in-depth exploration of a person's perspective through group interaction. Participants can be triggered by a comment from another participant [26,27], and by the concept of sharing and comparing [28]. Then, as an extension of the focus group study, the observational prospective cohort study will examine ASD, PTSD, anxiety and depressive symptoms, and QOL. This will be assessed up to one year after treatment for physical trauma. A flow diagram of the observational study design and the main procedures that patients will undergo during the course of the observational study are shown in Figure 1.

Participants and Centers of Recruitment

Trauma patients treated in the shock room in 2015 of the Elisabeth-TweeSteden Hospital are asked to participate in the focus group study. A shock room is situated at the Emergency

Department and is reserved for physical trauma patients (ie, all types of injury) with a potentially life-threatening situation.

Figure 1. Flowchart of the study design. ASD: acute stress disorder; IC: informed consent; PTSD: Posttraumatic stress disorder; QOL: quality of life.



Concerning the observational study, all adult patients who have been in the shock room at the Emergency Departments of the Elisabeth-TweeSteden Hospital (Tilburg) or the Erasmus Medical Centre (Rotterdam, The Netherlands) are asked to participate. The inclusion period is about 12 months after the start in November 2016.

Sample Size Calculation

This project is exploratory in nature. Moreover, the focus is on examining the stability of results. The sample size was calculated only for the observational study. According to the Dutch trauma registry, the shock room admission was about N=1440 in 2013 and N=986 in 2016 in the Elisabeth-TweeSteden Hospital. Using a mean of these admission numbers of (N=1213, alpha=0.05, beta=0.80, and effect size=0.4), it was estimated that N=300 would be sufficient. This was also based on Monte Carlo simulations [29].

Inclusion and Exclusion Criteria

In order to be eligible to participate, patients (1) are treated in the shock room and (2) are aged 18 or older. Patients are excluded from participation in case of (1) severe traumatic brain injury (ie, Glasgow Coma Score ≤ 8), (2) dementia, or (3) insufficient knowledge of the Dutch language (verbal and writing). These criteria are used in the focus group and the study observational study.

Study Procedures

Focus Groups

Trauma patients who were treated in the shock room of the Elisabeth-TweeSteden Hospital during 2015 were asked to participate in a qualitative focus group study. Patients were divided into 3 groups: (1) patients who went home after treatment in shock room (no hospitalization) or, in case of hospitalization, they had an ISS of less than 16; (2) ISS equal or higher than 16, and (3) mild or moderate traumatic brain injury (Glasgow Come Score > 8). Six to 10 patients were invited to participate in each group. To obtain a representative sample of the trauma population, the division into groups was based on type of injury, sex, and age. The purposive sampling method was used [26,27].

The focus group meetings took place in a conference room at the Elisabeth-TweeSteden Hospital. Each focus group was guided by a moderator and an assistant. The patients were asked

to share their experiences by answering the main question, "What experience related to your injury impressed you the most?" Their experiences were clustered on a flipchart on the basis of the trauma procedure: (1) moment of injury, (2) treatment in the ambulance or the trauma helicopter, (3) treatment in the shock room, (4) hospital stay, (5) moment of discharge, and (6) period after discharge and/or rehabilitation. Finally, another main question, "In what way did you need and received psychological treatment?", was discussed. At the end of each focus group, participants were asked to complete questions about their socio-demographic status (ie, age, sex, marital status, and education level). In addition, they completed the Impact of Event Scale revised (IES-R) for PTSD and the Hospital Anxiety and Depression Scale (HADS) for anxiety and depressive symptoms. All focus groups had the same structure and were audio-recorded. The duration of the meeting was about 90 minutes.

Observational Study

The emergency doctor or the resident will ask patients to participate in this study as soon as they can talk and are lucid. If the emergency doctor or the resident is not able to ask the patient to participate (eg, due to transferring the patient to another department in the hospital), the researcher will ask the patient as soon as possible to participate in this study. The researcher will check medical records to see whether there are patients that have not yet been asked to participate in the study.

Patients will sign two informed consents. First, in the emergency department (after being treated in the shock room and being informed by the doctor). Then 1-5 days later, the patient will be asked to confirm participation again to make sure that they have sufficient time to consider participation in the study. In the case of a patient who is unconscious, the patient will be informed by the researcher and asked to participate as soon as the patient is lucid. If a patient declines participation by not signing the second informed consent, all obtained information will be destroyed.

After confirming participation, the patient will complete a questionnaire on socio-demographic questions, ASD and PTSD, anxiety and depressive symptoms, personality, and QOL at the first time-point (ie, baseline). Clinical information will be retrieved from patients' medical records. The measurement points are at inclusion, 3, 6, 9, and 12 months after injury (see Figure 1).

Data Collection

Focus Groups

The topic of the interviews are focused on patients' experiences with the traumatic event (see Study Procedures). In addition, participants were asked to complete socio-demographic questions, the IES-R and the HADS. All focus groups have the same structure and are audio-recorded. The recorded focus groups are transcribed verbatim [26,27].

In case of observed severe symptoms of ASD or PTSD during focus group sessions, the treating physician was informed. The doctor could refer the patient for a consult with a psychologist in the department of Medical Psychology at the Elisabeth-TweeSteden Hospital who is specialized in psychological treatment after injury.

Observational Study

Data for the observational study will be collected using a structured interview—MINI-plus for ASD and PTSD—as well as self-report questionnaires: (1) the IES-R for ASD and PTSD, (2) HADS, (3) NEO Five-Factor Inventory (NEO-FFI) and the State Trait Anxiety Inventory (STAI) - Trait scale for personality, and (4) World Health Organization Quality of Life assessment instrument-Bref (WHOQOL-Bref) for QOL. All outcome measures will be assessed after treatment in the shock room (baseline), 3, 6, 9, and 12 months after injury. However, ASD and personality will only be measured at baseline (see Table 1).

Acute Stress Disorder and Post Traumatic Stress Disorder

The MINI-Plus [22] and the IES-R [30] assess ASD and PTSD symptoms. Since both instruments are often used (together) in clinical practice, we will use both in the current study.

The MINI-Plus is a short structured interview based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and it will be used to assess ASD and PTSD symptoms [22]. The items are dichotomous because symptoms are present or absent. The DSM-5 is a classification of mental disorders with associated criteria designed to facilitate more reliable diagnoses of these disorders compared to the DSM-IV. It is a standard reference for clinical practice in the field of mental health [22]. For diagnostic criteria for ASD, see Multimedia Appendix 1 and for PTSD, see Multimedia Appendix 2.

The IES-R is a self-report questionnaire to assess symptom severity of ASD and PTSD [30]. It consists of 15 items which measure intrusive re-experiences of the injury and avoidance of injury-related stimuli. The respondent states whether the content of each statement was present during the past 7 days. A 4-point Likert scale will be used ranging from 0 (*not at all*) to 5 (*often*). The cut-off score for a probable diagnosis of PTSD is ≥ 33 and have good diagnostic accuracy [31,32]. The IES-R has good psychometric properties [32] and the Dutch translation of the IES-R has been found to be valid and reliable [33].

Anxiety and Depressive symptoms

The HADS measures anxiety and depressive symptoms [34]. It is a generic questionnaire measuring levels of anxiety (7 items) and depression (7 items) with a 4-point rating scale ranging from 0 (*not at all*) to 3 (*very much*). Subscale values ≥11 for one of the subgroups are observed as an indication for a psychological disorder, as this cut-off score provides the lowest proportion of false positives (5% for anxiety and 1% for depression) [34]. The questionnaire is shown to be reliable and valid [34].

Table 1. Overview of self-report questionnaires

Study and related questionnaires	Domain	Outcome measures	Time point for retrieval
Focus group study			
Patients' experiences	N/A[a]	Primary outcome	N/A
IES-R[b]	PTSD[c]	Secondary outcome	Shortly after meeting
HADS[d]	• Anxiety • Depressive symptoms	Secondary outcome	Shortly after meeting
Sociodemographic questions	• Educational level • Living situation • Paid job	Secondary outcome	Shortly after meeting
Observational study			
MINI-Plus	• ASD[e] • PTSD	Primary outcome	• Baseline • 3 months • 6 months • 9 months • 12 months
IES-R	• ASD • PTSD	Primary outcome	• Baseline • 3 months • 6 months • 9 months • 12 months
HADS	• Anxiety • Depressive symptoms	Secondary outcome	• Baseline • 3 months • 6 months • 9 months • 12 months
NEO-FFI[f]	Personality	Secondary outcome	Baseline
STAI[g]-Trait	Personality	Secondary outcome	Baseline
WHOQOL-Bref[h]	QOL[i]	Secondary outcome	• Baseline • 3 months • 6 months • 9 months • 12 months

[a]N/A: Not applicable.

[b]IES-R: Impact of Event Scale-Revised.

[c]PTSD: posttraumatic stress disorder.

[d]HADS: Hospital Anxiety and Depression Scale.

[e]ASD: acute stress disorder.

[f]NEO-FFI: NEO Five-Factor Inventory.

[g]STAI: State Trait Anxiety Inventory.

[h]WHOQOL-Bref: World Health Organization Quality of Life assessment instrument-Bref.

[i]QOL: quality of life.

Personality

Personality will be assessed using the NEO-FFI [35] and the STAI-Trait scale [36]. The 60-item NEO-FFI measures the Big Five personality domains: (1) Neuroticism, (2) Extraversion, (3) Openness to experience, (4) Agreeableness, and (5) Consciousness from the five factor model [35]. Each statement is rated on a five-point rating scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*), resulting in dimension scores between 12 and 60. The psychometrics has been extensively assessed and the internal consistency, test-retest reliability, and validity are acceptable to good [37].

The STAI (short form) consists of 20 items for measuring state anxiety (10 items) and trait anxiety (10 items) [36]. In this study, only the STAI-Trait scale will be used. This scale describes the person's tendency to experience feelings of anxiety and stress. The STAI-Trait scale has a four-point rating scale ranging from 1 (*almost never*) to 4 (*almost always*). The Dutch version of the STAI is a reliable and valid instrument [38].

Quality of Life

QOL will be measured with the WHOQOL-Bref [39]. This 26-item questionnaire is a short version of the WHOQOL-100 and assesses four domains (Physical health, Psychological health, Social relationships, and Environment) as well as one general facet "Overall QOL and General Health". The questions in the domains are derived from the 24 facets of the WHOQOL-100, with one item from each of the facets. Each item is rated on a five-point rating scale. Higher scores indicate better QOL [39,40]. The WHOQOL-Bref has good psychometric properties as prior research shows that the WHOQOL-Bref is a reliable and valid instrument [40-43].

Additional Assessments

Socio-demographic information (ie, sex, age, marital status, and education level) will be obtained from patients at baseline. Clinical information, including date of trauma treatment, ISS, type of trauma mechanism (eg, traffic accident or fall), type of injury (eg, fracture), trauma treatment (eg, operation or medication), consult or treatment from medical psychology (yes/no and which type of treatment), hospital stay (yes/no), in case of hospital stay, admission to intensive care unit, and duration of hospital stay will be abstracted from the patients' medical records. Possible logistic problems will also be recorded.

Statistical Analysis

Focus Groups

The recorded focus groups are analyzed using open, axial, and selective coding technique [26,27]. Open coding is used to identify different domains: physical, psychological, social, and environmental. Then, axial and selective coding is conducted to determine different themes. These codes consist of single words or short sentences. Two reviewers independently reviewed and coded each of the transcripts and ensured data saturation. Atlas.ti is used for analyzing the transcripts [44]. In addition, patient characteristics, PTSD, anxiety and depressive symptoms, and responses on the questionnaires were analyzed using descriptive statistics in SPSS version 22.

Observational Study

The patient characteristic will be studied using descriptive statistics. Then, the baseline characteristics (ie, sociodemographic, clinical, and psychological variables) of participants versus nonparticipants, participants who complete versus drop out during follow-up, and participants who are discharged versus being in the hospital after treatment in the shock room will be compared using independent t-tests and Chi-squared tests. Nonnormal continuous data will be analyzed with Mann-Whitney U tests or Fisher's exact tests.

Repeated measures of latent class analysis will be used to analyze the courses (ie, time is independent variable) of ASD and PTSD (dependent variables). Moreover, to examine if these different courses of ASD and PTSD (independent variable) could be characterized by socio-demographic (eg, sex, age, education level, and living situation) and clinical (eg, type of trauma, ISS, Glasgow Coma Score, being hospitalized, being treated on the intensive care unit, complications during treatment, and treated by a medical psychologist or psychiatrist), and psychological (eg, anxiety, depressive symptoms, and personality) variables (dependent variables). As a result, each class will represent a different course of ASD and PTSD. By focusing on the characteristics of the different classes, a risk profile will, consequently, be developed to determine which patients are at risk for ASD or PTSD. Sociodemographic and clinical variables are examined as moderating effect, while psychological variables are studied as mediating effects.

Linear mixed models, repeated measures, will be used to examine the effect of ASD (independent variable) on PTSD, anxiety and depressive symptoms, and QOL domains (dependent variables) over time (see Table 2).

The ISS, type of injury and type of trauma mechanism (eg, traffic accident or fall) will be used as covariates.

Table 2. Overview of statistical analysis

Baseline analysis and aims[a]	Independent variables	Dependent variables	Analyses
Patient characteristics	Sociodemographics	N/A[b]	Frequencies Descriptives
	Clinical variables	N/A	Frequencies Descriptives
	Psychological variables	N/A	Frequencies Descriptives
Comparison of patient characteristics	Participants versus nonparticipant	• Sociodemographics • Clinical variables • Psychological variables	Continuous data: Independent t-test, Mann-Whitney U Categorical data: Chi-squared, Fishers' exact test
	Completers versus noncompleters	• Sociodemographics • Clinical variables • Psychological variables	Continuous data: Independent t-test, Mann-Whitney U Categorical data: Chi-squared, Fishers' exact test
	Participants being discharged versus being in the hospital	• Sociodemographics • Clinical variables • Psychological variables	Continuous data: Independent t-test, Mann-Whitney U Categorical data: Chi-squared, Fishers' exact test
Aim 2: Course of ASD and PTSD	Time	• ASD[c] • PTSD[d]	Repeated measures, latent class analysis
Aim 3: Risk profile	• ASD • PTSD	• Sociodemographics • Clinical variables • Psychological	Repeated measures, latent class analysis
Aim 4: Effect of ASD	ASD	• PTSD • Anxiety • Depressive symptoms • QOL[e]	Linear Mixed models, repeated measures

[a]The dependent and independent variables for aim 1 could not be provided because this aim focuses on qualitative data.

[b]N/A: Not applicable.

[c]ASD: acute stress disorder.

[d]PTSD: posttraumatic stress disorder.

[e]QOL: quality of life.

Results

Data collection and analysis for the focus group study are completed. Results will be reported in 2018. Enrollment of participants for the observational study began in November 2016. Data collection will be completed by the end of 2018. The study results will then be reported in 2019.

Discussion

This is the first multi-method study in trauma patients that examines psychological consequences after injury, using both a qualitative focus group study design as well as an observational prospective design. In the focus group study, the aim was to interview patients about their experiences with the injury, treatment, and rehabilitation. Since it is unknown if and in what way patients' experiences contribute to the development of psychological problems and disorders. The observational study will examine the course of ASD and PTSD, as ASD after injury is less studied and it is unknown how ASD and PTSD develop over time up to 12 months after injury. Moreover, as a result of all outcome measures, a risk profile of patients may be determined to predict which patients are at risk for developing ASD or PTSD. Altogether, this study will provide information concerning which patients to include in further research that focuses on psychological intervention.

Several factors related to the design and execution must be taken into account. First, response bias may occur in the focus group study. Patients may decline participation because they are not interested in discussing their experiences, or it might be too confronting to talk about their experiences and psychological problems. Second, it is known that the population of trauma patients has a broad variety of trauma mechanisms and injuries. Therefore, it might be difficult to generalize to the whole trauma population. However, concerning the observational study, almost all trauma patients being treated in the shock room will be included from two different Level-1 trauma centers so data saturation can be reached. These centers are located in different provinces and cities in The Netherlands. Therefore, a representative population in the observational study can be included. Third, patients with severe injuries might be less capable to complete the baseline questionnaire almost directly

after injury due to being treated at the intensive care unit. Patients will, therefore, be asked to fill in the date of completing the questionnaire and if they needed any help. Then, the time between injury and measurement can be analyzed. This provides information on what time severely injured patients are capable to complete the baseline questionnaire.

In conclusion, this study is exploratory in nature and it will contribute to the need for information on psychological consequences after injury. Then, awareness in clinicians about the consequences can be created so they are able to act more effective and patient-oriented care can be provided.

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Authors' Contributions

EV, TG and JDV have contributed to the study conception and design. EV is responsible for the data acquisition and drafting the manuscript. TG, BDO and JDV perform the general supervision of this multi-method study. All authors have critically revised the final manuscript. All authors have read and have given approval of the final manuscript to be published. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

None declared.

Multimedia Appendix 1

DSM-5 Diagnostic criteria for acute stress disorder (ASD).

[PDF File (Adobe PDF File), 29KB - resprot_v7i3e88_app1.pdf]

Multimedia Appendix 2

DSM-5 Diagnostic criteria for posttraumatic stress disorder (PTSD).

[PDF File (Adobe PDF File), 38KB - resprot_v7i3e88_app2.pdf]

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Abbreviations

ASD: acute stress disorder
DSM: Diagnostic and Statistical Manual of Mental Disorders
HADS: Hospital Anxiety and Depression Scale
IES-R: Impact of Event Scale-Revised
ISS: Injury Severity Score
NEO-FFI: NEO Five-Factor Inventory
PTSD: posttraumatic stress disorder
QOL: quality of life
STAI: State Trait Anxiety Inventory
WHOQOL-Bref: World Health Organization Quality of Life assessment instrument-Bref

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Corrigenda and Addenda

Conflict of Interest Addendum: Assessing the Efficacy of an App-Based Method of Family Planning: The Dot Study Protocol

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The authors of "Assessing the Efficacy of an App-Based Method of Family Planning: The Dot Study Protocol" (JMIR Res Protoc 2017;6(1):e5) have a previously undisclosed competing interest as follows:

> The product under investigation (the Dynamic Optional Timing [DOT] app) is the property of Cycle Technologies, Inc, a for-profit corporation based in Washington, DC. The CEO of Cycle Technologies is Leslie Heyer (née Jennings), who is the daughter of Victoria Jennings, one of the co-authors of this article. The efficacy study on DOT uses funds from a research grant awarded to the Institute for Reproductive Health at Georgetown. Cycle Technologies Inc or their employees do not receive any licensing fees, honoraria, or financial contributions related to the study.

The corrected article will appear in the online version of the paper on the JMIR website on March 16, 2018, together with the publication of this correction notice. Because this was made after submission to PubMed or PubMed Central and other full-text repositories, the corrected article also has been re-submitted to those repositories.

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Corrigenda and Addenda

Correction: An App to Help Young People Self-Manage When Feeling Overwhelmed (ReZone): Protocol of a Cluster Randomized Controlled Trial

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The authors of "An App to Help Young People Self-Manage When Feeling Overwhelmed (ReZone): Protocol of a Cluster Randomized Controlled Trial" (JMIR Res Protoc 2017;6(11):e213) would like to add the following Acknowledgments section as it is important funding information:

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The corrected article will appear in the online version of the paper on the JMIR website on March 16, 2018, together with the publication of this correction notice. Because this was made after submission to PubMed or PubMed Central and other full-text repositories, the corrected article also has been re-submitted to those repositories.

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Protocol

A Web- and Mobile-Based Map of Mental Health Resources for Postsecondary Students (Thought Spot): Protocol for an Economic Evaluation

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Abstract

Background: Youth demonstrate a low propensity to seek help for mental health issues and exhibit low use of health services despite the high prevalence of mental health challenges in this population. Research has found that delivering interventions via the internet and mobile devices is an effective way to reach youth. Thought Spot, a Web- and mobile-based map, was developed to help transition-aged youth in postsecondary settings overcome barriers to help-seeking, thereby reducing the economic burden associated with untreated mental health issues.

Objective: This paper presents the protocol for an economic evaluation that will be conducted in conjunction with a randomized controlled trial (RCT) to evaluate the effectiveness and cost of Thought Spot compared with usual care in terms of self-efficacy for mental health help-seeking among postsecondary students.

Methods: A partially blinded RCT will be conducted to assess the impact of Thought Spot on the self-efficacy of students for mental health help-seeking. Students from 3 postsecondary institutions in Ontario, Canada will be randomly allocated to 1 of 2 intervention groups (resource pamphlet or Thought Spot) for 6 months. The economic evaluation will focus on the perspective of postsecondary institutions or other organizations interested in using Thought Spot. Costs and resources for operating and maintaining the platform will be reported and compared with the costs and resource needs associated with usual care. The primary outcome will be change in help-seeking intentions, measured using the General Help-Seeking Questionnaire. The cost-effectiveness of the intervention will be determined by calculating the incremental cost-effectiveness ratio, which will then be compared with willingness to pay.

Results: The RCT is scheduled to begin in February 2018 and will run for 6 months, after which the economic evaluation will be completed.

Conclusions: We expect to demonstrate that Thought Spot is a cost-effective way to improve help-seeking intentions and encourage help-seeking behavior among postsecondary students. The findings of this study will help inform postsecondary institutions when they are allocating resources for mental health initiatives.

Trial Registration: ClinicalTrials.gov NCT03412461; https://clinicaltrials.gov/ct2/show/NCT03412461 (Archived at WebCite at http://www.webcitation.org/6xy5lWpnZ)

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KEYWORDS

economic evaluation; health economics; transition-aged youths; participatory action research; mental health

Introduction

Background

According to the National Alliance on Mental Illness [1], approximately 75% of mental illnesses develop by age 24. Additional evidence suggests that the first onset of mental disorders usually occurs between ages 18 and 24, which is the typical age range of postsecondary students [2].

Transition-aged youth in postsecondary school can face major barriers to academic success as a result of mental illness. Languishing mental health or the presence of mental illness can impair their ability to function [3]. Mental health challenges may adversely affect academic performance and educational attainment by reducing learning opportunities and decreasing the ability to absorb information and demonstrate learning [4,5]. Eisenberg and colleagues [6] found that college students with depression had lower productivity rates in school compared with students without the disorder [6]. This lower performance increases the risk of lower grade point averages and course or semester withdrawal.

Early onset of mental health issues, such as depression, is also associated with the early termination of schooling [4,7]. Adolescents with anxiety disorders are at increased risk of academic underachievement and school dropout compared with adolescents without these disorders [8]. Disruptions to educational attainment can have a wide range of effects on physical and mental health in adulthood [6,9] and on social ability [10]. They also reduce productivity and create large economic losses for the individual [5,11,12]. Students, who are unable to keep up with academic expectations and are thus at increased risk of withdrawing from the semester, may lose investments in their education in the form of nonrefundable tuition payments and lost future income due to delayed graduation and later entry into the workforce [13,14]. Moreover, disrupted education limits career prospects [5].

Mental health issues among students also have a large economic impact on postsecondary institutions [15]. The need for mental health services in colleges and universities has increased the financial burden on these institutions. Canadian postsecondary institutions continue to face challenges associated with limited resources and funding due to the greater costs associated with the high prevalence of mental health issues in young people [15].

Mental Health Climate in Canadian Postsecondary Institutions

The burden of mental illness and emotional crisis among students has been increasing at an exponential rate across Canadian postsecondary institutions: schools are seeing a 200% increase in the demand for counselling services and more than 50% of students report feelings of hopelessness and anxiety [16]. In an assessment of the mental health climate across 41 Canadian postsecondary institutions in 2016, the American College Health Association found that 58% to 73% of students reported feeling hopeless, overwhelmed, lonely or sad, and 13% had seriously considered suicide in the previous 12 months [17]. Approximately 1 in 10 students reported self-harm, including burning, bruising, and cutting. Moreover, although students indicated that mental health concerns, financial difficulties, gambling, relationship and roommate problems, drugs and alcohol use, and other factors affected their academic performance, less than half reported ever receiving help from a medical or mental health care provider or from on-campus counselling services [17].

Despite the high prevalence of mental health and addiction challenges among postsecondary students, there is a low propensity to seek professional or nonprofessional help, resulting in a low use of health and wellness services [3,18-22]. Barriers to seeking help include stigma and embarrassment, trust and confidentiality concerns, poor mental health literacy, negative attitudes or shame for seeking professional help, and lack of knowledge about where to get help [23-26]. These findings highlight the need for an intervention that helps students overcome barriers to seeking help. With 90% of youth using the internet, health interventions hosted on the Web (electronic health) or on mobile devices have been found to be effective methods for reaching this population [27-30]. In an effort to reach this population of postsecondary students (16-29 years of age), the University of Toronto's Faculty of Medicine and the Centre for Addiction and Mental Health worked with partners from Ryerson University, the Ontario College of Art and Design, and ConnexOntario to engage with university and college students to co-develop a mobile and online resource called Thought Spot. The project was funded by the Ontario Ministry of Training, Colleges and Universities.

The Thought Spot platform was created through collaboration with postsecondary students. The student-led project aims to improve postsecondary students' knowledge of, access to, and navigation within addiction and mental health services by digitally mapping mental health, health, and wellness services in the Greater Toronto Area in Ontario, Canada [31]. This Web- and mobile-based map strives to help students overcome barriers to help-seeking, such as health illiteracy and stigma, by increasing their knowledge of local services while simultaneously decreasing the need for intermediaries such as friends, family members, and physicians.

Objectives

This paper describes a proposed protocol for an economic evaluation of Thought Spot. The evaluation will be conducted using data from a randomized controlled trial (RCT) that evaluates the impact of the Web- and mobile-based app compared with usual care on self-efficacy for mental health help-seeking among university and college students [31]. By conducting an evaluation through an economic lens, researchers will be able to quantify the cost-effectiveness of the intervention. The evaluation will assess the cost and effect of the intervention on mental health help-seeking, and the findings will inform future recommendations regarding intervention use.

Methods

Study Design and Target Population

The Consolidated Health Economic Evaluation Reporting Standards guidelines were used to develop this protocol to ensure that the reporting of relevant information for the economic evaluation is consistent with the international standards set out by the International Society of Pharmacoeconomics and Outcomes Research [32].

The economic evaluation will be conducted using data from the primary study, which is a partially blinded RCT with two arms. The full protocol for the RCT has been published elsewhere [31]. The study will recruit 472 students, aged 17 to 29 years, at George Brown College, Ryerson University, and the University of Toronto, who have self-identified as having mental health concerns or an interest in managing their mental health. We will recruit participants through recruitment flyers and messaging, both online (eg, social media and listserv), and physical posters around campus. All participants must have functional competency in English and access to digital devices compatible with the Thought Spot digital platform. Participation is strictly voluntary, and participants may withdraw from the study at any time. Individuals who self-report being actively suicidal will be excluded from the study. Participants will be randomly assigned to the control arm or the intervention arm. The study will take place over 6 months, with measurements taking place at baseline, 3 months, and 6 months. Additional information on the study design and methods is available in the project protocol paper [31].

Intervention

Participants in the intervention arm will receive access to the Thought Spot platform. They will watch an online “tour the app” video and receive login instructions via email. Participants in the control arm will receive a resource pamphlet via email tailored to each school [31].

Perspective

The growing need for mental health services for young people has increased the economic burden on postsecondary institutions. A cost-effective intervention for students may reduce the financial strain. To this end, the analysis in this study will take the perspective of potential adopters and promoters of the Thought Spot platform, namely postsecondary institutions and other organizations supporting transition-aged youth.

Estimating Resources and Costs

The study will report the total resources and costs associated with researching, developing, implementing, and evaluating the Thought Spot platform. These values include costs of starting the project anew rather than costs associated with adopting the Thought Spot project. Because many of the research and development costs will not be relevant to future project adopters, only costs and resources associated with hosting and maintaining the Thought Spot platform will be included in the economic evaluation. Project costs that have already been incurred and that will not be assumed by future project adopters will be excluded in the cost-effectiveness calculations. All costs and effects will be valued using the study period as the time horizon (6 months). All costs will be reported in 2018 Canadian dollars.

Choice of Health Outcomes

The primary effect variable in the economic evaluation will be change in help-seeking intentions among participants for the duration of the RCT. This change will be assessed using the General Help-Seeking Questionnaire (GHSQ). Responses on this 10-item, 7-point Likert scale range from “extremely unlikely” to “extremely likely” to measure the likelihood that participants will seek help from various formal and informal sources. A higher score indicates greater intent to seek help. The GHSQ scale was chosen to measure the primary outcome because validation studies have suggested a positive and significant correlation between to seek mental health care and seeking care [33]. As a result, an assumption of the evaluation is that secondary outcomes (ie, positive changes in help-seeking behaviors among participants) are attributed to positive changes in the primary outcome, help-seeking intentions.

Analytic Methods

The evaluation will report the cost per change in help-seeking intentions among the target population. The cost-effectiveness of the intervention will be reported using the incremental cost-effectiveness ratio (ICER) [34], using the following formula:

$$ICER=\Delta C/\Delta E$$

where ΔC represents the difference in cost between the Thought Spot platform and usual care ($C_{treatment}–C_{usual\ care}$), and ΔE represents the change in help-seeking intentions among the intervention and control arms as measured by the GHSQ ($E_{treatment}–E_{usual\ care}$). The ICER will represent the extra cost per additional increase in help-seeking intentions. Cost-effectiveness acceptability curves and 95% confidence intervals will be generated to represent the uncertainty around this value [35].

The calculated ICER can subsequently be compared with willingness to pay (WTP) which allows individuals to value a benefit in terms of a monetary value. WTP allows for recommendations to be made about intervention use by determining whether a decision maker is willing to pay the cost to receive one additional outcome. WTP can be elicited in various ways including directly asking individuals whether they would pay an amount (which is varied) for one additional outcome. However, this WTP amount can be arbitrary and as such may not be entirely accurate. Also, different decision

makers may have different WTP values. Thus, in order to ensure this economic evaluation is generalizable across different settings, net benefit regression will be used to vary WTP to evaluate how recommendations about intervention use change based on the estimated ICER [36].

Recommendations about intervention use can be made by comparing the ICER with a threshold WTP. If the ICER value is less than the WTP, the intervention is considered cost-effective compared with usual care. Varying WTP allows researchers to determine how recommendations based on the ICER change. In this way, the incremental net benefit (INB) of the intervention against the expected net benefit of usual care can be calculated as follows:

$$INB = WTP^{*}\Delta E - \Delta C$$

$$WTP^{*}(E_{treatment} - E_{usual\ care}) - (C_{treatment} - C_{usual\ care})$$

$$[(WTP^{*}E_{treatment}) - C_{treatment}] - [(WTP^{*}E_{usual\ care}) - C_{usual\ care}]$$

$$= NB_{treatment} - NB_{usual\ care}$$

In this formula, NB represents net benefit, and INB is the additional value in monetary units created by the intervention compared with usual care [36]. By varying WTP using low, medium, and high estimates, a one-way sensitivity analysis can be conducted to assess the cost-effectiveness conclusion to WTP assumptions [36]. This method, net benefits regression, uses regression techniques to yield stronger estimates for cost-effectiveness [36].

Alternative costing scenarios for project adopters will be explored by varying the main incremental cost drivers: the cost of hosting the Thought Spot platform, which varies by the number of end users accessing the platform, as well as the cost of data maintenance (ie, creating, validating and maintaining new spots on the platform). This scenario analysis will demonstrate how the ICER changes as the cost of providing the platform to a greater number of users changes at postsecondary schools.

Results

Phase 1 of the project ran from September 2015 to December 2017 and informed the redevelopment and optimization of Thought Spot. Phase 2 began in early 2018. It will involve an RCT to evaluate the impact of Thought Spot 2.0 on help-seeking intentions and behavior.

The economic evaluation of Thought Spot will be conducted during Phase 2. Results will be used to report the costs associated with maintaining the Thought Spot platform from the point of view of future project adopters and to report outcomes for postsecondary students associated with using the platform. Ultimately, the evaluation will calculate the cost-effectiveness of the Thought Spot platform in improving health-seeking intentions and behaviors.

Discussion

Study Rationale

Research has found that postsecondary students tend to trust Web-based sources for health information and advice, and that they are likely to seek help online first [37,38]. This population reports wanting help in various areas: determining whether they have a mental health problem, finding support, becoming empowered through health information without the assistance of an intermediary, and connecting with peers [39,40]. Thought Spot provides a way for students with mental health concerns to engage in an online community anonymously, access information, and gain awareness of mental health and wellness services in the area. Consequently, we expect Thought Spot to promote help-seeking intentions and encourage help-seeking behavior among postsecondary students.

Generalizability and Future Research

The availability of resources and funding varies across Canadian postsecondary institutions, which leads to a disparity in mental health services offered to students as part of usual care. This situation limits the generalizability of the study's cost-effectiveness findings to all postsecondary institutions. To reduce inequity in health services across college and university campuses, a consistent provincial strategy could be developed that incorporates platforms like Thought Spot [15]. As individuals become more likely to seek help, the need for services aimed at improving self-management of mental health issues will increase. Therefore, it is important to simultaneously develop provincial strategies and resources to increase mental health support across campuses.

Thought Spot has the potential to benefit other populations facing similar barriers to mental health help-seeking, including secondary school students and young professionals. Further research would be required to determine the clinical significance and cost-effectiveness of this intervention for other populations. With relatively few studies that have assessed the clinical significance and cost-effectiveness of electronic mental health interventions, the current study will contribute to a growing body of evidence.

Limitations

A limitation of the evaluation is the assumption that choosing the perspective of postsecondary institutions, rather than a societal perspective, is the best approach. Conducting the evaluation from the viewpoint of potential project adopters excludes costs and benefits of the project to society, but we chose this approach under the assumption that the institutional perspective would include the most relevant costs and benefits of the Thought Spot project.

Another limitation is the assumption that the benefits of Thought Spot as measured by the GHSQ will persist beyond the 6-month RCT period. Using this time frame assumes that 6 months is sufficient to observe expected outcomes and that any benefits observed at that time will not change (ie, increase or revert to prestudy status) after the observation and evaluation period end.

Since participants in the study are identified through self-selection, the population is limited to those who identify as having mental health concerns. The participation is voluntary and participants may withdraw at any time. Consequently, the study population may exclude segments of the population who do not identify as having mental health challenges or who may not yet recognize the need for service or support.

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Conflicts of Interest

None declared.

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Abbreviations

GHSQ: General Help-Seeking Questionnaire
ICER: incremental cost-effectiveness ratio
INB: incremental net benefit
NB: net benefit
RCT: randomized controlled trial
WTP: willingness to pay

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