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Self-Management Support Program for Patients With Cardiovascular Diseases: User-Centered Development of the Tailored, Web-Based Program Vascular View

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Abstract

Background: In addition to medical intervention and counseling, patients with cardiovascular disease (CVD) need to manage their disease and its consequences by themselves in daily life.

Objective: The aim of this paper is to describe the development of "Vascular View," a comprehensive, multi-component, tailored, Web-based, self-management support program for patients with CVD, and how this program will be tested in an early randomized controlled trial (RCT).

Methods: The Vascular View program was systematically developed in collaboration with an expert group of 6 patients, and separately with a group of 6 health professionals (medical, nursing, and allied health care professionals), according to the following steps of the intervention mapping (IM) framework: (1) conducting a needs assessment; (2) creating matrices of change objectives; (3) selecting theory-based intervention methods and practical applications; (4) organizing methods and applications into an intervention program; (5) planning the adaption, implementation, and sustainability of the program, and (6) generating an evaluation plan.

Results: The needs assessment (Step 1) identified 9 general health problems and 8 determinants (knowledge, awareness, attitude, self-efficacy, subjective norm, intention, risk perception, and habits) of self-managing CVD. By defining performance and change objectives (Step 2), 6 topics were distinguished and incorporated into the courses included in Vascular View (Steps 3 and 4): (1) Coping With CVD and its Consequences; (2) Setting Boundaries in Daily Life; (3) Lifestyle (general and tobacco and harmful alcohol use); (4) Healthy Nutrition; (5) Being Physically Active in a Healthy Way; and (6) Interaction With Health Professionals. These courses were based on behavioral change techniques (BCTs) (eg, self-monitoring of behavior, modeling, re-evaluation of outcomes), which were incorporated in the courses through general written information: quotes from and videos of patients with CVD as role models and personalized feedback, diaries, and exercises. The adoption and implementation plan (Step 5) was set up in collaboration with the members of the two expert groups and consisted of a written and digital instruction manual, a flyer, bimonthly newsletters, and reminders by email and telephone to (re-)visit the program. The potential effectiveness of Vascular View will be evaluated (Step 6) in an early RCT to gain insight into relevant outcome variables and related effect sizes, and a process evaluation to identify intervention fidelity, potential working mechanisms, user statistics, and/or satisfaction.

Conclusion: A comprehensive, multi-component, tailored, Web-based, self-management support program and an early RCT were developed in order to empower patients to self-manage their CVD.

Trial Registration: Nederlands Trial Register NTR5412; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5412 (Archived by WebCite at http://www.webcitation.org/6jeUFVj40)

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KEYWORDS

intervention mapping; eHealth; self-management; cardiovascular diseases; tailoring; nursing care; chronic secondary care; outpatients; early RCT

Introduction

Cardio vascular disease (CVD) is the leading cause of death worldwide [1]. In 2012, 17.5 million people died of CVD, within which 7.4 million deaths were due to heart attacks and 6.7 million deaths resulted from strokes [1]. The incidence of CVD, and its consequences for chronic secondary care, continue to rise and place high demands on scarce health care resources [1].

CVD is predominantly caused by genetic and environmental factors, among which unhealthy lifestyle habits are the most important. Risk factors of CVD caused by atherosclerosis are divided into behavioral risk factors (physical inactivity, an unhealthy diet rich in salt, fat, and calories, tobacco use, and the harmful use of alcohol), metabolic risk factors (hypertension, diabetes, raised blood lipids, and overweight/obesity), and other risk factors (eg, advancing age, gender, stress, and depression). Since all risk factors interact with each other and play a key role in decreasing the process of atherosclerosis, they must be considered in the treatment of CVD and secondary prevention [1].

Health and social care services support patients with chronic diseases by providing specialized staff, medicines, and equipment to control symptoms. In addition to medical treatment and counseling, patients need to manage CVD and its consequences in daily life by themselves [2]. Self-management assumes that patients feel confident dealing with the symptoms, treatment, lifestyle changes, and physical and psychological consequences related to illness [3,4]; however, many patients do not feel confident enough to manage their CVD [5-7]. Self-management programs that encourage patients to identify problems, barriers and support, generate solutions, and develop and monitor long- and short-term goals may therefore help patients in actively controlling and improving their own condition [3,8].

Self-management programs have the potential to decrease the load on health and social services, to lower the high costs of chronic care, and to improve patient quality of life. Self-management in chronic care appears to be effective, especially when focusing on behavioral change, supporting self-efficacy, and implemented in wider initiatives (eg, information provision, online peer support, monitoring symptoms with technology, and psychological and behavior change interventions) [2]. Although the effectiveness of traditionally delivered, face-to-face, self-management programs is proven [9-11], the major part of their care depends on a patient's self-management skills, for which Web-based programs are expected to be helpful [12]. However, Web-based programs demonstrate varied and inconsistent effectiveness due to design limitations and lack of power [12]. Only a few studies suggest that these programs for CVD are effective in risk factor reduction, secondary prevention, clinical outcomes, reductions in hospital admissions, and mortality [12-15].

To our knowledge, there are no comprehensive, multi-component, Web-based, self-management support programs that focus on behavior change and support self-efficacy in secondary care patients with CVD. Within such programs, the tailoring of the content to a patient's profile is important in order to increase their level of understanding, information recall, and adherence to lifestyle interventions [16]. Therefore, we systematically developed a tailored, Web-based, self-management program that aims to change behavioral and metabolic risk factors and increase self-management behavior, based on the perceived problems and (support) needs of patients in managing secondary prevention after CVD.

The aim of this paper is to describe (1) the development of the "Vascular View" ("Vaat in Zicht" in Dutch) program for patients with CVD, according to six steps of the intervention mapping (IM) framework [17]; and (2) the plans we have made to systematically evaluate Vascular View in an early randomized controlled trial (RCT). The early RCT will test the viability of a larger clinical trial, including the ability to recruit a relatively small number of patients and to explore the potential efficacy and effectiveness of the intervention under study [18].

Methods

IM is an iterative, 6-step process for developing theoretically-based behavior change interventions [17]. The steps are (1) conducting a needs assessment among end-users according to the Predisposing, Reinforcing, and Enabling Constructs in Educational/Environmental Diagnosis and Evaluation (PRECEDE) model; (2) creating matrices of change objectives; (3) selecting theory-based intervention methods and practical applications; (4) organizing methods and applications into an intervention program; (5) planning the adaption, implementation, and sustainability of the program; and (6) generating an evaluation plan.

Throughout the entire development process for the Vascular View program, two expert groups (one of patients and one of professionals) explored and discussed, at each IM step, the specific issues (disease and treatment) that may influence self-management. The groups met up to three times to ensure

that the program would be tailored to the perceived problems and needs that are important to patients with CVD and their health professionals. The patient expert group consisted of 1 female and 5 males with CVD (stroke and/or cardiac events and/or peripheral artery disease). The professional expert group included a medical specialist in general and vascular medicine, a neurology nurse, a cardiology nurse, a vascular surgery nurse, a psychologist, a dietician, and a physical therapist. Two researchers (SPH and BvG) participated in both expert groups and SPH chaired each meeting. Before the start of each expert group meeting, the members were asked to prepare by reading information and finishing assignments on the themes of the meeting. The meetings were supported by PowerPoint presentations and the researchers emphasized the importance of the opinions and contributions of each member. This resulted in valuable discussions and agreements at the end of each meeting, which were audio recorded. After the meetings, the recordings were transcribed verbatim by a student. Analysis of all meetings took place by thematically verifying researcher's (SPH) notes with the typed results of the audio recordings, in summary.

Step 1: Conducting a Needs Assessment

The needs assessment focused on identifying perceived problems and (support) needs in the self-management of CVD using the Predisposing, Reinforcing, and Enabling Constructs in Educational/Environmental Diagnosis and Evaluation (PRECEDE) model [19]. First, we sampled the literature for perceived problems related to the self-management of CVD [5-7,20-23]. Second, the problems identified were extracted by the researchers and discussed with and prioritized by the members of both expert groups during one meeting to generate a complete list. The researchers then clustered the prioritized perceived problems into general health problems. In addition, they selected the underlying behaviors and environmental conditions of the health problems and the corresponding determinants (factors which were linked to the underlying behaviors and environmental conditions) from the literature. Finally, in two meetings, the members of the two expert groups discussed the selection and determined the most important and modifiable underlying behaviors and determinants required to self-manage CVD.

Step 2: Creating Matrices of Change Objectives

The aim of creating matrices of performance and change objectives was to provide a translation from needs to content in Vascular View. Behavioral and environmental conditions selected were related to self-management of the problems identified in Step 1. These were subdivided into performance objectives and combined with the important and modifiable determinants of the behavioral and environmental conditions based on the Integrated Change Model 2.0 (I-Change model 2.0) [24], and described in matrices of change objectives. For example, the performance objective "CVD patients understand their disease and the accompanying symptoms and consequences" was combined with the determinant "knowledge," which resulted in the change objective "CVD patients know their disease and accompanying symptoms and consequences." In one meeting with both expert groups, the identified performance and change objectives were then pointed out and validated by the members of the two expert groups to ensure the designed matrices did indeed address the problems of patients with CVD. Finally, in the same meeting, the two expert groups were asked to prioritize the topics that should be incorporated in the Vascular View program.

Step 3: Selecting Theory-Based Intervention Methods and Practical Applications

The purpose of Step 3 was to select theory-based intervention methods and practical applications based on the former steps. The Coding Manual for Behavior Change Techniques from de Bruin and colleagues [25] was used to select the methods used to change the sub-behaviors of self-management and the corresponding determinants from Step 2. This manual provides behavior change techniques (BCTs) in general (eg, tailoring) and on determinant level. The IM framework identifies the parameters under which a given technique is most likely to be effective [17,25]. Two researchers (SPH and BVG) determined relevant BCTs based on the selected determinants and translated these techniques into practical applications, such as text, personal stories, exercises, diaries, and videos. In one meeting, the selected BCTs and practical applications were then discussed with the members of the two expert groups to decide whether the techniques fit the target group.

Step 4: Organizing Methods and Applications Into an Intervention Program

The aim of Step 4 was to develop and pretest the program components and materials of Vascular View. The program outcomes, the selected BCTs, and the practical applications from Steps 2 and 3 were starting points for the development and pretest of the program. All members of the two expert groups were asked what the ideal Vascular View program should look like, in line with the message (eg, tailoring, text, video, and exercise), the channel (Internet), and the information sources (eg, websites, patient forum). All patients from the expert group were also asked for the most valuable perceived advices that they received during their treatment and rehabilitation, how these advices looked like, and from whom these messages came. All health professionals were asked how they adapted their advice given to a patient and how they validated this adaptation. The research group prepared blueprints for the production of the different program materials and discussed this within the two expert groups in one meeting. Based on the outcomes of this meeting, the final content (ie, text, personal stories, diaries, and videos) was determined and developed by the research group and incorporated into the Vascular View program by Mind District Development BV (The Netherlands), the information and communication technology (ICT) partner. Finally, the program was pretested by the members of both expert groups individually and their feedback was gathered by open-ended questionnaires in which the members could describe their comments on each page. All patients and health professionals were asked to use the program for one week and give feedback about the importance and comprehensibility of the information, quotes, pictures, videos, diaries, and exercises, and their views of the layout of Vascular View and whether it was user-friendly. All of the feedback was collected, structured

per training session and specific page, and incorporated into the final program. See also the results of Step 4.

Step 5: Planning for Program Adoption, Implementation, and Sustainability

The focus of Step 5 was to make an implementation plan for Vascular View during the planned evaluation study. The adoption and implementation of Vascular View started in the development process with the involvement of patients and professionals by taking their expertise into account. In addition to their role in the development of the program, the two expert groups played an important role in the determination of facilitators for, and barriers to, the adoption and implementation of this intervention. For example, all members were asked, via questionnaires, what facilitates dissemination and exposure (eg, logging in for the first time and subsequent logging in), in order to complete the different courses of Vascular View. The researchers also determined performance objectives for a patient's first visit and re-visits to Vascular View and combined these with the relevant determinants into change objectives, and discussed these results in one meeting with the members of the two expert groups. The findings of dissemination and exposure were incorporated in the final Vascular View program. The performance and change objectives, and the corresponding determinants, were included in the adoption and implementation plan for Vascular View.

Step 6: Generating an Evaluation Plan

The objective of the final step of IM was to design an evaluation study for Vascular View by conducting an early RCT to gain insight into relevant outcome variables and related effect sizes, and to perform a process evaluation to identify intervention fidelity, potential working mechanisms, and user satisfaction [26,27].

In this phase, we selected relevant measurable outcome variables related to the objectives of the Vascular View program, the defined performance outcomes, and whether the specific tailoring to changes in self-management behavior conformed to the applied I-Change Model 2.0. The process evaluation also includes a check of intervention fidelity (adherence to the program as proposed), incorporating outcomes compliant with the performance objectives and determinants as expressed in the matrix of change objectives in IM Step 2, as well as interviews with participants (program users and non-users) of the study, audio recordings of nursing visits with participating patients, and focus group interview(s) with health professionals.

Results

The involvement of the members of both expert groups for each IM step during the development of Vascular View is described in Table 1.

Table 1. Involvement of stakeholders in the development of Vascular View.

Step	Intervention mapping	Meetings, n	Patients, n (gender)	Health professionals, n
1	Needs assessment	3	6 (1 female, 5 males)	7[a]
2	Objectives	1	5 (males)	3[b]
3	Theory	1	6 (1 female, 5 males)	6[c]
4	Intervention program	1	4 (males)	5[d]
	Pretest Vascular View	N/A	6 (1 female, 5 males)	7[a]
5	Implementation	1	4 (males)	5[d]
6	Evaluation	1	4 (1 female, 3 males)	4[e]

[a]Neurology nurse, cardiology nurse, vascular surgery nurse, psychologist, dietician, physical therapist, and medical specialist in general and vascular medicine

[b]Neurology nurse, vascular surgery nurse, and medical specialist in general and vascular medicine.

[c]Neurology nurse, cardiology nurse, vascular surgery nurse, psychologist, dietician, medical specialist in general and vascular medicine.

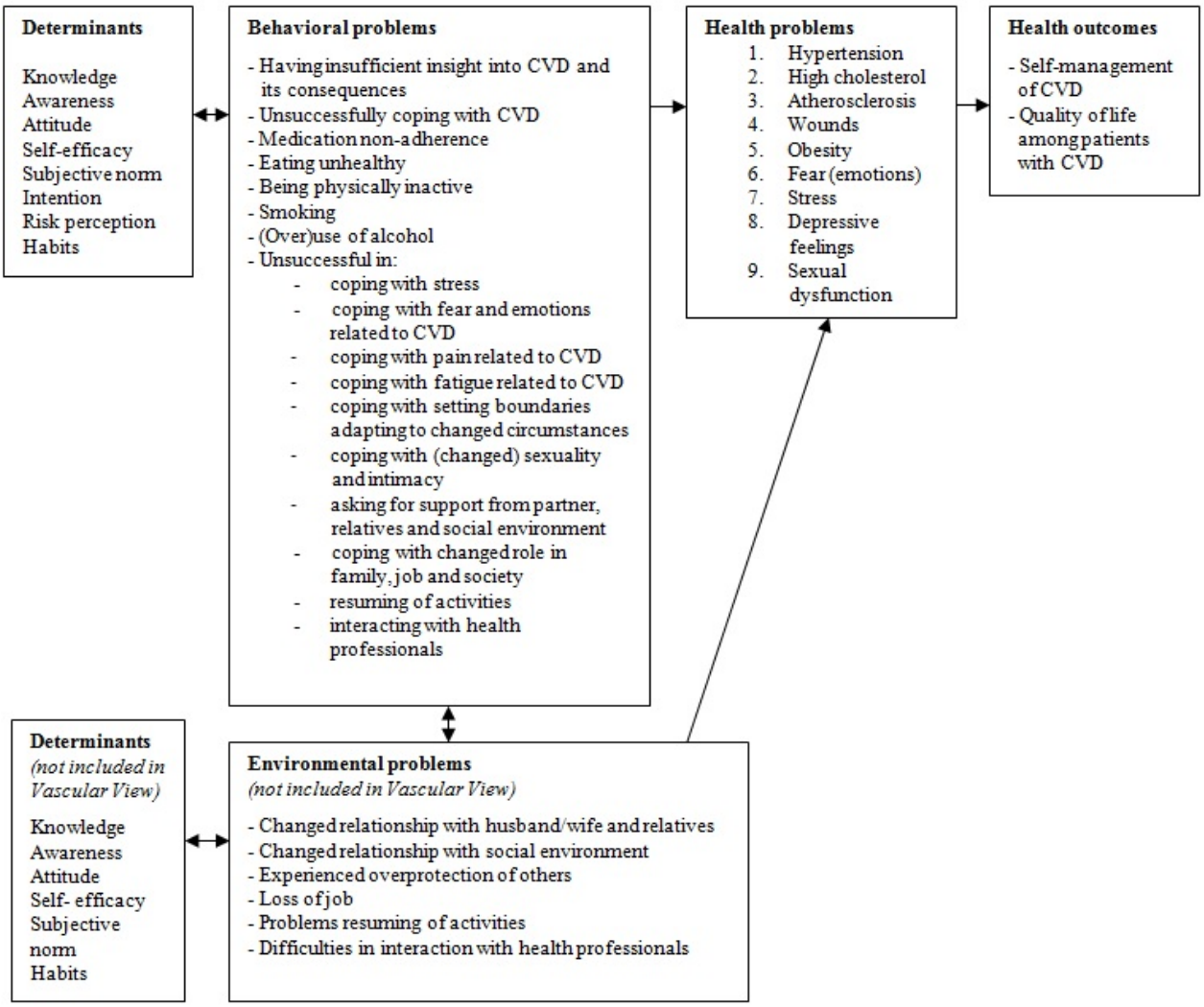
[d]Neurology nurse, cardiology nurse, vascular surgery nurse, dietician, medical specialist in general and vascular medicine.

[e]Neurology nurse, cardiology nurse, vascular surgery nurse, medical specialist in general and vascular medicine.

Step 1: Needs Assessment

A literature search and three meetings with the two expert groups (Table 1) elicited perceived and experienced problems related to self-managing CVD [5-7,20-23]. The comprehensive results of the first meeting were clustered into 9 general health problems and the accompanying important symptoms (fatigue and pain), which were applied specifically to self-management in CVD (Figure 1).

Figure 1. Contextualized Predisposing, Reinforcing, and Enabling Constructs in Educational/Environmental Diagnosis and Evaluation (PRECEDE) model as a logic model for the needs assessment of self-managing cardiovascular disease.



The second and third meetings provided the selected underlying behaviors and environmental conditions of these health problems and symptoms, which varied from having insufficient insight into CVD to having an unhealthy lifestyle, and being unsuccessful in setting boundaries, or inadequate interaction with health professionals (Figure 1). The following corresponding determinants of these underlying behaviors and environmental conditions were extracted from the literature: (1) knowledge, (2) awareness, (3) attitude, (4) self-efficacy, (5) subjective norm, (6) intention, (7) risk perception, and (8) habits. Because the Vascular View program will focus on patients' behavior, we did not explicitly involve environmental factors and corresponding determinants. For example, the health problem "obesity" is related to the behavior "eating unhealthy" with the corresponding determinants knowledge (patients know what healthy nutrition is) and self-efficacy (patients believe they are able to eat healthy).

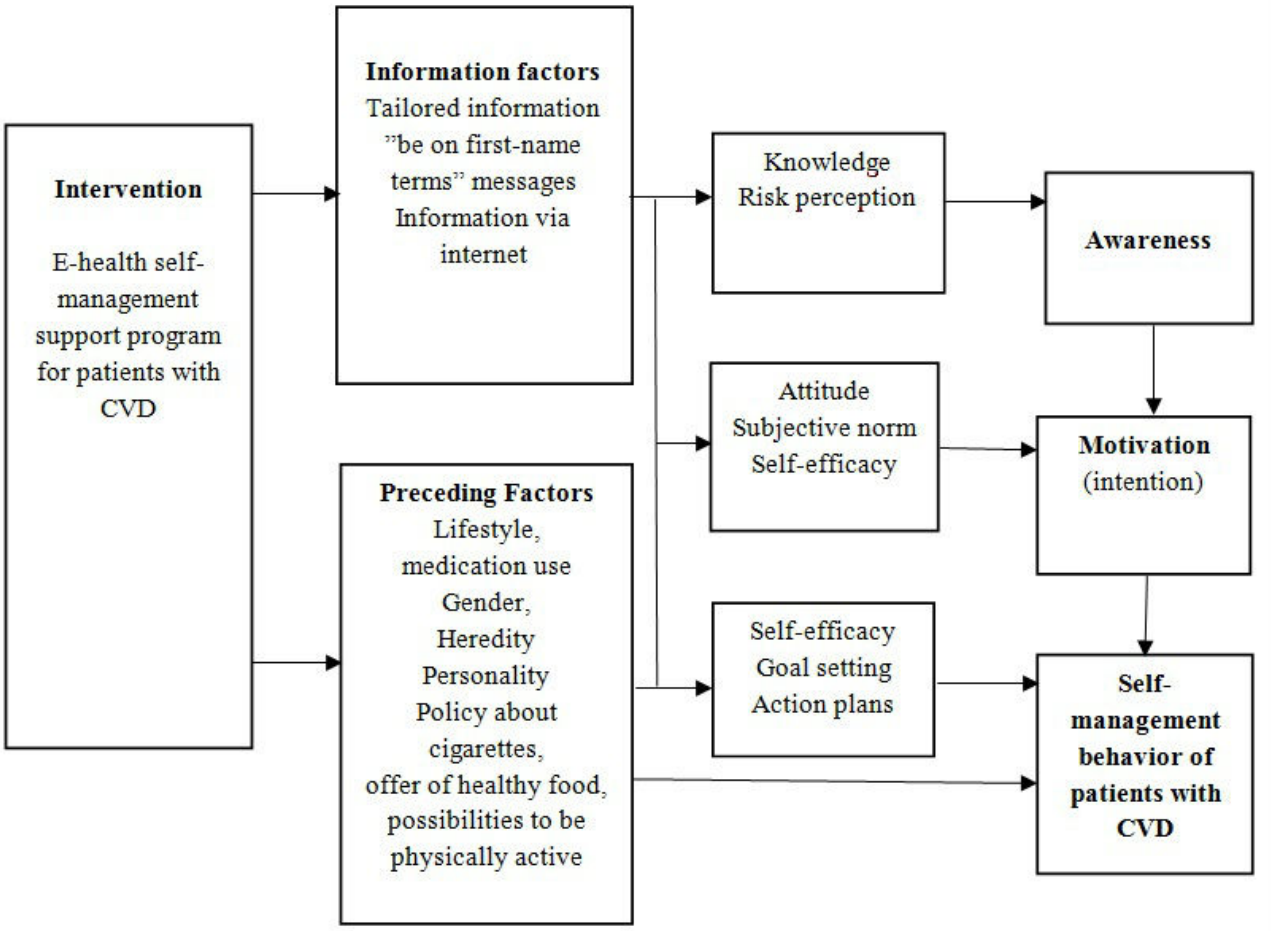
Step 2: Matrices of Change Objectives

We selected the three most important and modifiable determinants of self-managing CVD from the I-Change Model 2.0 [24]: awareness, motivation, and action. A patient should have accurate knowledge and risk perception to be aware that self-managing CVD is a possibility and a choice. A patient's motivation (intention) to increase self-management behavior depends on the patient's attitude (perceived pros and cons), beliefs about subjective norms (reactions and expectations of important others), and self-efficacy expectations (perceived ability to perform self-management behavior). Action is needed to increase self-management behavior, which is determined by self-efficacy, goal setting, action-planning, and the development of the skills needed for CVD self-management. Finally, we defined predisposing factors, such as lifestyle, gender, heredity, personality, policy about cigarettes, supply of healthy food, and potential to be physically active. The applied I-Change Model 2.0 for increasing self-management behavior in CVD patients is shown in Figure 2.

In one meeting, the members of the two expert groups (Table 1) validated the designed matrices of performance and change objectives and prioritized the following topics of the performance and change objectives: (1) lifestyle (nutrition, physical activity, smoking and use of alcohol); (2) setting boundaries; (3) medication adherence; (4) emotions (fear); and (5) interaction with the health professional.

Multimedia Appendices 1 and 2 show matrices in which the selected most important and modifiable determinants were added to the performance objectives of each topic according to the I-Change Model [24], and combined with change objectives.

Figure 2. Applied Integrated Change Model (I-Change) 2.0 for increasing the self-management behavior for cardiovascular disease.



Step 3: Theory-Based Intervention Methods and Practical Applications

For each selected determinant of self-management behavior (eg, knowledge, risk perception, awareness, attitude, self-efficacy, subjective norm, intention, and habits), the BCTs were selected [25] and discussed with both expert groups (Table 1) during one meeting. According to the Coding Manual for Behavior Change Techniques [25], a patient's knowledge will be influenced by providing general information and increasing the memory and/or understanding of transferred information. Awareness will be influenced by self-monitoring and delayed feedback of behavior (eg, by providing an overview of recorded, self-reported, behavior) (see Multimedia Appendix 3 for a screenshot of a diary of Vascular View) whereas risk communication will change a patient's risk perception. Intention will be modified by specific goal setting and review of general and/or specific goals (see Multimedia Appendix 4 for a screenshot of a step-by-step plan of Vascular View), and modeling, setting graded tasks, and goal setting will influence self-efficacy (see Multimedia Appendix 5 for a screenshot of role models in Vascular View). Attitude will be modified by a reevaluation of outcomes, self-evaluation, persuasive communication, and belief selection and providing information about peer behavior and mobilizing social norm will change subjective norm. The maintenance of a patient's behavior change will be influenced by formulating goals for maintenance of behavior and relapse prevention. Finally, it is suggested that a behavior change program in which the content and exercises can be adapted to a patient's profile is most likely to be effective [11,12]. Therefore, personalized tailoring is integrated in Vascular View in a number of ways (described below).

In translated these BCTs to practical applications, the parameters under which a given technique is most likely to be effective were taken into account. For example, self-reevaluation can use feedback and confrontation; however, raising awareness must be quickly followed by increase in problem-solving ability and self-efficacy. Multimedia Appendix 6 shows how we developed the practical applications from determinants (awareness, intention, and self-efficacy), BCTs, and parameters [17,24].

Step 4: Intervention Program

In one meeting, the two expert groups (Table 1) emphasized the use of brief sentences, dynamic content (different videos, quotes, exercises, diaries, pictures/cartoons), and to write on first-name terms in the Web-based program. It was also found that the program should enable patients to write down their questions (question prompt sheet), which can be taken to a consultation with their health professional. The program should enable a patient to make a printable, personal plan for

improvement. The meetings with the two expert groups and the results of IM Steps 1 to 3 resulted in the current Vascular View program. The program starts with a welcome for every patient, in which the courses (Coping with CVD, Setting Boundaries in Daily Life, Lifestyle, Healthy Nutrition, Being Physically Active in a Healthy Way, and Interaction with Health Professionals) are explained (Multimedia Appendix 7). A patient can randomly visit and complete every individual course. In the welcome section, patients fill in a short questionnaire, which guides their choice of preferred courses.

The course "Coping with CVD" addresses the determinants knowledge, awareness, risk perception, attitude, self-efficacy, subjective norm, intention, and action plans. The patient learns about dealing with CVD and its impact on daily life (eg, medication adherence, sexuality, emotions, fatigue, and pain), relatives, social environment, and resuming activities.

In the course "Setting Boundaries," patients learn to clearly communicate with their social environment (eg, relatives, colleagues) about perceived boundaries in daily life and in resuming activities with respect to their current ability. This course addresses the determinants knowledge, awareness, attitude, self-efficacy, and subjective norm.

The course "Lifestyle" addresses the determinants knowledge, awareness, attitude, self-efficacy, subjective norm, intention, habits, and skills, and consists of information about a healthy lifestyle (eg, risk information about tobacco and alcohol use in CVD, and their health), and information to support abstention from tobacco and alcohol use.

In the courses "Healthy Nutrition" and "Being Physically Active in a Healthy Way," patients gain insight into what they eat and drink, how physically active they are, and how to change their habits to healthier ones, step by step. These courses address the determinants knowledge, awareness, attitude, self-efficacy, subjective norm, intention, habits, and skills.

The course "Interaction With Your Health Professional" teaches patients to effectively communicate with the health professional (eg, preparing a consultation, asking questions, sharing worries). This course addresses the determinants knowledge, awareness, attitude, self-efficacy, and subjective norm.

The sessions in the courses are personalized and are supported by written information, quotes, pictures, videos, diaries, and exercises. In the courses "Healthy Nutrition" and "Being Physically Active in a Healthy Way," two case studies involving two imaginary patients (a man and a woman) support the information and exercises offered through the sessions and courses (Multimedia Appendix 7).

In all courses of Vascular View, tailoring was done using variables or factors related to behavior change (such as stage of change), or to relevance (such as culture or socioeconomic status) [17,25]. A patient is able to choose preferred courses in the welcome section. The "Lifestyle" course also contains a short questionnaire about nutrition, weight, height, physical activity, and tobacco and alcohol use, which is transformed into tailored, written feedback including red (unhealthy behavior) and green (healthy behavior) emoticons, followed by tailored guidance to undertake different courses of Vascular View (Setting Boundaries, Healthy Nutrition, and Being Physically Active in a Healthy Way). The healthy nutrition advice is also tailored to age using an algorithm (ages 19 to 50 years, 51 to 70 years, and greater than 70 years), to fit the age-based Dutch guidelines for a healthy diet [28]. Tailoring takes place according to the detail of the information ("read more" options in all of the courses). To support the change processes in patients, we used the short form version of the Scale for Interpersonal Behavior (s-SIB) [29] and motivational interviews [30].

The feedback of the pretest by all patients and health professionals of both expert groups (Table 1) consisted of usability issues (eg, problems with logging in) and feedback on text issues (patronized texts, typological and layout errors, the amount of "passive" texts). This resulted in the adaption of Vascular View (eg, text of all courses were shortened, medical information was rewritten, the Healthy Nutrition and Being Physically Active courses were rewritten in a more interactive way, and typological and layout errors were removed) and different implementation strategies (see also Step 5). For example, we simplified the user manual by reducing text and including screenshots of Vascular View to guide the use of the program.

Step 5: Program Adoption, Implementation, and Sustainability

As a result of the first 4 Steps and one meeting with both expert groups (Table 1), we developed different implementation strategies for patients as well as health professionals. For patients, we determined that motivation and perceived personal relevance on the first visit were the most important factors in the dissemination of, and exposure to, Vascular View. Important facilitators of re-visiting Vascular View were tailored feedback, new, relevant, and reliable information, a user-friendly program, reminders to re-visit the program and repeating personal points of improvement, and the possibility of email contact [31,32]. Therefore, the following implementation strategies were developed for patients: patients receive a written instruction manual for Vascular View and the diaries (nutrition and physical activity) are made available before receiving the codes to log in. Upon the start of the program, a digital flyer is sent to patients, which promotes the benefits of using the program and contains information about contact persons. Patients receive a code to log in when they receive the flyer. The patients who do not visit the program within one month receive an email reminder. If patients do not log in after another week, they receive a phone call from a researcher. Patients also receive an email when they visit the program but do not finish a task or a course. Finally, every 2 months a newsletter is sent to all participants to informally remind them of Vascular View with news about the program, the ongoing research project, and contact details in case of questions or problems with logging in.

The members of the two expert groups also emphasized the importance of being motivated to use Vascular View by their health professionals, whether or not this was supported by a brochure. They added that health professionals should also be interested in the progress of a patient's self-management

behavior, and be able to answer questions during the study in order to show their involvement.

The key persons in adoption and implementation are the medical specialists in Internal and Vascular Medicine, and the nurse specialists in Neurology, Cardiology, and Vascular Surgery, because of their crucial roles in the recruitment of patients. They also brought Vascular View to the attention of patients during regular consultations across the study period by asking about the program. Before the program started, the nurse specialists were instructed in how to support a patient's use of Vascular View.

Step 6: Evaluation Plan

Design

A mixed-methods study design will be conducted with an early RCT and a process evaluation to (1) evaluate the potential effectiveness and effect size of Vascular View; (2) identify the outcome measures most likely to capture potential patient benefit; and (3) evaluate continued participation or withdrawal from Vascular View. The early RCT and the process evaluation will be performed at four outpatient clinics in one university hospital in the Netherlands (Internal Medicine, Cardiology, Neurology, and Vascular Surgery).

Participants

We will recruit 400 to 600 potential participants diagnosed with CVD, to allow the participation of 200 patients. Inclusion criteria are that patients (1) manifest atherosclerotic vascular disease, including ischemic heart disease, cerebrovascular disease (eg, stroke or transient ischemic attack), and peripheral artery disease (eg, claudication intermittens), or a combination; (2) are aged 18 years or older; (3) can speak, read, and understand the Dutch language; and (4) have access to a computer, the Internet, and an email account. Exclusion criteria are patients with (1) comorbidities, which may hinder the use of Vascular View, as defined by the medical specialist; and (2) psychiatric disorders.

Procedure

The medical specialists will inform patients about the content and aim of the study via an information letter. After signing the informed consent and completing the baseline questionnaire (T0), patients will be included and randomized to an intervention group (access to Vascular View for 1 year on top of usual care) and a control group (usual care). Randomization will take place at the individual level, will be stratified for diagnoses, and will be executed by a statistician who will use a computer program. Patient characteristics will be assessed at baseline via an online questionnaire (T0) and medical file research. Repeated measures will be conducted 6 months (T1) and 12 months (T2) after baseline. Semi-structured interviews will be performed with patients and focus group interview(s) will be conducted with health professionals at 12 months.

Ethical Approval

This study has been improved by the Medical Ethical Research Committee of Arnhem - Nijmegen, Nijmegen, the Netherlands (registration number: 2015/1908), and is registered in the Netherlands Trial Registry (registration number: NTR5412).

Measurements

The quantitative data will be collected via an online questionnaire and medical file research. The online questionnaires consist of patient demographics and the following, described 11 measurements. Illness attribution will be assessed by one question in the Illness Perception Questionnaire (IPQ) [33]. The health-related quality of life survey (RAND-36) measures a patient's general health status in 8 dimensions including physical and social functioning, role limitations (physical and emotional problems), mental health, vitality, and pain [34]. Self-management will be evaluated using Patient Activation Measurement (PAM-13) [35]. Self-efficacy will be assessed through self developed questions in which patients will be asked how confident they feel about self-managing CVD based on the program outcomes and corresponding determinants. Patient trust in their communication skills will be measured by the Perceived Efficacy in Patient-Physician Interactions (PEPPI-5) [36]. Patient attitudes to prescription medicine will be evaluated using the Beliefs about Medicines Questionnaire (BMQ) [37]. The Morisky Medication Adherence Scale (MMAS-8) will assess medication adherence [38]. Finally, lifestyle will be evaluated using the Fägerstrom Test for Nicotine Dependence [39] for tobacco use, the Alcohol Use Disorders Identification Test (AUDIT) [40] for testing harmful alcohol use, the International Physical Activity Questionnaire (IPAQ) [41] to identify a patient's physical activity, and eating habits will be evaluated by the Dutch Healthy Diet Index [42]. We will sample biometrics from patient medical files, including blood pressure, BMI, etc.

Process Evaluation

To investigate the factors that influence user statistics, intervention fidelity, and user satisfaction in the Vascular View program, a process evaluation will be performed based on the framework of Saunders et al [27]. This is a comprehensive and systematic framework for developing a process-evaluation plan to evaluate the implementation of a targeted health promotion intervention, which comprises components including fidelity, dose (delivered and received), reach, recruitment, and context [27]. Data for the process evaluation builds on different sources. An extra questionnaire will be completed at T1 and T2, in which experiences and opinions of the written manual, use and non-use of the program, layout, content, exercises, and diaries of the program will be asked of patients in the intervention group. Data obtained from the Web-based program will be used, including login data (exposure and continued participation or dropping out), data about using different courses, sessions, and the use of the diaries. Qualitative interviews with users and non-users will be conducted to explore their experiences and satisfaction with Vascular View. Patients will be asked how Vascular View supported the self-management of their CVD, including coping with CVD and its consequences, setting boundaries, changing lifestyles (being physical active, eating healthily, cessation of smoking, and the harmful use of alcohol), and communicating with health professionals. Patients who do not log in, or log in only once, will be asked about their reasons for not visiting the Vascular View program and the barriers they perceived. Nursing visits with participating patients will be audio recorded and analyzed to explore the role of nurses and

activities related to the introduction of Vascular View. Finally, focus group interview(s) with health professionals in chronic diseases will be conducted to determine their opinions of the adaptation and implementation of a Web-based program and their own role in this process and in patient treatment.

Analyses

Quantitative and qualitative analyses will be performed. Patient outcome measures will be treated as dependent and continuous variables and will be analyzed on the basis of intention-to-treat. All variables will be presented in percentages or in means and standard deviations of the sum-scores. Repeated measures analyses will be performed to explore effect sizes and the responsiveness of outcome measures. Multilevel analyses will be applied to compensate for the clustered nature of the data using mixed linear modeling techniques. The qualitative data gathered in semi-structured interviews and the focus group interviews will be analyzed using content analyses.

Discussion

Principal Findings

The aims of this paper are (1) to describe the development of the tailored, Web-based, self-management support program Vascular View for patients with CVD according to the 6 steps of the IM framework; and (2) to describe how the program will be evaluated. The 6 steps of IM provide a well-balanced processual guide for tailoring to the preferences and support needs of patients with CVD, by combining evidence and the perceived experiences of patients and their health professionals. A unique feature of the program is that it is based on the perceived problems of patients with CVD and that the corresponding determinants were combined with theory-based intervention methods into practical applications. This resulted in a Web-based program which may influence the relevant determinants—knowledge, awareness, attitude, self-efficacy, subjective norm, risk perception motivation (intention), habits, and maintenance—of self-management in patients with CVD by applying different methods through the courses. The Vascular View program was tailored to patient preferences, the level of elaborateness of the information, the content, factors related to behavior change, and relevance. To our knowledge, such a comprehensive, tailored, Web-based, self-management program for secondary care patients with CVD has not been previously developed; other programs have mainly focused on one or two risk factors or risk factor determinants only [12-15].

Strengths and Limitations

A strength of the Vascular View program is the intensive cooperation of the two expert groups in every step of IM. The two expert groups ensured that the general information from the literature fitted the target group. Their knowledge, experiences, and visions led to the comprehensive, Web-based program developed.

Vascular View was developed for a heterogeneous population of patients with manifest CVD, including, among others, ischemic heart disease, cerebrovascular disease, and peripheral artery disease. This diversity in patients and diagnoses required a well-balanced approach from the Web-based program. To overcome this possible limitation, we tailored the content of the courses to patient diagnoses and interests by using short questionnaires before or during a course and “read more” options within the courses.

Despite the comprehensiveness of this Web-based program, Vascular View is limited in its influence over the different environmental factors of patients with CVDs. Different interpersonal (eg, partner, relatives, colleagues), organizational (eg, unavailability of accompanied exercise facilities by a health professional), community (eg, availability of work and income), and societal (eg, no smoking allowed in public buildings) factors were incorporated in Vascular View because the program aimed to increase self-management behavior and the way patients living in this (interpersonal, organization, community, and society) environment are able to cope, via the patients themselves. However, we do not know how these different environmental factors interact in order to change behavior [17]. In designing Vascular View, we made use of two highly relevant theoretical models [17,25]. For future studies, to prevent confusion, attention should be paid to the similarities and dissimilarities between the terminology and terms used in these different models. The composition of the patient expert group might be considered a limitation, because only 1 female patient as opposed to 5 males participated, which is not a representative reflection of the population. It might be considered as a limitation that we left out interventions on smoking and drinking behavior. Because of their availability, we give general information and provide links to already existing, highly effective programs. Finally, the pilot testing of Vascular View will take place in one university hospital in the Netherlands only. For an early RCT that aims to obtain insight into the relevant outcome variables and related effect sizes, such a mono-centered study is considered to be the most convenient [18,26].

Conclusions

This paper describes the systematic development of the comprehensive, tailored, Web-based self-management support program Vascular View for patients with CVD, according to the IM framework. Vascular View aims to increase self-management behavior in patients with CVD by influencing the risk factors of CVD and through an improvement in quality of life, via a unique combination of tailoring, personalizing, and behavior change, by influencing determinants (knowledge, awareness, attitude, self-efficacy, subjective norm, risk perception, intention, and habits) of self-management behavior. The proposed early RCT will indicate whether these aims can be achieved. Furthermore, this feasibility study will give insight into relevant outcome variables and related effect sizes and allow us to identify any flaws or technical difficulties. This information will be used to set up a larger RCT. A process evaluation will identify, amongst other things, patient experiences in using the program and at which level the Vascular View program is helpful in supporting self-managed CVD. This information will be used in the future development of the Vascular View program.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Matrix of performance and change objectives for patients with cardiovascular disease (according to the boxes in the applied Integrated Change Model 2.0).

[PDF File (Adobe PDF File), 229KB - resprot_v6i2e18_app1.pdf]

Multimedia Appendix 2

Matrix of performance and change objectives for patients with cardiovascular disease (according to the boxes in the applied Integrated Change model 2.0).

[PDF File (Adobe PDF File), 234KB - resprot_v6i2e18_app2.pdf]

Multimedia Appendix 3

Screenshot of Vascular View ("Awareness").

[JPG File, 136KB - resprot_v6i2e18_app3.jpg]

Multimedia Appendix 4

Screenshot of Vascular View ("Intention").

[JPG File, 116KB - resprot_v6i2e18_app4.jpg]

Multimedia Appendix 5

Screenshot of Vascular View ("Self-efficacy").

[JPG File, 197KB - resprot_v6i2e18_app5.jpg]

Multimedia Appendix 6

Development of Vascular View from determinants to practical applications.

[PDF File (Adobe PDF File), 165KB - resprot_v6i2e18_app6.pdf]

Multimedia Appendix 7

An overview of the 6 courses of Vascular View.

[PDF File (Adobe PDF File), 293KB - resprot_v6i2e18_app7.pdf]

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Abbreviations

BCTs: behavior change techniques
BMI: body mass index
CVD: cardiovascular disease
I-Change model 2.0: Integrated Change Model 2.0
IM: intervention mapping
PRECEDE: Predisposing, Reinforcing, and Enabling Constructs in Educational/Environmental Diagnosis and Evaluation
RCT: randomized controlled trial

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Protocol

Protocol for a 24-Week Randomized Controlled Study of Once-Daily Oral Dose of Flax Lignan to Healthy Older Adults

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Abstract

Background: Increased oxidative stress and inflammation are associated with aging, and contribute to an increased risk of chronic disease in older adults. Flaxseed lignans demonstrate antioxidant and anti-inflammatory activity, but their ability to reduce oxidative stress and inflammation markers in older adult populations has received limited investigation.

Objective: This is a chronic intervention trial of community-dwelling healthy older adults to examine the effects of a flaxseed lignan (secoisolariciresinol diglucoside; SDG) enriched supplement (BeneFlax) compared to a placebo. The primary aim was to demonstrate the safety of BeneFlax and confirm its anti-inflammatory efficacy on markers of oxidative stress and inflammation, and subsequent functional outcomes, including those associated with its anti-inflammatory efficacy. A secondary aim was to determine flaxseed lignan metabolite concentrations in blood.

Methods: A double-blind randomized clinical trial was conducted. Subjects were healthy community-dwelling adults aged 60-80 years. Testing was performed at baseline, 8, 16, and 24 weeks. The 24-week intervention consisted of 600 milligrams (mg) of SDG daily or an equivalent amount (volume) of placebo. All participants received 1000 international units of vitamin D to ensure adequate vitamin D status. Measurements consisted of blood pressure, hematology, and tolerability for safety assessments; blood oxidative stress and inflammatory biomarkers for efficacy; and cognition, muscle strength, and pain as functional outcomes. Secondary endpoints of plasma levels of lignan metabolites were analyzed by mass spectrometry. Other tests, such as bone turnover markers and fecal levels of flax cyclolinopeptides, will be performed at a later date.

Results: Thirty-two participants were recruited (19 intervention and 13 control) and all completed the trial. Numerous Health Canada-imposed exclusion criteria limited recruitment success. Analyses are ongoing, but the baseline data available for a number of parameters indicate no differences between treatment groups. Safety measures (vital signs) did not change from baseline and were not significantly different between treatment and placebo groups at 24 weeks.

Conclusions: Preliminary results indicate that no safety concerns are associated with administering 600 mg SDG for 24 weeks to adults between the ages of 60 and 80 years.

Trial Registration: Clinicaltrials.gov NCT01846117; https://clinicaltrials.gov/ct2/show/NCT01846117 (Archived by WebCite at http://www.webcitation.org/6nlDZNjmA)

(JMIR Res Protoc 2017;6(2):e14) doi:10.2196/resprot.6817

KEYWORDS

flax; lignan; inflammation; oxidative stress; clinical trial; older adults

Introduction

Oxidative stress and inflammation are associated with a number of chronic diseases that are common among older adults [1,2]. Decreasing these processes may ameliorate problems associated with aging, such as hypertension and inflammation, which promote the development of vascular dementia and Alzheimer's disease (resulting in cognitive impairment) [3], and muscle wasting promoted by proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [4]. Increased oxidative stress also appears to be an early instigator of metabolic syndrome [5]. Evidence from animal and human studies demonstrates that flax lignans, such as secoisolariciresinol diglucoside (SDG), may delay the development of diseases associated with inflammation (ie, type 2 diabetes [6]), decrease hypertension [7,8], and lower serum cholesterol levels [9], among other actions. SDG supplementation in adults is associated with decreased levels of cholesterol and glucose in hypercholesterolemic individuals [9], reduced concentrations of C-reactive protein [10], and decreased metabolic syndrome composite score [7].

While older individuals would be expected to benefit more from anti-inflammatory compounds, most studies have focused on adults <60 years of age [9]. Consequently, limited information is available in seniors, and studies are necessary to confirm the safety and efficacy of anti-inflammatory compounds in this subpopulation of older adults. When SDG was tested in younger adults in a human clinical trial, there were no safety concerns associated with intake of 600 milligrams (mg) SDG, ingested for 8 weeks in participants between 53 and 58 years of age [9]. We also previously conducted two trials of SDG. One trial used a dose of 500 mg SDG in older (60-70 years of age) community-dwelling adults [7] but that trial had exercise in both the treatment and control groups, so assessment of SDG-only treatment was not possible. We then conducted a trial in older residential care (nursing home) adults aged 60-80 years, but that trial used a dose of only 300 mg SDG, as per Health Canada permission, and suffered from low recruitment (due to multiple exclusion criteria) and low retention (due to subject frailty) [11].

The present study was designed to examine whether consumption of a pharmacological dose (ie, 600 mg/day) of the flax lignan SDG for approximately 6 months (which was predicted to reduce oxidative stress and inflammation [12]), would show evidence of efficacy and safety in community-dwelling healthy older adults. A battery of biochemical and functional tests was applied. A 1000 international unit (IU) vitamin D supplement was given to all participants to ensure similar vitamin D status, in order to avoid confounding effects of differing status. The hypothesis being tested was that consumption of SDG, in persons with adequate vitamin D status, will decrease oxidative stress and associated inflammation, and improve secondary measures of function at the 6-month time point. In addition, data regarding blood lignan metabolites was gathered.

Methods

Intervention and Participant Recruitment

A 24-week double-blind randomized clinical trial was conducted, in which the intervention consisted of 600 mg flax lignan SDG daily or an equivalent amount of placebo. Participants were healthy community-dwelling men and women between the ages of 60 and 80 years, living in Saskatoon, Canada. The study was conducted in 2013-2014. Exclusion criteria included: age below 60 or above 80 years at initiation of the study; living in long term care (nursing) homes; individuals at risk of hypotension or with symptomatic hypotension; fasting hypoglycemia; unstable diabetes, or diabetics taking insulin; current cancer or diagnosed with cancer in the past 2 years; women with an immediate family history or personal history of breast cancer or ovarian cancer; significant liver (or other gastrointestinal) disorder, including inflammatory bowel disease; significant kidney disorder; unstable or severe cardiac disease, recent myocardial infarction, or stroke (either in past 6 months or significantly affecting physical mobility); unstable other medical disease including, but not limited to, pulmonary disorder, epilepsy, and genitourinary disorder; migraine with aura within the last year (as this is a risk factor for stroke); current diagnosis of a bleeding condition, or at risk of bleeding; significantly immunocompromised; current use of hormone replacement therapy (except thyroid medication); current use of warfarin, clopidogrel, ticlopidine, dipyridamole, or their analogues; intolerances or allergies to flax or vitamin D; allergy to whey (placebo); surgery within the last six months; and participation in any other clinical trial with an investigational agent within one month prior to randomization.

Recruitment of participants was undertaken using posters and newspaper advertisements. Study posters were displayed in local hospitals, on the University of Saskatchewan campus, and in several senior residences. The contact information of the study coordinator was provided. Interested volunteers called the study coordinator, who reviewed inclusion and exclusion criteria over the phone. Volunteers who met the inclusion criteria were asked to visit the study coordinator's office at the College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon (one time only) where inclusion and exclusion criteria were again reviewed and information in the consent form (10-page document) was explained, including purpose (Figure 1) and procedures (Figure 2), along with the possible risks and benefits of the study. Volunteers were given sufficient time to think about their participation. All volunteers were given the opportunity to ask questions and were made aware that they could withdraw from this study at any time for any reason. At the end of the consent process, volunteers gave permission to use and disclose their deidentified information that was collected for research purposes. A signed copy of the consent form was provided to each study participant. After participants signed up for the study, a study number was assigned and participants were given a map of the Saskatchewan Centre for Patient-Oriented Research (SCPOR) facility. Participants were

also given a toilet hat and instructions regarding the collection of fecal samples for baseline. All study visits took place at the SCPOR facility located at City Hospital in Saskatoon, Canada.

Figure 1. Schematic of trial design, procedures, and stages.

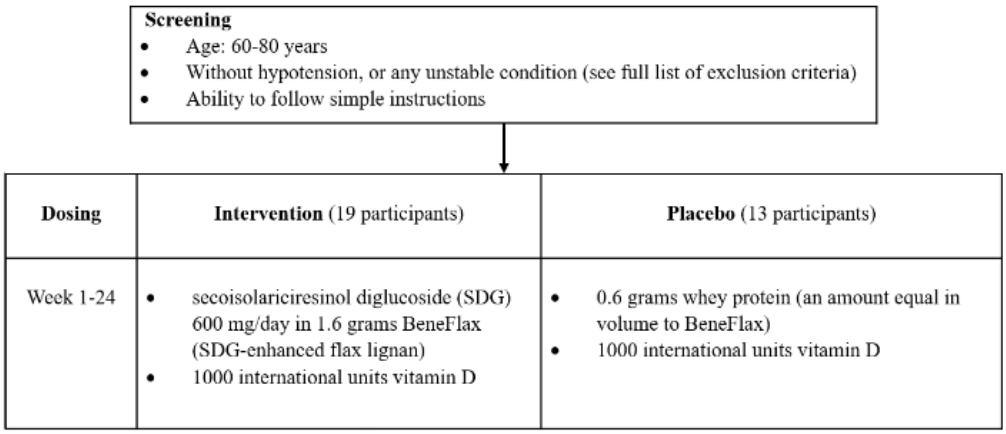
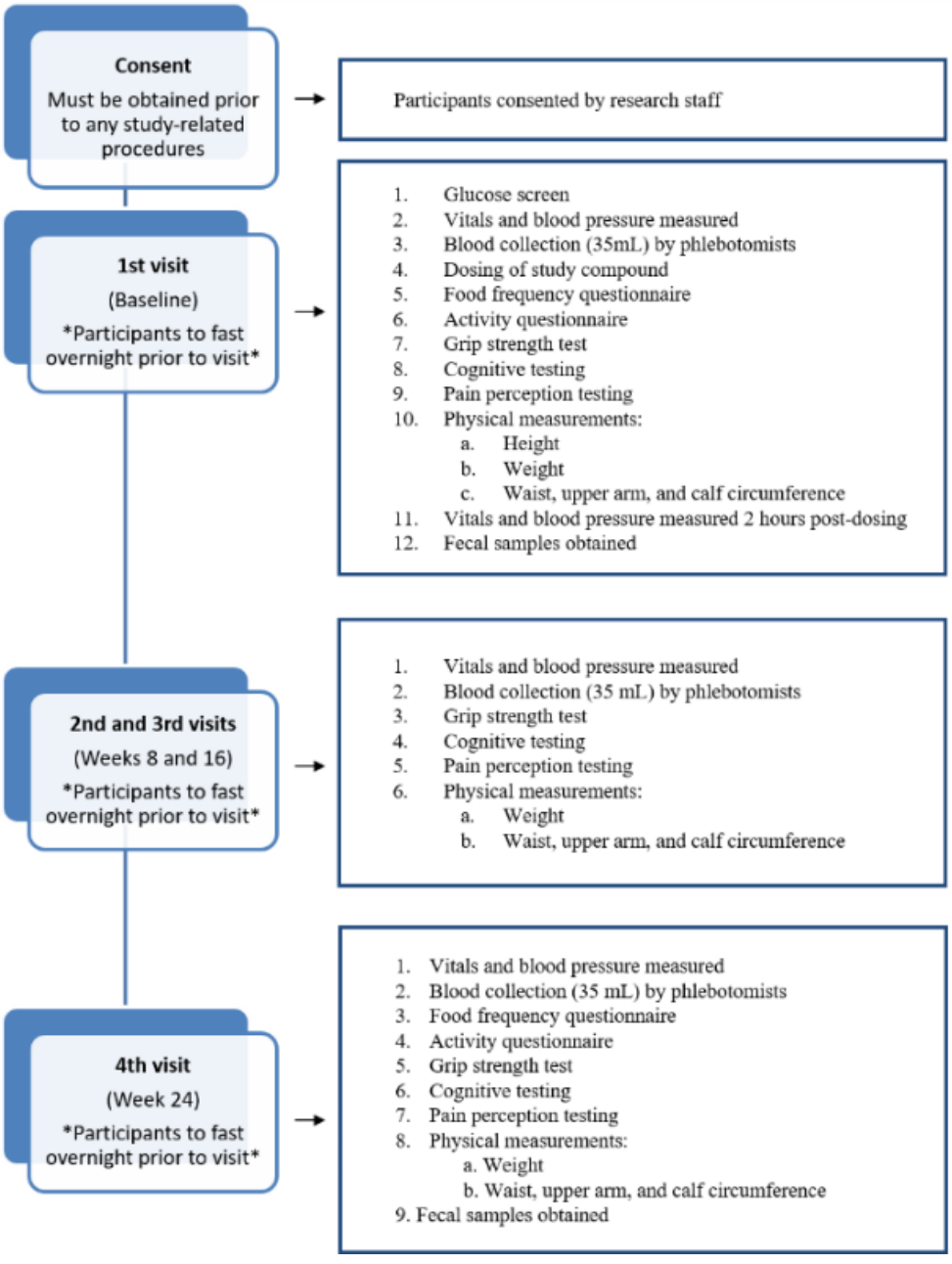


Figure 2. Flow chart of events for study.

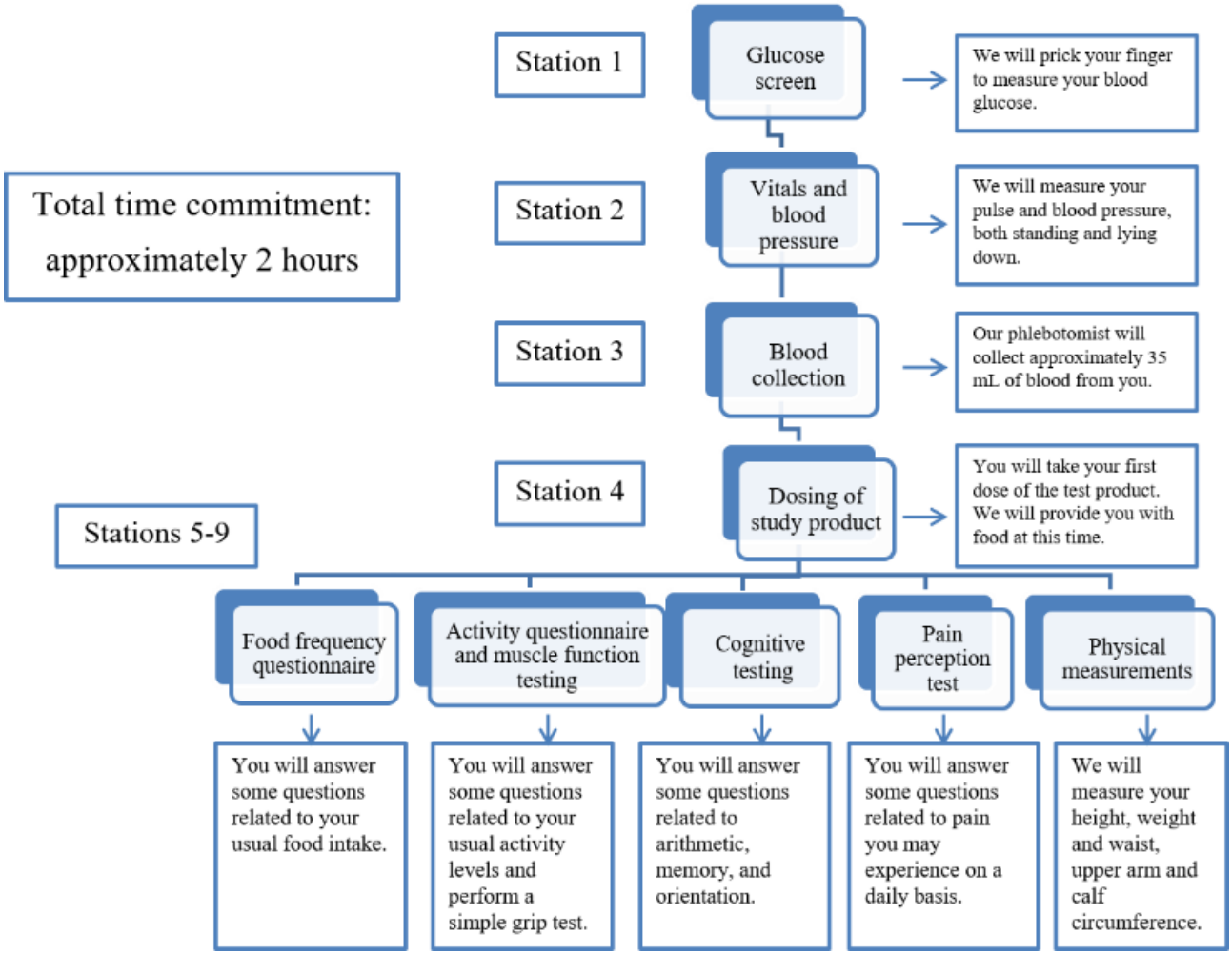


Study Procedures

The details of tests and timing are described in Figure 2. After obtaining informed consent from the participants, research staff collected demographic information, including age, date of birth, race, sex, and personal health number (required for blood collection). Screening for inclusion and exclusion criteria was done before each visit (ie, baseline, week 8, week 16, and week 24). The list of medications (including vitamins, supplements, natural health products, over the counter medications, and prescription medications; total daily dose if regular or individual dose if used as needed) was obtained from all study participants at baseline, and changes to medications were enquired at every consecutive visit with the review of inclusion/exclusion criteria.

A flowchart of the study procedures corresponding to visits 1 through 4 is shown in Figure 2. Clinical facilities and lounge areas at SCPOR were available for the study. Some measures were assessed at all visits while others were completed only at visit 1 (eg, the two-hour postdosing measurements), and fecal samples were collected only at visits 1 and 4. Figure 3 shows instructions given to the participant upon his or her arrival at the study center. Nine stations were set up in four different areas (to allow for privacy) and participants went from station 1 to station 4 in order, and then stations 5 through 9 in any order. At the end of each visit, a checklist was signed off by research staff to ensure that all study tests and procedures were completed. Upon completion of the checklist, participants were given a light lunch.

Figure 3. The flowchart of procedures that was handed to participants at each visit. Visit 1 had an additional reminder regarding the 2-hour post dosing measures.



Randomization and Blinding

We aimed to recruit a total of 60 participants (30 per treatment group) per protocol analysis. We calculated that a blood pressure change of 10 mmHg (inducing hypotension as a safety concern) would require 30 participants per group. However, recruitment proceeded slowly; thus, we started the study with 32 participants, with 19 in the intervention group and 13 in the control group. This distribution was generated randomly to allow for an equitable sex distribution.

BeneFlax or placebo were administered in a double-blind fashion. Only the pharmacist, who used a computer-aided randomization system, knew group assignments; all personnel performing the data collection and analyses were blind to group assignment. The pharmacist kept a secure copy of the randomization codes during the study. The code was broken only after results were analyzed. Some tests have yet to be been run (ie, some of the cytokine markers of inflammation, bone turnover markers, and fecal cyclolinopeptides).

Accountability Procedures

The placebo (whey powder, Natural Factors) was purchased from a health food store in Saskatoon, Canada. The flax lignan supplement BeneFlax was shipped to the College of Pharmacy and Nutrition Saskatoon, Canada (a secured facility) from Archer Daniels Midland (Natural Health Products File # OF2-31-3-13412-2-4), and stored at –20°C. The analyzed content of SDG in BeneFlax was measured prior to the study (samples were shipped to Archer Daniels Midland for quantitative analysis). The packets of BeneFlax and whey were prepared by the research staff following safe food preparation procedures. Study compounds were sent to a designated pharmacy where the pharmacist oversaw the dispensing of products into packets, which were labelled and packaged into 12-week supplies in child-proof amber containers, with instructions to store the containers in the fridge. The pharmacist kept accurate records of the study compounds dispensed, with identification of the participant to whom they were dispensed and the date of the dispensing. During the course of the study all unused study compounds were returned to the researchers. The 1000 IU vitamin D supplements were purchased from the pharmacist and were dispensed in their original packaging.

Intervention

This study used a two-group randomized design with an intervention group and a control group. The intervention group received 1.6 grams of SDG-enriched food-grade flaxseed lignan complex BeneFlax containing 600 mg SDG, plus 1000 IU vitamin D, while the placebo control group received 0.6 grams of whey protein (similar in volume to the intervention compound) plus 1000 IU vitamin D. Vitamin D tablets were provided separately. The daily dose could not be delivered in one packet, so instructions indicated that two packets were to be consumed per day. Each packet contained 0.8 grams of BeneFlax or 0.3 grams of placebo (a volume equivalent to the volume of BeneFlax given). The product was taken at the same time each day (eg, always with breakfast or always with dinner). Either compound (lignan or whey powder) could be added to a tablespoon of applesauce or equivalent food.

Usual medications were allowed except for warfarin, clopidogrel, ticlopidine, dipyridamole (or their analogues), and female hormone replacement therapy. Participants took at minimum 1000 IU vitamin D and were allowed other multivitamin/mineral formulations containing vitamin D as part of their supplemental routine. Participants were also asked to refrain from consuming flax-containing foods throughout the 24-week period of the study. All participants were provided with a diary at baseline to assess compliance, medication use, and bowel health monitoring. The initial pages included a checklist, and participants were instructed to place a checkmark in a square to indicate if they took the study product and vitamin D for each day in the 24 weeks of the study period. The medication list included all prescriptions, natural health products, vitamins, and supplements that they were using at baseline, along with any that were added during the duration of this study. Bowel health monitoring was assessed by study participants making note of any changes that differed from usual bowel health. These changes included alterations in bowel movement frequency, consistency, or any discomfort felt in the gastrointestinal tract. The last section of the diary was used to keep record of any illnesses along with the date, duration of symptoms (eg, once; number of days), and symptoms (date symptoms started and date symptoms ended).

Samples and Testing

Primary outcome measures were those of safety, related to 6-month administration of 600 mg SDG per day in healthy older adults. We included the reporting of clinical adverse signs and symptoms, vital signs, serum clinical chemistry, and hematology parameters for safety. SDG is known to be anti-inflammatory [10], so we also sought to confirm this property in older adults by examining the effects of flaxseed lignan supplementation on biomarkers of inflammation, risk factors of cardiovascular disease, and functional (ie, quality of life) indicators. Secondary outcomes included measuring plasma concentrations of lignans, fecal levels of flax cyclolinopeptides, and plasma levels of cyclolinopeptides.

Blood was collected on four visits: at baseline before taking the first dose of test product; and at weeks 8, 16, and 24. Phlebotomy staff at Saskatoon City Hospital collected a total of 35 milliliters (mL) of blood at each visit. Blood was collected in three 4.5 mL plasma separation tubes, two 10 mL tubes containing the anti-coagulant dipotassium ethylenediaminetetraacetic acid (K_2 EDTA), and two 4 mL K_2 EDTA tubes (or three 4 mL K_2 EDTA tubes in the case of diabetic participants), and all tubes were placed on ice packs. After centrifugation for 10 minutes at 1500 revolutions per minute (rpm), plasma was aliquoted into clearly labelled microcentrifuge vials to a volume of 500 microliters (µL) and placed at –20°C immediately, and research staff recorded the number of vials aliquoted each time. Subsequently, samples were stored at –80°C until analysis.

Two fecal samples were collected: once at the beginning of the trial, and again at the 24-week visit at the end of the trial. All required supplies and instructions to collect fecal samples were provided to participants. Participants were informed that fecal collection was to be made on the first bowel movement of the day of visit (baseline and 24-week) or samples collected at an earlier date (if they could not produce a fecal sample on the morning) were placed in freezer at home and brought to SCPOR by participants. Fecal samples were labeled by research staff and stored at –20°C immediately. Subsequently, fecal samples were also stored at –80°C until analysis.

Blood analysis was primarily carried out by the Saskatoon Health Region through the company Gamma Dynacare. Gamma Dynacare analyzed the following at all four time points (unless stated otherwise): urea, creatinine, glucose, liver enzymes (alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP]), total bilirubin, total protein, albumin, total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, low density lipoprotein cholesterol, total cholesterol to HDL ratio, total calcium, electrolytes (sodium, chloride, potassium), magnesium, prealbumin, complete blood count (platelets, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular volume, white blood cell count),

plasma C-reactive protein, and 25-hydroxyvitamin D. Research staff measured markers of oxidative stress, inflammation, and flaxseed lignan metabolites. Fecal samples will be analyzed for cyclolinopeptides by research staff.

A battery of functional tests was carried out. Cognitive function was assessed by research staff using the Mini-Mental State Examination, a clinical practice and research tool that takes 5-10 minutes to systematically assess mental status. The tool measures five areas of cognitive functionality: orientation, registration, attention and calculation, recall, and language, with 11 predefined questions. The maximum score is 30 and a score of 23 or lower is indicative of cognitive impairment [13]. Pain was assessed by research staff using the Brief Pain Inventory (BPI) Short Form [14]. Using BPI, participants rated the severity of their pain along with the degree to which it interfered with feeling and function.

Physical function was assessed by research staff via grip strength, using a Baseline Hydraulic Hand Dynamometer (Fabrication Enterprises Incorporated, White Plains, NY). Participants were seated comfortably with their upper arm in a normal neutral position alongside the body, and the elbow joint bent at 90°. The Hand Dynamometer was set to position 3 (or position 2 for females). The handgrip device was positioned vertically in the hand during the contractions (no rotating or twisting). Participants were instructed to squeeze the handle as hard as possible for a count of 3 (3-second long *isometric* contraction). Each participant's dominant side was tested first and 3 maximal repetitions with 30 seconds of rest between attempts were collected. Grip strength testing was completed on one hand before switching to the nondominant hand. Participants were not informed of the scores on each repetition until all repetitions were completed. If the participant was not able to complete the test, it was recorded as *unable*. If the participant could not complete the test due to a medical reason (ie, having had a past stroke), details were recorded in comments. Measurements were recorded to the nearest kilogram (kg). Height, weight, and circumference of the waist, mid-upper right arm, and right calf were measured by research staff using standard procedures [15].

The University of Saskatchewan version of the Block Food Frequency Questionnaire, modified to reflect Canadian fortification and to collect data on flax use, was administered to participants at each visit [7]. Activity was assessed by brief four-item queries of usual leisure-time exercise habits using the Godin Leisure-Time Exercise Questionnaire. Participants were asked during a typical 7-day period (one week), how many times (ie, each time = 1 unit) on average they did strenuous (eg, one's heart beating rapidly) **,** moderate (not exhausting), and mild (minimal effort) exercise for more than 15 minutes. Scoring in Godin Leisure-Time Exercise Questionnaire was based on a cut point at 24 units, which represented the cumulative score of two intensities: strenuous and moderate. A score of >24 units is categorized as active with substantial benefits, 14-23 units are moderately active with some benefits, and <14 units indicate insufficiently active with less substantial/low benefits [16].

Other Efficacy Measures

C-reactive protein was measured by Pathology and Laboratory Medicine, Saskatoon Health Region. Other oxidative stress measurements (plasma malondialdehyde) and proinflammatory measurements (IL-6, TNF-α) were measured by the research staff using kits purchased from Cayman (Ann Arbor, Michigan, US). All other solvents were specified as mass spectrometry grade and all other chemicals were reagent grade. Plasma 25-hydroxyvitamin D was measured in-hospital for vitamin D assessment.

To further understand the pharmacology of SDG, plasma levels of SDG metabolites (secoisolariciresinol, enterodiol, enterlactone) were analyzed using various methods. Plasma trough concentrations of flaxseed lignan metabolites were measured to provide important information regarding lignan levels with chronic oral administration of a pharmacological dose of SDG contained in BeneFlax (approximately 38% SDG). Participant plasma samples were collected and stored as stated above. Stock solutions (1 mg/mL) of lignan metabolites and their respective stable isotope-labelled internal standards (Toronto Research Chemicals) were prepared in methanol and stored at –20°C. Working solutions were prepared by serial dilution of the stock solution to produce a standard calibration curve of 0.2-50 nanograms (ng)/mL for enterolactone and enterodiol, and 1-50 ng/mL for secoisolariciresinol. Previous studies have indicated that SDG is not absorbed and therefore was not analyzed. Quality control (QC) standards were prepared for acceptance criteria of the analytical assay. Calibration and QC samples were prepared on ice for each day of sample analysis. A linear least-squares regression analysis using $1/X^2$as weighting factor was conducted to determine slope, intercept, and coefficient of determination (r^2) to demonstrate linearity of the method.

The sample extraction procedure involved the addition of 30 µL of internal standard and 4 mL diethyl ether to 300 µL of thawed plasma samples, and the mixture was shaken vigorously for 10 minutes. Samples were centrifuged at 2500 rpm for 5 minutes to separate the organic layers and transferred to –80°C to freeze the aqueous layer. The organic phase was then transferred to a glass tube and dried by rotary vacuum. Samples were reconstituted in 150 µL of mobile phase (85:15 solvent ratio [A:B] containing 0.1% formic acid) and filtered through Whatman Mini-UniPrep Syringeless Filter vials. For measuring the total lignans in plasma (free and conjugated lignans), 300 µL plasma and 60 µL beta-glucuronidase were added to 300 µL sodium acetate buffer (0.1 molar, pH 5.0) and incubated at 37°C for 4 hours before proceeding to the extraction procedure.

For high-performance liquid chromatography, 5 µL of sample was injected onto a Porshell 120 EC-C18 2.1 x 50 millimeter (mm), 2.7 micrometer (µm) column and 2.1 x 5 mm, 2.7 µm guard column (Agilent Technologies) with the column temperature set at 20°C. Samples were separated using an Agilent series 1200 binary pump (Agilent Technologies, Mississauga, Ontario, Canada) with an online degasser and auto sampler set at 4°C. Analytes were detected with an AB Sciex API 4000 Q-TRAP mass spectrometer (AB Sciex, Concord, Ontario, Canada). The mobile phase was 0.1% formic acid in

liquid chromatography-mass spectrometry (LC-MS) grade water (Solvent A) and LC-MS grade acetonitrile (Solvent B). The flow rate was set to 250 µL/min. Samples were separated using the 10-minute gradient method. The mobile phase was started with 85:15 A:B at 0 minutes and dropped to 50:50 A:B from 0 to 1.5 minutes. The gradient continuously changed to 5:95 A:B from 1.5 minutes to 2.5 minutes and remained the same to 4.5 minutes. The mobile phase was quickly returned to 85:15 A:B from 4.5 minutes to 5 minutes and held for another 5 minutes to equilibrate the column.

LC-MS was performed in the negative ion mode. The AB Sciex 4000 Q-TRAP mass spectrometer utilized a curtain gas pressure of 10 pounds per square inch and GS1 and GS2 parameters were set at 50 pounds per square inch. The ionspray voltage was set at 4500 V and the temperature of the electrospray ionization source interface was maintained at 700°C. The mass spectrometer utilized multiple reaction monitoring to quantify the analytes, by using the transition of mass (M) and charge number (z) such that [M]+ (m/z 361.019>164.800; declustering potential of 90, collision energy of 36, collision cell exit potential of 11) for secoisolariciresinol, transition of [M]+ (m/z 301.000>253.000; declustering potential of 95, collision energy of 32, collision cell exit potential of 5) for enterodiol, and transition of [M]+ (m/z 297.000>189.000; declustering potential of 90, collision energy of 30, collision cell exit potential of 7) for enterolactone. The peak areas were summed through use of Analyst Software. The ratio of peak areas of lignan metabolites to their respective internal standards were plotted against the nominal concentrations to construct the calibration curve. Analytical method validation was performed in accordance with the United States Food and Drug Administration (FDA) guidelines [17]. The assay was specific and linear, extraction efficiency ranged from 50% to 72%, and intraday and interday precision and accuracy of the method was within 15%.

Safety Parameters

Urea, creatinine, total bilirubin, platelets, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular volume, white blood cell count, total calcium, glucose, liver enzymes (AST, ALT, ALP), total protein, albumin, lipids, glycated hemoglobin for diabetic participants, and electrolytes were measured for safety assessment. Vital signs, including blood pressure, heart rate, and respiration rate were also assessed, with a copy of these results sent to the participant's physician. Blood pressure using a standard hospital sphygmomanometer was measured as resting blood pressure for all participants, in addition to standing blood pressure using the blood pressure monitor. All vital signs (except respiratory rate) were taken when study participants were either lying down or standing. Study participants would lie quietly for 3-5 minutes prior to blood pressure and pulse readings being taken; they then stood for 1 minute prior to blood pressure and pulse being taken again. If blood pressure measurements exceeded the inclusion criteria of *mild* hypertension (140-159 mmHg/90-100 mmHg) or fell below cutoffs for systolic hypotension (systolic blood pressure <80 mmHg) or orthostatic hypotension (reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 minutes of standing after restful sitting for at least five minutes) at visit 1, participants would have been excluded; however, no participants met these extreme cut-offs. During the study, hypoglycemia, systolic hypotension, and orthostatic hypotension episodes were used as indicators of adverse effects. Respiration rate was measured by the number of breaths in one minute by counting how many times the chest rose.

A research assistant reviewed the results and flagged any values that were outside of the normal range; values were signed off by a designated physician, and those of concern were discussed with the principal investigator or study physician. Diabetic participants had fasting glucose monitored for hypoglycemia using Rapid Response test strips on Rapid Response blood glucose meter (BTNX Inc, Markham, Ontario, Canada).

Ethics

Ethical approval was obtained from the University of Saskatchewan/University of Regina Ethics Review Board for Biomedical Research in Human Subjects. Approval from Health Canada was obtained for use of BeneFlax, a natural health product approved by both the FDA and Health Canada. This study is one of a series of studies that were supported by a Team Grant from the Saskatchewan Health Research Foundation to the University of Regina. This particular substudy was undertaken at the University of Saskatchewan and fell under the insurance of that institution.

Adverse Events Monitoring

Adverse events were recorded throughout the study. An *adverse event* was defined as any untoward medical occurrence in a patient or clinical investigation participant that was administered a pharmaceutical product. All research team members in contact with participants were responsible for noting adverse events, which were reported by the participants. Participants were advised to communicate the adverse event at the time of occurrence to the Physician Responsible for Trial Site Medical Decisions during office hours, or to the on-call study physician if outside of office hours. The 24-hour contact numbers for study physicians were made available to all participants. Adverse events were documented with clinical details, as well as the date, start and stop time of the event, and severity. All actions taken and outcomes were documented. All potentially adverse experiences, including illnesses, unpleasant symptoms, and falls and injuries were charted. Upon the occurrence of a serious adverse event, Internal Serious Adverse Event Reporting Form from University of Saskatchewan (page 39) and Adverse Reaction Report Form for Clinical Trials from Health Canada (page 41) forms were to be filled; however, none occurred during this clinical trial.

Statistics

The data will be descriptively analyzed using frequencies, means, and standard deviations. The data will be assessed for potential outliers or extreme observations, and for adherence to the assumptions underlying the analytic model. The data will be analyzed using a random-effects regression model for repeated measures data. A random-effects model is an appropriate and valid choice for these data given the potential for a high proportion of missing observations due to loss to follow-up, as a random-effects model does not require complete

data and does not rest on the stringent assumptions regarding the covariance structure of the data that underlies the repeated measures analysis of variance (ANOVA). Any deviations from the original statistical plan will be described and justified in the final report. Model effects will include group (intervention, control) and time (baseline, 8, 16, and 24 weeks). Analyses will be conducted using body weight, blood pressure, age, and body mass index (kg/m^2) as potential confounding covariates in the model. Likelihood ratio tests will be used to test for differences between treatment and control groups at each measurement occasion and/or between baseline and 24 weeks. A Cronbach alpha level of 0.05 will be used as the level of significance.

Data will be analyzed on an intent-to-treat basis; an attempt will be made to remeasure participants that did not adhere to supplementation. Analyses will also be performed by received dose (ie, analysis by the actual amount of supplement consumed by subtracting missed doses) using the diary information. A consort checklist for this study was completed according to established protocol and is presented as Multimedia Appendix 1 [18].

Results

This trial was started on May 8, 2013. We screened 173 potential participants (92 females, 81 males) who responded to advertisements that listed inclusion criteria of 60-80 years of age, and "healthy." There were 34 potential participants (16 females, 18 males) who consented to be in the study; however, after consenting two participants (one male and one female) withdrew. The 32 participants remaining in the study came to all four visits except one participant who missed the 16-week time point. Of the data from 128 total possible visits from 32 participants, we obtained data from 127 visits. Information on study participants is provided in Table 1, showing no differences between those randomized to intervention with those randomized to control treatment, using one-way ANOVA.

Here we report on some of the safety parameters. Systolic blood pressure, diastolic blood pressure, and heart rate measurements were completed in duplicate for all participants at each visit. Table 2 shows blood pressure (systolic and diastolic), heart rate, and respiration rate two hours after the BeneFlax or placebo was administered for the first time, and after 24 weeks of chronic ingestion (in fasting subjects). There was no significant change in any of these parameters with treatment, using one-way ANOVA.

Table 1. Study participants at baseline.

Parameter	BeneFlax	Placebo
Total (males, females)	19 (10, 9)	13 (7, 6)
Age in years, mean (SD)	67.9 (5.2)	68.1 (4.7)
Body mass index, mean (SD)	26.0 (3.3)	28.8 (5.0)
Systolic blood pressure, mean (SD)	129.5 (23.6)	138.3 (19.9)

Table 2. Vital signs after acute (2-hour) and chronic (24-week) ingestion of BeneFlax or placebo.

Outcome	Treatment	n	Baseline	2-hour	24-week	Range
Systolic blood pressure, mean (SD)	BeneFlax	19	130 (24)	136 (20)	132 (14)	100-178
	Placebo	13	138 (10)	134 (21)	138 (21)	99-167
Diastolic blood pressure, mean (SD)	BeneFlax	19	79 (10)	80 (9)	79 (9)	64-109
	Placebo	13	77 (6)	74 (5)	76 (7)	64-89
Respiratory rate, mean (SD)	BeneFlax	19	16 (5)	13 (3)	13 (3)	7.0-24
	Placebo	13	15 (4)	15 (4)	14 (3)	9.0-24
Heart rate, mean (SD)	BeneFlax	19	63 (9)	66 (7)	69 (11)	47-88
	Placebo	13	64 (9)	67 (7)	63 (11)	49-86

Discussion

Data analyses for this intervention trial are ongoing and flaxseed lignan metabolite measurements are underway. Results and findings will be reported in several publications. In terms of further analyses, the determination of the differences in the inflammatory and oxidative stress markers between the SDG- and placebo-supplemented group are in progress. This research will contribute to the literature on the efficacy and safety of SDG supplementation in healthy older adults. Data from other tests such as grip strength, pain measures, activity, anthropometrics, and cognitive testing will help in better understanding the effects of flaxseed lignan supplementation on functionality. Associations with oxidative stress and inflammation will be made.

In terms of safety, our data (Table 2) are compatible with our other studies in which we reported that SDG supplementation (300 mg/day of BeneFlax) in a very frail, complex patient population 60-80 years of age caused no significant adverse

outcomes [11], and that 543 mg daily for 6 months produced no incidents of hypoglycemia or hypotension among participants 49-87 years of age [19].

Compliance with the Flax Product Study compound was monitored with the participant diary. Although participants did not consistently return all used and unused product packets of Beneflax and vitamin D supplements, most returned diaries outlining the compliance to study test products, vitamin D, medication change, illnesses, and bowel health monitoring.

Strengths of the study included the commitment of participants who presented themselves at 127 of 128 visits (32 participants and 4 visits), which represents 99.2% compliance to the study. Conducting this trial at SCPOR was another strength, as this facility had adequate space and rooms for all tests and procedures, which were simultaneously performed by the research staff during the visits. The centrifuge for obtaining plasma was in place at SCPOR and Pathology and Laboratory Medicine, Saskatoon Health Region was situated in the hospital as well, for immediate transfer of blood samples. The equipment used at SCPOR, such as blood pressure monitors and weighing scales, were calibrated by the technicians there, providing accuracy and precision to the tests. Also, SCPOR is located in the downtown area, making it easily accessible to the study participants. All tests and procedures performed by research staff were conducted using standard operating procedures; training was provided to staff.

The foremost study limitation and challenge was the recruitment of healthy older adults due to our extensive exclusion criteria. Of the 173 potential participants initially screened by research staff, only 34 participants met the inclusion/exclusion criteria, representing approximately 20% of the potential participants. After the withdrawal of two participants, we had only 32 final participants. Our previous work [11,19] demonstrated the safety of BeneFlax in older healthy and frail populations, therefore the inclusion and exclusion criteria could be revised/reviewed in further clinical trials of BeneFlax in older healthy and frail populations for better recruitment, and to allow for larger scale clinical trials.

Conclusion

We are comparing flax lignan to a placebo (whey powder) to examine whether a dietary intervention (ie, flaxseed lignan-enriched product) might decrease oxidative stress and inflammation in older adults. This intervention consisted of 600 mg of the flaxseed lignan SDG, taken daily for 24 weeks in healthy older adults. SDG is broken down in the gastrointestinal tract to produce the health benefits of flax. Results from this study will demonstrate whether SDG supplementation decreases oxidative stress and inflammation in community-dwelling healthy older adults. These findings might help in maintaining/improving functionality markers such as cognition, muscle strength, and other inflammation-associated problems of aging.

To the best of our knowledge this is the first study testing the efficacy and safety of flaxseed lignan in community-dwelling healthy older adults. Our findings will contribute significantly to the knowledge base on flaxseed lignan safety and efficacy.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

CONSORT-EHEALTH checklist V1.6.1 [18].

[PDF File (Adobe PDF File), 7MB - resprot_v6i2e14_app1.pdf]

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Abbreviations

ALP: alkaline phosphatase
ALT: alanine transaminase
ANOVA: analysis of variance
AST: aspartate transaminase
BPI: Brief Pain Inventory
FDA: Food and Drug Administration
HDL: high density lipoprotein
IL-6: Interleukin-6
IU: international unit
K_2 EDTA: dipotassium ethylenediaminetetraacetic acid
kg: kilogram
LC-MS: liquid chromatography-mass spectrometry
M: mass
mg: milligram
mL: milliliter
mm: millimeter
ng: nanogram
QC: quality control
RPM: revolutions per minute

SCPOR: Saskatchewan Centre for Patient-Oriented Research
SDG: secoisolariciresinol diglucoside
TNF-α: tumor necrosis factor-alpha
µL: microliter
µm: micrometer

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Protocol

Local Anesthesia Versus Local Anesthesia and Conscious Sedation for Inguinal Hernioplasty: Protocol of a Randomized Controlled Trial

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Abstract

Background: Conscious sedation is regularly used in ambulatory surgery to improve patient outcomes, in particular patient satisfaction. Reports suggest that the addition of conscious sedation to local anesthesia for inguinal hernioplasty is safe and effective in improving patient satisfaction. No previous randomized controlled trial has assessed the benefit of conscious sedation in this regard.

Objective: To determine whether the addition of conscious sedation to local anesthesia improves patient satisfaction with inguinal hernioplasty.

Methods: This trial is designed as a single-center, randomized, placebo-controlled, blinded trial of 148 patients. Adult patients diagnosed with a reducible, unilateral inguinal hernia eligible for hernioplasty using local anesthesia will be recruited. The intervention will be the use of intravenous midazolam for conscious sedation. Normal saline will be used as placebo in the control group. The primary outcome will be patient satisfaction, measured using the validated Iowa Satisfaction with Anesthesia Scale. Secondary outcomes will include intra- and postoperative pain, operative time, volumes of sedative agent and local anesthetic used, time to discharge, early and late complications, and postoperative functional status.

Results: To date, 171 patients have been recruited. Surgery has been performed on 149 patients, meeting the sample size requirements. Follow-up assessments are still ongoing. Trial completion is expected in August 2017.

Conclusions: This randomized controlled trial is the first to assess the effectiveness of conscious sedation in improving patient satisfaction with inguinal hernioplasty using local anesthesia. If the results demonstrate improved patient satisfaction with conscious sedation, this would support routine incorporation of conscious sedation in local inguinal hernioplasty and potentially influence national and international hernia surgery guidelines.

Trial registration: Clinicaltrials.gov NCT02444260; https://clinicaltrials.gov/ct2/show/NCT02444260 (Archived by WebCite at http://www.webcitation.org/6no8Dprp4)

(JMIR Res Protoc 2017;6(2):e20) doi:10.2196/resprot.6754

KEYWORDS

inguinal hernioplasty; local anesthesia; conscious sedation; patient satisfaction; randomized controlled trial

Introduction

Inguinal hernia repair is one of the most commonly performed surgical procedures in the world. It is estimated that 20 million inguinal hernia repairs are performed globally every year [1]. Inguinal hernia repair prevents the development of complications of inguinal hernias such as incarceration, obstruction, and strangulation with their ensuing morbidity and mortality. Mesh repair (ie, hernioplasty) is superior to suture repair and is now standard for inguinal hernia repair [2].

There are a variety of anesthetic options available for this procedure. These include infiltration of the inguinal region using local anesthesia (LA), the use of regional anesthesia such as a subarachnoid block, or general anesthesia. For suitable inguinal hernias, the use of LA has been a simple and very popular option [3]. Several high-quality studies have suggested numerous advantages of LA over both regional and general anesthesia techniques. These include shorter operative time [4], reduced nausea [4,5], less urinary retention [4,6,7], increased day-case rates [6,7], less postoperative analgesia [6,7], faster return to normal activity [5], reduced costs [8], and greater patient satisfaction [4,9]. Patient tolerance and satisfaction for hernioplasty performed using LA may be as high as 82%-98% [4].

One adjunct that is utilized to improve patient experience with ambulatory surgical procedures is the addition of conscious sedation. Conscious sedation refers to the use of sedative or dissociative agents and analgesics to induce a state that enhances patient tolerance of unpleasant procedures while maintaining cardiorespiratory function. Use of sedation in addition to LA for surgical procedures allays patient anxiety, reduces autonomic arousal, and often provides amnesia for the procedure. However, evidence linking conscious sedation to improved patient satisfaction and its effect on other patient outcomes has been lacking.

Potential issues with the use of conscious sedation include delayed awakening and impairment of psychomotor function that may prolong postoperative recovery and reduce the rate of same-day discharge [10,11]. These issues initially limited the use of sedation for inguinal hernioplasty using LA. The use of midazolam, with its high therapeutic index and relatively short duration of action, has allayed these concerns [12]. This high therapeutic index has facilitated the use of midazolam for sedation by nonanesthetists with the presence of appropriate monitoring. Inguinal hernioplasty using LA with conscious sedation (LACS) has demonstrated acceptable patient outcomes with no mortality and acceptable morbidity [13-16]. A study from the University of the West Indies prospectively evaluated 90 patients undergoing inguinal hernioplasty using LA combined with midazolam. Operative morbidity was low, with all patients discharged ambulant and same day. No adverse reactions to sedation were demonstrated [17].

Inguinal hernioplasty using either LA or LACS has demonstrated good patient outcomes, patient satisfaction, and low morbidity. No study has directly compared LA to LACS in patients undergoing inguinal hernioplasty in order to establish superiority of either method.

It was hypothesized that the addition of conscious sedation to local anesthesia would result in improved patient satisfaction with no change in the rate of same-day discharge or perioperative complications when compared to the use of LA alone.

Methods

Trial Design

The trial will be a single-center, randomized, blinded, placebo-controlled trial of 148 participants with an allocation ratio of 1:1. Patients, surgeons, outcome assessors, and data analysts will be unaware of the treatment assignments.

Primary and Secondary Endpoints

The primary endpoint of this trial is patient satisfaction with the method used: anesthesia alone or anesthesia plus sedation. Patient satisfaction will be assessed using the Iowa Satisfaction with Anesthesia Scale (ISAS) [18]. ISAS is a validated scale consisting of 11 parameters measured on a 6-point Likert scale. ISAS has been used to assess patient satisfaction with anesthesia across various surgical specialties, including ophthalmology and orthopedic surgery, and for various types of anesthesia. It will be administered at the time of discharge from hospital following the surgical procedure and at the 2-week follow-up visit.

The secondary endpoints include measurement of pain during and following the procedure, the quantity of anesthetic and/or sedation required, the frequency of complications, the frequency of functional incapacity [19], and the time to discharge [20] from hospital. A complete list of these secondary endpoints is provided in Table 1.

Table 1. Complete list of secondary endpoints.

Study endpoint	Definition
Intraoperative pain	Patient's perception of pain felt during the procedure as measured by a visual analog scale
Postoperative pain	Patient's perception of pain being experienced at the time of discharge as measured by a visual analog scale
Operative time	Time from incision to wound closure
Volume of local anesthetic	Total volume of local anesthetic administered during the procedure
Volume of conscious sedation	Total volume of conscious sedative agent administered during the procedure
Time to discharge	Time from transfer to the recovery room to scoring at least 9 out of 10 on the Modified Post-Anesthetic Discharge Scoring System [20]
Frequency of early postoperative complications	Any postoperative complication occurring within 30 days of the surgical procedure, including wound hematoma, scrotal hematoma, surgical site infection, seroma, and wound dehiscence
Frequency of late postoperative complications	Any postoperative complication occurring between 30 days and 1 year following the surgical procedure, including chronic pain, hydrocele, and recurrence
Frequency of functional incapacity	Impairment in functional abilities following the surgical procedure as measured by a 13-parameter, 6-point Likert scale by McCarthy et al [19]

Inclusion and Exclusion Criteria

The trial (ClinicalTrials.gov identifier: NCT02444260; protocol number: ECP 342, 12/13) was approved by the Ethics Committee of the Faculty of Medical Sciences, University of the West Indies at Mona. All patients will be informed about the purpose of the trial, the two study arms, and the potential benefits and risks. Eligible patients will be 18-75 years of age and diagnosed with a reducible inguinal hernia. Patients will be selected solely based on suitability for inguinal hernioplasty with local anesthesia and not because of easy availability, diminished autonomy, or social bias. Exclusion criteria are listed in Textbox 1.

Textbox 1. Exclusion criteria for the study.

Exclusion criteria:

- Age less than 18 years or greater than 75 years
- Known renal, hepatic, respiratory, cardiovascular, neurologic, or psychiatric disease
- Body mass index >30 kg/m^2
- Bilateral, recurrent, inguinoscrotal, or incarcerated/irreducible hernia
- Allergy to local anesthetic or sedative agents
- Pregnancy, lactating, or breastfeeding patients
- Chronic pain syndromes, such as sickle cell disease
- Anxiety disorder
- Regular opioid analgesia or sedative use
- Serious medical condition likely to impede successful completion of the study
- Current participation in other therapeutic clinical trials

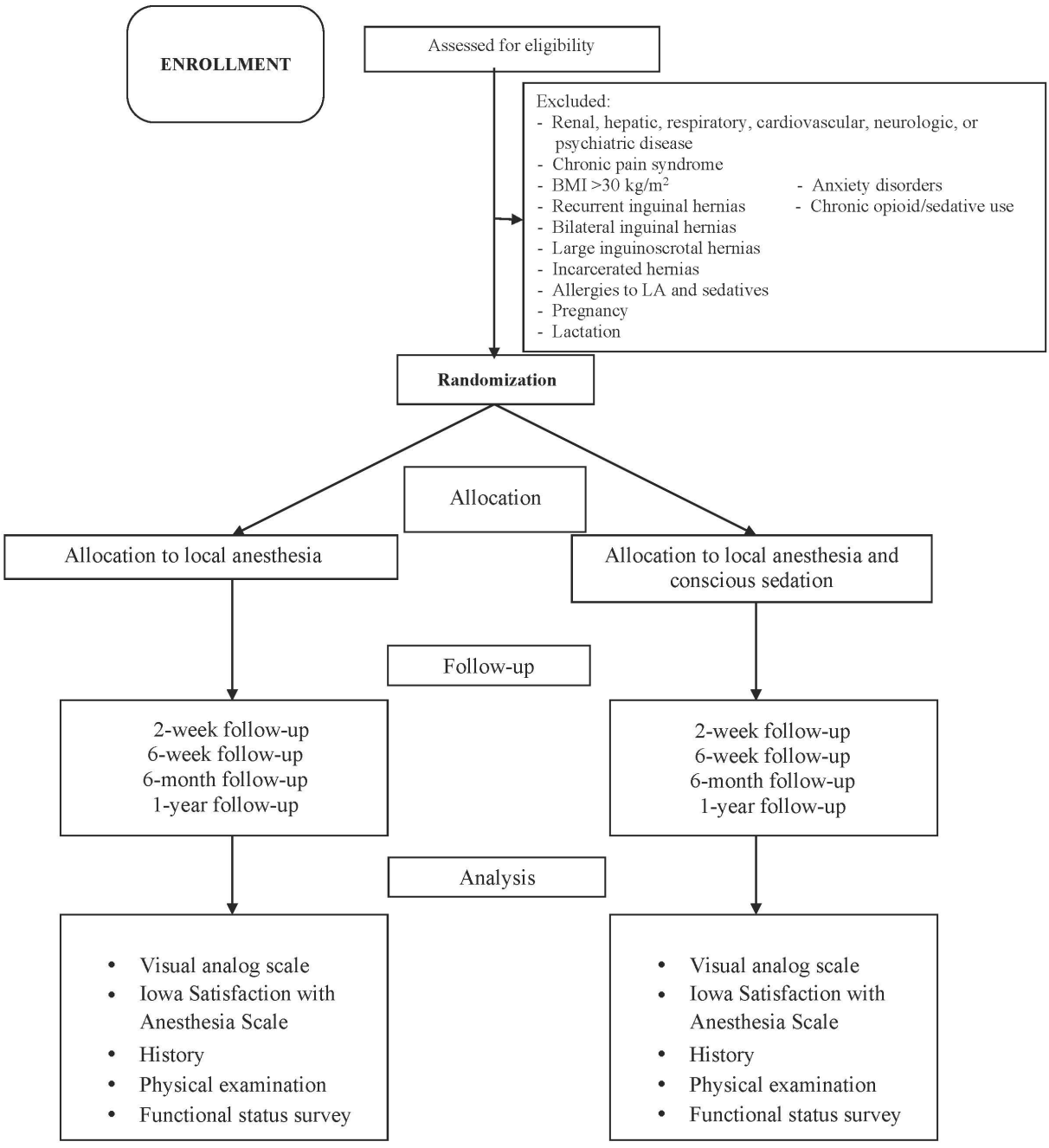
Determination of Sample Size

Assuming a variance of 1.3, as established by Dexter et al [18], a sample size of 74 participants per subject group (ie, a total of 148 participants) would provide 80% power to detect a difference in ISAS score of 0.6 at 5% significance between the two subject groups—LA versus LACS. These values were derived from data by Candiotti [21] in a randomized controlled trial showing a 0.6 ISAS score difference between two intervention arms. To mitigate the effects of dropouts, we proposed to recruit 90 subjects per group for a total of 180.

Study Procedures

The study procedures and participant flow through each stage are summarized in the flowchart in Figure 1.

Figure 1. Flowchart summarizing study procedures and participant flow through each stage. BMI: body mass index; LA: local anesthesia.



Screening and Recruitment

Subjects will be recruited as they are evaluated in the surgical outpatient department (SOPD) at the University Hospital of the West Indies (UHWI). Clinical staff will review new patients referred to the SOPD for management of inguinal hernias and those previously seen but awaiting surgical management. Following initial clinical assessment for study suitability by the clinical staff, the research nurse coordinating the study will approach potential study patients and assess them for

participation. These potential subjects will complete an eligibility-screening questionnaire to document fulfillment of the entry criteria. Eligible patients will have the study explained to them and provided with full study information prior to consent being obtained. Patients will be given ample opportunity to review the information provided and have any questions answered prior to making the decision to consent. Once the informed consent document is signed, the subject will be considered *registered* in the study. Patients that are not eligible for the study and eligible patients that decline to participate in the study will continue the usual assessment and therapy as dictated by the practice guidelines of UHWI.

General Scheduling

Once consent is given, a study number will be assigned and this will be used to identify the subject throughout the study. Once registered, scheduling of study evaluations will proceed. Patients will be sent to the minor operating theater of the UHWI where a date for surgery will be issued and surgical preparation instructions given. A total of six visits are scheduled for the trial (see Table 2). Follow-up visits will be carried out at 2 weeks, 6 weeks, 6 months, and 1 year where patients will be examined and issued questionnaires evaluating patient satisfaction, pain evaluation, and functional status [19].

Table 2. Schedule of visits during the course of the trial.

Study step	Visit					
	1 (SOPD[a])	2 (Operation)	3 (2 weeks postop[b])	4 (6 weeks postop)	5 (6 months postop)	6 (1 year postop)
Demographics and baseline clinical data collected	X	X				
Eligibility criteria determined	X					
Randomization performed		X				
History and clinical examination performed			X	X	X	X
Visual analog scale administered		X	X			
Iowa Satisfaction with Anesthesia Scale administered		X	X			
Functional status determined			X	X	X	X

[a]SOPD: surgical outpatient department.

[b]postop: postoperation.

Randomization

The study will be blinded. Randomization will be done using the *ralloc* command in Stata (StataCorp LLC) version 14. In order to reduce the risk of breaking the blind because of small block sizes or alternately to prevent unequal sample sizes if the trial is stopped prematurely, treatment allocation will be done according to a 1:1 ratio and block sizes will be allocated in proportion to elements of Pascal's triangle. The ensuing allocation table will be kept in a secure file on the study statistician's computer and will be made available to the anesthetist on a per-enrolled-patient basis when required in a sealed envelope immediately prior to the procedure.

Preoperative Assessment and Preparation

On the day of their procedure, all patients will be seen in the holding area. A presurgery checklist will be completed to ensure that the patient has no immediate contraindications to surgery. All parameters must be within specified ranges in order to proceed. If there are abnormalities that preclude safe conduct of the procedure, the procedure will be postponed and the patient returned to the SOPD. Reevaluation for participation in the study will be possible once the identified abnormality is corrected. The patient will have to reenter the study at the eligibility-screening phase, though the study identifier will remain the same.

Standardized Treatment

Perioperative and intraoperative care will be standardized, except for the administration of conscious sedation, which will be randomized by the attending anesthetist according to the allocated study group. Prophylactic antibiotics will not be administered.

Local anesthesia will be administered by the surgeon and will be used in all cases. A mixture of 1% lignocaine and 0.25% bupivacaine to a maximum of 4.5 mg/kg and 2 mg/kg, respectively, will be infiltrated. An initial dose will be administered prior to skin incision with subsequent doses administered during the procedure. Protocols for rescue intraoperative analgesia have been established in the event that the maximum amount of local anesthetic has been infiltrated without effective pain control.

The operative technique will be a standardized Lichtenstein repair using polypropylene mesh. A single consultant surgeon will be supervising surgical residents. During the procedure, the ilioinguinal nerve will be spared.

Trial Interventions

Following placement on the operating table and the attachment of monitoring devices, the anesthetist will open the randomization envelope. Only she or he will know the allocated study intervention.

In the LACS group, the sedative agent being used will be midazolam. This will be administered at an initial dose of 2 mg, with incremental doses of 0.5-1 mg to a maximum of 10 mg. Additional doses of midazolam will be administered based on assessment of the patient's level of sedation at 15-minute intervals using the Ramsay Sedation Scale [22] (see Table 3). A score of 2-3 on the Ramsay Sedation Scale will be maintained. In the LA group, the anesthetist will administer placebo (ie, intravenous normal saline) to the patient in a similar manner to the midazolam in order to maintain blinding.

Table 3. The Ramsay Sedation Scale scores and their definitions.

Score	Definition
1	Anxious and agitated, restless, or both
2	Cooperative, oriented, and calm
3	Responsive to commands only
4	Exhibiting brisk response to light glabellar tap or loud auditory stimulus
5	Exhibiting a sluggish response to light glabellar tap or loud auditory stimulus
6	Unresponsive

Blinding

The patient and surgeon will be blinded to the randomization. We recognize that both the patient and surgeon may have an opinion as to the randomization based on known effects of sedative agents (ie, sleep). However, neither will be made aware directly of the allocation. The patient will be draped in such a manner that the surgeon will not be able to see the patient during the procedure. Conversation between patient and surgeon during the procedure will be discouraged. The allocation of the participant to the study group will be unmasked prior to the end of the trial only if a serious adverse event occurs.

Outcome Assessment and Follow-Up

At Discharge

Patient demographic data and medical history, operative time, volume of local anesthetic, and volume of conscious sedation used (if applicable) will be recorded. Following inguinal hernioplasty, the subject will be transferred to the recovery room where she or he will be monitored by nursing staff. The nursing staff will be trained to determine the subject's readiness for discharge based on specified discharge criteria [20]. The discharge criteria questionnaire will be administered 1 hour after admission to the recovery room and thereafter at 30-minute intervals until the patient has achieved the appropriate score for discharge. Once the subject has fulfilled the criteria for discharge, the time of discharge will be recorded on the subject's research operative chart. A questionnaire assessing surgical experience and satisfaction will be administered at the time of discharge. It will include a previously validated visual analog pain scale [23] and the Iowa Satisfaction with Anesthesia Scale [18].

Prior to discharge, all patients will be given a supply of oral analgesics, which will include acetaminophen and diclofenac. Instructions on the dosages and administration schedule for these drugs will be included with the medications. Patients will be given a telephone number to contact if they have any questions about postoperative analgesia administration or instructions.

Follow-Up Visits

Subjects will return for routine interval follow-up visits 2 weeks, 6 weeks, 6 months, and 1 year following the surgical procedure. The 1-year visit will be considered the study exit visit. At the time of discharge following surgery, the study coordinator will calculate the follow-up dates. These will be indicated in the subject's research chart as well as the hospital chart. A special sticker will be placed on the hospital chart to indicate that the subject is involved in this study and should be seen by the study coordinator.

Table 2 shows the mode of assessment and the outcome measures evaluated at each follow-up visit.

Assessment of Safety

From the time of consent until completion of the study at 1-year follow-up or premature withdrawal, all serious adverse events will be reported to the Ethics Committee and the Data Safety Monitoring Board within 24 hours of the principal investigator learning of its occurrence. All adverse events occurring from the time of consent until 30 days following completion of the last follow-up visit will be recorded; those at grade 2 or higher using the Common Terminology Criteria for Adverse Events version 4.0 [24] will be reported to the Ethics Committee and the Data Safety Monitoring Board. Information to be submitted will include the study identifier, the nature and grade of the adverse event, and the outcome or nature of the event.

The Data Safety Monitoring Board will be responsible for assessing adverse outcome data collected during the course of the trial at 6-month intervals and communicate findings to the Ethics Committee. Unacceptable findings will be an indication for early termination of the study.

Data Management and Monitoring

Subjects enrolled in this study will be assigned and tracked according to a unique study identifier assigned at the time of the subject's registration. A log report will be kept to track each subject that is registered. This log will be kept as a hard copy in the regulatory binder and stored securely in a locked cabinet in the office of the principal investigator. All data collected in the trial, including on the day of the procedure and during follow-up visits, will be collected on case report forms. The

completed case report forms will be reviewed by the principal investigator and data from the forms will be transferred to a database on a secure computer. The case report forms will be stored as hard copies in a locked cabinet. All data are managed and analyzed at the Tropical Metabolic Research Institute, University of the West Indies.

Monitoring is carried out in accordance with the Declaration of Helsinki, International Conference on Harmonization Guidelines for Good Clinical Practice (codification E6) and standard operating procedures of the Faculty of Medical Sciences, University of the West Indies.

Statistical Analysis Plan

Demographic variables and quantitative data will be displayed in tables. Summary measures of continuous variables will be expressed as means with standard deviation, minimum, and maximum. Categorical variables will be expressed as counts. Differences in mean values by group will be tested with an independent *t* test while differences in proportions for categorical variables by group will be assessed with chi-square statistics. A *P* value of <.05 will be considered significant.

Dissemination of Results

Data will be collated, analyzed, and submitted for publication as soon as possible following completion of the study. The results of this study will be submitted for publication whether or not a significant difference is found in the outcomes for the two groups.

Results

This trial has been designed as a single-center, randomized controlled trial and was initiated at the Department of Surgery, University of the West Indies at Mona, in February 2014. To date, a total of 171 patients have been recruited. Surgery has been performed on 149 patients, meeting the sample size requirements. Follow-up assessments are still ongoing. Trial completion, with completed follow-up, is expected in August 2017.

Discussion

We present a study protocol for a randomized controlled trial to assess the effect of adding conscious sedation (ie, midazolam) to local anesthesia (ie, lignocaine and bupivacaine) on patient satisfaction with inguinal hernioplasty. Patient satisfaction is an indirect indicator of the quality of health care. Its impact extends beyond the patient to also include the hospital staff, the institution, and potentially national policy making. It influences patient loyalty and retention, patient and staff morale, staff productivity, and overall profitability [25].

Inguinal hernioplasty using local anesthesia alone has long been a standard for ambulatory hernia surgery, with reports of reasonable patient satisfaction [4]. With increasing use of conscious sedation in ambulatory surgery [26-28], it is prudent to establish its utility for ambulatory hernia surgery.

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Conflicts of Interest

None declared.

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Abbreviations

BMI: body mass index
ISAS: Iowa Satisfaction with Anesthesia Scale
LA: local anesthesia
LACS: local anesthesia with conscious sedation
postop: postoperation
SOPD: surgical outpatient department
UHWI: University Hospital of the West Indies

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Protocol

VESPRO: An Individual Patient Data Prospective Meta-Analysis of Selective Internal Radiation Therapy Versus Sorafenib for Advanced, Locally Advanced, or Recurrent Hepatocellular Carcinoma of the SARAH and SIRveNIB Trials

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Abstract

Background: Untreated advanced hepatocellular carcinoma (HCC) has an overall poor prognosis. Currently there are 2 ongoing prospective randomized controlled trials that are evaluating the efficacy and safety of sorafenib and selective internal radiation therapy (SIRT) with yttrium-90 resin microspheres in patients with advanced HCC. The SorAfenib versus Radioembolisation in Advanced Hepatocellular carcinoma (SARAH; 459 patients) trial is being performed in Europe and the SIRt VErsus SorafeNIB (SIRveNIB; 360 patients) trial in the Asia Pacific region. Prospectively combining the results, these trials will not only allow for increased precision to estimate efficacy (in terms of survival), but will also provide increased statistical power for subgroup analyses.

Objective: To ensure the prospectivity and transparency of the meta-analysis.

Methods: The sirVEnib and SARAH merge PROject (VESPRO) is an individual, patient-data prospective meta-analysis of the SIRveNIB and SARAH randomized trials. The VESPRO protocol includes prespecified hypotheses, inclusion criteria, and outcome measures. The primary outcome measure is overall survival and secondary outcomes include tumor response rate, progression-free survival, progression in the liver as first event, and disease control in the liver. Pooling of toxicity results will allow for robust safety profiles to be established for both therapies, and provides increased statistical power to investigate treatment effects in key subgroups. Analyses will be performed in the intent-to-treat population stratified by trial.

Results: Both studies are expected to demonstrate a survival benefit for SIRT together with a better toxicity profile compared with sorafenib. It is also anticipated that liver progression as the first event would be longer in the intervention compared with the control.

Conclusions: As the results of the 2 trials are not yet known, the methodological strength is enhanced, as biases inherent in conventional meta-analyses are avoided. This has the effect of providing this meta-analysis with the advantages of a single, large,randomized study of 819 patients. It is anticipated that the SARAH and SIRveNIB trial results will be published separately

and together with the combined meta-analysis results from VESPRO. The combined dataset will allow the effect of the interventions to be explored with improved reliability/precision with respect to prespecified patient and intervention-level characteristics.

Trial Registration: Australian New Zealand Trials Registry: ACTRN12617000030370.

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KEYWORDS

advanced hepatocellular carcinoma; individual patient data prospective meta-analysis; sorafenib; selective internal radiation therapy; noninferiority; percentage of active control retained

Introduction

Hepatocellular carcinoma (HCC) is the most common type of malignant primary liver tumor, accounting for 80% to 90% of all liver cancers, and most frequently develops in patients with chronic liver disease [1]. HCC is the second leading cause of cancer-related death worldwide and incidence and mortality rates are expected to increase in the coming decades [2,3]. At the time of presentation, the clinical presentation and tumor characteristics of HCC vary considerably; while approximately 40% of HCC patients present with advanced tumors with a high tumor burden or with decompensated liver disease, some patients present with small tumors and compensated chronic liver disease. Thus, the management of HCC is complex, and must take into consideration both patient and tumor characteristics as well as the severity of underlying chronic liver disease.

Curative treatment (by surgical resection, liver transplantation, or radiofrequency ablation) is feasible in very early or early stage HCC, but most patients with intermediate or advanced HCC receive palliative treatment. Advanced HCC is defined as stage C of the Barcelona Clinic Liver Cancer (BCLC) staging system, Eastern Cooperative Oncology Group (ECOG) performance status 1 to 2, portal invasion or extrahepatic spread, and Child-Pugh A-B. The prognosis is poor for patients with untreated advanced HCC, but survival varies depending on the Child - Pugh score [4-6]. Sorafenib is the only systemic therapy shown to confer survival advantages compared with placebo in patients with advanced unresectable HCC. Two phase III randomized controlled trials (RCTs; the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol [SHARP] study and the Asia-Pacific trial) showed significant increases in median overall survival (OS) in patients treated with sorafenib, compared with placebo [7,8]. However, median OS was different in the sorafenib-treated patients from Western countries (SHARP study) and patients from the Asia Pacific region (10.7 months and 6.5 months, respectively). As a result of these data, sorafenib is currently recommended as first-line treatment for advanced HCC [9]. Sorafenib was associated with an overall adverse event incidence of 80%, the most frequent being diarrhea, asthenia, hand-foot reaction, and erythema or desquamation leading, on average, to dose reduction or treatment interruptions in 26% to 44% of patients [7].

Radioembolization (also called selective internal radiation therapy, or SIRT) with yttrium-90 (Y-90) resin microspheres delivered into the hepatic arteries via transfemoral catheterization, is an alternative treatment for advanced unresectable HCC. Several retrospective cohort trials have suggested that SIRT with Y-90 resin microspheres offers similar OS in patients with BCLC stage B or C diseases compared with sorafenib, but with fewer adverse events and better quality of life [10-12]. A recent Cochrane review concluded that there is insufficient evidence to assess the beneficial and harmful effects of Y-90 SIRT for people with unresectable HCC [13]. The authors state that "Further randomised clinical trials are mandatory to better assess the potential beneficial and harmful outcomes of Y-90 microsphere transarterial radioembolisation … for people with unresectable hepatocellular carcinoma" [1].

Several RCTs comparing SIRT with Y-90 resin microspheres with sorafenib for the treatment of HCC are currently underway. The SorAfenib versus Radioembolisation in Advanced Hepatocellular carcinoma (SARAH; [ClinicalTrials.gov identifier NCT01482442]) [14] and SIRt VErsus SorafeNIB (SIRveNIB; [ClinicalTrials.gov identifier NCT01135056]) trials [15] are randomized, open-label phase III studies making head to head comparisons of SIRT and standard of care (ie, sorafenib) in patients with locally advanced HCC. SARAH was performed in France and follow-up is completed, and SIRveNIB is ongoing in countries in the Asia Pacific region. These 2 investigator-based RCTs enrolled patients with advanced or intermediate HCC that did not respond to transarterial chemoembolization with OS as the primary endpoint. Recruitment in these studies is now completed; the survival results by a randomized treatment group and other measures have not yet been reported.

A prospective meta-analysis on individual patient-level data from the SARAH and SIRveNIB studies would increase the power of the studies to assess the treatment effects in this population with advanced HCC and also in key subgroups. This will be useful as treatment effects may differ between patients with HCC in Western and Asian populations. Individual patient data overviews provide more information than conventional meta-analyses. They allow more a detailed investigation and a common statistical analysis plan with an agreement on a standardized methodological approach to the examination.

This study, sirVEnib and Sarah merge PROject (VESPRO), is an individual patient data prospective meta-analysis (IPD-PMA) of the OS survival data of the SARAH and SIRveNIB studies. The primary aim of this meta-analysis is to improve the strength of the evidence on the benefit or potential noninferiority of SIRT compared with sorafenib with respect to OS.

Methods

Included Studies

The core trials that make up VESPRO are conducted in accordance with the Declaration of Helsinki and current Good Clinical Practice guidelines, and all participating centers will have obtained the relevant ethics committee approval before patient enrollment.

The primary endpoint of VESPRO is to compare the efficacy of a single SIRT procedure with daily sorafenib, assessed by OS in patients with advanced HCC. Secondary endpoints are to compare the following: cumulative incidence of progression in the liver; progression-free survival (PFS); tumor response rate; disease control rate; and safety and tolerability measured by the incidence of serious adverse events (SAEs).

Eligible Patients

All patients from the SARAH and SIRveNIB trials will be included in this IPD-PMA. Patients had to satisfy the inclusion and exclusion criteria for the respective trials. These are summarized in Textbox 1 and [14,15].

Textbox 1. Inclusion criteria for respective trials.

SARAH trial and SIRveNIB trial

- Written informed consent provided
- Aged ≥18 years of age
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- Liver cirrhosis Child-Pugh A-B (up to 7 points)
- Adequate hematological function
- Adequate renal function
- Adequate hepatic function

SARAH trial

Histologically or cytologically confirmed diagnosis, or American Association for the Study of Liver Disease criteria for the diagnosis of hepatocellular carcinoma (HCC) and at least one measurable lesion on a computed tomography (CT) scan according to response evaluation criteria in solid tumors (RECIST) criteria

- Patients not eligible for surgical resection, liver transplantation, or radiofrequency ablation who have advanced HCC according to the Barcelona criteria (stage C), with or without portal invasion, or patients with recurrent HCC (new lesion in a different place) after surgical or locoregional treatment who are not eligible for any other treatment or patients in whom chemoembolization has failed after 2 rounds. Treatment failure is defined as the absence of objective response in the treated nodule after 2 rounds (objective response according to the modified RECIST criteria and/or European Association for the Study of the Liver [EASL] criteria)
- Affiliated to a social security scheme or beneficiary

SIRveNIB trial

Unequivocal diagnosis of locally advanced HCC without extrahepatic metastases

- Patients with HCC that is not amenable to surgical resection, immediate liver transplantation, or that could be treated with local ablative techniques (eg, radiofrequency ablation)
- Locally advanced HCC as defined by Barcelona Clinic Liver Cancer (BCLC; B) intermediate stage or BCLC (C) advanced stage.
- At least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with spiral CT scan or magnetic resonance imaging (MRI)
- Life expectancy of at least 3 months without active treatment

Textbox 2. Exclusion criteria for respective trials.

SARAH and SIRveNIB trials

- Advanced liver disease with a Child-Pugh score >B7 or active digestive hemorrhage or encephalopathy or refractory ascites
- Extrahepatic metastases except nonspecific pulmonary tumors <1 cm and abdominal lymph node tumors <2 cm
- Patient unable or unwilling to provide informed consent or comply with the treatment and follow-up required by the trial
- Previously treated advanced hepatocellular carcinoma (excluding chemoembolization)
- Contraindication to hepatic artery catheterisation
- Allergy to trial medications or contrast agents
- Pregnant or breastfeeding women

SARAH trial

- Other primary tumor except for basal-cell carcinomas or superficial bladder cancers
- Unable to take oral medication

SIRveNIB trial

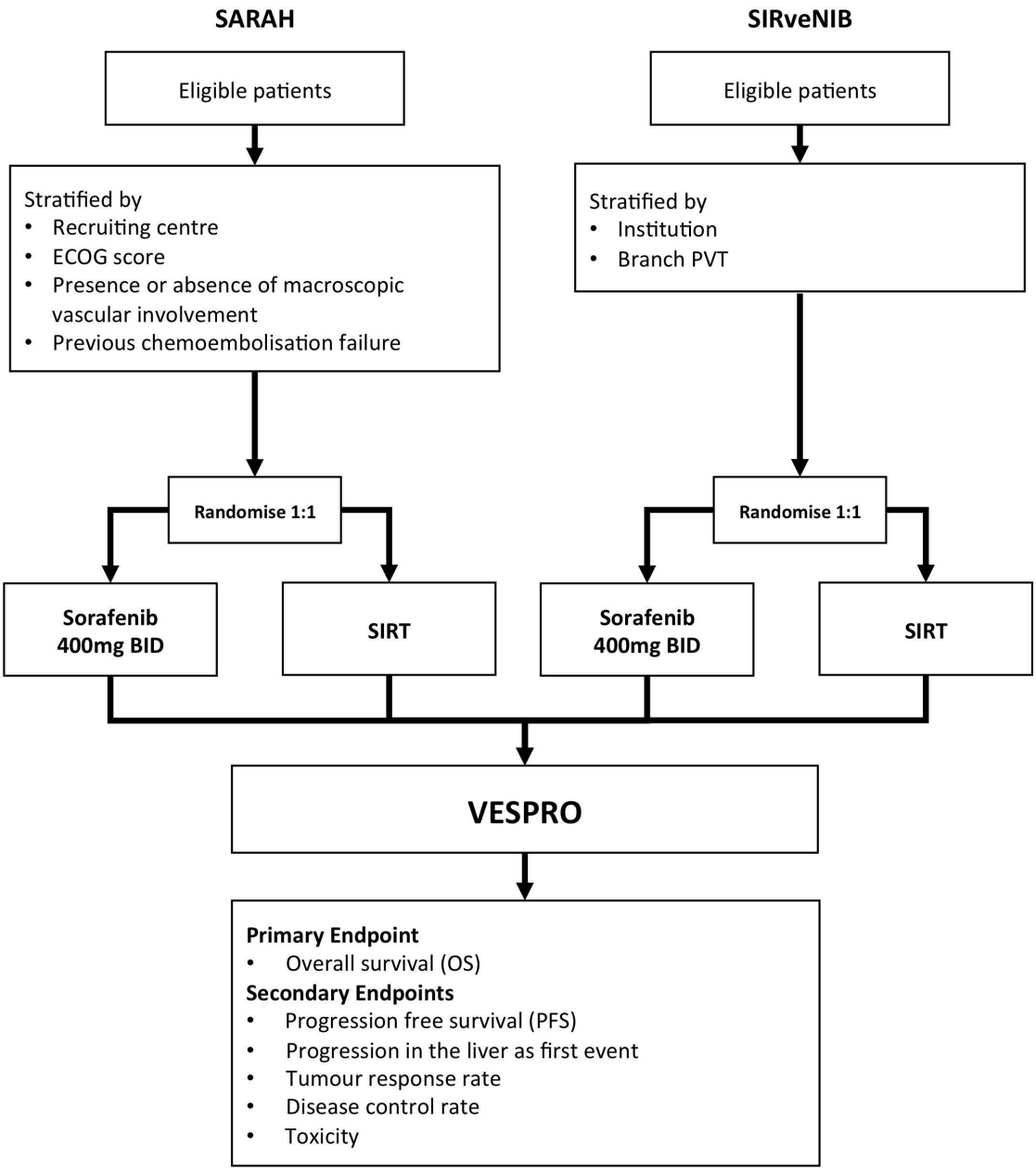
- Intractable ascites, or other clinical signs of liver failure
- Complete thrombosis of the main portal vein
- Other concurrent malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient has been disease free for ≥5 years
- Uncontrolled intercurrent illness
- Currently enrolled in another investigational therapeutic drug or device study
- Men unwilling to use effective contraception during the course of the trial

Adequate hematological function was defined in SARAH as hemoglobin ≥9 g/100 mL, neutrophils ≥1500/mm^3, platelets ≥50,000/mm^3, and international normalized ratio () ≤1.5; and defined in SIRveNIB as hemoglobin >9.5 g/dL, leukocytes ≥2500/mm^3, platelets ≥80,000/mm^3, and INR ≤2.0. Adequate renal function was defined in SARAH as creatinine <150 µmol/L, and defined in SIRveNIB as albumin ≥2.5 g/dL and creatinine ≤2.0 mg/dL. Adequate hepatic function was defined in SARAH as bilirubin ≤50 µmol/L, aspartate transaminase (AST) or alanine aminotransferase (ALT) ≤5 × upper limit of normal (ULN), and defined in SIRveNIB as bilirubin <2 mg/dL; alkaline phosphatase (ALP), AST, or ALT ≤5 × ULN.

Study Design

VESPRO is an IPD-PMA of the results of the SARAH and SIRveNIB trials (Figure 1). As these trial results are not yet published, this protocol and the corresponding statistical analysis plan were prepared blinded to any trial results, with the aim of documenting methodology and outcomes prior to knowledge of any outcome results from the individual trials.

Figure 1. Overview of the VESPO trial design.



Trials Included in the Meta-Analysis

The SARAH and SIRveNIB trials are randomized open-label trials comparing OS in advanced HCC patients who received SIRT using Y-90 resin microspheres or standard of care (sorafenib). The designs, objectives, and patient recruitment into these trials are summarized in Table 1 [14,15].

Table 1. Characteristics of studies included in VESPRO.

Characteristics		SARAH	SIRveNIB
Trial design		Multicenter, open-label, randomized controlled phase III trial comparing SIRT using Y-90 resin microspheres with sorafenib 800 mg/day	Multicenter, open-label, randomized controlled phase III trial comparing SIRT using Y-90 resin microspheres with sorafenib 800 mg/day
Primary objective		To compare the efficacy of Y-90 SIRT with that of sorafenib in the treatment of advanced HCC	To compare the efficacy of Y-90 SIRT with that of sorafenib in the treatment of advanced HCC
Secondary objectives		To compare: Progression free survival (PFS) according to response evaluation criteria in solid tumors (RECIST) and European Association for the Study of the Liver (EASL) at 6 months; tolerability and safety of Y-90 SIRT with those of oral sorafenib; quality of life in the 2 treatment groups; costs in the 2 treatment groups and calculate a cost-effectiveness ratio	To compare: PFS in the liver; PFS at any site; tumor response rate; disease control rate; toxicity and safety; health-related quality of life; liver resection rate; liver transplantation rate; time to disease progression
Primary endpoint		Overall survival (OS)	OS
Secondary endpoints		Adverse events reported according to the National Cancer Institute criteria version 3.0; PFS at 6 months according to RECIST and EASL criteria; response rate (complete, partial or stability) measured according to RECIST and EASL criteria; general and liver disease-specific quality of life scores; cost of each strategy comprising 2 parts: (1) the cost of Y-90 SIRT from the hospital's perspective; (2) the total cost of each strategy	PFS in the liver; PFS at any site; tumor response rate; disease control rate; toxicity and safety; health-related quality of life; liver resection rate; liver transplantation rate; time to disease progression
Sample size			
	Planned	400	360
	Accrued	467	360
	Sample size assumptions	4.3-month increase in median survival from 10.7 to 15 months (hazard ratio [HR] 0.71) 80% power, 95% confidence	4.65-month increase in median survival from 9.35 to 14 months (HR 0.67) 90% power, 95% confidence
Required number of events		Time driven and not event driven	266
Accrual time		24 months	36 months
Follow-up time		12 months	24 months
Randomization		1:1 randomization (stratified blocks).	1:1 randomization (stratified blocks)
Stratification factors		Center; Eastern Cooperative Oncology Group (ECOG) score (0 vs 1); presence of macroscopic vascular invasion (obstruction of the portal vein or its branches); previous chemoembolization failure	Center; presence of branch portal vein thrombosis
Recruiting countries/ regions		France	Asia Pacific

Treatments

Patients were randomized to either receive sorafenib or SIRT with Y-90 resin microsphere on a 1:1 basis.

In the sorafenib arms, patients received oral treatment with sorafenib (400 mg, twice daily), commencing as soon as possible after randomization in SIRveNIB, but at most within 35 days, and in SARAH within 1 week (7 days) of randomization. Treatment was continued until disease progression, with an anticipated duration of at least 3 months. Treatment suspensions or dose reductions were permitted.

Patients randomized to SIRT were required to have a hepatic angiogram and a liver-to-lung shunt preassessment with technetium-99 m (^{99m}Tc)-marked human serum albumin to determine their suitability for the SIRT procedure. The activity of SIRT was calculated using the body surface area or partition model method. SIRT was administrated within 35 days after randomization in SIRveNIB and between 2 and 5 weeks after randomization in SARAH, to allow time for the pretreatment assessments.

Trial Schedules

Patients in SIRveNIB were assessed monthly for the first 3 months during protocol treatment and then at 3-month intervals until 24 months following randomization or death. In SARAH, patients were followed up with monthly with an assessment of response every 3 months from randomization until disease progression, death, or the end of the trial. The last enrolled patient was followed up with for up to 12 months after the start of treatment, and all other patients followed up until the final visit of the last enrolled patient; expected duration of patient follow-up was between 12 and 51 months. The full treatment trial schedules are shown in Tables 2 and 3.

Table 2. SARAH trial assessment schedule.

Visits	Enrollment	D0[a]	D15	M1[b]	M2	M3	M4	M5	M6	M7	M8	M9	End of participation
Identification	X												
Verification of selection criteria	X												
Consent signature	X												
Initial assessment/history	X												
CT[c]scan	X			X		X			X			X	X
CT perfusion	X			X		X			X				
Lab tests	X	X	X	X	X	X	X	X	X	X	X	X	X
Classification	X			X	X	X	X	X	X	X	X	X	X
Clinical examination				X	X	X	X	X	X	X	X	X	X
Quality of life questionnaires	X			X		X			X			X	X
Preparatory angiography		X											
Scintigraphy		X											
SIRT		X											
Start of sorafenib treatment		X											
Retreatment[d]				X	X	X	X	X	X	X	X	X	
Cancer progression monitoring				X	X	X	X	X	X	X	X	X	X
Sorafenib monitoring				X	X	X	X	X	X	X	X	X	X
Concomitant medication				X	X	X	X	X	X	X	X	X	X
Adverse events				X	X	X	X	X	X	X	X	X	X

[a]D, day.

[b]M, month.

[c]CT, computed tomography.

[d]Timing of retreatment depends upon type of retreatment (see text).

Table 3. SIRveNIB trial assessment schedule.

Schedule		Screening/ baseline (eligibility) randomization[a]	During protocol therapy					Trial conclusion	Post trial conclusion follow-up
			Week 2[b]	Week 4	Week 8	Week 12	12-weekly thereafter	As appropriate[c]	12 weekly
	Informed consent	X							
	Demographics	X							
	Medical and surgical history	X							
	Concurrent illness	X							
Concomitant medications[g]		X[d]	X[d,e]	X[d]	X[d]	X[d]	X[d]	X[d]	
Clinical assessment and physical examination									
	Height (baseline only)	X		X	X	X	X	X	
	Weight	X		X	X	X	X	X	
	Blood pressure	X		X	X	X	X	X	
	Body temperature	X		X	X	X	X	X	
Performance status	Eastern Cooperative Oncology Group	X		X	X	X	X	X	
Hematology									
	Leukocytes	X		X	X	X	X	X	
	Platelets	X		X	X	X	X	X	
	Hemoglobin	X		X	X	X	X	X	
	International normalized ratio (INR)	X		X	X	X	X	X	
Hepatitis serology									
	Hepatitis Bsag	X[e]							
	Anti-hepatitis C virus immunoglobulin (IgG)	X[e]							
	Hepatitis B core antibody IgG (optional)	X[e]							
Renal function	Creatine	X		X	X	X	X	X	
Liver function									
	Aspartate transaminase (AST)/ alanine aminotransferase (ALT)	X		X	X	X	X	X	
	Alkaline phosphatase (ALP)	X		X	X	X	X	X	
	Total bilirubin	X		X	X	X	X	X	
	Albumin	X		X	X	X	X	X	
	Pregnancy test (as appropriate)	X[f]							
Tumor marker	Serum alpha-fetoprotein (AFP)	X[f]				X	X[f]	X[f]	

Schedule	Screening/ baseline (eligibility) randomization[a]	During protocol therapy					Trial conclusion	Post trial conclusion follow-up
		Week 2[b]	Week 4	Week 8	Week 12	12-weekly thereafter	As appropriate[c]	12 weekly
EuroQol five dimensions questionnaire (EQ-5D) health-related quality of life	X		X[g]	X	X	X[g]	X[g]	X[g]
Computer tomography or magnetic resonance imaging scan: chest/abdomen/pelvis[h,i]	X				X	X		
SIRT-arm only								
Hepatic angiogram	X[e]							
^{99m}Tc-microaggregated albumin (MAA) lung shunt study	X[e]							
Response assessment[i]					X	X	X	
Sorafenib arm only								
Toxicity assessment		X[b]	X	X	X	X	X	
Dose delay/modification		X[b]	X	X	X	X	X	
Adverse events (AE)/serious adeverse events (SAE)	AE/SAE for the Sorafenib arm will be recorded from the time of signing the informed consent form (ICF) until 30 days after the final dose of Sorafenib, or until commencement of the next alternative therapy, whichever is earlier. AE/SAE for the SIRT arm will be recorded from the time of signing the ICF until 30 days post-SIRT regardless of causality and for a further 5 months thereafter if judged by the investigator to be causally related to SIRT or Sir-Spheres, or until commencement of the next alternative therapy, whichever is earlier. If the AE/SAE is a Sorafenib- or SIRT-related toxicity follow-up will continue until resolution.							
Survival								X

[a]Screening assessments performed within 28 days before signing of informed consent can be used to confirm eligibility

[b]Sorafenib arm only. Sorafenib patients contacted at week 2 to assess treatment related toxicity and interrupt/modify the dose as necessary

[c]Disease progression, death, complete regression, unacceptable toxicity, patient responds to treatment and becomes eligible for surgical resection, liver transplantation or ablative therapy, lost to follow-up, patient's request for withdrawal

[d]Concomitant medication to be recorded from screening/baseline up to 30 days post study conclusion (or until commencement of the next alternative therapy, whichever is earlier).

[e]Hepatic angiogram and Tc-99m MAA lung shunt study to be performed after randomization and prior to treatment commencement ONLY for SIRT Arm group

[f]Serum AFP to be performed during screening/baseline and every 12 weeks from date of randomization thereafter. Serum AFP does not need to be repeated for study conclusion visit if it has been performed within the last 28 days.

[g]EQ-5D quality of life questionnaires to be filled out at baseline, while on study (ie, week 4, 8, 12, and every 12 weeks thereafter), at study conclusion, and 12 weekly during post study conclusion follow-up. EQ-5D quality of life questionnaire does not need to be repeated for study conclusion if it has been performed within the last 28 days.

[h]The same radiological assessment method must be used throughout the study.

[i]Assessment for tumor response rate to be done every 12 weeks plus at first disease progression. Radiological assessment for tumor response rate to be done every 12 weeks from date of randomization until first evidence of disease progression.

Outcome Measures

The primary endpoint of VESPRO is all-cause mortality measured by OS time. Secondary endpoints include: cumulative incidence of progression in the liver; PFS time; tumor response rate; disease control rate; and incidence of grade 3-4 SAEs. The outcomes are defined in Textbox 3.

Textbox 3. Outcome definitions.

- Overall survival is defined as the time from randomization to death from any cause, with living patients censored on the date of last follow-up.
- Progression-free survival is defined as the time from randomization until disease progression at any site (response evaluation criteria in solid tumors criteria 1.1) [16] or death. Living patients will be censored on the date of last evaluable tumor assessment.
- Progression in the liver as first event is defined from randomization until the first progression in the liver. Patients alive and progression free will be censored on the date of last evaluable tumor assessment.
- Tumor response rate is defined as the number of patients whose best overall response is complete response (CR) or partial response (PR), divided by the total number of patients in the analysis population.
- Disease control rate is defined as the number of patients whose best overall response is PR, CR, or stable disease, divided by the total number of patients in the analysis population.

Toxicity Profile

The toxicity profiles of the 2 groups will be described as the frequency of the worst toxicity grade of adverse event (AE) experienced (according to National Cancer Institute Common Terminology Criteria for Adverse Events). AE rates for the pooled data from the studies will be compared between treatment groups, stratified by trial, using the Mantel-Haenszel technique. The principal comparison will be the proportion of grade 3-4 AEs in each group. In an observational series of 325 patients, SIRT for HCC showed grade 3-4 toxicity profile of: 2.5% fatigue; 1.5% abdominal pain; and 1.5% gastrointestinal (GI) ulceration [17]. In the placebo-controlled SHARP study, patients with advanced HCC who received sorafenib demonstrated serious adverse event/grade 3-4 toxicity profile comprising: 8% diarrhea; 8% hand-foot reaction; 7% liver dysfunction; 5% ascites; 4% other hepatobiliary; 3% fatigue, dehydration, hemoglobin, and cardiac ischemia/infarction; and 2% abdominal pain, hyperbilirubinemia, and weight loss [7]. Other toxicity profiles to be considered include: infection; fever; GI and non-GI bleeding; renal dysfunction; radiation hepatitis; GI ulceration; pulmonary embolism; rash or desquamation; hyponatremia; hypertension; abdominal pain; alopecia; anorexia; ascites; and nausea/vomiting.

Sample Size Calculation and Statistical Considerations

Sample Size Calculation for Individual Trials

In the SARAH trial, hypothetical median survival times, estimated from OS data reported in previous studies [7,18-22], were 10.7 months and 15.0 months in the sorafenib and SIRT arms, respectively, corresponding to a hazard ratio (HR) of 0.71. Enrollment of 400 patients (200 in each treatment arm) would provide 80% power with 95% confidence to detect this risk reduction, based on an accrual period of 24 months and a minimum follow-up of 12 months. The final sample size was 467 patients (459 actually randomized), which allows for an approximately 8.1% rate of patient noncompliance and dropout. The expected number of events was 153 in the SIRT arm and 179 in the sorafenib arm.

In the SIRveNIB trial, the hypothetical median survival times based on OS data reported in previous clinical trials [23,24] were 9.35 and 14.0 months in the sorafenib and SIRT arms, respectively, corresponding to a HR of 0.67. Enrollment of 360 patients (180 per group) would provide 90% power with 95% confidence to detect this risk reduction with an accrual of 36 months and minimum follow-up of 24 months. This sample size also allows for an up to 20% dropout rate. Factoring in this high dropout rate was a pragmatic decision due to the patient recruitment being in developing countries. The expected number of events was 127 in the SIRT group and 139 for the sorafenib group.

Prospective Meta-Analysis and Noninferiority

Regardless of the results of the individual trials (statistical significance, or extent of therapeutic benefit), a prospectively designed pooled analysis may help clarify several findings useful for medical decision-making. Thus, the total number of events for the 2 trials combined will provide increased power or precision for assessing the overall treatment effect, and for performing additional analyses among prespecified subgroups. However, pooled analyses resulting in estimates of benefit, which may be small and/or statistically not significant, will raise challenges as to how the results should be clinically interpreted. In this context, a complementary approach is to define a noninferiority (NI) margin to not be appreciably worse clinically .

As it is anticipated that both trials will show a benefit, no specific hypotheses will be tested, and issues of statistical power do not arise. The question of interest is whether the 95% confidence interval (CI; one-sided) crosses the NI margin if the pooled result does not reach statistical significance. By exploiting the prospective nature of determining the NI margin, a scientific underpinning can be provided for subsequent clinical interpretation of the results. This approach is based on the assumption that, beside the specific therapeutic actions of SIRT, other aspects of the SIRT intervention could be advantageous, compared with the standard of care (sorafenib). For example, SIRT with Y-90 resin microspheres is administered in a single procedure, while sorafenib is taken daily until disease progression; consequently a better toxicity profile and lower cost could be anticipated with SIRT. In the absence of superiority over sorafenib, SIRT may still be considered a desirable option if the NI boundary is satisfied.

Determining the Noninferiority Margin: Fraction of Active Control Retained

To establish a NI margin, the minimum fraction of retained benefit from the active control (sorafenib) is determined. The International Committee on Harmonization E10 guidance from the Food and Drug Administration (FDA) recommends that NI margins should not exceed the smallest effect size that would

be expected if the intervention were compared with placebo [25]. The SHARP study showed a 31% risk reduction for mortality with soranifeb versus placebo (HR: 0.69; 95% CI 0.55-0.87) [2]. Likewise, the Asia-Pacific trial showed a 32% risk reduction for mortality with soranifeb versus placebo (HR: 0.68; 95% CI: 0.50-0.93) [8,26]. The pooled overall HR for mortality for sorafenib over placebo is 0.69 (95% CI: 0.57-0.83); or if placebo is compared with sorafenib, there is a 1.46 (95% CI: 1.21-1.75) increase in mortality risk, which equates to an increase of at least 21% (the lower limit of the CI) with placebo over sorafenib. The FDA recommends that the minimum fraction of active control retained should not be lower than 50% [25]. NI margins, based on a one-sided 95% CI, for different fractions of active control retained are shown in Table 4.

Table 4. Fractions of active control retained noninferiority (NI) margins.

Active control retained (from a hazard ratio of 1.21)	NI boundary
50%	1.10
70%	1.06
75%	1.05
80%	1.04

A boundary of 10% is considered to be clinically acceptable for potential relative detriment of SIRT compared with sorafenib. Assuming a pooled median survival for sorafenib of 9.5 months, such a margin would translate to an absolute detriment between the 2 groups of less than 5% at 9.5 months. With a 10% NI margin and a fixed sample size of the pooled cohort of 819 with greater than 495 expected events, a survival benefit with SIRT compared with sorafenib of at least 7% (HR: 0.93) would be needed to satisfy this margin at a median survival with sorafenib of 9.5 months.

Statistical Analyses

Primary Endpoint

Statistical analysis of the primary endpoint will be performed in the intent-to-treat population, keeping patients in their randomization groups. The primary outcome (OS) will be compared between treatment arms using the inverse-variance weighted HR of the individual trials. A sensitivity analysis using a stratified log-rank test and an unadjusted stratified proportional hazards model test (stratified by trial) will also be performed. The comparison will be based on superiority. In the event that the 95% CI for the HR crosses the null, if the one-sided upper 95% CI for this HR does not breach the NI boundary of 1.10, this will be interpreted as supporting evidence that SIRT is not appreciably worse than sorafenib.

Planned Subgroup Analyses

Subgroup analyses will be performed according to the following baseline characteristics: age (<65 years, ≥65 years); sex; ECOG performance status (0, 1); tumor size (≤50% of liver, >50% of liver); presence or absence of portal vein thrombosis; BCLC stage (B1 and B2, B3 and B4 and C; using Bolondi Criteria); previous treatment for HCC (yes, no); hepatitis status (B, C, both); unilobal versus bilobal disease; single focal versus multifocal disease; and serum alpha-feto protein level (≤100 vs >100 ng/mL).

Additional Analysis

As advanced HCC has a poor prognosis, a landmark analysis [27] will be performed at 2 months post-randomization. This conditional analysis will exclude patients that die within 2 months of randomization as such patients are deemed to have disease so severe that neither treatment would be expected to provide any therapeutic benefit.

As SIRT is a locoregional treatment, treatment effect based on progression in the liver as the first event, will be investigated using a competing risk analysis. In this analysis, death or progression outside the liver as the first event will be considered as a competing risk for liver progression. The Gray method [27] will be used to compare groups with HRs and 95% CI estimated from the proportional hazards approach detailed by Fine and Gray [28].

Results

Patient follow-up in the SARAH trial was completed in March 2016 and patient follow-up in the SIRveNIB trial is currently ongoing (expected completion September 2017).

It is anticipated that the results of SARAH, SIRveNIB, and VESPRO will be published soon after the results are released. As per the individual study protocols, it is anticipated that each study will demonstrate a survival benefit favoring treatment with SIRT. However, practically the intervention could not be given to some patients who were allocated SIRT due to clinical suitability and the results may not be as strongly in favor of SIRT as anticipated. SIRT is a local therapy directed at the liver and the expectation is an increased time to liver progression as the first event in the SIRT cohort compared with sorafenib. It is expected that SIRT will have a lower toxicity profile than sorafenib, which may help guide clinical choice in the event of either or both studies failing to show a significant survival benefit.

Discussion

Advantages of Prospective Pooling

The meaningful and relevant data that can be obtained from any clinical trial is restricted by several factors, including the ability to obtain complete outcome data on all (or most) participants, the accuracy and quality of outcomes measurement, and patients' adherence to the allocated treatment. The SARAH and

SIRveNIB trials are evaluating therapies with different modes of delivery; sorafenib is taken orally, twice daily until disease progression or death, whereas SIRT is administered in a single application. The problems of nonadherence that may be encountered with sorafenib include unplanned interruption or cessation of treatment or dose reduction; whereas with SIRT, some patients initially randomized to receive SIRT will be deemed unsuitable after clinical workup and will subsequently receive other treatment. The ability to prospectively pool results from clinical trials in an IPD-PMA will increase the amount of meaningful data available to address important clinical questions.

In a single trial, the ability to draw relevant conclusions from subgroup analyses is also restricted by the low statistical power of the multiple tests in small patient populations. Therefore, there is a disparity between the aim of identifying heterogeneity in the responses of trial participants to treatments and the ability to achieve this goal. Pooling data will provide larger sample sizes that will attenuate the impact of multiple comparisons and enable the detection of small but potentially clinically important differences. The prospective design of such comparisons will add to the credibility of the interpretation of these differences. Additionally, a prospective pooled analysis will facilitate the recognition of signals of clinical interest that in each of the individual trials could potentially be regarded as spurious, and thus disregarded.

If the individual trials and the pooled analysis do not demonstrate statistical significance on the primary endpoint, the question of how the totality of evidence should be interpreted then becomes an issue. These so-called ‘negative results’ may arise due to: a small true benefit; the patients enrolled having a different risk profile to that anticipated; issues with study conduct (nonadherence, lost to follow-up, etc); or changes in clinical practice during the trials. Faced with a ‘negative result’ clinicians may choose to continue with standard care (sorafenib) or introduce the new intervention (SIRT) without strong clinical evidence.

Defining Margin of Noninferiority Prospectively to Improve Clinical Interpretation

The originality of the VESPRO study is to go beyond classical meta-analysis goals. It is why we propose to consider all the results of the primary and secondary outcomes, and prospective subgroup analyses of the pooled analysis. On a superiority analysis basis, if equality between the 2 treatments is rejected, then due to the greater power the meta-analysis compared with the individual trials a more precise estimate of treatment effects can be provided. If the null hypothesis cannot be rejected, it will be very interesting to determine the reasonable limit within which treatments will be deemed comparable. This margin, while not formally a component of a NI design, will guide interpretation of the results when there is uncertainty. The casual observation suggests that SIRT has a better safety profile than sorafenib, which may be important if efficacy is similar between treatments

Using this information, pooled toxicity profiles and cost estimates will allow clinicians to make informed decisions as to the most appropriate treatment choice for patients with advanced HCC.

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An ethics committee approved both the SARAH and SIRveNIB trials. Patients consenting to participate in either trial were required to sign an ethically approved patient informed consent form.

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Authors' Contributions

VG drafted the manuscript and managed the incorporation of comments from all authors. All authors have made substantial contribution to design this study. All authors have reviewed the manuscript and given final approval to be published. The authors had full access to the appropriate study data, which are included in the VESPRO project.

Conflicts of Interest

PKHC has received honorariums and research grants from Oncosil, pSivida, SIRTEX, Bayer, Ipsen, and Merck Sharp & Dohme. VG has received honorariums and VV has received speaker fees from SIRTEX. All other authors declare that they have no competing interests.

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Abbreviations

AE: adverse event
AFP: serum alpha-fetoprotein
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate transaminase
BCLC: Barcelona Clinic Liver Cancer
CI: confidence interval
CR: complete response
CT: computed tomography
ECOG: Eastern Cooperative Oncology Group
EQ05D: EuroQol five dimensions questionnaire
FDA: Food and Drug Administration
GI: gastrointestinal
HCC: hepatocellular carcinoma

HR: hazard ratio
ICF: informed consent form
IgG: immunoglobulin
INR: international normalized ratio
NI: noninferiority
MMA: microaggregated albumin
MRI: magnetic resonance imaging
OS: overall survival
PR: partial response
PFS: progression-free survival
RCT: randomized control trial
RECIST: response evaluation criteria in solid tumors
SAE: serious adverse event
SARAH: sorafenib versus radioembolization in advanced hepatocellular carcinoma
SIRveNIB: selective internal radiation therapy versus sorafenib in locally advanced
SHARP: sorafenib hepatocellular carcinoma assessment randomized protocol
SIRT: selective internal radiation therapy
ULN: upper limit of normal
yttrium-90: Y-90

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Protocol

Statins and Fibrates for Diabetic Retinopathy: Protocol for a Systematic Review

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Abstract

Background: Diabetic retinopathy (DR) is a common microvascular complication of diabetes mellitus, and more than 75% of patients who have had diabetes for more than 20 years will have some degree of DR. This disease is highly destructive to self-esteem and puts a high burden on public health and pension systems due to the effects that it has on people of working age. The current mainstay of treatment is laser photocoagulation, which causes impairment of vision and discomfort to patients. Thus, finding a systemic drug that could act on all microcirculation and prevent direct manipulation of the eyes would be highly desirable.

Objective: To assess the efficacy and safety of the drugs in the statin and/or fibrate groups for the prevention and treatment of DR.

Methods: In this systematic review, we will select randomized controlled trials of fibrates or statins used for the treatment or prevention of DR. Our search strategy will include free text terms and controlled vocabulary (eg, MeSH, Emtree) for, “diabetic retinopathy”, “statins”, “fibrates”, “hypolipidemic agents”, and for drugs from both groups. Databases that will be used include Medical Literature Analysis and Retrieval System/PubMed, Embase, Cochrane Central Register of Controlled Trials, Latin American and Caribbean Center on Health Sciences Information, Clinicaltrials.gov, World Health Organization International Clinical Trials Registry Platform, and OpenGrey, and we will not have language or date limits. Two review authors will independently select eligible studies and assess the risk of bias using the Cochrane Collaboration’s tool. We will report structured summaries of the included studies and, if possible, conduct meta-analyses.

Results: This is a protocol for a systematic review, therefore results are not available. We registered a short version of this protocol before progressing in the review and we are currently in the process of selecting the studies for inclusion.

Conclusions: Intensive glucose control and lowering blood pressure and lipids are mechanisms that protect macrocirculation in diabetic patients. Both macrovascular and microvascular events in diabetic patients appear to have a common pathway, starting with endothelial injury. Thus, prevention and treatment of microvascular events may benefit from the same interventions. In the review for which we have written this protocol, we will assess whether the use of lipid-lowering oral drugs of the statin and/or fibrate groups may prevent and/or retard progression of DR, with the added benefit of preserving visual acuity.

Trial Registration: PROSPERO CRD42016029746

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KEYWORDS

diabetic retinopathy, hypolipidemic agents, hydroxymethylglutaryl-CoA reductase inhibitors, fibric acids, ETDRS, HMG-CoA reductase inhibitors

Introduction

Diabetic retinopathy (DR) is a common microvascular complication of diabetes mellitus, and more than 75% of patients who have had diabetes for more than 20 years will have some degree of DR [1]. This disease is the leading cause of blindness among working-age Americans [2]. It is estimated that 33,000 new cases of diabetic macular edema, 86,000 new cases of proliferative DR, and 12,000-14,000 new cases of blindness are caused by DR each year in the United States alone [1]. Projections compute that by 2050 the number of Americans aged 40 years and older with DR and vision-threatening DR will triple compared to 2005 numbers (from 5.5 million to 16.0 million for the former and 1.2 million to 3.4 million for the latter) [3].

A putative pathophysiological mechanism of the disease is through products of nonenzymatic glycosylation, named advanced glycosylation end products (AGEs) [4,5]. AGEs are proteins or fats that become glycated after exposure to sugar, and the oxidative stress that occurs in diabetes is one of the probable causes that triggers this reaction [6]. AGEs bind to receptors in the retinal vessel endothelium and trigger the extrinsic pathway of coagulation, along with the inhibition of protein C (a physiological anticoagulant), and increase production of endothelin-1 (a potent vasoconstrictor) [7]. Together, these cascades lead to narrower vessels, increased permeability of the vascular wall, and consequently tissue ischemia. Ischemia, in turn, attracts angiogenic factors that promote neovascularization [8]. Lipids also presumably play an important role in the exudative stage of DR. The increased permeability of retinal capillaries causes extravasation of plasma lipoproteins that (along with degenerating cells) are engulfed by macrophages and form hard exudates, which is a defining characteristic of this stage of the disease [9].

Numerous studies on the newer antivascular endothelial growth factor drugs for the treatment of DR have been conducted, but laser photocoagulation persists as the treatment with the highest level of efficacy and safety [10]. However, even being the first option of treatment, laser photocoagulation is frequently associated with irreversible side effects caused by the ablation of retinal tissue. Visual field loss and impairment of night vision are frequent, and the procedure itself is very painful [11]. In this capacity, systemic drugs are highly desirable since they might prevent the onset and progression of DR, thereby avoiding the harms of manipulating the eye. Drugs might also allow for the chance to act in a preventive manner across the entire vascular endothelium.

It is known that all vascular diabetic alterations, whether in macrocirculation or microcirculation, have a common endothelial start. It is also well known that inadequate glycemic control, hypertension, and dyslipidemia are risk factors for the development of macrovascular disease in diabetics. Although the importance of the first two factors in microcirculation have already been addressed by previous systematic reviews [12,13], the relationship between lipids and the development and severity of DR is complex and remains unclear [14].

A recent update of The Wisconsin Epidemiologic Study of Diabetic Retinopathy, a 30-year follow-up of approximately 903 patients, found no association between total cholesterol or high density lipoprotein (HDL) and incidence of DR or macular edema, while there was a modest association between higher levels of HDL and decreased prevalence of proliferative DR [15]. The investigators then concluded that total cholesterol and HDL (as well as statin use) had a modest impact on DR [15]. Studies examining dietary lipid interventions showed favorable variable results in DR progression [16-18]. Other studies with clofibrate found reductions in hard exudates, but did not find differences in visual acuity [19-21].

Conversely, some randomized controlled trials (RCTs) showed beneficial effects of hypolipidemic drugs, suggesting that they may slow the progression of DR. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study, for example, evaluated the effects of specific strategies for managing blood glucose levels, serum lipid levels, and blood pressure on cardiovascular events in participants with type 2 diabetes [22]. This study also assessed the effects of these medical strategies on the progression of DR in a subgroup of trial participants: results showed that patients with type 2 diabetes who received fenofibrate and simvastatin had less progression of DR at 4 years when compared to placebo (6.5% vs 10.2% respectively; P=.006) [22]. Similarly, the Fenofibrate Intervention and Event Lowering in Diabetes study concluded that monotherapy with fenofibrate resulted in a significant reduction in the need for laser therapy at 5 years for either macular edema or proliferative retinopathy when compared to the placebo group (3.4% vs 4.9%; P<.001) [23]. Nevertheless, in the study that followed ACCORD patients (known as the Action to Control Cardiovascular Risk in Diabetes Follow-On Eye Study), this difference disappeared 8 years after randomization in the original ACCORD study (11.8% vs 10.2% respectively; P=.60) [22].

In light of these conflicting results, and considering the absence of the highest level of evidence for this question, it is critical to summarize the efficacy and safety of statins and fibrates for the prevention and treatment of DR through a systematic review of RCTs.

Objectives

To assess the efficacy and safety of the drugs of the statins and/or fibrates groups for the prevention and treatment of DR.

Methods

This protocol is registered in PROSPERO (CRD42016029746). We developed the protocol according to the Cochrane Handbook of Interventions Reviews [24] and report it according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols [25].

Types of Studies

For the purposes of this systematic review, only RCTs will be included. Given the progressive nature of the clinical situation, cross-over designs will not be considered.

Types of Patients

Patients with type 1 or 2 diabetes, with or without nonproliferative retinopathy (for treatment and prevention, respectively) will be considered. Patients with proliferative retinopathy will be excluded.

Types of Interventions

The interventions considered will be any drug from the statin or fibric acid groups, either in isolation or compared to placebo, no intervention, or a different type of statin or fibrate. We will also consider any statin or fibric acid as adjunctive therapy if we find RCTs of main therapy with statin or fibrate versus main therapy with placebo, no intervention, or a different type of statin or fibrate. Photocoagulation may be considered as a main therapy in this schema. In each situation (isolation or adjunctive) we will consider studies with any dose or any duration course of the intervention.

Types of Outcome Measures

Primary Outcomes

Our primary outcomes will include: (1) aiming prevention, the proportion of patients that develop DR; (2) aiming treatment, the proportion of patients with progression of DR; and (3) aiming safety, the proportion of patients with at least one serious adverse event (ie, those that are immediately life-threatening, or resulted in hospitalization, incapacity, malignant disease, or death).

DR will be defined as 35 or more points in the Early Treatment Diabetic Retinopathy Study (ETDRS) scale [26], based on evaluation of stereoscopic color fundus photographs of the eyes of participants who did not have retinopathy at baseline. This score is equivalent to the categories of mild nonproliferative DR, or more severe DR [27].

Progression will be defined as a change from baseline of 2 or more steps on the same scale. We will accept trials that describe outcomes in terms of steps in the ETDRS scale and trials that described outcomes that can be converted to the ETDRS scale (eg, for older trials). For the adverse events outcome, we will not conduct additional searches in nonrandomized studies, which are not included in this review.

We plan to assess these outcomes at 2, 6, 12, 18, and 24 months, and annually thereafter, grouping the trials that fall within these time points (eg, group trials that assess the outcomes up to 2 months).

Secondary Outcomes

We will assess the proportion of patients with: (1) decrease of visual acuity (any decrease) measured by Snellen or LogMAR charts, and (2) proliferative DR (measured by the ETDRS scale) with at least one minor adverse event (ie, adverse events not included in the serious adverse event outcome). We will also evaluate quality of life measured by the National Eye Institute Visual Functioning Questionnaire 25 or another validated vision-related scale. These outcomes will be assessed at the same time points as the primary outcomes.

Methods for Search

Electronic Search

We will systematically search the following databases: Medical Literature Analysis and Retrieval System (via PubMed), Embase (via Elsevier), Latin American and Caribbean Center on Health Sciences Information (via Virtual Health Library), and Cochrane Central Register of Controlled Trials (via Wiley). The search strategy will include controlled vocabulary (eg, MeSH, Emtree) and free-text terms related to, “diabetic retinopathy”, “hypolipidemic agents”, “statins”, “fibrates”, and drugs from both groups. No limits for data, language, or status of the publication (eg, conference abstracts, full-text, ongoing studies) will be used. Additional searches will be conducted in the clinical trial registries of Clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform, and in the grey literature source OpenGrey.

Hand Search

We will assess reference lists of all included studies and review articles for additional references. We will contact authors of identified trials and ask them about other published and unpublished studies. We will also contact manufacturers and specialists in the field of ophthalmology.

Selection of Studies

Two authors (VM and CGF) will independently read the references and select the studies according to the inclusion and exclusion criteria. We will exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, will be the unit of interest in the review. After the initial step of screening titles and abstracts of the records, we will read the full text articles for the potentially includible studies, finally deciding on the included ones and giving reasons for the exclusions in this step. A third reviewer (RR) will resolve any disagreements. We will record the selection process in sufficient detail to fulfill a PRISMA flow diagram and a *characteristics of excluded studies* table [28].

Data Extraction and Management

We will use a standard data collection form for extracting study characteristics and outcome data. Two reviewers (VM and CGF) will extract the study characteristics outlined in Textbox 1.

Textbox 1. Characteristics that will be extracted from the included studies.

- Methods: study design, total duration of study and run-in, number of study centers and location, study setting, withdrawals, and date of study.
- Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications, and excluded medications.
- Outcomes: primary and secondary outcomes (the final outcomes reported and those planned), and time points reported.
- Notes: funding for trial and notable conflicts of interest of trial authors.

One reviewer (VM) will copy the data from the data collection form into the Review Manager (RevMan 5.3) file [28]. We will double check that the data is entered correctly by comparing the study reports with how the data is presented in the systematic review.

Assessment of Risk of Bias in Included Studies

Two reviewers (VM and CGF) will independently judge the risk of bias of each study using the Cochrane Collaboration's tool for assessing risk of bias [29]. The tool comprises the following domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other bias. Each domain will be judged as *high risk*, *low risk*, or *unclear risk* of bias according to the criteria described in the risk of bias table in the Cochrane Handbook [29]. We will consider blinding separately for different key outcomes when necessary (eg, regarding unblinded outcome assessment, risk of bias for all-cause mortality may be very different than that of a patient-reported quality of life scale [28]). When considering treatment effects, we will take into account the risk of bias of the studies that contributed to that outcome.

Data Synthesis

We will use a software Review Manager (RevMan 5.3) to perform meta-analyses whenever possible. We plan to use random-effects meta-analyses except when involving up to 3 studies in the pooled estimate; a situation in which we will use fixed-effects. This approach is a change from our previous protocol, in which we would use fixed-effects models for homogeneous studies and random-effects otherwise; however, random-effects models result in pooled estimates similar to fixed-effects models when there is little or no heterogeneity within studies. Additionally, random-effects analyses provide poor estimates for the confidence interval when examining few studies or when the studies are small [30]. If we are not able to analyze studies due to a lack of data for any comparison, or high heterogeneity as specified in the *assessment of heterogeneity* section, we will report the result of each individual trial narratively.

Measures of Treatment Effect

We will analyze dichotomous data as risk ratios and continuous data as mean differences or standardized mean differences. We will undertake meta-analyses only when meaningful (ie, if the treatment participants and the underlying clinical question are similar enough for pooling to make sense). If multiple trial arms are reported in a single trial, we will include only the relevant arms, and if two comparisons from the same trial (eg, *drug X vs placebo* and *drug Y vs placebo*) must be included in the same meta-analysis, we will halve the control group to avoid double counting [28].

Dealing with Missing Data

We will contact authors or study sponsors to verify key study characteristics or to obtain missing numerical outcome data when possible (eg, when a study is identified as *abstract only).* If outcome data are missing in both intervention groups, but reasons for these are both reported and balanced across groups, important bias would not be expected unless the reasons have different implications in the compared groups. In dichotomous studies, the potential impact of missing data depends on the frequency or risk of outcomes. In continuous outcomes, the potential impact increases with the proportion of participants with missing data [29].

Assessment of Heterogeneity

We will assess studies regarding clinical and methodological heterogeneity. If studies are deemed homogeneous in these criteria, we will conduct meta-analyses and analyze statistical heterogeneity by visual inspection of the forest plots, and use Chi-squared and I^2tests. Results of Chi-squared <0.10 and I^2>50% will be considered heterogeneous; in these cases, we will try to explain heterogeneity by the prespecified groups for the subgroup analysis and also by the possible findings of the assessment of publication bias [30].

Assessment of Reporting Bias

If 10 or more studies are included in the meta-analysis, we will assess reporting biases using funnel plots and visually inspect the plots for asymmetry [29].

Subgroup Analyses and Investigation of Heterogeneity

Subgroup analyses for the primary outcomes will be conducted and consider the following groups: the different types of diabetes, the different kinds of hypolipemic drugs (statins, fibrates), the different doses of these drugs (eg, high-dose fibrates), and the dyslipidemia and/or diabetic macular edema status of the patients [30].

Sensitivity Analyses

Sensitivity analyses will be conducted to determine the impact of exclusion of studies with overall high risk of bias. Such studies will include those judged to harbor *high risk* of bias in at least one of the main domains in the Risk of Bias Table (generation of randomization sequence, allocation concealment, and blinding) [30].

Summary of Findings

Using GRADEpro software we will generate two summary of findings (SoF) tables, one for each key question of this review: development and progression of DR. We will use the five Grading of Recommendations Assessment, Development, and Evaluation criteria (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence that contributes data to the meta-analyses for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 [29] and Chapter 12 [31] of the Cochrane Handbook for the judgment of these criteria. We will justify all decisions to downgrade or upgrade the quality of studies using footnotes, and make comments to aid readers' understanding of the review when necessary. We will consider whether there is any additional outcome information that was not incorporated into meta-analyses, note this in the comments, and state if it supports or contradicts the information from the meta-analyses. The SoF table regarding the prevention of DR will comprise the following outcomes: (1) the proportion of patients with DR, (2) the

proportion of patients with at least one serious adverse event, (3) the proportion of patients with proliferative DR, and (4) the proportion of patients with any decrease in visual acuity. The comparison for this table will be hypolipidemic drugs versus placebo or no intervention.

The SoF table regarding the treatment of DR will comprise the following outcomes: (1) the proportion of patients with progression of DR, (2) the proportion of patients with at least one serious adverse event, (3) the proportion of patients with proliferative DR, and (4) the proportion of patients with any decrease in visual acuity. The comparison for this table will be laser photocoagulation with hypolipidemic drugs versus laser photocoagulation with placebo or no intervention. The outcomes for both SoF tables will be reported at 6 months and 5 years (short- and long-term, respectively).

Results

This is a protocol for a systematic review, therefore results are not available. We registered a short version of this protocol before progressing in the review and we are currently in the process of selecting the studies for inclusion.

Discussion

Dyslipidemia is one well-known risk factor for the development of vascular disease in diabetics. However, to date the effects of statin and/or fibrate use have not been addressed by a systematic review. The findings of this review will provide an assessment of the existing evidence for patients and health care providers that deal with this severe and prevalent complication of diabetes.

Authors' Contributions

RR, VM, and CGF developed the review protocol (VM as content specialist, RR and CGF as method specialists). VM, CGF, and RR drafted the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACCORD: Action to Control Cardiovascular Risk in Diabetes
AGE: advanced glycosylation end products
DR: diabetic retinopathy
ETDRS: Early Treatment Diabetic Retinopathy Study
HDL: high density lipoprotein
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial
SoF: summary of findings

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Protocol

Rationale and Design of a Genetic Study on Cardiometabolic Risk Factors: Protocol for the Tehran Cardiometabolic Genetic Study (TCGS)

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Abstract

Background: Cardiometabolic risk factors comprise cardiovascular diseases and/or diabetes, and need to be evaluated in different fields.

Objective: The primary aim of the Tehran Cardiometabolic Genetic Study (TCGS) is to create a comprehensive genome-wide database of at least 16,000 Tehranians, who are participants of the ongoing Tehran Lipid and Glucose Study (TLGS) cohort.

Methods: TCGS was designed in collaboration with the Research Institute for Endocrine Sciences and the genetic company deCODE. Participants had already been followed for over a 20-year period for major cardiometabolic-related health events including myocardial infarction, stroke, diabetes mellitus, hypertension, obesity, hyperlipidemia, and familial hypercholesterolemia.

Results: The TCGS cohort described here comprises 17,186 (86.3%) of the 19,905 TLGS participants who provided a baseline blood sample that was adequate for plasma and deoxyribonucleic acid analysis. This study is comprised of 849 individuals and 3109 families with at least one member having genotype information. Finally, 5977 males and 7422 females with the total genotyping rate of 0.9854 were genotyped with HumanOmniExpress-24-v1-0 bead chips (containing 649,932 single-nucleotide polymorphism loci with an average mean distance of 4 kilobases).

Conclusions: Investigations conducted within the TCGS will seek to identify relevant patterns of genetic polymorphisms that could be related to cardiometabolic risk factors in participants from Tehran. By linking genome-wide data to the existing databank

of TLGS participants, which includes comprehensive behavioral, biochemical, and clinical data on each participant since cohort inception in 1999, the TCGS will also allow exploration of gene-gene and gene-environment interactions as they relate to disease status.

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KEYWORDS

cardiometabolic disorders; cardiovascular; genetic; genome-wide association study

Introduction

Noncommunicable Diseases and Their Health Burden

A noncommunicable disease (NCD) is a medical condition or disease that can be defined as nontransmissible among people. NCDs refer to chronic diseases or conditions in which progression is slow and may last for a long period, or may be lifelong. NCDs, being life threatening conditions, drain economic resources, increase mortality and morbidity in society, and have negative effects on development and economic growth [1]. Claiming 63% of all deaths worldwide, these diseases are currently the world's most common killer [2], and 80% of these deaths now occur in low- and middle-income countries [3]. This finding also shows that half of those who die of chronic NCDs are in the prime of their productive years, and thus the disability imposed and the lives lost are also endangering industrial competitiveness across borders [3]. Therefore, managing and preventing NCDs are national priorities for several countries, as well as the World Health Organization [4].

The term cardiometabolic is intended to cover cardiovascular and metabolic diseases including diabetes, obesity-related traits, and biomarkers known to be associated with the risk of cardiovascular disease [5,6]. Genetically predisposed individuals have inherent risks independent of environmental factors. Nevertheless, at-risk individuals can adopt healthy lifestyles so that other factors do not augment their risk for the disease. Genetic susceptibility implies an increased likelihood for an individual developing a particular disease, based on his/her genetic makeup. Such predisposition results from specific genetic variations that are often inherited from an individual's parents [7]. Accumulating evidence supports the role of genetic changes in major NCDs including cancer, diabetes, cardiovascular diseases, mental health, and asthma [8].

With advances in our understanding of the genetic basis of human disease, it has become apparent that the underlying causes of many chronic disorders are multifactorial and involve the complex interplay between acquired and inherited risk factors [9,10]. In most cases copresence or interactions between several molecular changes across the genomic landscape will work together to make one prone or resistant to a given condition. With the advent of genome-wide scanning technologies, it is now possible to obtain information on most of the common genetic variations in individual patients. Obtaining this genome-wide information in well-characterized patient groups (with or without risks for disease) is a critical step in moving toward a genome-based practice of medicine that not only provides insights into the root causes of disease, but also forms the basis for discovery of new and specific targets for drug therapies. Genome-based medicine may also fulfill the promise of personalized medicine and provide the means to implement patient-specific preventive programs years in advance of clinical symptoms [11,12].

A favored analytic approach for such discovery is the genome-wide association study (GWAS), in which genetic variation across the human genome is compared between patients with different disease states or different risk-factor profiles. Success in GWAS requires a comprehensive knowledge of genome-wide variation and linkage disequilibrium patterns, the availability of dense genotyping chip sets containing several hundred thousand single-nucleotide polymorphisms (SNPs), and the availability of large, well-phenotyped patient populations [13].

A potentially more powerful approach than GWAS is the large-scale prospective cohort study, in which initially healthy individuals are followed over long periods of time and assessed for disease development, and all members of the cohort undergo comprehensive genotyping. Such prospective cohort studies have the advantage of avoiding bias in the selection of case and control subjects, and enable simultaneous evaluation of many environmental exposures and potential disease states in an epidemiologically efficient manner. In the present study, we aimed to analyze the genomic chip type of all Tehran Cardiometabolic Genetic Study (TCGS) participants to estimate the genetic pattern of this population. After deep sequencing to generate the Iranian reference panel, the imputation will be performed for each trait, and associations will be analyzed.

Knowledge Gap

We aimed to undertake a GWAS to evaluate genetic patterns for cardiometabolic risk factors in a Tehranian population, and compare these patterns to other reference genetic databases. This is one of the first studies of its kind in the Middle East, and addresses the knowledge gap on allele frequencies, genetic associations, and the role of consanguineous marriage among Iranian families.

Methods

Objectives and Study Variables

The primary objectives of this study are: (1) to measure and analyze deoxyribonucleic acid (DNA) sequence variations from across the Tehranian human genome, in an effort to identify genetic patterns for cardiometabolic risk factors in the population; and (2) to conduct a GWAS to identify genetic variants that are associated with cardiometabolic disorders, use genetic risk factors to predict those at risk, and identify the biological underpinnings of cardiometabolic disease susceptibility to develop new prevention and treatment

strategies. The secondary objectives of this study are: (1) to determine inheritable genetic risk factors among families of the TCGS with heritability analyses; and (2) to compare the different genetic patterns that contribute to cardiometabolic outcomes among this population, in different case and control groups.

Overall Study Design

The TCGS is a prospective family-based GWAS cohort that has been followed since 1999 within the Tehran Lipid and Glucose Study (TLGS), which includes over 15,000 initially healthy subjects >3 years old, who have already been followed for more than 20 years. Participants have been followed for the development of common disorders such as myocardial infarction, stroke, diabetes mellitus, hypertension, obesity, familial hypercholesterolemia, hyperlipidemia, habitation (eg, smoking and physical activity), and biochemical factors (ie, high cholesterol, low high-density lipoproteins, high triglycerides).

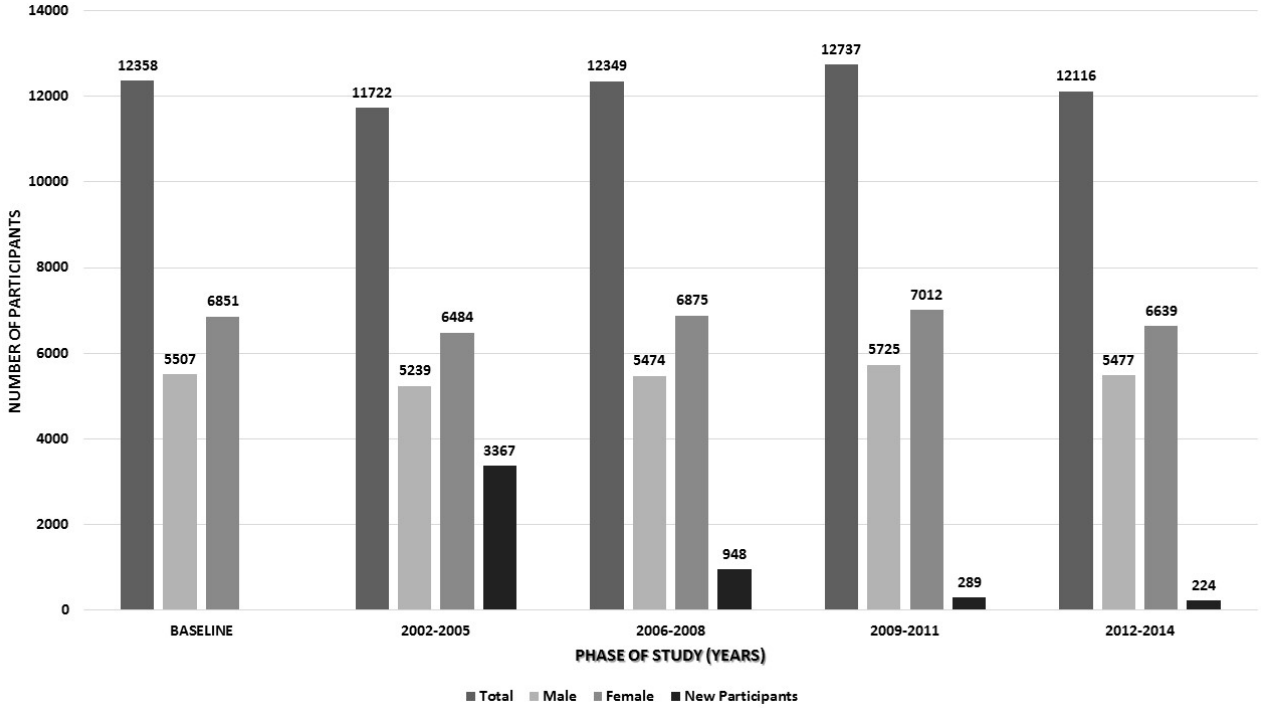
The concept of designing a genomic bank from TLGS samples was first presented to the Endocrine Research Center (ERC) and the Iranian molecular medicine network, and was funded by FA and MSD (grant number 147, 2004; grant number 265, 2008). In 2008, a project determining pedigrees according to genetic relationships was funded by ERC (grant number 321), with MSD and AAM as principal investigators. Funding of the main study began in June 2012 with an agreement between the Research Institute for Endocrine Sciences (RIES) and the deCODE genetic company (Reykjavik, Iceland), with FA and MSD as primary investigators. The final protocol for the genetic study was written by FA, MSD, MSF, and DK, and was submitted to the Ministry of Health and Medical Education in August 2012. The protocol was approved by the National Committee for Ethics in Biomedical Research in December 2012.

In this paper, we describe the TCGS (and its parent TLGS) from the perspectives of cohort assembly, follow-up, endpoint validation, baseline plasma phenotyping, DNA extraction, genotyping, participant confidentiality, power, and sample size, and discuss the TCGS in the context of other ongoing GWASs being performed in related areas. The study is organized into 5 phases: (1) cohort assembly and prospective follow-up, (2) genomic sample extraction, (3) phenotype and outcome gathering, (4) chip typing and genotype analysis, and (5) drawing family trees.

Cohort Assembly and Prospective Follow-Up

All members of the TCGS cohort were participants in the TLGS who had provided an adequate baseline blood sample for plasma and DNA analysis, and had given written consent for blood-based analyses and long-term follow-up. The TLGS is a long-term integrated community-based program for the prevention of NCDs by developing of a healthy lifestyle and reducing NCD risk factors. The study began in 1999, and will be continued for at least 20 years. A primary survey was performed to collect baseline data for 15,005 Iranian individuals born between 1912 and 2008, and was selected from cohorts at three medical heath centers [14]. The study designs for TLGS and TCGS were approved by the Institutional Review Board of the RIES, Shahid Beheshti University of Medical Sciences, and all participants provided written informed consent for genetic analyses. The presence of participants in each phase of study shown in Figure 1.

Figure 1. Cohort participation and gender distribution of the study phases.



Genomic Sample Extraction

At the TLGS sample collection center, a blood sample was drawn into vacationer tubes from all study participants, between 7:00 and 9:00 a.m. after 12-14 hours of overnight fasting. Two blood samples were taken in a sitting position per standard protocol. The blood collected in ethylenediaminetetraacetic acid-containing test tubes was used to obtain DNA samples, which were immediately sent to the genomic laboratory. All TLGS samples were recoded as a genomic sample that connected to the TLGS code in a database. DNA samples were extracted from buffy-coat samples from each participant using a proteinase K/salting out standard method [15]. The quality and quantity of extracted DNA were evaluated. A Thermo Scientific NanoDrop 1000 Spectrophotometer was used to qualify samples, which were aliquoted into 1.5 milliliter tubes and stored in -80°C ultra-freezers for future studies.

Phenotype and Outcome Gathering

A broad range of epidemiologic data related to behavioral, dietary, and environmental risk exposures were received from TLGS as a parent study to TCGS. Each TCGS participant also provided a baseline blood sample that had already been evaluated for multiple disease biomarkers, including total cholesterol, high-density lipoprotein-C, low-density lipoprotein-C, triglycerides, fasting plasma glucose, fasting insulin, and creatinine. Individuals with genomic samples that had full familial information will be included in the TCGS, and cardiometabolic risk factors will be measured and defined in this dataset. The specified families with multiple signs of these risk factors will be followed-up.

Chip Typing and Genotype Analysis

Portions of DNA samples were genotyped with HumanOmniExpress-24-v1-0 bead chips (containing 649,932 SNP loci with an average mean distance of 4 kilobases) at the deCODE genetics company (Reykjavik, Iceland) according the manufacturer's specifications (Illumina Inc., San Diego, CA).

Drawing Family Trees

At this step, TCGS focuses on drawing all genetic relationships. On the initial day of examination, the TLGS participants were interviewed to obtain demographic data and relationship information, or update existing data. Genealogy data was drawn in Genepro (V 2.0.1.6) and checked by Family-Based Association Tests (FBAT-Toolkid V 1.7.3) [16]. Family data, pedigree information, phenotype, and genotype data were stored, manipulated, and error-checked using the genetic data management system (Progeny Clinical Version 7) from Progeny Software (Progeny Software LLC, Delray Beach, FL). The name of the father was checked for all individuals, and if duplicate names were identified their genetic relationship was checked with their genotype information. If the genetic relationship was confirmed with genotype information, the family tree joint was merged to generate a mega family.

Genetic Association

The present study aims to genotype TLGS participants. Genotyping will be based on a standard SNP array platform suitable for performing a GWAS comprising tag SNPs from all three HapMap phases, and has been strategically selected to capture the greatest amount of common variation and drive the discovery of novel associations with traits and diseases. Incidence rates of cardiometabolic risk factors (ie, diabetes mellitus, angina pectoris, myocardial infarction, hypertension) will be estimated, and adjusted for age and sex. Other variables, such as education level, physical activity, smoking habits, nutritional habits, and drug use will be use as covariables. Relative risks for different factors and their 95% CIs will be reported. Longitudinal linkage analyses will be performed for families, and selected genetic regions will be examining via association analyses. By using common genetic polymorphisms with well-understood effects on exposure patterns, a causal effect from observational data in the presence of confounding factors will be estimated by Mendelian randomization. The most important phenotypes in this project are cardiometabolic risk factors, including diabetes, cardiovascular disease, obesity, and metabolic syndrome. All phenotypes will be analyzed using a case-control and familial based design, and the related genetic regions will be analyzed and replicated in other populations. An Iranian reference panel will be designed and imputed based on a reference panel that will be performed to obtain information about a higher number of variants.

Multifactoriality is expected to play a pivotal role, and this study is currently focused on collecting information on the genetic and environmental factors that potentially influence cardiometabolic diseases. For the gene-gene and gene-environment interaction analyses, it will be assumed that genetics may influence disease risk either directly or via environment effects. The genetic loci can have either independent or epistatic effects, so the model will be a multilogistic model. However, if nonparametric gene-gene interaction is desired, semiparametric regression and least square kernel machines will be used occasionally.

According to the outcome and phenotype information, different ethnicities, and homozygosity fraction, samples will be selected for whole genome analysis to make an Iranian reference panel in deCODE (Reykjavik, Iceland). After making the reference panel, the genotype data set will be imputed to larger data set.

Epigenetic Analyses

To explore the association between the methylation pattern of cytosine phosphate guanine (CpG) islands in the regulatory regions of determined genes and main outcomes (ie, obesity, cardiovascular diseases), we will examine the methylation alterations in the CpG regions of determined genes among TCGS participants using methylation-specific polymerase chain reaction, bisulfite-sequencing polymerase chain reaction, and epigenome-wide analysis techniques. Identifying epigenetic modifications associated with cardiometabolic risk factors, including DNA methylation variation, may point to genomic pathways that are dysregulated in numerous conditions. The Illumina Bead Chip array will be use to assay DNA methylation in leukocyte DNA obtained from TCGS participants. Mixed-effects regression models will be used to test the association of methylation beta value with cardiometabolic risk factor changes, adjusting for batch effects and potential

confounders. Association analyses of the DNA methylation patterns and TCGS phenotypes will subsequently be performed.

Sample Size and Power

Sample size and power calculation were estimated according to the TLGS [14] criteria, with the total TCGS duration of 20 years. Due to the wide scope of the project and variety of measured variables, different types of analyses will be performed, depending on the type of report, or the variables and outcomes. Continuous data will be expressed as their measures of location and spread in total, and in subgroups. For qualitative and categorized continuous variables, percentages and frequency distributions will be reported.

Normality of distribution of the continuous variables will be examined using histograms, measures of skewness and kurtosis, Kolmogrove-Smirnove tests, and Chi-square tests. When log-transformed values are used, geometric means will be computed. Percentiles will be used to describe the high or low values of the skewed variables. When assumptions of the parametric statistical methods are not met, nonparametric methods of their counterparts will be used. These methods will also be used for analyses of variables that are not originally continuous, such as attitudes or quality of life.

Results

Participant Confidentiality

Participant confidentiality in the TCGS is maintained throughout all aspects of the study, as is the case in the TLGS. Investigators within the TCGS have no access to any direct patient identification information; these data are held confidentially by staff members of the TLGS, who are involved in patient contact and follow-up, but not in any data analysis or interpretation. Separate data files are kept for participants' clinical covariate and endpoint data, plasma phenotyping data, and genomic data. Blood samples sent to the plasma phenotyping laboratory and the genetic laboratories are labeled only with a sample identification number that cannot be tracked by laboratory personnel to any patient identification variables, or to any clinical covariate data. All TCGS data included in the TLGS are maintained on a separate and fully protected computer system that is isolated and distinct from computing systems used for the parent study. A unique and fully distinct participant identification number is used in the TCGS, making direct linkage to the TLGS impossible for scientific investigators.

Participants' DNA Information

Since the establishment of the genomic bank in 2004, some subjects only participated in Phase 1 of the study (1999-2002), and their data has been excluded from this study. The TCGS has a genomic bank with over 16,000 samples. The TCGS cohort described here comprises 17,186 (86.34%) of the 19,905 TLGS participants, who provided baseline blood samples that were adequate for plasma and DNA analyses (Multimedia Appendix 1). This study is comprised of 849 individuals and 3109 families with at least one member who had genotype information.

Familial Information

The pedigrees were drawn (based on questionnaire information) for all biologically related TCGS participants. Total family data of Tehranian residents (consisting of 3109 families) were collected; 849 unrelated persons, adopted persons, childless bride and groom couples, and individuals who lacked information were marked as *independent persons*. The mean pedigree size in the study population was 6.76 (range 3-52). Placeholding individuals were imputed when necessary to reflect kinship relations among participants, and a total of 6158 individuals were added as virtual persons that were recorded by special codes for further tracking. For example, parents who had not participated in the TLGS were added during the drawing of pedigrees to identify sibships in the TCGS.

Demographic, Clinical, and Biochemical Information

Demographic, clinical, and biochemical information of participants (categorized by year) in each period of study are presented in Multimedia Appendix 2 and Multimedia Appendix 3. Most the study population was in the range of 31-50 years old. Phenotype frequencies of hypertension, dyslipidemia, diabetes, obesity, and metabolic syndrome were described in adults, and being overweight was the most frequent among them (Multimedia Appendix 4).

Genotype Quality Control Analysis

PLINK program (V 1.07) and R statistic (V 3.2) were used for quality control procedures. 13,894 samples were arrayed, consisting of 6274 males and 7614 females, with the total genotyping rate of 0.9774.

To increase the power of the analyses, some markers (and some samples) were removed from TCGS database after quality control [17]. In the first step of sample quality control, individuals with discordant sex information were identified. In total, 15,031 X chromosome variants were detected in 397 samples, which were removed from analyses. To evaluate heterozygosity among genotyped samples, plots were drawn and the observed heterozygosity rate per individual was examined to decide reasonable thresholds for excluding individuals based on elevated missing heterozygosity or extreme heterozygosity (Multimedia Appendix 5). In this step, 243 individuals were excluded with a genotype failure rate (>0.03) and/or heterozygosity rate >3 standard deviations from the mean. To eliminate the genetic influence of sample contamination, duplications and cryptic first-degree relative sibling pairs, genome-wide average identity by state (IBS)/identity by descent (IBD) values were calculated for each pair of individuals in the present GWAS data set using pruned SNPs (649,932). To check kinship relationships, IBDs were calculated and all relationships were confirmed.

To find individuals with large-scale differences in ancestry, a principal component analysis was conducted and 47 subjects were removed (Multimedia Appendix 6). For marker quality control, those with a minor allele frequency less than 0.01 (n=24,860) and genotype failure rate less than 0.95 (n=2620) were removed. After excluding markers that did not satisfy the Hardy Weinberg Equilibrium (n=14,032, $P<.001$), 608,420 remained for analyses. Multimedia Appendix 7 shows the

distribution of SNP call rate after the cleaning process. In summary, the clean data set included 13,399 individuals consisting of 5977 males and 7422 females, with 608,420 markers and a total genotyping rate of 0.9854.

Discussion

The genetic findings of this study could help us to understand the genetic pattern of our population and design association studies. The results of the TLGS indicated that the prevalence of cardiometabolic risk factors is speedily increasing in our population, necessitating further investigations for genetic background information to study the interactions between environmental and genetic factors. The incidence of NCDs, especially cardiometabolic diseases, is increasing worldwide due to changes in lifestyle [18], and various countries have investigated their populations using genetic dissection to understand the genetic pattern of these complex disorders. Unfortunately, established health education and lifestyle interventions in American and European populations cannot be implemented in other regions of the world (such as Iran) due to differences in susceptibility, nutrition, social circumstances, and culture.

The TCGS was designed in Iran as a population-based genetic study, and is one of the very first studies of its kind in the Middle East, addressing the knowledge gap on the genetic patterns of the Iranian population. This study will clarify the role of environmental factors in Iran, along with environmental-genetic interactions. Combining the epidemiological findings in TLGS with genetic data has led to the design of Mendelian randomization studies to change some concepts about the interaction of lipid variation and cardiovascular diseases. In addition, this study may clarify missing heritability data and aid in the understanding of NCD-related problems [19].

However, the delineation of shared phenotypes facilitated by GWAS is of great interest, such as the recent insight into the relationship between height and cardiovascular disease [20]. Results of this study will provide a comprehensive understanding of personalized genomic data and could be used to help to governmental organizations use genetic knowledge to promote personalized health care that facilitates the prevention and management of NCDs.

Strengths and Weaknesses

This study was based on a national project that selected a representative sample of residents in district-13 of Tehran, the capital of Iran. The project included detailed information on individuals, households, and family relationships (along with environmental, biomedical, and biochemical factors that could be linked to the rate of NCDs) to create a cohort of the entire population residing in Tehran. We recently reviewed the literature in this field, and to our knowledge the present study is the first population-based cohort study for cardiometabolic genetic risk factors in Iran.

In the TCGS, data have been thoroughly and robustly collected on a wide range of clinical parameters, focusing on quantitative traits that are well established as risk factors for cardiometabolic disease. This cohort includes substantial numbers that represent the full adult spectrum of ages, lifestyles, and demography, and includes important phenotypes and quantitative traits to allow population-based genetic and epidemiological research on many important diseases/risks related to NCDs. The family-based approach of the TCGS enables the study to take a flexible approach to gene discovery, encompassing association and linkage approaches, and gives the potential to study aspects such as heritability of disease-related traits and parent-of-origin effects. The combination of linkage and association approaches has proven very effective in studies of various diseases/disease traits [21].

Data in this study can be linked anonymously to routinely collected samples from different cohorts in Iran. This linkage effectively converts this longitudinal study into a national study, with pluripotential outcomes. The TCGS can contribute as a major partner to GWAS meta-analysis consortia, enabling the study of SNPs of low minor allele frequency (1-10%). The TCGS is one of the largest family-based genetic epidemiology studies in Iran and the Middle East.

Although the family-based nature of the cohort is an important strength of this study, providing an efficient strategy for DNA sequence-based studies, relatedness of cohort members will be a confounding factor in some analyses, and may require statistical adjustment. The other weakness of the study is related to the Tehranian nature of the population, rather than a comprehensive Iranian cohort.

Acknowledgments

The authors would like to express their gratitude to the patients participating in the TLGS. Special thanks to the deCODE genetic company for performing the genetic screening. This study was funded by the RIES, Shahid Beheshti University of Medical Sciences (Tehran, Iran) and recognizes the scientific support of deCODE (Reykjavik, Iceland). The Iranian Molecular Medicine Network supported the genomic bank.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Phases of the Tehran Lipid and Glucose Study (duration and number of participants) from 1999 to 2014. Horizontal arrows show the number of people entering and exiting in each phase. Vertical lines show the number of the individuals moving between phases.

[JPG File, 90KB - resprot_v6i2e28_app1.jpg]

Multimedia Appendix 2

Demographic and laboratory information for children and young Tehran Cardiometabolic Genetic Study participants.

[PDF File (Adobe PDF File), 37KB - resprot_v6i2e28_app2.pdf]

Multimedia Appendix 3

Demographic and laboratory information for adults and the elderly among Tehran Cardiometabolic Genetic Study participants.

[PDF File (Adobe PDF File), 41KB - resprot_v6i2e28_app3.pdf]

Multimedia Appendix 4

Phenotype frequency among adult Tehran Cardiometabolic Genetic Study participants.

[PDF File (Adobe PDF File), 26KB - resprot_v6i2e28_app4.pdf]

Multimedia Appendix 5

Genotype failure rate versus heterozygosity across all individuals in the study. The vertical dashed line shows all individuals with a genotype failure rate >0.03 who were excluded, and the horizontal dashed lines represent a heterozygosity rate 3 standard deviations from the mean.

[PNG File, 92KB - resprot_v6i2e28_app5.png]

Multimedia Appendix 6

PCAAncestry clustering based on genome-wide association data.

[PNG File, 30KB - resprot_v6i2e28_app6.png]

Multimedia Appendix 7

Histogram of missing data rate across all individuals passing per-individual quality control. SNP: single-nucleotide polymorphism; K: thousand.

[PNG File, 39KB - resprot_v6i2e28_app7.png]

Multimedia Appendix 8

Peer review report of the grant reviewers.

[PDF File (Adobe PDF File), 35KB - resprot_v6i2e28_app8.pdf]

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Abbreviations

CpG: cytosine phosphate guanine
DNA: deoxyribonucleic acid
ERC: Endocrine Research Center
GWAS: genome-wide association study
IBD: identity by descent
NCD: noncommunicable disease
RIES: Research Institute for Endocrine Sciences
SNP: single-nucleotide polymorphism

TCGS: Tehran Cardiometabolic Genetic Study
TLGS: Tehran Lipid and Glucose Study

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Protocol

Feasibility of Implementing a Patient-Centered Postoperative Wound Monitoring Program Using Smartphone Images: A Pilot Protocol

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Abstract

Background: Surgical site infections (SSI) represent a significant public health problem as the most common nosocomial infection and a leading cause of unplanned hospital readmissions among surgical patients. Many develop following hospital discharge and often go unrecognized by patients. Telemedicine offers the opportunity to leverage the mobile technology to remotely monitor wound recovery in the transitional period between hospital discharge and routine clinic follow-up. However, many existing telemedicine platforms are episodic, replacing routine follow-up, rather than equipped for continued monitoring; they include only low-risk patient populations and those who already have access to and comfort with the necessary technology; and transmit no visual information.

Objective: Drawing upon the Coleman model for care transitions and the Proctor model for implementation, we propose a protocol of postoperative wound monitoring using smartphone digital images. In this study, we will establish the feasibility of such a program, both for patients and for the clinical care team.

Methods: We will recruit 40 patients or patient/caregiver pairs from our inpatient vascular surgery service. Eligible patients will be English-speaking, 18 years of age or older, and have an incision at least 3 cm in length. Participants will receive a training session, during which they will learn to use the device and the wound monitoring smartphone app. Following hospital discharge, they will submit digital images of their wound and responses to a survey about their recovery for 14 days. Experienced health care providers on the vascular surgery inpatient service will review transmitted data daily and contact patients for any concerning findings.

Results: Primary outcomes will include participant adherence to the protocol, time required for providers to review submissions, time from submission to provider review, and participant satisfaction. Secondary outcomes will include SSI detection and hospital readmission.

Conclusions: Health systems are increasingly dedicating efforts to transitional care improvement programs. This feasibility trial will confirm whether patients and their caregivers can learn to use a postdischarge wound monitoring smartphone app and will assess patient and provider satisfaction. This protocol will provide preliminary evidence for a shift in the delivery of postdischarge care in a patient-centered and cost-effective manner.

Trial Registration: Clinicaltrials.gov NCT02735525; https://clinicaltrials.gov/ct2/show/NCT02735525 (Archived by WebCite at http://www.webcitation.org/6oIvN4Mab)

(JMIR Res Protoc 2017;6(2):e26) doi:10.2196/resprot.6819

KEYWORDS

telemedicine; smartphone; surgical site infection; transitional care; feasibility study; clinical research protocol

Introduction

Background

Surgical site infection (SSI) represents a significant public health problem as the most common nosocomial infection and the leading cause of unplanned hospital readmissions among surgical patients [1-4]. SSI can be intractable because up to 84% develop in the critical interval between hospital discharge and routine follow-up [1,5]. Moreover, since the majority of patients have little experience caring for a surgical wound, they rarely recognize early stage wound infections and often present with an advanced infection that requires rehospitalization [6,7]. Conversely, SSI diagnosed at an early stage can be treated in the outpatient setting with oral antibiotics and wound care, precluding the need for readmission, intravenous antibiotics, and reintervention. The fact that SSI develops or progresses in the outpatient setting makes transitional care coordination a promising area of focus in the management of SSI.

Hospitals are incentivized to improve transitional care for surgical patients as the Center for Medicare and Medicaid Services (CMS) increasingly imposes financial penalties for unplanned readmissions after surgery through the Readmissions Reduction Program as part of the Patient Protection and Affordable Care Act [8]. However, transitional care coordination following surgical procedures has received less attention from researchers and hospital systems relative to medically managed conditions [9,10]. Although the Centers for Disease Control and Prevention have long monitored SSI rates through the National Healthcare Safety Network, the majority of prevention efforts occur during the operative procedure and any associated inpatient stay; few early detection and prevention efforts crosscut care settings. We leverage the alignment of national policy and gaps in existing SSI surveillance to implement a patient-centered mobile health (mHealth) intervention focused on stemming the burden of SSI and readmissions through image capture of wound healing.

Telemedicine, and mHealth specifically, offers an opportunity to leverage technology for the remote monitoring and early detection of SSI during the transitional care period, including wound monitoring using smartphone digital images [11]. However, significant barriers have restricted adoption of telemedicine, particularly in the United States where regulatory and reimbursement policies present unique challenges. The few studies examining continued monitoring of recovery following hospital discharge have been performed outside of the United States [12-14] and have not adhered to privacy standards set forth by the Health Insurance Portability and Accountability Act (HIPAA) [15]. Moreover, sustainable implementation of mHealth protocols for wound monitoring requires that they support existing patient-provider-caregiver relationships, fit into patients' daily routines following hospital discharge, and provide visibility of the wounds' healing for both patients and providers [16]. Therefore, the design of a wound monitoring protocol using telemedicine must support both patients and providers in their existing roles without creating a significant burden.

Another essential feature of such a protocol is scalability to a full patient panel, particularly with respect to novice-user patient populations. The cost effectiveness and widespread accessibility of a telemedicine protocol for wound monitoring can help to ensure scalability. Specifically, the cost per enrolled patient must be sufficiently low to justify targeted enrollment among patient populations who are at high risk of developing a complication requiring readmission following discharge in the context of quality-based payment and financial penalties for readmission. In addition, health systems must allocate resources to ensure that patients who have no experience using smartphones are empowered and equipped to participate. A majority of published studies rely on self-selection into telemedicine, conferring "digital access" to technologically savvy patients who tend to be younger, more educated, and wealthier [11]. Telemedicine thus has demonstrated potential to exacerbate existing access and utilization care disparities, and dedicated resources are required to mitigate this gap.

Objectives

Overview

We propose to address identified shortcomings in published mHealth studies with a patient-centered, mHealth outpatient wound surveillance program designed to promote early recognition of SSI following discharge. The current trial is part of a larger project funded by Agency for Healthcare Research and Quality R21 HS023395. The goals of this larger project are (1) to empower patients, particularly novice smartphone users, to be mindful of their wounds and to partner with their surgeons in monitoring their postoperative recovery; (2) to diagnose SSI, when it occurs, at an early stage, enabling outpatient management; and (3) to prevent hospital readmission and the serious morbidity and mortality associated with wound complications. The project entails teaching vascular surgery patients to use a simple, linear smartphone app to take and transmit images of their postoperative wounds and symptom information (as yes/no questions) daily for the first 2 weeks following hospital discharge; surgical staff then review the submissions to discern the presence of a complication.

Prior work from our group and others has demonstrated enthusiasm from patients and their families regarding participation in transitional care programs [17]. In addition, we have shown that digital images are sufficient for diagnostic and therapeutic decision making, resulting in decisions comparable to those based on in-person evaluation [18]. Using an internally developed smartphone app with an accompanying training program grounded in tenets of adult learning and memory retention, we have also demonstrated that patients and their caregivers can learn to use the app with a high level of independence and satisfaction [19].

The next step in the project is to pilot test the full patient-centered outpatient wound surveillance program to

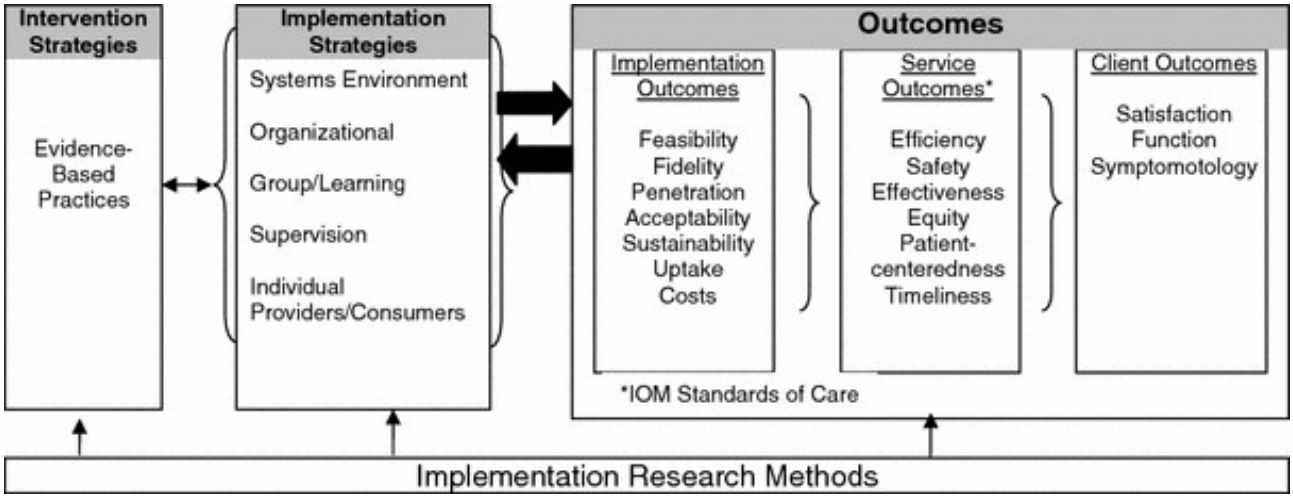
establish its feasibility for both patients and the service line of a large academic tertiary care institution. With a targeted enrollment of 40 patients, outcomes will include evaluation of the module's technological capability, including (1) barriers to participation, (2) patient attrition/adherence, (3) picture and information quality, (4) successful information transmission and assimilation into clinical workflows, (5) ease of integration into the clinical service line, and (6) the ability of health care professionals to identify early wound infection from photographs.

Theoretical Foundation

We use Proctor's model of implementation research to structure the evaluation of our feasibility trial (Figure 1) [20]. This framework integrates 3 bodies of theory, including multilevel organizational models of change, stage pipeline models of implementation that accelerate interventions from development to real world practice settings, and structure-process-outcome models of health services use. This model is particularly suited to our project because our intervention cross cuts care settings (inpatient, outpatient, and home), requires integration at multiple organizational levels (clinical, patient/caregiver, information technology infrastructure, and leadership), and necessitates real-world feasibility testing at bedside prior to widespread implementation. Accordingly, this framework facilitates defining outcomes on different organizational levels: implementation, service, and client. Although this model is largely a heuristic model, it is useful here because our trial is a small, research-focused feasibility trial rather than a large-scale implementation study involving widespread uptake of an established intervention. Moreover, Proctor's emphasis on diffusion of innovation theories lends itself to studying a new mHealth technology in a clinical setting.

Interdisciplinary collaboration and stakeholder engagement are fundamental to this model. During intervention and app development, we engaged patient advocates, physicians, surgical nursing staff, and community members to provide structured feedback via focus groups and interviews on app content and ancillary training materials to ensure that all functionalities and language used are clear and consistent with discharge instructions. Additionally, formal usability tests involving 9 postoperative vascular surgery patients at our institution established acceptance by the target population and patients' and their caregivers' capacity for completion after a short training session, with a median training time of 8.5 minutes and an average System Usability Scale score of 83.3 [19]. We also involved surgical leadership, surgeons, nurse practitioners, physician assistants, information technology personnel, and nurses in the vascular surgery inpatient unit to develop clinical implementation strategies that can be easily integrated into their daily workflow. Defined outcomes, described in detail in the Methods section, are mapped onto 3 organizational levels: implementation, service, and client outcomes.

Figure 1. Conceptual model of implementation research. Reprinted with permission from Procter et al [20].



Objectives and Hypotheses

Our overall objective is to evaluate the feasibility and effectiveness of a protocol for postdischarge wound monitoring using a smartphone app and its ability to detect postoperative wound complications and reduce hospital readmissions in a vascular surgery patient population. In this phase of the larger project, we focus on feasibility of the protocol from both the patient and the provider perspectives. We hypothesize the following:

1. Patients can be engaged in their postoperative care by participating in a smartphone protocol to monitor wound healing, completing the protocol daily for 2 weeks.
2. Reviewing received submissions and acting on any detected abnormalities can be integrated into existing service lines without overburdening clinical staff.

Methods

Participants

We will recruit 40 patients or patient/caregiver pairs for participation in our pilot study, aiming for 20 independent participants and 20 patient/caregiver pairs, in an effort to capture all eligible patients over the study duration based on our institution's annual volume. Recruitment will occur primarily in the University of Wisconsin Hospital and Clinics (UWHC) vascular clinic at the time of consent for surgery and the

postoperative inpatient vascular surgery service; UWHC performs more than 600 inpatient vascular procedures annually, a majority of which are open rather than endovascular [21]. As a major referral center for the state of Wisconsin, our institution performs a relatively high number of nonelective procedures necessitating additional recruitment in the postoperative period before hospital discharge. English-speaking patients over the age of 18 with an incision at least 3 cm in length will be eligible. All eligible patients will be approached for participation in a consecutive fashion. Patients and their caregivers will receive training to learn to use the smartphone itself as well as the wound monitoring app during their stay with a refresher session on the day of discharge including a test image transmission prior to discharge. This will allow for reinforcement of the initial training session as well as the acquisition of a baseline image for later comparison. Smartphones will be provided for use during the study, which participants will be able to keep as remuneration after study completion.

Participants will be enrolled in waves of approximately 5, with time between waves for protocol evaluation and to identify areas for intervention improvement. Patients who are approached but decline to participate will be asked to provide their reason for declining.

Ethics Approval and Consent to Participate

The University of Wisconsin Institutional Review Board (IRB) approved this study (UW IRB #2015-1581). All future modifications to the protocol or to the consent process will go through this IRB for review and approval.

Participants (and their caregivers, where applicable) will be approached for informed consent in person during the postoperative, predischarge period. Eligibility will be determined by medical record review and consultation with service providers. Proxy consent will be obtained for participants who are unable to participate if a competent family member or caregiver can be identified. Participants will receive copies of all signed consent forms.

Intervention

WoundCheck is an internally developed and user-tested iOS app that enables patients to transmit daily wound images and symptom information from their home or postacute care facility to the surgical care team in the hospital (Figure 2) [19]. There are 2 phases of the app: an image-taking phase where patients take up to 4 digital images of their surgical wound and a brief survey of 6 yes/no questions regarding recovery (Textbox 1). Survey questions were developed based on prior work from our group validating smartphone digital images for postoperative wound monitoring and were designed to capture information not as easily appreciated from the submitted images [18]. Information generated from the app is automatically transmitted to our research server as the final step of the app. The app, which features large font, large buttons, and simple language and design, is accompanied by a training program that is delivered in person prior to discharge along with a written instructional packet.

Textbox 1. WoundCheck survey module yes/no questions.

- Have you had fevers or chills in the past 24 hours?
- Have you changed how you take your medication in the last 24 hours?
  - If yes, is this change related to your pain medication?
  - If yes, did you increase your pain medication?
- Has the area around your wound become red in the past 24 hours?
- Has the area around your wound become swollen in the past 24 hours?
- Is there a bad smell coming from your wound?
- Is fluid leaking from your wound?
  - If yes, is the fluid white, yellow, or green?
  - If yes, do you change your dressing more than once per day because fluid soaks through?

We developed the app using the Coleman model transitional care framework to guide content [22-24]. The Coleman model is specifically designed to reduce discontinuity in care transitions and addresses the needs of elderly patients and patients with complex, chronic conditions [25]. Moreover, it focuses on patients and caregivers as the "common thread linking differing providers and settings," emphasizing patient education and empowerment as essential for facilitating (1) medication self-management, (2) use of a dynamic patient-centered record, (3) completion of follow-up care, and (4) knowledge of red flags that could indicate a worsening of their condition. Our smartphone-based intervention is designed to promote mindfulness of the wound, identify red flag symptoms and medication misuse, and direct and document communication between the patient/caregiver and the surgical service.

At the time of recruitment, we will introduce patients and any caregivers to the smartphone and teach them to complete the app independently, a process that takes between 3.9 and 23.0 minutes, based on our preliminary results from usability testing [19]. We developed the training drawing on the following tenets from the adult learning and memory literature: the need for repetition and multiple formats of educational materials [26], the decline in motivation when not experiencing success [27]

or when the purpose of the task is not clear or relevant [28], the need for active engagement with teach-back [29], and the importance of letting the learner set the pace of learning [30].

The patient will take a baseline digital image on the day of discharge to serve as a reference for future comparison. Participants will be asked to transmit a digital image and complete the survey regarding their recovery within the app once per day for 14 days. For those patients discharged to a postacute care facility, the participant or their specified caregiver will still be responsible for submission. We will not rely on the staff of the facility to complete the protocol. Transmissions will be sent through an encrypted connection to a secure research server, a process which has been designed to be HIPAA compliant (Figure 3). Once transmitted, the images are no longer stored on the device.

Participants are provided an iPhone 5S that is theirs to keep at the end of the study. At the time of training, they are counseled that the cost of the phone and the data plan are paid for through the research study, but they are asked not to use the phone for other purposes for the duration of the study protocol. They are also counseled that this protocol of wound monitoring is a supplement to usual care rather than a replacement. As such, they are given the number to our vascular surgery clinic and encouraged to communicate with them as they would outside the study protocol. During training, participants are told that the nurse practitioners (NPs) will review the submissions daily, usually at the end of their workday in the later afternoon. Phone calls from the NPs to participants for concerning findings will likely be made at that time. If a participant has a concern and either does not receive a phone call or does not wish to wait to receive one, they are encouraged to call the clinic or the research contact. Contact information for the vascular surgery clinic and study personnel is provided at 2 points in the app itself and in the provided instructional packet so that patients and their caregivers can easily call with questions or concerns.

Each afternoon, at a time designated by clinical personnel as most accommodating of existing clinical workflows, a vascular surgery service NP or researcher with MD surgical training will review the transmitted images as well as the responses to the survey questions within the app. A short form checklist documenting the appearance of the surgical wound will be completed for each image received [18]. This checklist was previously developed and validated by our research group, drawing upon definitions of surgical site infection and other wound complications from the Centers for Disease Control and Prevention and measures compiled by Cutting and colleagues [31,32]. The checklist also includes a question regarding whether the image is adequate for evaluation, and if an image is found inadequate, space is available to explain why (eg, insufficient light, out of focus, parts of the wound excluded from view). The time required to review the images will be recorded as will the time between submission and review. Any concerning findings prompt a phone call from the surgical service NP to the patient to gather more information and recommend additional intervention/treatment as indicated, which may include antibiotics or a clinic visit. If there is uncertainty about evaluating or interpreting submitted information, the NP will contact the operating surgeon or the vascular surgeon on call to discuss concerning findings.

If a participant has not submitted information for 24 hours, research staff will phone him or her to troubleshoot barriers to completion; these unscheduled calls will be recorded for analysis. Similarly, if the digital images are inadequate for diagnostic purposes, research staff will contact the participant to remind them the goals for the image and help them strategize how to take an effective image on their subsequent submissions. Calls will not be punitive but aimed at minimizing study attrition, identifying reasons why patients are unable to complete the protocol, and identifying possible measures to improve the protocol. Additionally, all participants will receive a phone call on postdischarge day 6 to assess use of the app and continued willingness to participate. A final phone call will be made at the end of 2 weeks, when the participant has completed submissions, to evaluate satisfaction with the protocol. The details of these phone calls will be recorded on a secure data collection spreadsheet. The feasibility trial for the intervention is registered at ClinicalTrials.gov [NCT02735525].

Figure 2. WoundCheck iOS app: image taking and survey sample screenshots. Picture from Shutterstock.

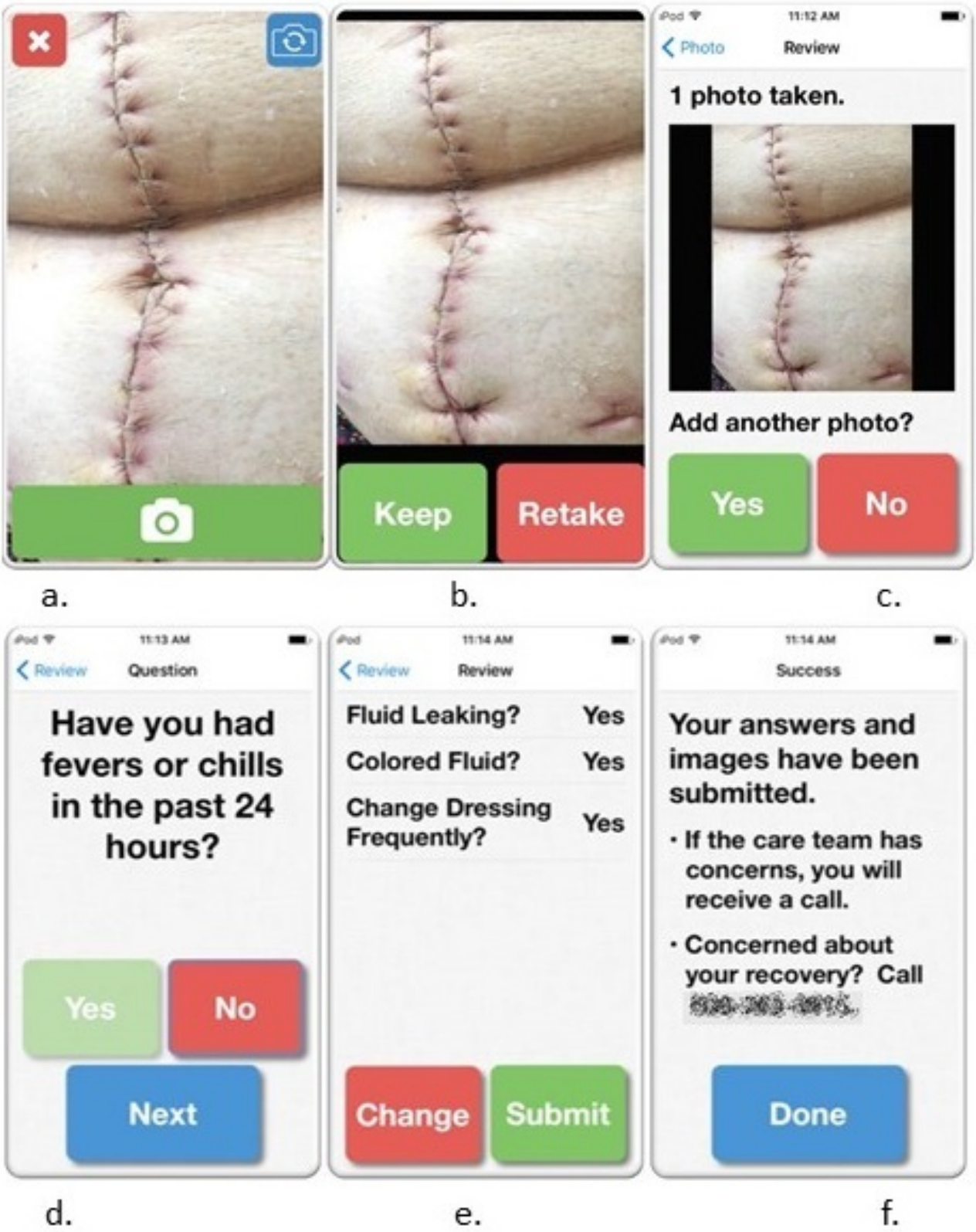
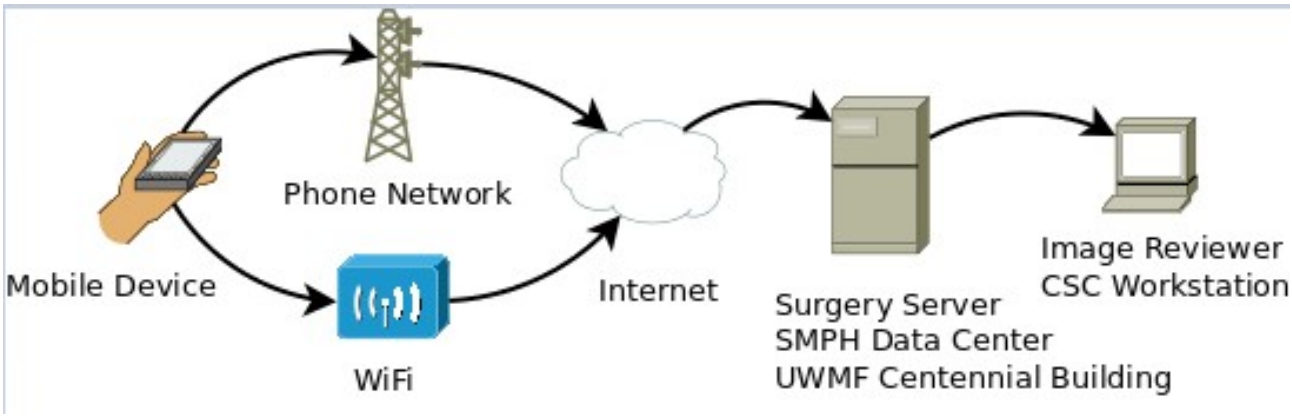


Figure 3. WoundCheck workflow.



Implementation

Organization

Multilevel organizational implementation strategies include information systems implementation, legal compliance, clinical integration, and administrative engagement. To that end, we engaged stakeholders within hospital and surgical leadership to ensure that our mHealth intervention is consistent with existing quality improvement initiatives within the hospital and can be used to augment existing transitional care programs; during this process, we were able to garner enthusiasm for the intervention among clinical and administrative leadership. We also engaged hospital information systems personnel to verify that the hospital had not already licensed a software platform that we could modify for our intervention and to explore the possibility of future medical record integration. Our human subjects review process mandated legal review of app security, cloud-based workflow, and electronic data storage in conjunction with our cybersecurity department to ensure HIPAA compliance. Finally, we solicited input from surgeon-scientists in the Wisconsin Surgical Outcomes Research Program and the Institute for Clinical and Translational Research to leverage existing infrastructure to support clinical evaluation and clinical trials in the department of surgery.

Group/Team

We opted to assess intervention feasibility on the vascular surgery service line within the department of surgery to assess clinical implementation and workflow for a defined patient population with (1) a high base rate of postoperative SSI and readmission, (2) a high number of novice smartphone users, and (3) a high number of regional referrals (making travel for postoperative care potentially burdensome to the patient). Vascular surgery is comprised of a patient population with the highest readmission rate among surgical specialties, most commonly for SSI [3,21,33]. Vascular surgery also has the highest projected demand growth among medical specialties (31% by 2025) after adjusting for expanded coverage under the Patient Protection and Affordable Care Act due to the aging US population and the prevalence of underlying disease burden, such as diabetes [34].

Our vascular surgery service line is comprised of 10 board certified vascular surgeons, 3 inpatient NPs, and a team of nurses and outpatient physician assistants. We engaged the vascular surgery division chief and the service NPs early in the intervention design process to make sure the protocol addressed priority areas of transitional care and to ensure clinical buy-in. Interviews with these clinical stakeholders and ongoing feedback ensured that the intervention is consistent with service line quality improvement efforts and is integrated into existing workflows, particularly that of the NPs undertaking daily wound image review, as smoothly as possible. We presented the proposed protocol at clinical and quality improvement standing meetings and made additional adjustments to the protocol based on feedback. We also notified our 12 regional clinics about the protocol to make sure participants with questions who called the clinic could be directed to the research and app support contact. Whereas participant recruitment, image review, and any follow-up resulting from anomalous findings in the images will take place in the clinical setting, protocol support, materials sourcing and design, teaching patients to use the app, and phone calls associated with the protocol will be performed by 3 research staff.

Individual Providers/Consumers

Given the high prevalence of novice users in the vascular surgery patient population, vetting app and training content in focus groups as well as subsequent formal usability testing provided essential foundations for implementation. The use of published user interface standards (International Organization for Standardization 9241-12) similarly facilitated ease of use [35]. Leveraging state-negotiated rates for mobile phones, we purchased generation-old iPhone 5Ss at a cost of $0.99 per unit and provided the phone as remuneration for study participation to remove the burden associated with having to return the phones. Study service plans cost $34.50 per month per patient, bringing estimated materials costs to $53.50, including a protective phone case and written training materials. Essential features of patient-level implementation include conducting training during the postoperative inpatient stay; this allows us the attention of the patients and assessment of their capacity, caregiver interaction, and engagement during both the inpatient and outpatient settings.

Outcomes

We have defined our outcomes in 3 domains: implementation outcomes, service outcomes, and client outcomes. The primary, multidimensional outcomes of interest are protocol completion by participants and the burden of the protocol on clinician

workflow. Our implementation outcomes include patient adherence to the protocol, cost, clinician/service investment, and technological system compatibility. Service outcomes include the incidence of advanced stage SSI diagnosis, readmissions, and service integration (patient/caregiver participation and follow-up by clinical staff). Client outcomes include satisfaction measured using both previously validated questionnaires and internally developed project-specific measures. We describe our specific measures below.

Implementation outcomes include patient adherence, cost, clinician/service investment, and technological system compatibility. We will calculate the number of eligible patients approached to participate in the protocol relative to the number who consent to participate. Reasons for declining to participate will be recorded. We will also report the percentage of patients who completed the app for the full length of the protocol (daily from the day of discharge until the day of scheduled clinic follow-up) without requiring a reminder phone call. Likewise, the percentage of participants who required a reminder phone call when they did not submit an image or their survey responses within a 24-hour period will be recorded, as well as their reasons for not completing the protocol. The number of phone calls required to reach the participant will be logged, as will the day the phone calls were made. Participant sociodemographic information and relevant comorbidities will be collected from the medical record to ensure that the protocol was accessible to a diverse patient population. We will also identify participant characteristics that would preclude full participation in the absence of a caregiver.

We will calculate the per-patient cost of the protocol including device and plan cost, ancillary materials costs (phone use, written training materials, iPhone cases), and researcher/clinical person-hours spent on the protocol. To determine the burden of the protocol on the clinical workflow, we will determine the time required to complete the review of submitted images and survey responses by the service NPs or study personnel. The time required to make follow-up phone calls will also be recorded. Finally, we will evaluate the data assimilation and review process. To ensure that the service NPs or research personnel review transmitted information within a clinically appropriate timeframe, we will measure time from receipt of transmission to diagnostic review and the time from diagnostic review to follow-up call to the patient, when indicated. Upon trial completion, we will ask all participating clinical staff to anonymously complete the Patient-Centered Care Improvement Guide's Self-Assessment Tool and to provide open-ended feedback on the protocol, their perceptions of its utility, and areas for improvement for long-term sustainability [36]. Finally, we will ask NPs whether they would prefer medical record integration of the app images and content or whether they find our custom provider review interface better suited to their practice.

Service outcomes include late stage SSI diagnosis, readmissions (using a modified CMS definition of any unplanned recurrent admission to an acute care facility before routine follow-up in the 30 days following discharge, subject to certain exclusions including same-day readmission and discharge against medical advice), and service integration (patient/caregiver participation and follow-up by clinical staff) [37]. Although the design and sample size are insufficient to evaluate a significant change, we will track the percent of SSI diagnosed at an early stage (ie, managed on an outpatient basis) and the percent of readmissions; specifically, any late stage SSI diagnosis or unplanned readmission among participants will be thoroughly evaluated for process/diagnosis failures. We will also record the percentage of patients who require intravenous antibiotics or surgical reintervention and whether these patients missed 1 or more of their daily submissions.

To assess client outcomes associated with patient and caregiver perceptions, we will ask participants to complete 2 established, validated scales: the Care Transitions Measure from the Coleman Care Transitions Program and the "After surgery" questions from the Consumer Assessment of Healthcare Providers and Systems (CAHPS) Surgical Care Survey during the phone call made at the end of the protocol [22,38]. The Coleman Care Transitions Program was conceived through the use of focus groups and validated in a large randomized controlled trial among older adults; the CAHPS Surgical Care Survey is a National Quality Forum–endorsed measure of the patient experience following surgery. During the phone call at the end of the protocol, open-ended qualitative interviews will be performed to evaluate participant satisfaction and to elicit feedback regarding barriers to protocol completion and suggestions for possible areas of improvement. Our preliminary goal for patient adherence for the study period is 90% over the first week and 70% over the full 2 weeks; all participants will be queried for barriers to adherence during a routine day 6 follow-up phone call. Our goal for diagnostic quality of all photos submitted, as judged by reviewing clinicians, is 95%. Any instances of photos not being reviewed within 24 hours of transmission will be investigated for process failures.

We will also evaluate the success of the training protocol and participant satisfaction and confidence following training. We will record the time required to successfully complete the training module and patient/caregiver ability to independently complete the app following the training session. We will collect sociodemographic information and smartphone experience from participants, in part to evaluate subgroups of patients whose training needs are unmet by the protocol. Any redesign of the training module will be based on the questions asked and evaluation of the module. At the end of training, we will elicit free response written feedback on the training module from all participants. Responses will be cataloged and content analysis will evaluate themes, pitfalls, and potential barriers to implementation. The training module will be redesigned iteratively based on these results.

Data Confidentiality and Access

All medical record information and study devices will be stored in a secure, locked research office or on a secure server in the department of surgery. When possible, identifiable information will be kept separately from information that is not readily identifiable, and the 2 will be linked with a randomly generated identifying number. Digital images and symptom information collected through the smartphone app will be stored in the department of surgery server behind a firewall; none of this

information will be stored on the smartphone on which it was generated.

All smartphones will be password protected, allowing only patients and their caregivers access to the phone. Transmitted data will include only the study identifier, digital images of the wound, and symptom information; there will be no personal health information recorded in the transmission itself. Upon protocol completion, the service plan will be discontinued, and participants will be given instructions to return the phone to its original factory settings. Participants can keep the erased phone for personal use.

All of our data security measures will be fully outlined in all recruitment and consent materials.

Dissemination

Results of this feasibility trial will be disseminated through peer-reviewed publications as well as at scientific conferences. Lay summaries and presentations at standing meetings will provide feedback to clinical and administrative stakeholders in the hospital. Our results will inform a larger multi-institutional trial using this app as part of a larger transitional care intervention aimed at readmission reduction among complex vascular and colorectal surgery patients.

Results

This feasibility trial began enrolling patients in June 2016. Enrollment and data collection continued until 40 patients completed the protocol, with study completion in December 2016.

Discussion

Summary

As the medical community has increasingly dedicated its efforts to improving transitions of care, particularly transitions from an inpatient stay back to the community, the majority of solutions involve assigning patients a discharge advocate, transition coach, or nurse case manager to provide close follow-up during the transition [22,39]. However, while these methods are effective in reducing hospital readmissions in medical patients, they have frequently not included the crucial visual component needed to fully monitor surgical patients in the postoperative period. The rise of smartphones capable of transmitting visual information and their increasing market penetration have generated enormous opportunities for the incorporation of mobile devices as extensions of care traditionally provided in person.

Through prior work, we have demonstrated that patients and their caregivers are accepting of a protocol of postdischarge monitoring using smartphone technology, that digital images can be used to make diagnostic and therapeutic decisions comparable to those made in person, and that patients and their caregivers can learn to use the postdischarge monitoring app after a short training session tailored to their needs. This feasibility trial will confirm whether patients can complete a smartphone protocol and assess patient and provider satisfaction. In an era of shortened hospital lengths of stay and increasing penalties for higher than expected readmission rates, this protocol provides preliminary evidence for changing the way postdischarge care is delivered with the goal of providing it in a cost-effective manner.

Limitations

This is a feasibility study without a control arm and thus cannot draw conclusions in reference to usual care. Although we will be enrolling only vascular surgery patients, we feel confident that if a patient population that is largely elderly with limited technology exposure can complete the protocol, it can be generalized to a wider surgical population with some caveats. Specifically, our surgical population is racially and culturally homogeneous (over 95% white) and largely comprised of native English speakers. In addition, we are pursuing implementation on a single specialty service and cannot discern whether our intervention scales to a larger service or surgical care teams with different organization of services. Moreover, our hospital has substantial information technology and nursing resources to support our intervention, and significant changes to the protocol might be required for implementation at a hospital with limited resources.

Acknowledgments

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Authors' Contributions

KCK and SFT are the primary investigators on this trial. LA, RLG, KMB, and CCG provided guidance on methodology and optimization of study design. All authors were involved in drafting the manuscript and take responsibility for the contents therein. RLG and SR will be primarily responsible for data collection. SFT, KMB, CCG, and KCK will provide oversight to ensure the protocol is adhered to during participant recruitment and data collection.

Conflicts of Interest

None declared.

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Abbreviations

CAHPS: Consumer Assessment of Healthcare Providers and Systems
CMS: Centers for Medicare and Medicaid Services
HIPAA: Health Insurance Portability and Accountability Act
mHealth: mobile health
NP: nurse practitioner
SSI: surgical site infection
UWHC: University of Wisconsin Hospital and Clinics

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Original Paper

A Prospective, Multicenter, Single-Blind Study Assessing Indices of SNAP II Versus BIS VISTA on Surgical Patients Undergoing General Anesthesia

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Abstract

Background: Traditionally, anesthesiologists have relied on nonspecific subjective and objective physical signs to assess patients' comfort level and depth of anesthesia. Commercial development of electrical monitors, which use low- and high-frequency electroencephalogram (EEG) signals, have been developed to enhance the assessment of patients' level of consciousness. Multiple studies have shown that monitoring patients' consciousness levels can help in reducing drug consumption, anesthesia-related adverse events, and recovery time. This clinical study will provide information by simultaneously comparing the performance of the SNAP II (a single-channel EEG device) and the bispectral index (BIS) VISTA (a dual-channel EEG device) by assessing their efficacy in monitoring different anesthetic states in patients undergoing general anesthesia.

Objective: The primary objective of this study is to establish the range of index values for the SNAP II corresponding to each anesthetic state (preinduction, loss of response, maintenance, first purposeful response, and extubation). The secondary objectives will assess the range of index values for BIS VISTA corresponding to each anesthetic state compared to published BIS VISTA range information, and estimate the area under the curve, sensitivity, and specificity for both devices.

Methods: This is a multicenter, prospective, double-arm, parallel assignment, single-blind study involving patients undergoing elective surgery that requires general anesthesia. The study will include 40 patients and will be conducted at the following sites: The Ohio State University Medical Center (Columbus, OH); Northwestern University Prentice Women's Hospital (Chicago, IL); and University of Miami Jackson Memorial Hospital (Miami, FL). The study will assess the predictive value of SNAP II versus BIS VISTA indices at various anesthetic states in patients undergoing general anesthesia (preinduction, loss of response, maintenance, first purposeful response, and extubation). The SNAP II and BIS VISTA electrode arrays will be placed on the patient's forehead on opposite sides. The hemisphere location for both devices' electrodes will be equally alternated among the patient population. The index values for both devices will be recorded and correlated with the scorings received by performing the Modified Observer's Assessment of Alertness and Sedation and the American Society of Anesthesiologists Continuum of Depth of Sedation, at different stages of anesthesia.

Results: Enrollment for this study has been completed and statistical data analyses are currently underway.

Conclusions: The results of this trial will provide information that will simultaneously compare the performance of SNAP II and BIS VISTA devices, with regards to monitoring different anesthesia states among patients.

ClinicalTrial: Clinicaltrials.gov NCT00829803; https://clinicaltrials.gov/ct2/show/NCT00829803 (Archived by WebCite at http://www.webcitation.org/6nmyi8YKO)

(JMIR Res Protoc 2017;6(2):e15) doi:10.2196/resprot.6741

KEYWORDS

Bispectral index; SNAP II; BIS VISTA; EEG monitoring

Introduction

Anesthesiologists have relied on patients' somatic signs (motor response, alteration in respiratory patterns) and autonomic signs (hypertension, tachycardia, lacrimation, sweating), and eliciting responses using tactile and verbal stimulation when assessing patients' depth of anesthesia and comfort level [1,2]. Based on this data, anesthetic agents are used to achieve hypnotic effects, blocking somatic motor response and suppressing autonomic response to noxious stimulation [1,2]. Although objective physiological signs are easy to observe in nonresponsive patients, these signs may be nonspecific [1].

Intraoperative awareness has been a concern among surgical patients undergoing anesthesia and it may be responsible for postoperative major depression and/or suicide secondary to posttraumatic stress disorder [3,4]. The incidence of intraoperative awareness is approximately 0.1-0.2% among the general surgical population, and approximately 1% among patients with reduced cardiac reserve, or those undergoing cardiac surgery or caesarean section [3-5].

Commercially available electrical monitors have been developed to enhance the assessment of patients' levels of consciousness, using both low- and high-frequency electroencephalogram (EEG) signals [6,7]. SNAP II is a single-channel EEG device that monitors brain activity [8], and is intended to monitor the state of the brain by acquiring EEG signals [9]. A derived measure provided by the SNAP II index indicates the patient's brain activity level [9]. The SNAP II index is based on a unique combination of low-frequency (0.1-40 hertz) and high-frequency (80-420 hertz) EEG analysis that is processed for display in a time-based trend [8].

Conversely, the bispectral index (BIS) VISTA is a dual-channel EEG device that monitors brain activity [8]. The BIS VISTA index is based on bispectral analysis of the EEG [8]. BIS VISTA is a dimensionless number between 0 and 100 [8,10] (Table 1). The 40-60 range is suitable for surgical anesthesia, 0 indicates flat line EEG, and 100 indicates that the patient is fully awake [3,10-15]. SNAP II records a value every second, whereas BIS VISTA is usually set up to provide indices every 5 seconds [10,16]. Studies have shown that monitoring a patient's consciousness level during a procedure leads to a reduction in drug consumption, which helps in earlier recovery and reduces anesthesia-related adverse events [3,15,17].

This clinical study will provide information by simultaneously comparing the performance of SNAP II and BIS VISTA, by assessing their efficacy in monitoring different anesthetic states in patients undergoing general anesthesia.

Table 1. BIS VISTA index ranges [10].

Index	BIS VISTA
100	Awake: responds to normal voice
80	Light/moderate sedation: may respond to loud command or mild prodding/shaking
60	General anesthesia: low probability of explicit recall and unresponsive to verbal stimulus
40	Deep hypnotic state
20	Burst suppression
0	Flat line electroencephalogram

Methods

This is a multicenter, prospective, double-arm, parallel assignment, single-blind study involving patients undergoing elective surgery that requires general anesthesia. The study will examine the predictive value of Stryker Instruments' SNAP II versus the BIS VISTA indices at various anesthetic states during a surgical procedure under general anesthesia.

Information obtained during the study will be used to identify and evaluate the benefit of using SNAP II in different types of surgical procedures. This data will include electronic records from the devices undergoing study, electronic records from physiological monitor(s), the anesthesia provider's notes, case notes from a clinical observer, patient demographic information (gender, age, weight, height, medical history, and handedness), and record of Post-Anesthesia Care Unit (PACU) follow-up.

The primary objective of this study is to establish the range of index values for the SNAP II corresponding to each anesthetic state (preinduction, loss of response, maintenance, first purposeful response, and extubation). The secondary objectives will assess the range of index values for BIS VISTA corresponding to each anesthetic state compared to published

BIS VISTA range information, and estimate the area under the curve (AUC), sensitivity, and specificity for both devices.

After Institutional Review Board (IRB) approval, all clinical investigation sites will enroll a total of 40 patients. All surgeries will be performed at the following sites: The Ohio State University Medical Center (Columbus, OH); Northwestern University Prentice Women's Hospital (Chicago, IL); and University of Miami Jackson Memorial Hospital (Miami, FL).

Eligibility requirements include: patients 18 to 65 years of age, American Society of Anesthesiologists (ASA) physical status classification system I-III, body mass index <40, weight >41 kilograms, undergoing elective surgery (expected length <4 hours) under general anesthesia, and signing informed consent. Exclusion criteria include: prisoners, pregnant women, taking psychoactive medication within the past 7 days, known alcohol or narcotic abusers within the last 6 months or reporting narcotic use 24 hours prior to surgery, history of any adverse incident with anesthesia, head or neck surgery, recent trauma, active seizure disorder, dementia, Alzheimer's disease, or active infection.

Data collection for all devices in the study (SNAP II, BIS VISTA, and the physiological monitor) will be performed electronically, enabling the monitors to record case events. Case event recording will be done using a master clock (operating room wall clock) synchronized with the SNAP II device, the BIS VISTA device, the physiological monitor, or a laptop computer used to collect data from the physiological monitor.

Clinical consciousness assessments will be standardized using the Modified Observer's Assessment of Alertness and Sedation (MOAAS; Table 2 [18]) and the ASA Continuum of Depth of Sedation (Table 3 [19]) criteria.

Table 2. Modified Observer's Assessment of Alertness and Sedation Scale.

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Table 3. American Society of Anesthesiologists Continuum of Depth of Sedation.

	Minimal Sedation (Anxiolysis)	Moderate Sedation/ Analgesia (Conscious Sedation)	Deep Sedation/ Analgesia	General Anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response following repeated or painful stimulation	Unarousable even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

Five anesthetic states will be monitored in this study, as follows:

1. Preinduction baseline: time between application of the electrodes and induction.

2. Loss of response: occurs within the induction phase of anesthesia, defined as the period of time starting with the delivery of the induction agents and ending at the beginning of maintenance. During anesthesia induction, patients will be instructed to hold onto a weighted object as long as possible using a supinated hand. The moment that the object is dropped will be considered the *loss of response* time.

3. Anesthesia maintenance: this time starts 10 minutes after completion of induction medication administration, and ends when the anesthetic agent delivery stops.

4. First purposeful response: defined as a definitive response after anesthesia is discontinued and the MOAAS score is >1 and ASA status is *deep sedation* or lighter.

5. Extubation or laryngeal mask airway (LMA) removal: as per meeting clinical criteria for extubation or discontinuation of the LMA.

Delivery of anesthesia will be standardized, and the use of anesthetic agents will be controlled and carefully documented during the study to avoid confounding results. Tapering of inhalation agents in anticipation of the end of a surgical case will not be allowed, as this could skew study results. Allowable agents for this study are outlined in Textbox 1.

Textbox 1. Agents eligible to be used in the study.

- Preinduction (anxiolytics) agents such as Versed (0.04 milligrams/kilogram, maximum 2 milligrams).
- Induction agents such as propofol (2 milligrams/kilogram) delivered as a continuous infusion at the rate of 300 micrograms/kilogram/minute; succinylcholine is optional for endotracheal tube placement only.
- Prior to intubation or LMA placement, use up to 0.5 micrograms/kilogram fentanyl, plus timely delivery of succinylcholine if needed.
- After the administration of fentanyl, face mask ventilation (FMV) will be performed with sevoflurane (1.0-1.5 minimum alveolar concentration adjusted per age) for 3 minutes. Partial pressure of carbon dioxide <50 mmHg and minimum peripheral capillary oxygen saturation of 94% will be maintained. Nitrous oxide is not allowed.
- After 3 minutes of FMV, intubation or LMA placement will be performed.
- Optional agents will be used as per investigator criteria and ondansetron (4 milligrams intravenous) and/or other antiemetic will be administered for postoperative nausea and vomiting prophylaxis. Fentanyl will be used as a narcotic only (not as induction or maintenance agent) for intraoperative analgesia. Analgesia upon PACU arrival will follow institutional standard operational procedures (may use drugs other than fentanyl) or toradol (30 milligrams intravenous) will be used as an alternative.
- The following agents/techniques are not allowed during the study: ketamine, total intravenous anesthesia, and prolonged use of neuromuscular blocking agents beyond dose required for intubation or LMA placement.

Electronic and Clinical Consciousness Level Monitoring

Placement of SNAP II and BIS VISTA electrode arrays will be based on the manufacturers' recommended locations (as instructed on electrode packaging materials) and never on the same side of the forehead. Placement of the electrode arrays (left or right) will be allocated based on the study patient number indicated by the study design: even patient numbers will have the SNAP II electrode placed on the right side and the BIS VISTA electrode on the left, and odd patient numbers will have the SNAP II electrode placed on the left side and the BIS VISTA electrode on the right. SNAP II electrodes will be placed as follows: circle number 1 (or number 3) at the center of the forehead above the nose approximately 1.5 inches (approximately 4 centimeters) above the bridge of the nose; circle number 2 (middle sensor) over the arch of the eyebrow; and circle number 3 (or number 1) at the end of the eyebrow line just above the temple. BIS VISTA electrodes will be placed as follows: circle number 1 at the center of the forehead, approximately 2 inches (approximately 5 centimeters) above the nose; circle number 4 directly above and parallel to the eyebrow; and circle number 3 on the temple area between corner of eye and hairline.

Preoperative baseline indices from SNAP II and BIS VISTA monitors will be collected to assess the baseline indices and sensors' impedance checks. Prior to the baseline indices, an impedance check for both devices will be performed and manually recorded. The SNAP II electrode impedances will be checked with a third-party impedance meter to assess the stability of the indices (<10% variation). These preoperative readings will be obtained in the preoperative holding area or in the operating room ten minutes after placing the electrodes from both devices, and before the administration of midazolam; the SNAP II and BIS VISTA baseline index readings will be collected and manually recorded 4 times in a 15 second interval. Consequently, baseline MOAAS and ASA assessments will be performed.

Upon the patient's arrival in the operating room, electrode impedances from both devices will be checked and recorded again to assess the stability of the indices. Preinduction MOAAS and ASA assessments will be performed, then both electrodes will be connected to their respective monitors before induction time, to assess the indices from both devices 4 times in a 15 second interval.

After the patient shows a loss of response, 4 MOAAS and ASA assessments will be performed at 15 second intervals to confirm the loss of response event. In addition, a manual impedance check of both devices will be performed, and time and value will be recorded to confirm the stability of the indices.

After intubation or LMA placement, MOAAS and ASA assessments will be performed every 2 minutes until sevoflurane administration is discontinued. Furthermore, the time and description of all significant events or maneuvers/procedures performed during maintenance will be recorded.

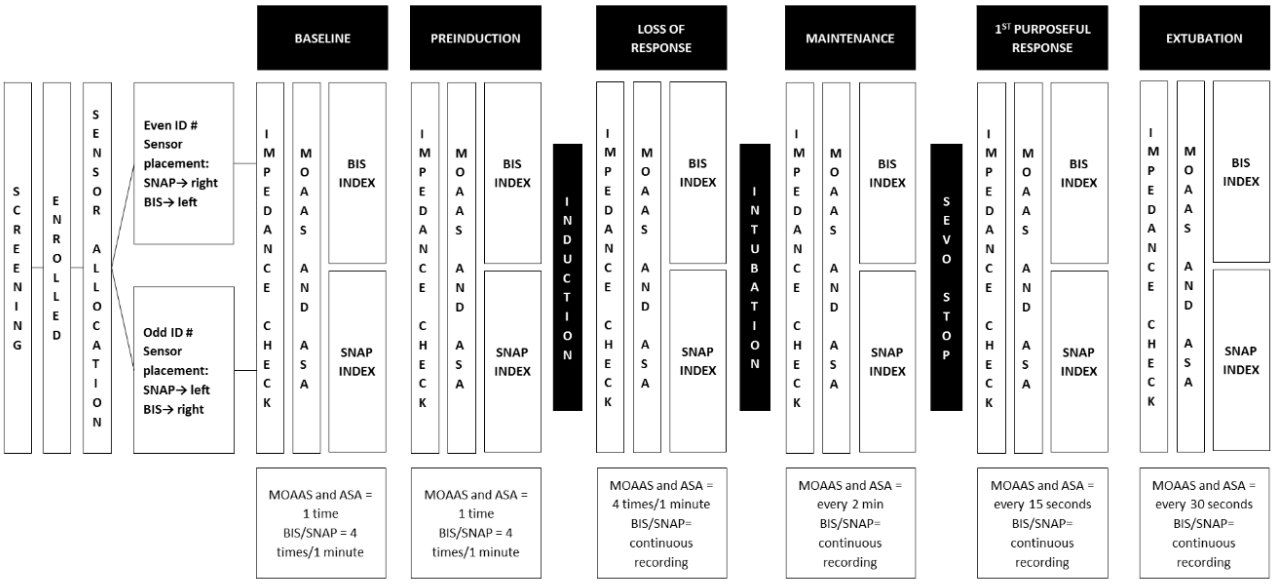
Prior to sevoflurane discontinuation, additional impedance checks will be performed on both devices, and the corresponding times and values will be recorded. At incision closure, sevoflurane administration will be discontinued (tapering of sevoflurane will not be allowed). Consequently, MOAAS and ASA assessments will be performed every 15 seconds until the first purposeful response is observed. From this moment, these assessments will be performed every 30 seconds until patients meet clinical criteria for extubation or LMA removal. Additionally, impedance checks will be performed and recorded immediately before extubation or LMA removal time. The study procedure is outlined in Figure 1.

Postsurgical pain assessment will be conducted upon PACU arrival by using a numeric pain rating scale, and asking the patient to rate their pain ranging from 0 to 10: 0 indicates no pain and 10 indicates the worst possible pain. PACU discharge will be determined by institutional standard of practice.

There is no patient follow-up in this study beyond pain assessment in the PACU. Any deviations from the protocol will be documented and the appropriate report will be submitted to the participating IRB and sponsor. All postoperative complications/concurrent medical events and follow-up on existing complication/adverse events will be documented and

reported accordingly. The investigator will immediately notify the monitor and the sponsor regarding all adverse product-related events until the patient's admission to PACU. The event is to be appropriately documented by the investigator on a serious adverse event form.

Figure 1. Procedural flow chart. BIS: bispectral index; ASA: American Society of Anesthesiologists Continuum of Depth of Sedation; MOAAS: Modified Observer's Assessment of Alertness and Sedation; SEVO: Sevoflurane.



Statistical Methods

In this study, for a given pair of clinical states, our goal is to choose a threshold in SNAP II values that best distinguishes the two states, and to precisely estimate the accuracy associated with this threshold. We define this accuracy as the average of the sensitivity and specificity (if an equal number of values for both states exist, this is simply the proportion of the index values during both states correctly classified). This accuracy calculation will first be done for each patient, and then the patient-level accuracies will be averaged to determine an overall estimate of accuracy. We assume an overdispersed binomial variance, which depends not only on the true accuracy but also on a within-patient correlation of the correct classification indicator variables. We will calculate the standard deviation of the overall estimated accuracy under varying values of number of patients, number of SNAP II index values per patient per state, true mean accuracy, and within-patient correlation. Assuming the true accuracy is 0.95, the number of index values per state is at least 10, and the within-patient correlation is 0.25, a sample of 30 patients will result in a standard deviation of approximately 0.02, which we deem sufficiently small.

There are four pairs of clinical states that we wish to distinguish using the SNAP II index values. For each pair of states, the nonparametric estimate of the area under the receiving operating characteristic (ROC) curve will be computed at the patient-level. An overall AUC will be computed as the average of the patient-level values. Confidence intervals (95%) will be computed as mean (standard error 1.96), where the standard error of the mean is based on patient-level values. An overall ROC curve for each pair of states will be estimated by pooling observations across patients. Ranges of typical index values for each of the 5 clinical states will be identified and reported. Correlation between MOAAS values and the SNAP II and BIS VISTA index values will be assessed with the nonparametric Spearman's rank-based correlation. Only the index value closest in time to each MOAAS value will be used in estimating this correlation. In addition, box plots of SNAP II and BIS VISTA index values versus MOAAS values will be created. Plots showing SNAP II and BIS VISTA index values over time for each patient, with annotated clinical states, will also be created.

Both BIS VISTA and SNAP II index values will be assigned to a clinical state based on the time of index value collection. Only values of SNAP II and BIS VISTA taken at the same time will be used. SNAP II records a value every second, whereas BIS VISTA records a value every 5 seconds, so every fifth SNAP II value will be used in analyses [10,16]. For baseline, loss of response, maintenance, first purposeful response, and extubation, the 10 values of BIS VISTA immediately following the clinical event (covering approximately 50 seconds of time) and the 10 matching SNAP II values will be assigned to that state. All BIS VISTA values and matching SNAP II values obtained from 10 minutes after loss of consciousness until the inhalation anesthesia is turned off will be assigned to maintenance state.

Results

Enrollment for this study has been completed and statistical data analyses are currently underway.

Discussion

This part of the study will be elaborated when data analyses are completed. The results of this clinical trial will provide information by simultaneously comparing the performance of

SNAP II and BIS VISTA by assessing their efficacy in monitoring different anesthetic states in patients undergoing general anesthesia. Due to the complexity of the study procedures and anesthesia regimen used for this trial, we anticipate a moderate to high incidence of screen failures during enrolment.

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Authors' Contributions

SB participated in literature searches, study design, methodology, data collection, and manuscript writing. AU participated in methodology, data collection, and manuscript writing. EP participated in literature searches, study design, methodology, and manuscript writing. RM, RS, and KC participated in data collection. RK and SD participated in literature searches, study design, and methodology.

Conflicts of Interest

This study was funded by Stryker Corporate.

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Abbreviations

ASA: American Society of Anesthesiologists
AUC: area under the curve
BIS: bispectral index
EEG: electroencephalogram
FMV: face mask ventilation
IRB: Institutional Review Board
LMA: laryngeal mask airway
MOAAS: Modified Observer's Assessment of Alertness and Sedation
PACU: Post-Anesthesia Care Unit
ROC: receiving operating characteristic

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Protocol

Irreversible Electroporation for the Ablation of Renal Cell Carcinoma: A Prospective, Human, In Vivo Study Protocol (IDEAL Phase 2b)

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Abstract

Background: Irreversible electroporation (IRE) is an emerging technique delivering electrical pulses to ablate tissue, with the theoretical advantage to overcome the main shortcomings of conventional thermal ablation. Recent short-term research showed that IRE for the ablation of renal masses is a safe and feasible treatment option. In an ablate and resect design, histopathological analysis 4 weeks after radical nephrectomy demonstrated that IRE-targeted renal tumors were completely covered by ablation zone. In order to develop a validated long-term IRE follow-up study, it is essential to obtain clinical confirmation of the efficacy of this novel technology. Additionally, follow-up after IRE ablation obliges verification of a suitable imaging modality.

Objective: The objectives of this study are the clinical efficacy and safety of IRE ablation of renal masses and to evaluate the use of cross-sectional imaging modalities in the follow-up after IRE in renal tumors. This study conforms to the recommendations of the IDEAL Collaboration and can be categorized as a phase 2B exploration trial.

Methods: In this prospective clinical trial, IRE will be performed in 20 patients aged 18 years and older presenting with a solid enhancing small renal mass (SRM) (≤4 cm) who are candidates for ablation. Magnetic resonance imaging (MRI) and contrast-enhanced ultrasound (CEUS) will be performed at 1 day pre-IRE, and 1 week post-IRE. Computed tomography (CT), CEUS, and MRI will be performed at 3 months, 6 months, and 12 months post-IRE.

Results: Presently, recruitment of patients has started and the first inclusions are completed. Preliminary results and outcomes are expected in 2018.

Conclusions: To establish the position of IRE ablation for treating renal tumors, a structured stepwise assessment in clinical practice is required. This study will offer fundamental knowledge on the clinical efficacy of IRE ablation for SRMs, potentially positioning IRE as ablative modality for renal tumors and accrediting future research with long-term follow-up.

Trial Registration: Clinicaltrials.gov registration number NCT02828709; https://clinicaltrials.gov/ct2/show/NCT02828709 (archived by WebCite at http://www.webcitation.org/6nmWK7Uu9). Dutch Central Committee on Research Involving Human Subjects NL56935.018.16

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KEYWORDS

irreversible electroporation; IRE; ablation; kidney; renal cell carcinoma; cancer; safety; efficacy

Introduction

Ablative Therapy in Renal Cell Carcinoma

Due to widespread detection of small renal masses (SRMs), a gradual but sustained rise in incidence of renal tumors 4 cm or less (cT1a, according to the TNM [tumor/node/metastasis] staging system) has been observed [1-4]. At present, the reference standard therapy in the management of SRMs is nephron sparing surgery like partial nephrectomy [5]. However, a significant interest is sparked in minimally invasive therapies, including cryoablation and radiofrequency ablation (RFA). Literature shows that thermal ablation compared to partial nephrectomy is characterized by a slightly higher recurrence rate but also accompanied by a lower complication rate [6,7]. Nevertheless, a growing body of research advocates that in selected patients similar oncological results can be obtained compared to those accomplished in surgical resection [8]. Current guidelines recommend primary ablative therapy in patients who are (1) not suitable for surgery, (2) have a genetic predisposition for developing multiple tumors, and (3) are diagnosed with bilateral tumors or have a solitary kidney and are at risk of complete loss of renal function after surgery [9-11].

Ablation of undesirable tissue depends on accurate dosing and adequate targeting of tumor destruction while sparing vital structures such as adjacent organs, collecting system, or major vessels [12,13]. Due to temperature fluctuations that are accompanied with the thermal character of cryoablation and RFA, it is thought that the destruction process of the tumor is unselective [14,15]. Ablation effects and tissue heating may be less effective in proximity to blood vessels as a result of thermal drainage by regional vascular flow impairing the extent of coagulation, in the literature termed as a “heat sink” effect [9,16]. Additionally, collateral damage to underlying vital structures can occur, as the natures of these structures are susceptible to extreme temperatures. Therefore according to guidelines, renal tumors located near the hilum or near the proximal ureter are not suitable for thermal ablation, forming a niche in ablative treatment of renal tumors [10].

Irreversible Electroporation in Renal Cell Carcinoma

An emerging technique among the assortment of ablative modalities is called irreversible electroporation (IRE). It is based on high-voltage electrical pulses transferred between 2 or more needle electrodes. Charging the cell membrane causes holes in the membrane called nanopores, resulting in increased permeability of the cell and subsequent cell death [13,17-20].

Theoretically, the mechanism of action of IRE does not rely on temperature changes. Therefore it has been postulated that it has the potential to overcome the current limitations of thermal ablative modalities like cryoablation and RFA [12]. However, using the current clinical device settings, a rise in temperature is to be expected as shown by Wagstaff et al in an animal model [21].

With regard to IRE ablation in renal tumors, 4 studies have been performed in humans [20,22-24]. All studies concluded that safety of IRE in humans is warranted as long as electrocardiogram (ECG) synchronization is used.

Trimmer et al made a start in clinical efficacy, describing postablation features on cross-sectional imaging. Although these initial results seem promising and appear similar to conventional ablative techniques, a few limitations deserve consideration. The study design is retrospective, and the follow‐up was limited. Imaging was available in 15 out of 20 patients (75%) at 6-month follow-up and only in 6 out of 20 patients (30%) at 1-year follow-up [23].

Thomson et al performed IRE in various organs, including 10 renal tumors in 7 patients. One patient (14%) developed an ureteral stricture after IRE ablation in an area of the ureter that previously had been obstructed by RFA. Other centrally located tumors did not show any major complications. A total of 2 patients (29%) experienced minor complications consisting of transient hematuria [24]. Wendler et al were the first to provide histopathological data of IRE in renal tumors of 3 patients, showing complete coverage of the tumor within the ablation zone with preservation of the renal parenchyma [25]. Very small tumor residues of unclear malignant potential were found within the ablation zone. Unfortunately, clinical significance of these residues remained unclear and impossible to follow up since the tumors had been resected.

Rationale

The first human studies have proven the safety of IRE for the ablation of SRMs. Initial results on clinical efficacy of IRE are promising and imply that effective oncological management is achievable. Clinical outcomes should be investigated in a small patient population to provide essential data before embarking on a randomized trial. We therefore plan to perform a study aiming at the clinical efficacy and safety of IRE in SRMs, with a specific focus on postablation follow-up with cross-sectional imaging. Research on IRE in liver tumors has demonstrated that ablation success of IRE decreases with tumor size above 4 cm [24]. According to current guidelines, ablative treatment is only offered to patients with SRMs (≤4 cm) [10]. Therefore, we aim to investigate IRE ablation in renal masses up to 4 cm. This prospective, human, in vivo trial is an essential step in order to safely progress to larger randomized trials on IRE of SRMs. This study conforms to the recommendations of the IDEAL (idea, development, exploration, assessment, long-term study) Collaboration and can be categorized as a phase 2B exploration trial [26] .

Methods

Study Objectives

- To determine the clinical efficacy of IRE ablation for SRMs (≤4 cm) assessed by the recurrence and residual disease rate at follow‐up using cross‐sectional imaging

- To evaluate the use of computed tomography (CT), magnetic resonance imaging (MRI), and contrast-enhanced ultrasound (CEUS) in the visualization of (non)complete ablation to assess the radiological extent of the ablation zone at 1 week, 3 months, 6 months, 9 months and 1 year after IRE
- To evaluate perioperative outcomes after IRE ablation of SRMs (≤4 cm) such as (1) renal function, measured by creatinine levels and estimated glomerular filtration rate (eGFR), (2) average length of hospital stay, (3) quality of life, and (4) postoperative pain score after IRE, measured by a visual analog scale (VAS) and analgesics use
- To determine the safety and feasibility of IRE ablation of SRMs (≤4 cm) by evaluating device and procedural adverse events using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

Population

A total of 20 patients with solid enhancing SRMs on cross-sectional imaging qualifying for ablative therapy will be enrolled in this study. Eligible patients are 18 years of age and older and will receive a biopsy of the SRM before procedure. All inclusions are reviewed for safety and eligibility by a nephrologist participating in the research project. The inclusion and exclusion criteria for this study are listed in Textbox 1.

Textbox 1. Selection criteria. Severe cardiovascular disease is defined as the diagnosis of myocardial infarction, uncontrolled angina, significant ventricular arrhythmias, stroke or severe cardiac failure (New York Heart Association class III and IV) within 6 months prior to inclusion.

Inclusion criteria:

- Age 18 years and older
- Solid enhancing SRM on cross-sectional imaging
- Candidate for ablation
- Signed informed consent

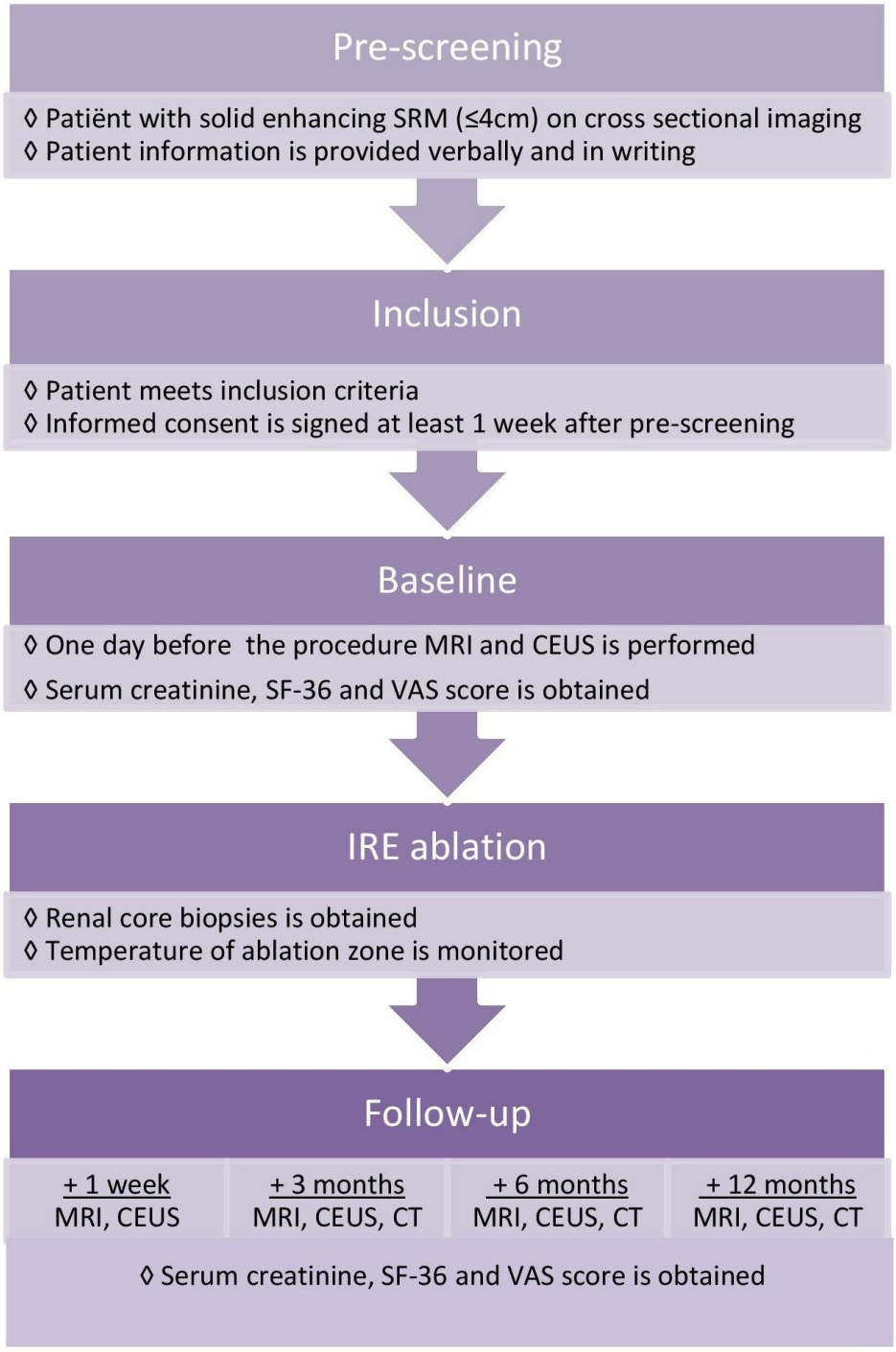
Exclusion criteria:

- Irreversible bleeding disorders
- Inability to stop anticoagulation therapy
- Implantable cardioverter-defibrillator or pacemaker
- Severe cardiovascular disease

Study Design

This is a prospective, human, in vivo study among 20 patients presenting with solid enhancing SRM on cross-sectional imaging suspect for RCC. Preoperatively, imaging is required through CT, MRI, and CEUS. Furthermore, serum creatinine levels and VAS scores are obtained. A biopsy of the SRM will be performed prior to the ablation. IRE ablation will be performed using CT guidance, and ablation success will be measured directly after the ablation through contrast-enhanced CT. Device-related adverse events will be registered using the CTCAE version 4.0 guideline. At 1 week postablation, only CEUS and MRI will be performed to limit exposure to ionizing radiation. At 3 months, 6 months, and 12 months postablation, CEUS, MRI, and CT will be performed. Additionally at these time points, serum creatinine levels and VAS scores will be obtained, and quality of life will be assessed through Short Form 36 (SF-36) questionnaires. Residual and recurrent disease will be assessed through tissue enhancement on cross-sectional imaging. When imaging appears suspicious for recurrence or residual disease, a percutaneous renal core biopsy will be performed. A study flowchart demonstrating the investigations is outlined in Figure 1.

Figure 1. Study design flowchart.



Study Procedures

Renal Core Biopsy (Standard)

According to the ablation protocol of the Academic Medical Center University Hospital, percutaneous renal core biopsies will be obtained prior to the IRE procedure if patient desires. At least 2 core biopsies will be acquired for pathological examination.

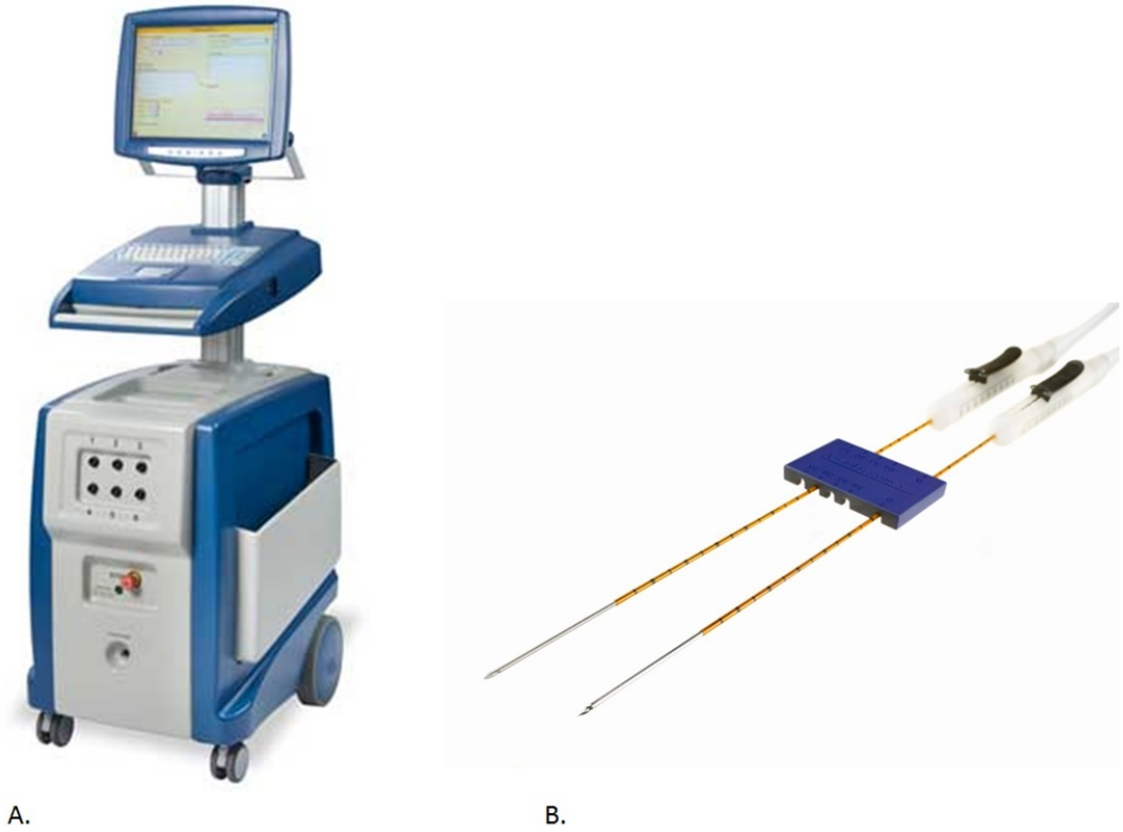
Irreversible Electroporation Ablation (Study Intervention)

In this study, IRE ablation is performed using the NanoKnife IRE device (AngioDynamics Inc) (Figure 2, A), also registered as the HVP-01 electroporation system. The IRE system contains a low energy direct current generator, a foot switch, and 19G monopolar needle electrodes (15 or 25 cm length). Regulatory authorities have approved both the device and the electrodes through a Conformité Européenne certificate for the use of cell membrane electroporation. Additionally, the US Food and Drug Administration has granted 510(k) clearance with premarket notifications (K060054, K080202, K080376, K080287). Granted 510(k) components are all approved for surgical ablation of soft tissue.

The IRE procedure will be performed at the radiology department CT room with the patient under general anesthesia including deep muscle relaxation to prevent severe muscle contraction [27]. CT imaging will be performed with the patient in the prone or lateral position, dependent on tumor location and position of adjacent organs such as intestines. An interventional radiologist cooperating with a urological surgeon, both experts on percutaneous ablative procedures, will perform the IRE procedure. IRE pulses will be synchronized with ECG under supervision of an anesthesiologist. Prior to ablation, a (second) set of biopsies will be obtained to confirm histopathology. Guided by CT and accompanied by an external spacer for fixation, needle electrodes will be placed (Figure 2, B). The amount of probes and probe placement will be attuned for specific tumor size and location, granting 15 mm between the electrodes with an active tip length of 15 mm. IRE pulses with pulse intensity of 1500 V/cm will be delivered in 90 consecutive pulses of 90 µs . Settings are used to disrupt the cell membrane potential in order to achieve irreversible permeability of the cell and subsequent apoptosis. Van den Bos et al demonstrated that with current settings the ablation zone is completely ablated without leaving any skip lesions within the electrode configuration [28].

The primary cycle of IRE will take 5 to 10 minutes with a total operating time (including anesthesia) of approximately 90 minutes. Immediately after IRE has been performed, a contrast-enhanced CT will be made to assess adequate ablation. It is expected that patients will be discharged 24 to 36 hours after the IRE procedure. Before patient's discharge, quality of life and postprocedural pain will be assessed through SF-36 questionnaire and VAS score respectively. At 1 week after the procedure, VAS score and SF-36 questionnaire will be obtained and cross-sectional imaging by CEUS and MRI will be performed.

Figure 2. A. The NanoKnife IRE console. B. The console operates with 19G monopolar needle electrodes, which are bundled together using the external spacers.



Computed Tomography Imaging (Standard)

As provided per ablation protocol, CT imaging will take place during the diagnostic phase and during the procedure. According to our ablation surveillance protocol, follow-up CT imaging will be performed at 3 months, 6 months, 1 year, 1.5 year, 2 years, 2.5 years, and 3 years after IRE ablation. After this, patients will be followed up yearly up to 10 years. This is the standardized follow‐up after ablative therapy at our institution (see Figure 1). Patients with an eGFR below 60 mL/min/1.73 m^2 will undergo pre- and posthydration in order to prevent contrast-induced nephropathy. Patients with an eGFR below 30 mL/min/1.73 m^2 are excluded from CT imaging.

CT imaging will be performed in a supine position in a dual source CT system, SOMATOM Force (Siemens Medical Solutions), or in a Sensation 64-slice CT scanner (Siemens Medical Solutions). First, a survey scan from the upper border of the diaphragm to the ischium bone will be made. Next, noncontrast series in the same section will be performed. Subsequently, 120 mL of Ultravist-300 diluted with NaCl 0.9% will be administered intravenously with a speed of 4 mL/s. Following contrast injection, arterial, venous, and delayed series will be obtained after 45 seconds, 115 seconds, and 600 seconds, respectively. Source images will be recontructed in coronal and sagittal planes using multiplanar reconstruction in the venous and delayed series.

Contrast-Enhanced Ultrasound and Magnetic Resonance Imaging (Study Intervention)

Baseline CEUS will take place 1 day before IRE, and 1 week, 3 months, 6 months, and 12 months after IRE. MRI imaging will take place 1 week, 3 months, 6 months, and 12 months post-IRE (see Figure 1). This frequency was established in order to assess lesion size and characteristics.

CEUS imaging encompasses microbubbles of 3 to 5 μm as a contrast agent to visualize blood flow. The phospholipid-coated microbubbles demonstrate regional tissue vascularization, including the tissue-specific microvasculature. This study uses a Philips iU22 (Phillips Healthcare) device united with a third-generation intravenous ultrasound contrast agent (SonoVue) for optimal imaging. Sonovue contrast agent is characterized by a distribution half-life of 1 minute and an elimination half-life of 6 minutes when intravenously administered [29].

MRI will be performed with the patient in the supine position using a 1.5 Tesla AVANTO MRI scanner (Siemens Healthcare) with a 16-channel body matrix array coil. According to our kidney tumor protocol, a minimum of 9 sequences will be performed: T2-trufi with fat suppression, T1-fl2d contrast-enhanced in and out of phase, T2-haste, T1-vibe unenhanced, and dynamic series at 30 seconds, 60 seconds, and 15 minutes . Intravenous contrast agent Gadovist (Bayer Pharma) of 0.1 mmol per kg of body weight will be administered for enhancement.

Sample Size

Our sample size was deliberated on the basis of previous similar study designs that used comparable sample sizes of 6 to 20 patients [20,23-25]. In this phase of research (phase 2B IDEAL Collaboration), a small cohort of N=20 was chosen to acquire first results in order to progress to a large trial. A sample size of 20 patients does not permit reliable comparative statistical analysis. In this study, IRE is intended as a curative therapy. Consequently, there will be no exploration in number of probes and configuration settings. Hence, analysis will be restricted to averages and standard deviations of assessed radiologic features.

Potential Benefits and Risks

Conventional focal ablative therapies, RFA and cryoablation, are indicated in patients presenting with an SRM who are poor surgical candidates or who are genetically predisposed to develop multiple tumors. For this study, IRE ablation will be offered to this group of patients in our institution. Early research into renal IRE has proven that the procedural safety and the periprocedural burden are comparable to conventional ablative therapies. The lack of long-term oncological follow-up poses a potential risk as patients cannot be counseled on the risk of residual or recurrent tumor. Post-IRE follow-up will be equal to postcryoablation and post-RFA follow-up and therefore does not carry additional burden with regard to ionizing radiation. When renal function appears to decrease to eGFR below 30 mL/min/1.73 m^2, only MRI and CEUS will be performed to prevent contrast-induced nephropathy. Furthermore, potential risks associated with IRE ablation for renal tumors using the NanoKnife system are listed in Table 1.

Table 1. Potential risks associated with irreversible electroporation of renal tumors.

Potential hazards	Potential effects
Excessive energy delivery	Muscle contraction, burn, damage to critical anatomical structure, unintended tissue ablated, bradycardia/hypotension, vagal stimulation/asystole, electrical shock, myocardial infarction, stroke, death
Insufficient/no energy delivery	Ineffective ablation, no ablation
Unintended mains or patient circuit voltage exposure to patient or user	Electrical shock
Incorrect timing of pulse delivery	Transient arrhythmia, prolonged arrhythmia, stroke, death
Unintended interference with implanted devices containing electronics or metal parts	Myocardial infarction, stroke, death
Unexpected movement of the device and displacement of the electrodes	Hypotension, damage to critical anatomical structure, pneumothorax, mechanical perforation, hemorrhage, unintended tissue ablated, electrical shock, death
Sterile barrier breach	Infection, sepsis

Data Safety Monitoring Board

The study will be monitored by a data safety monitoring board (DSMB) consisting of an independent urologist and a clinical epidemiologist. This team will monitor patient safety and treatment efficacy data during the study. Monitoring procedures are predetermined and described in the DSMB charter, approved by the institutional review board (IRB) of the Academic Medical Center University Hospital in Amsterdam. Additional DSMB meetings can be called at any time if deemed necessary by the DSMB or the principal investigator.

Analysis

The NanoKnife console produces 2-dimensional images including a prediction of the ablation zone, which is perpendicular to the needle. The AMIRA (FEI) software package system will bundle the 2-dimensional ablation zone cross-sections around the length of the exposed tip. This will estimate the following:

- Ablation zone volume (cm^3)
- 3-Dimensional reconstruction
- Ablation zone shape/symmetry

An experienced uroradiologist will evaluate CT and MRI images for the following characteristics *:*

- Volume of ablation zone (cm^3)
- Shape of ablation zone
- Residual tumor on ablation zone border
- Skip lesions or signs of recurrence within ablation zone
- Transition zone between ablated and normal renal tissue
- Damage to adjacent vital structures

For MRI and CT, whole-mount kidney and ablation zone will be calculated. The AMIRA software system will be used to obtain a 3-dimensional kidney and ablation zone. CEUS will be performed by an interventional radiologist and will be used for 2-dimensional imaging only.

Ethical Consideration

The IRB of the Academic Medical Center, Amsterdam, approved this study protocol (2016_055). The protocol has been registered with the Dutch Central Committee on Research Involving Human Subjects (NL56935.018.16) and is entered in the ClinicalTrials.gov database (NCT02828709). The study is conducted in accordance with the ethical principles and standards of Good Clinical Practice which have their origin in the Declaration of Helsinki (Fortaleza, Brazil, October 2013). Potential candidates will receive the study information both verbally and in writing. They will be granted at least 1 week to decide on participation. Written informed consent will be acquired from all participants. If deemed necessary, supplementary information will be provided verbally or in writing.

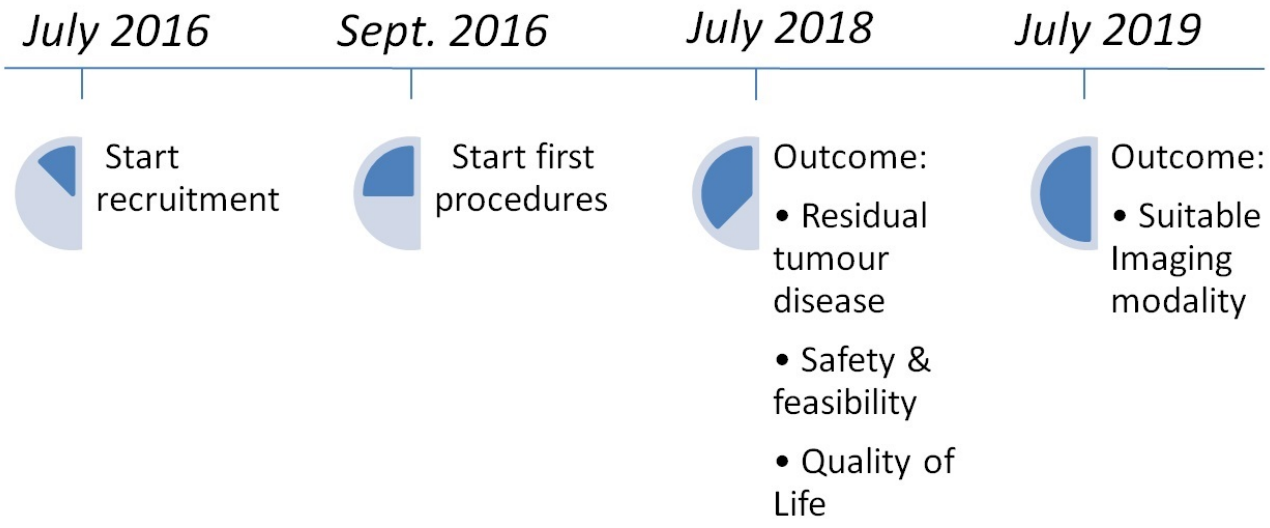
Availability of Data and Materials

The study initiator, international coordinating researcher, and biostatistician have access to all data. All data is available for audit, and all data will be published in an international peer-reviewed medical journal. The datasets created in the current study are not publicly available due to protecting the privacy of participants but are available from the corresponding author on reasonable request.

Results

At time of writing the trial is recruiting patients, with 2 inclusions completed. The expected inclusion rate is 1 patient every 6 weeks, resulting in an estimated inclusion period of 2 years. Hence we calculate that we will recruit the full sample size within 2 years. Additionally, early results on outcome of residual tumor disease, quality of life, and safety and feasibility will be acquired within 2 years (see Figure 3). The imaging follow-up in this study is 1 year for each patient (see Figure 1); therefore, we expect to complete the study in 2019.

Figure 3. Planned timeline of recruitment, enrollment, and outcome.



Discussion

Principal Findings

IDEAL phase 1 and 2A research into IRE in renal tumors has shown encouraging short-term outcomes, paving the way for small-scale follow-up studies. In our opinion, it is crucial to investigate the clinical efficacy of IRE in renal tumors to serve as a solid base for a large randomized trial. We aim to determine the clinical effect of IRE by assessing the presence of enhancement on cross-sectional imaging during follow-up as it is advised in thermal ablation [30]. Whereas IRE is a novel ablation technology, posttreatment radiological features in CT scan or MRI are still ill-defined. However, retrospective preliminary research suggests the radiological pattern is similar to the one described after thermal ablation [23].

Limitations

A limitation within our study is the absence of histopathological confirmation post-IRE. In literature, 2 in vivo studies have revealed the IRE ablation effects in a histopathologic analysis. The first study resected the renal tumor immediately after ablation, demonstrating preliminary IRE ablation effect on a cellular level. In this study no definite cell death was observed, implying that IRE effects are not directly established. Wendler et al resected the ablated tumors 4 weeks after the IRE procedure, showing that the ablation zone covered the renal tumors completely. Nonetheless, within the ablation zone very small residues of tumor have been found of uncertain malignancy [22] in 3 cases described. Studies in animal models have demonstrated that the effect of IRE is partially achieved after 3 to 4 weeks [31-33]. Yet resecting ablated RCCs in humans after longer than 4 weeks is not acceptable when ablation is used in curative setting. Hence, the only way to provide insight into the clinical value of these minimal tumor residues is to thoroughly follow patients with intensive imaging studies after IRE ablation. Despite the fact that biopsy during the follow-up targeting the ablation zone may contribute to histopathological confirmation, it would have brought additional burden in a fragile population and would not have been an irrefutable proof of complete ablation. Therefore, as provided by the consensus that ablation success in kidney tumors is assessed by radiological characteristics [30], success in our study will be assessed exclusively based on radiological features.

Conclusions

In our study, IRE parameters (1500 V/cm, active tip length 15 mm, interelectrode spacing 1 to 2 cm, 90 treatment pulses after 10 sufficient test pulses) were chosen because several studies confirmed that on a histopathological level the ablation zone is completely ablated within the electrode configuration without leaving skip lesions [25,28]. Due to the small sample size and the design of the study, we do not intend to explore different IRE configurations and probe settings.

IRE promises consistent ablation results due to its nonthermal character and is therefore theoretically suitable for centrally located tumors. However, recent literature has investigated the temperature rise of IRE ablation in porcine kidneys and livers, demonstrating a significant temperature rise when repetitive high-intensity pulses are applied [21,34]. Al-Sakere et al showed that when a high amount of energy is applied in a small number of pulses, significant rise in temperature occurs (a phenomenon called Joule heating). In current literature, a solution has been suggested in which the same amount of energy is applied in more pulses, which could result in a mild temperature increase [18,35]. Other factors that can influence the temperature in IRE ablation are varying voltage, pulse length, distance between electrodes, active tip length, and electrode configuration [35]. Furthermore, early clinical practice of IRE in renal tumors close to vital structures demonstrated that no major complications occurred, suggesting that thermal damage of IRE is not clinically significant, and centrally located tumors are suitable for IRE [24].

For the follow-up of renal masses, the most frequently used imaging modality is contrast-enhanced CT. Multiple studies have demonstrated that MRI and CEUS are adequate imaging techniques for follow-up after IRE [36-40]. However, the use of contrast-enhanced CT scan in the follow-up after kidney ablation might be precluded because of potential nephrotoxicity

or ionizing radiation exposure in young patients. In the population of patients that receive ablation for their renal mass comorbidity, older age and decrease in renal function are common since their presence entails a clear indication for ablative therapy. Furthermore MRI, applicable to a broader range of the ablated population, may not be easy available and may increase costs. Hence, in this population it is vital to investigate whether other imaging modalities will detect recurrences and residual disease in renal masses with the same accuracy as CT and MRI.

Nononcological outcomes of IRE have been minimally investigated in renal tumors. A total of 2 small studies described serum creatinine levels and demonstrated no significant changes in renal function or transient increase of creatinine which resolved after 1 month [23,24]. Postprocedural pain and length of stay is described by Thomson et al in liver, kidney, and lung (N=36, kidney tumors n=4). While 4 patients were admitted longer than 24 hours, none of these patients had kidney tumors. Postprocedural pain was registered through analgesics use, demonstrating 2 patients who required intravenous or intramuscular analgesics. No patient required prolonged analgesic use after discharge. Quality of life has not been reported in current IRE literature. Insight in nononcological outcomes, including quality of life, is urgently required since treatment decision making is often influenced by this. Particularly in the ablation population, meaning elderly patients with multiple comorbidities, quality of life after an intervention is of great importance.

Categorized as a level 2b study according to the IDEAL classification, this study will provide prospective information on kidney IRE ablation with an extensive description on the radiological evolution of the ablated lesion along time as well as mid-term oncological outcomes. Lastly, we will provide prospective data on quality of life, kidney function, pain level, and duration of admittance after IRE.

Acknowledgments

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Authors' Contributions

MB, KPvL, DMdB, JJMCHdlR, and MPLP conceived the trial concept and designed the protocol. PGKW, PJZ, OMvD, MJVS, and TGvL helped develop the trial design and protocol. MPLP is the principle investigator and responsible for trial design, protocol, and trial conduct. All authors aided in drafting the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

JJMCHdlR is a paid consultant to AngioDynamics Inc.

Multimedia Appendix 1

Peer-review report IRB (Dutch).

[PDF File (Adobe PDF File), 87KB - resprot_v6i2e21_app1.pdf]

Multimedia Appendix 2

Peer-review report IRB (English).

[PDF File (Adobe PDF File), 33KB - resprot_v6i2e21_app2.pdf]

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Abbreviations

CEUS: contrast-enhanced ultrasound
CT: computed tomography
CTCAE: Common Terminology Criteria for Adverse Events
DSMB: data safety monitoring board
ECG: electrocardiogram
eGFR: estimated glomerular filtration rate
IDEAL: idea, development, exploration, assessment, long-term study
IRE: irreversible electroporation
IRB: institutional review board
MRI: magnetic resonance Imaging
RFA: radiofrequency ablation
RCC: renal cell carcinoma
SF-36: Short Form 36
SRM: small renal mass
TNM: tumor/node/metastasis
VAS: visual analog scale

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Viewpoint

For You and Your Baby (4YYB): Adapting the Centers for Disease Control and Prevention's Text4Baby Program for Saudi Arabia

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Abstract

Background: Poor birth outcomes in the Kingdom of Saudi Arabia (KSA) have been found to be partially due to missed prenatal appointments as well as lack of knowledge of healthy pregnancy behaviors.

Objective: The objectives are to summarize birth outcomes and the antenatal care system in KSA, summarize research related to the US Text4Baby mobile health program, and outline the development of an Arabic version of the Text4baby app, For You and Your Baby (4YYB).

Methods: First, birth outcomes, health care access, and smartphone usage among Saudi Arabian women are reviewed. Next, the current evidence behind Text4Baby is described. Finally, a plan to develop and test 4YYB is proposed. In the plan, studies will need to be conducted to determine the effectiveness of 4YYB in educating pregnant Saudi women on healthy knowledge and behaviors. This will create an evidence base behind 4YYB before it is launched as a full-scale public health effort in KSA.

Results: The KSA offers public medical services but remaining challenges include poor birth outcomes and health care access barriers. An estimated 73% to 84% of Saudi women of child-bearing age use smartphone social media apps. A total of 13 published articles on Text4Baby were identified and reviewed. Due to design limitations, the studies provide only limited evidence about the effectiveness of the program in increasing healthy pregnancy knowledge and behaviors. To be useful for Saudi women, the educational messages in 4YYB will need to be translated from English to Arabic and tailored for cultural norms.

Conclusions: Developing the 4YYB Arabic-language app for use by pregnant Saudi Arabian women based on Text4Baby is a viable approach, but a rigorous study design is needed to determine its effectiveness in improving healthy pregnancy knowledge and behaviors.

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KEYWORDS

Saudi Arabia; telemedicine; text messaging; health knowledge, attitudes, practice; pregnant women

Introduction

Background

Although the health care system in the Kingdom of Saudi Arabia (KSA) is undergoing a dramatic expansion and there is a government-sponsored health system, not all health outcomes are being impacted optimally. There are remaining challenges with poor birth outcomes [1], and Saudi women still experience health care access barriers. Since a majority of Saudi women are users of smartphone social media apps [2], a mobile health platform for delivering messages to increase healthy pregnancy knowledge and behaviors could help address this important public health issue.

Text4Baby is a mobile health text messaging (short message service, SMS) program developed in the United States that has been disseminated nationally [3]. While Text4Baby has received much praise [3], the program has been criticized for lacking a scientific evidence base [4]. The aim of this paper is to discuss how we plan to adapt the Text4Baby program to serve Saudi Arabian women in an Arabic-language mobile app, For You and Your Baby (4YYB). The objectives of this paper are to summarize birth outcomes and the antenatal care system in KSA, summarize research related to the US Text4Baby mobile health program, and outline the development of an Arabic version of Text4Baby, 4YYB. Our hypothesis is that there are poor birth outcomes and obstetrical care in KSA, and a 4YYB program could improve this situation.

Poor Birth Outcomes in Saudi Arabia

KSA is currently challenged with unacceptably high rates of poor birth outcomes and neonatal complications in women. This includes issues with infants born with very low birthweight (VLBW), spontaneous preterm birth (SPTB), obstetric complications, unacceptable neonatal mortality rates, and other medical issues. This section will review the evidence regarding risk factors for poor birth outcomes in KSA.

Infants born at VLBW (defined as less than 1500 g) are at high risk for infant mortality, morbidity, and neurological developmental disabilities [5]. A 1994 case-control study of SPTB in Saudi Arabian women found associations with several risk factors including first or second trimester vaginal bleeding, previous preterm birth, consanguinity, low maternal body mass index, shorter interpregnancy interval, and inadequate prenatal care [6]. The authors concluded that “Awareness of such risk factors is essential in planning public education programs and in considering appropriate perinatal care options for women at potentially higher risk for preterm delivery” [6]. Another 1994 study of 880 pregnant Saudi Arabian women attending appointments at 75 primary health care centers found that 15.8% had experienced previous obstetric complications during their pregnancies and 12% experienced complications during delivery [7].

A 2001 study at King Abdulaziz University Hospital (KAUH) estimated the incidence of VLBW at 0.52% (133 out of 25,753 live births) over a 10-year period [1]. VLBW infants experienced an early neonatal mortality rate of 22.8% (21 out of 92 infants of gestational age 22 to 26 weeks) with 1 additional late neonatal death (gestational age 27 to 31 weeks), resulting in a total neonatal mortality rate of 23.9% (22 out of 92). [1]. In this study, the authors looked at maternal characteristics associated with 2 groups of VLBW infants with a gestational age of less than 32 weeks and found that the number of antenatal visits was only 2 on average [1].

A 2010 study of the prevalence of SPTB in Jazan, KSA, estimated it at 8.24% (34 of 420) [8]. The authors noted that this was “high compared to that in other cities in KSA and other developing countries” [8]. These authors identified 22 significant risk factors for SPTB in multiple regression analysis [8]. They recommended early identification of high-risk women for further management, which could bring about a decrease in both neonatal complications and health care expenditure [8]. However, it is important to recognize that Saudi women who do not encounter the health care system are unlikely to be identified as high-risk and receive necessary services.

Other authors have identified overlapping sets of risk factors for poor birth outcomes in KSA [5]. A 2014 study of anemia in 31 women of reproductive age attending an obstetrics and gynecology outpatient center at a university in Saudi Arabia reported that 64.7% of anemic respondents were pregnant, so anemia may be one of the risk factors for poor birth outcomes in KSA [9]. Another study in 2014 of 1182 postpartum women at a university hospital in Riyadh, Saudi Arabia, found that while 80% were aware of the negative effects of environmental smoke on the fetus, their knowledge of the specific effects on the fetus was lacking [10].

Overall, many of these articles point to the lack of prenatal care as a key risk factor [6]. As seen with the 2014 studies, health care interventions focused on eliminating anemia in pregnant women and counseling them on smoking cessation could be completed in the context of prenatal care. However, these are missed opportunities if pregnant women do not present for prenatal care. For example, Almalki studied reasons for missed appointments at maternal health care clinics in primary health care centers in Riyadh, noting that international rates of missed appointments range from 2% to 30% and are higher in maternal health care [11]. Almalki found that the 2 main reasons that women missed their appointments were lack of adequate tools at the medical clinic to do the examination (such as unavailability of a ultrasound machine, 143/200, 71.50%) and the unavailability of transportation (142/200, 71%) [11]. These barriers to completing a successful prenatal appointment may be enough to dissuade a woman from persevering through them.

Missed Appointments as a Risk Factor

As described earlier, 1 study quoted an average of 2 appointments in high-risk women prior to a VLBW infant being born, and 1 of the main reasons was lack of the availability of adequate tools for the examination [11]. This impacts the patient on the day the failed appointment takes place but can have future effects. Women who attend an appointment but cannot be served would likely be deterred from overcoming any barriers to attending future appointments, which would increase the risk of poor neonatal outcomes. While prenatal care is universally available, arranging transportation for women in KSA can be difficult and presents a barrier to attending appointments [11].

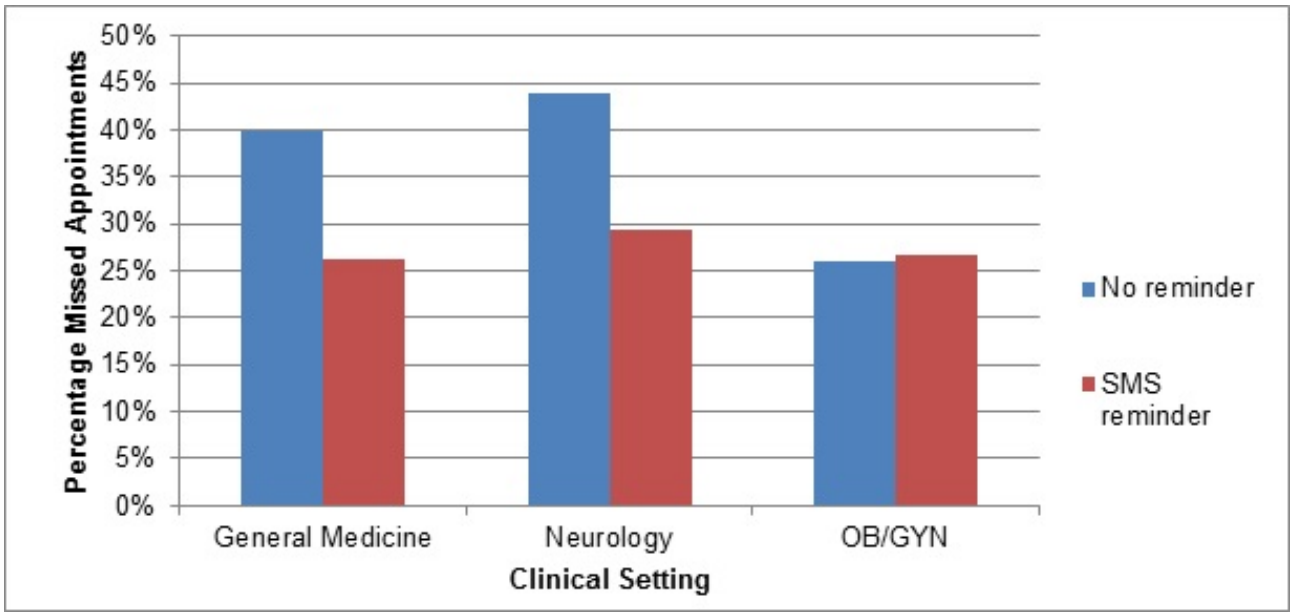
However, there may be also a cultural component [12]. Missed appointments are a problem in KSA in general, not just in obstetrics and gynecology (OB/GYN) clinics. Noting the high usage of text messaging in Saudi Arabia, Youssef et al studied the effect of sending SMS messages as appointment reminders in KSA compared to no appointment reminders to improve nonattendance [13]. They aimed to improve appointment attendance in 3 clinical settings: general medicine, neurology, and OB/GYN [13]. Figure 1 shows their results.

As shown in Figure 1, rates of nonattendance in the no reminder groups were higher in both general medicine (100/251, 39.8%) and neurology (87/198, 43.9%) compared to OB/GYN (104/350, 29.7%) [13]. The use of the appointment reminder did not

improve appointment attendance among the OB/GYN patients, but that may have been because of the other barriers identified in earlier studies, such as lack of transportation [11].

In summary, use of prenatal services by pregnant women in KSA appears to be low, and this contributes to poor birth outcomes. Using text messaging could improve appointment compliance, but given the barriers listed to completing appointments, a technological application that actually provides knowledge and guidance to pregnant women might be more helpful than 1 that simply provides appointment reminders.

Figure 1. Results of study of clinical appointment nonattendance and short message service use (adapted from Youssef et al [13]).



Antenatal Care in Saudi Arabia

The Saudi Arabian health care system is divided into a government sector, which offers free care, and a private sector, where fees are paid for care [14]. The private sector provides all levels of care, and the public sector is further divided into Ministry of Health–run facilities, which provide all levels of care, and facilities run by other agencies, which also provide all levels of care [14]. These other agencies include teaching hospitals, military health facilities, and school health units, among others [14]. More recently, Saudi Arabia has been transitioning from a curative medicine model to more public health and prevention, and this is seen by its enhancement and expansion of primary health care [14]. Although the Saudi Arabian health care infrastructure continues to expand and mature, it currently still faces challenges with "health workforce, financing and expenditure, changing patterns of diseases, accessibility to health care services, introducing the cooperative health insurance scheme, privatization of public hospitals, utilization of electronic health (e-health) strategies and the development of a national system for health information" [14].

Because of the availability of free care, there are few economic barriers to health access for pregnant women [14]. Public hospitals and medical complexes such as the Ministry of National Guard Health Affairs (NGHA) in Jeddah allow for women to receive health care at no cost [15]. This hospital serves families of those in the National Guard and has OB/GYN clinics to serve pregnant women.

The NGHA clinic is similar to other public clinics in that when women are found to be pregnant, they are enrolled in a pregnancy health program. In this program, the woman is scheduled for a second appointment during the first trimester (at 8 to 10 weeks), an appointment during the second trimester (at 18 to 20 weeks), and appointments in the third trimester at 28, 32, 35, 37, 39, and 41 weeks.

Women are also offered antenatal education classes taught by midwives. Women may decline to participate in these classes. The classes provide videos and pamphlets aimed at increasing pregnancy knowledge. When women are preparing for pregnancy, they are encouraged to take folic acid starting 3 months prior to pregnancy. They are told to continue folic acid until 16 weeks and then switch to iron tablets, calcium, and a multivitamin. Even though clinics like the one at NGHA are very accessible, pregnant women in KSA have reported barriers to accessing health care [11]. As described before, a 2012 study reviewed reasons 250 maternal health patients missed appointments and found that the most frequent reasons were lack of supplies and medical equipment such as ultrasound machines, the unavailability of transportation, and lack of respect from the primary health care center staff [11].

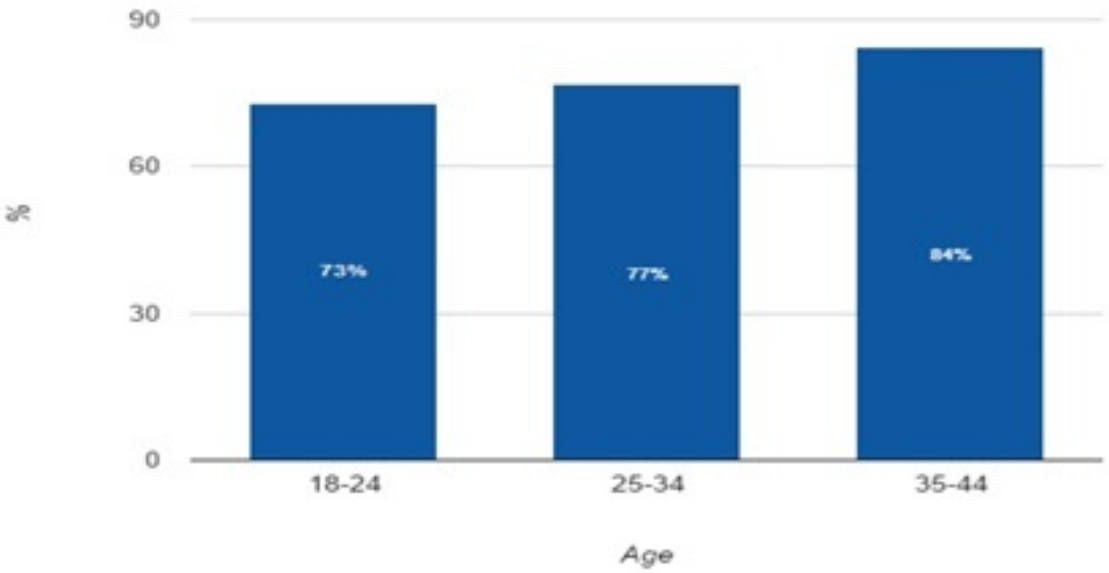
Saudi Women and Mobile Health

A large proportion of Saudi Arabian women of child-bearing age use smartphones and are adept at texting. The Our Mobile Planet online dataset provided by Google shows that 73% of Saudi Arabians regularly use smartphones [2]. Figure 2 shows the 2013 distribution of Saudi Arabian women's smartphone use specifically of social networking apps (as Text4Baby was characterized) stratified by age. Per the figure, the use in this group of social networking apps is between 73% and 84%.

Because of the high adoption of mobile technology in KSA, a messaging application that goes beyond the walls of the clinic could deliver important information these women are missing by missing their appointments. Nutrition information, guidelines

about attending prenatal care visits, and recommendations for adopting certain health behaviors (such as getting a flu shot or quitting smoking) could be provided to these women without the need of a clinic appointment. A similar rationale was behind the development of the Text4Baby program in the United States, which was aimed at underserved pregnant women who may not have had access to health care.

Figure 2. Distribution of Saudi Arabian women's 2013 smartphone use of social networking apps stratified by age (from Our Mobile Planet).



The Text4Baby Program

Text4Baby is a texting health education system developed in an effort led by the US Centers for Disease Control and Prevention (CDC) to reach low socioeconomic status (SES) pregnant women who are thought to be at high-risk for negative birth outcomes such as VLBW and SPTB [16]. This system was initially developed and piloted in 2011 and 2012 [17-19]. The main themes included in the messages are information about healthy weight, nutrition, and exercise; information about depression and anxiety; encouragement and information for seeking care; breastfeeding information; roles of partners in pregnancy; the celebration of pregnancy; prevention strategies including vaccinations, contraception, and sudden infant death syndrome prevention; and information on avoidance of toxic exposures [20].

Currently, to participate in Text4Baby, pregnant women sign up on the Text4Baby website [21]. Participants enter personal information, such as when the baby is due and their cell phone numbers [21]. Each week, the pregnant woman receives pregnancy health messages appropriate for her week of pregnancy. Text4Baby offers colorful and attractive apps for both iPhone and Android [21].

The Text4Baby site offers true stories from users who endorse the support and health education that Text4Baby has provided [21]. The CDC and state health departments are actively promoting Text4Baby [22]. Text4Baby has been adapted for a Russian population [23] and has been tested extensively in the US military [16]. Therefore, it appears to be an excellent system to adapt for the KSA pregnant population.

However, Text4Baby has also been criticized for redundant messages [20] and for lacking an evidence base [4]. The next section will review the current evidence regarding the public health implications of the Text4Baby program.

Methods

Although the program was launched in 2010, evidence regarding the effect of the messages on the knowledge and behavior of pregnant women remains largely elusive. This study will use a traditional or narrative type of literature review, which critiques and summarizes a body of literature and draws conclusions about the topic [24,25]. This type of literature review is important for identifying both gaps and inconsistencies in a body of literature on a scientific topic but requires an extremely focused topic [24,25]. This can be contrasted to the systematic review and meta-analysis approach, which relies on combining findings from many studies of similar study design conducted on the same topic [24,25]. Because Text4Baby was launched relatively recently and because the study designs and research questions in published reports are diverse, these approaches could not be taken at this time with this topic.

Articles were reviewed if they met the following criteria: (1) the main topic of the article was the Text4Baby program and (2) the article was in English. Articles were originally identified by searching for Text4Baby in Google Scholar. An initial search generally returns approximately 670 results; this was conducted first in June 2014 and then periodically over the next 2 years, with the most recent search being conducted on August 5, 2016. Each entry was reviewed for meeting qualifying criteria, and each article that was found to meet qualifying criteria underwent

a source review to identify cited articles that met qualifying criteria.

Results

Overview

The literature review resulted in the identification of 14 articles directly related to Text4Baby. Only 7of these articles [16,18,20,26-30] represented actual studies; the others described the program [3,4,17,31] or described a study that was going to take place [19,23]. Of the 7 that described actual studies, 2 focused on the American military population [16,28], 1 was a pilot study [18], 2 focused on the health literacy of Text4Baby participants [26,27], and 2 focused on the content of the messages [20,29].

Pilot Study

The earliest study published was a pilot study conducted with pregnant women in Fairfax County, Virginia, who presented for care at their Virginia health department. Participants were randomized to receive Text4Baby plus usual care or usual care [18]. Participants were surveyed at baseline and at approximately 28 weeks of the baby's gestational age [18]. There was a 73% retention rate, and results were determined using multivariate analysis [18].

Unfortunately, the questions asked in the survey were not related directly to Text4Baby messages and instead were copied from surveillance questions: "The variables for behavioral outcomes were derived from existing, validated instruments, including the Behavioral Risk Factor Surveillance Survey and National Health and Nutritional Examination Survey" [18]. Therefore, the questions were not worded to directly measure if any specific messages in Text4Baby were successful at imparting knowledge or changing behaviors. For example, one of the questions was "During the last 3 months, about how many servings of fruit did you have in a day?" However, there was no corresponding message or set of messages in Text4Baby that targeted changing the behavior of how much fruit the pregnant woman should eat.

Because of this mismatch, the results of the pilot study were hard to interpret. First, the groups were not comparable at baseline. For example, at baseline, the proportion who agreed with the statement "Eating 5 or more fruits and vegetables per day is important to the health of my developing baby" was about 71% in the control group versus 56% in the Text4Baby group, suggesting that either there was a randomization problem or the authors did not use an intent-to-treat analysis and simply removed the Text4Baby dropouts from their analysis [18]. Next, the authors performed bivariate statistical tests between both groups but did not find differences [18]. Further, because of a lack of an attention control [32], it was not possible to have the usual care only group, which was the control group, drop out, so rate of dropping out of using the app could not be compared [18].

Studies of Health Literacy

The next study published was on the health literacy of users of Text4Baby in the Atlanta area [26]. The reason this was a focus of study is that Text4Baby was aimed at a low health literacy population. Their results suggested that those who successfully self-enrolled in Text4Baby were already more health literate than those who did not, which prompted the authors to recommend the need for additional outreach efforts to enroll low literacy women [26]. The same team later studied factors related to the enrollment process and reception of Text4Baby and found that even though there was a high interest among public health practitioners to use Text4Baby to help underserved populations, there remained challenges to making sure women with significant disadvantages could enroll and receive uninterrupted messages [26]. Currently, it seems that the Text4Baby program is not serving the low literacy populations it was aimed to serve adequately, and public health efforts need to be employed to connect underserved women to the Text4Baby program.

Studies of Health Messages in Text4Baby

Lewkowitz and colleagues produced first a conference abstract and then a paper comparing the content of Text4Baby messages with messages from other pregnancy apps, such as the one sponsored by the American College of Obstetrics and Gynecology and March of Dimes [20,29]. Their analysis suggested that Text4Baby could improve by decreasing the number of messages about obtaining medical care and increasing the number of messages about healthy eating, normal weight gain, exercise, and nutrition without increasing the overall number of messages [20]. The paper later also recommended that Text4Baby replace messages on recruitment with messages about normal pregnancy symptoms, fetal development, and postpartum contraception [29].

Studies of Text4Baby in Specific Populations

Two studies focused on the American military [16,19] and 1 on women in a homeless shelter [30]. The American military studies were headed by the same researcher who did the pilot study in the Virginia health department cohort, and therefore, the results are similarly difficult to interpret. The first military study was designed similarly to the pilot study—using surveillance questions in the data collection and not using an attention control for the control group [19]. Although the number of participants was significantly larger than the pilot study, the same issues plagued this study, the main results are presented with 1 *P* value, and it is not clear what is being compared in this analysis [19].

Ultimately, due to these design issues with the study and the analysis, it was not possible to determine from the analysis whether Text4Baby increased healthy pregnancy knowledge or was associated with changes in behaviors. The authors did not provide an interpretation of their results in their abstract and said in their discussion that Text4Baby appears to improve "specific targeted beliefs" such as those about the importance of prenatal health care, risks of alcohol use, and importance of prenatal vitamins [28] but did not reference the findings in their analysis to which they were referring.

This military study was followed by another one with the same research team about the dose-response effect of Text4Baby [16]. Again, this study suffered from the same design issues, but authors were able to report that the more messages women

received through Text4Baby, the lower likelihood they had of self-reported alcohol consumption [16]. There were no other particular findings reported speaking to the effect on knowledge and behavior change due to Text4Baby.

The third study of a particular population focused on enrolling pregnant mothers in a homeless shelter into Text4Baby [30]. This study did not focus on knowledge and behavioral change; rather, it tried to implement the findings from the studies on health literacy by actively facilitating enrollment in Text4Baby by a low literacy, underserved population [30]. Researchers found that the facilitative, on-site support provided to these homeless pregnant women to help them enroll and use Text4Baby was successful at increasing enrollment and retention rates [30].

Analysis of Existing Evidence

Currently, it has been shown that women who enroll in Text4Baby have higher health literacy and enrolling lower literacy women will require facilitative support [26,27,30]. However, studies of the efficacy of Text4Baby in increasing healthy pregnancy knowledge and behaviors has not been clearly demonstrated. Although 1 military study shows that women decreased their alcohol intake [16], this is not a problem in Saudi Arabia, where alcohol intake is illegal. Therefore, it is currently unclear how Text4Baby impacts healthy pregnancy knowledge and behaviors.

This particular aspect of the development of the Text4Baby program has been criticized. Before the launch of Text4Baby, there was a lack of evidence supporting the claim that Text4Baby would be effective in changing knowledge and behavior [4]. Even though Text4Baby has now been widely implemented, this evidence base is still modest. In all, 2 studies reviewed [26,27] found that Text4Baby is not currently reaching the low literacy population it is targeting and 1 study showed that on-site enrollment may improve adoption in this population [30].

However, Text4Baby has not been consistently shown to improve pregnancy health knowledge and increase healthy behaviors in users, mainly due to errors in the design and analysis of the few existing studies [16,18,28]. Per the review of the message content, it is unlikely that Text4Baby messages are ineffective or even harmful [20,29]. A likelier scenario is that Text4Baby messages actually do increase pregnancy health knowledge and healthy behaviors, but due to lack of a rigorous study design and execution, this evidence is not currently available.

Discussion

For You and Your Baby: Text4Baby for Saudi Arabia

The aim of this project is to develop a similar program as Text4Baby aimed at Saudi Arabian pregnant women. The rationale is that this app would be able to deliver information on healthy pregnancy knowledge and behaviors even if these people do not go to a health care facility. Because Saudi Arabian women have widely adopted smartphone apps and social media, it is reasonable to expect that they would accept the dissemination of health information in this medium. A main health behavior that would be targeted for change in the Saudi Arabian app is missing health care appointments. Other behaviors that would be targeted for changes are consistent with those targeted by Text4Baby: smoking cessation, taking pregnancy vitamins regularly, improving nutritional intake, and avoiding toxic exposures such as contraindicated medications.

The results of our review demonstrate that although there are several publications on the Text4Baby program, a strong evidence base does not currently exist demonstrating that Text4Baby is effective at its original intention, which is to increase healthy pregnancy knowledge and behaviors in US women, especially those of low health literacy and SES. This should not dissuade researchers from seeking to adapt and improve this program for other populations, provided that sufficient evidence is gathered prior to launching the program. As described with the Russian effort [23], international partnerships are needed to properly adapt and study different Text4Baby programs before they are implemented. Although there is a lack of evidence of efficacy, the implementation has been highly studied and therefore provides an efficient starting point for 4YYB.

We plan to develop a culturally tailored Arabic-language version of Text4Baby and examine its effectiveness in increasing healthy pregnancy knowledge and behaviors in Saudi Arabian pregnant women. The new program, 4YYB, would be a mobile health app that runs on iPhone and Android platforms and provides culturally appropriate health information to pregnant Saudi women. Like with Text4Baby, women could download the app, enter their due dates, and receive health messages appropriate to their week of pregnancy. The app would also include diagrams of the baby's size at various weeks as well as health information on topics such as exercise during pregnancy (see Figure 3). The goals of the messages in the app would be to encourage women to present for prenatal visits and provide knowledge about healthy pregnancy behaviors that should be provided at prenatal visits, whether or not they attend them. The healthy pregnancy behaviors targeted by the app would be similar to those in the original Text4Baby: healthy nutrition, exercise, prenatal care, celebrating pregnancy, and avoidance of toxic exposures, as described earlier.

Messages would need to be not only translated into Arabic but adapted for the Saudi population. Alcohol is forbidden in Saudi Arabia while on the other hand, hookah smoking is popular. Messages will need to reflect cultural norms and practices and be culturally appropriate.

Figure 3. Screen shots from 4 You and Your Baby. Left panel shows message from pregnancy week 20. Center panel shows diagrams of baby's size at various weeks. Right panel shows dashboard for health information.

Anticipated Use of For You and Your Baby

As described earlier, missed appointments are a problem throughout the Saudi Arabian health care system. This is possibly compounded by the common cultural belief among pregnant women in KSA that they are not sick, so they do not need to attend health care appointments. Further, many pregnant women rely on their families rather than medical professionals when they have symptoms [12]. On the other hand, women in KSA are on average highly educated and tend to actively seek knowledge, especially health knowledge [33]. Also, women of child-bearing age are typically active users of smartphones and social media [2]. As a result, this population will be likely to adopt 4YYB because it delivers health information tailored to their specific week of pregnancy via a smartphone app. Further, a review of Arabic-language apps in Apple's App Store reveals a lack of apps aimed at this population providing this type of information. We expect the 4YYB app will fill the gap for an Arabic-language app devoted to pregnancy.

Development of For You and Your Baby

Text4Baby was designed to provide healthy pregnancy information to low-income US residents who may experience access to care barriers [26,27]. Many aspects of the design were evidence-based, such as having an expert panel develop the messages and modifying the app based on results from preliminary focus groups and interviews [3,31]. However, even with these promising elements, early studies of the efficacy of a prototype Text4Baby program in terms of successfully increasing knowledge and healthy behaviors in pregnant women from use of the app were not conducted [4]. Therefore, the actual impact of Text4Baby on these parameters remains unknown.

To avoid this problem in the development of 4YYB, research will first be conducted to determine the efficacy of a prototype 4YYB app in Saudi Arabian populations who may experience health care access barriers and inadequate information about maternal and newborn health. Studies should be conducted of the impact of the messages on users of the public health infrastructure, like those at the OB/GYN clinic at NGHA. As was pointed out by Gazmararian and colleagues, the program is designed to target those with low health literacy [27], and this population would be more likely to use public services.

Proposed Research

Ultimately, an evidence base for the effectiveness of 4YYB should be developed before it is launched in Saudi Arabia or other Arabic-speaking countries. So far, a randomized controlled trial (RCT) has not been published that demonstrates the efficacy of increasing healthy pregnancy knowledge and behavior in users of the Text4Baby program. In order to do that type of study, a control app providing nonhealth pregnancy messages should be developed. Participants in the study will then be randomized to either the control app group or the 4YYB app group and later followed for increases in healthy pregnancy knowledge and behavior. The use of a control app will offer an attention control [32] and a comparable comparison as to the uptake in knowledge and change in behaviors that take place during use of the app that are attributable specifically to the 4YYB messages.

During the RCT, questions used in the research data collection will be structured such that health knowledge and behaviors targeted by the app's messages will be measured at baseline. These questions will be developed around domains of knowledge such as healthy eating and avoiding smoking. Next, the same knowledge and behaviors will be measured after use

of the 4YYB or control app, with the time frame specified to start when the user starts using the app. This will facilitate evaluating whether the 4YYB messages have a differential impact on knowledge and behaviors in different domains.

This app, once developed and tested, can prove useful for dissemination of healthy pregnancy knowledge and behaviors in other Middle Eastern countries where Arabic is the main spoken language. These countries are predominantly Islamic, so messages would already be culturally acceptable. The other countries on the Arabian Peninsula, such as Qatar, Yemen, United Arab Emirates, and Kuwait, would likely easily be able to adopt this app as these countries are more affluent and tend to have higher rates of smartphone use. However, a leaner text-only version could be used in Egypt, which is a low- to middle-income country where cell phone use (but not necessarily smartphone use) is prevalent.

Conclusions

As KSA seeks to improve its pregnancy outcomes, it can leverage Saudi women's natural adoption of smartphone apps as a communication channel for delivering pregnancy health information by way of an Arabic-language mobile app adapted from Text4Baby. Although messages will need to be adapted and the app redesigned and enhanced, the development of 4YYB offers the opportunity for developing a rigorous evidence base behind the efficacy of the mobile app. By introducing the use of a control message app and using questions targeting knowledge in the apps domains, studies of 4YYB should provide clear evidence of the differential impact of the app's messages on healthy pregnancy knowledge and behaviors in Saudi Arabian women.

Conflicts of Interest

None declared.

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Abbreviations

4YYB: For You and Your Baby
CDC: United States Centers for Disease Control and Prevention
KAUH: King Abdulaziz University Hospital
KSA: Kingdom of Saudi Arabia
NGHA: Ministry of National Guard Health Affairs (Saudi Arabia)
OB/GYN: obstetrics and gynecology
RCT: randomized controlled trial
SES: socioeconomic status
SMS: short message service
SPTB: spontaneous preterm birth
VLBW: very low birthweight

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Protocol

Epigenetic Alterations and Exposure to Air Pollutants: Protocol for a Birth Cohort Study to Evaluate the Association Between Adverse Birth Outcomes and Global DNA Methylation

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Abstract

Background: Prenatal exposure to air pollutants can increase the risk of adverse birth outcomes and susceptibility to a number of complex disorders later in life. Despite this general understanding, the molecular and cellular responses to air pollution exposure during early life are not completely clear.

Objective: The aims of this study are to test the association between air pollution and adverse pregnancy outcomes, and to determine whether the levels of maternal and cord blood and of placental DNA methylation during pregnancy predict adverse birth outcomes in polluted areas.

Methods: This is a birth cohort study. We will enroll pregnant healthy women attending prenatal care clinics in Tehran, Iran, who are resident in selected polluted and unpolluted regions before the 14th week of pregnancy. We will calculate the regional background levels of fine particulate matter (particles with a diameter between 2.5 and 10 μm) and nitrogen dioxide for all regions of by using data from the Tehran Air Quality Control Company. Then, we will select 2 regions as the polluted and unpolluted areas of interest. Healthy mothers living in the selected polluted and non polluted regions will be enrolled in this study. A maternal health history questionnaire will be completed at each trimester. During the first and second trimester, we will draw mothers' blood for biochemical and DNA methylation analyses. At the time of delivery time, we will collect maternal and cord blood for biochemical, gene expression, and DNA methylation analyses. We will also record birth outcomes (the newborn's sex, birth date, birth weight and length, gestational age, Apgar score, and level of neonatal care required).

Results: The project was funded in March 2016 and enrollment will be completed in August 2017. Data analysis is under way, and the first results are expected to be submitted for publication in November 2017.

Conclusions: We supposed that prenatal exposures to air pollutants can influence fetal reprogramming by epigenetic modifications such as DNA methylation. This could explain the association between air pollution and adverse pregnancy outcomes.

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KEYWORDS

epigenomics; DNA methylation; air pollutants; pregnancy; adverse birth outcomes; placenta

Introduction

Air pollution, the most pervasive environmental concern, is estimated to cause around 800,000 deaths every year worldwide. Among air pollutants, fine particulate matter is known as a possible cause or exacerbator of diseases [1]. Previous studies showed significant associations between fine particulate matter (particles with a diameter between 2.5 [PM2.5] and 10 μm [PM10]) and mortality from complex disorders such as cardiovascular disease, cardiopulmonary disease, and lung cancer [2].

The highest number of estimated annual premature deaths due to fine particulate matter occurs in the developing countries of Asia [3]. In most Asian cities, sulfur dioxide, nitrogen dioxide, PM2.5 and PM10 levels are above the World Health Organization (WHO) guidelines [3]. Although Tehran, Iran, is rated as one of the world's most polluted cities, there are few reports on this matter [4,5]. Naddafi et al reported an annual average of 71 $\mu g/m^3$, which is 4.5 times the values recommended by the WHO [4]. Based on a WHO estimation, the average urban PM10 concentration in Iran is 68 $\mu g/m^3$, about 3.4 times higher than the WHO's air quality guidelines, which is estimated to cause about 9100 deaths per year [6].

Evidence shows that the elderly, children, and pregnant women appear to be more susceptible than the general population to the adverse health effects of air pollution, although people of all age groups are affected by air pollution [7-12]. In addition, growing evidence has been reported of the impact of environmental pollution on adverse birth outcomes [13-15]. Birth outcomes are important for public health policy, because health in early life is crucial for health later in life. Based on a life course approach, most epidemiologic research on chronic diseases has demonstrated that intrauterine and early life conditions significantly affect the occurrence of complex disorders that are of interest to public health [16,17].

Low birth weight, intrauterine growth retardation, and impaired growth in the early years of life are known to increase mortality and morbidity in childhood and the susceptibility of an individual to several complex disorders later in life, such as hypertension, coronary heart disease, and diabetes [15,18]. Despite this general understanding, the biological interactions responsible for impaired development and adverse birth outcomes are not completely clear.

The underlying mechanisms by which air pollutants may induce adverse birth outcomes are not clear. The hypothesis of fetal programming could explain some part of this interaction [19]. This hypothesis states that exposure to endogenous or exogenous factors during a sensitive period can lead to responses at a molecular and cellular level. However, environmental influences on metabolism could persist even under normal conditions or in the absence of stimulating factors [19]. Furthermore, long-term or permanent alterations in the function of target cells can lead to an increased risk for adult-onset diseases such as type 2 diabetes mellitus, hypertension, cardiovascular disease, and cancer [20-22]. The underlying biological mechanisms of fetal programming can be explained by epigenetic modifications such as DNA methylation [23-25], which is one important regulatory mechanism in cell development and differentiation [26,27]. It seems that maternal exposure to air pollutants is associated with an epigenetic modification such as DNA methylation. DNA methylation of cytosine residues is a heritable epigenetic modification that can maintain specific gene expression patterns in different cell types. Alterations in DNA methylation due to metabolic exposure during gestation or after birth may increase the susceptibility of an individual to complex disorders such as cancer and metabolic disorders later in life [28-30].

We systematically searched PubMed and SCOPUS up to December 1, 2016 for literature addressing adverse pregnancy outcomes (infant mortality, postneonatal mortality, birth weight, intrauterine growth retardation, premature birth, birth outcomes, and fetal development), pollution, and DNA methylation. This systematic search identified a few studies that assessed air pollution's effect on global and gene-specific methylation [31-36]; 2 studies focused on the association of DNA methylation of repetitive elements and global DNA methylation of placental tissue with air pollution in early life [32,36].

An environmental inputs birth cohort study [31] showed that "epigenetic modifications in the mitochondrial genome, especially in the MT-RNR1 region, substantially mediate the association between PM2.5 exposure during gestation and placental mtDNA content, which could reflect signs of mitophagy and mitochondrial death."

Another study [32] showed "a lower degree of placental global DNA methylation in association with exposure to particulate air pollution during early pregnancy". It seems that exposure to particulate matter during fetal development can lead to alterations in genomic DNA methylation and affect gene-specific DNA methylation and gene expression patterns during this crucial time. Consistent with this hypothesis, recent evidence from both human subjects and animal models has indicated that exposure to airborne particulate matter is associated with changes in DNA methylation patterns. Alterations of DNA methylation patterns are postulated to modulate immune responses and regulate inflammatory genes in response to inhalation of particulate matter.

Among intracellular pathways, the glutathione pathway's role in the lung is to defend the airway epithelium from damage in response to oxidants and inflammation [37]. Glutathione is a tripeptide, γ-glutamyl-cysteinyl-glycine (GSH), and is defined as the "body's master antioxidant" [37]. At the molecular level, nucleotide variation in the glutathione gene has been associated with differences in susceptibility to adverse effects of air pollutants on lung function and growth [38]. Emerging evidence has shown that *S*-adenosylmethionine (SAMe) increases cellular glutathione content and has an important role in the methylation

cycle [39,40]. SAMe is the main cosubstrate involved in methyl group transfers in the methylation cycle.

However, it is important to assess whether there is an association between air pollution and adverse birth outcomes, how it is modulated by alteration of genomic DNA methylation in the fetus and placental tissue, and how the adverse effects of air pollution on birth outcomes can be reduced by intervention strategies.

Study Objective

The primary objective of the study is to compare the incidence of adverse birth outcomes in a polluted urban area with that in an unpolluted urban area.

The secondary objective is to investigate the association between adverse birth outcomes and global changes in fetal and maternal DNA methylation.

In addition, we aim to determine the association between gene expression of GSH and alteration of global DNA methylation.

Methods

Study Design

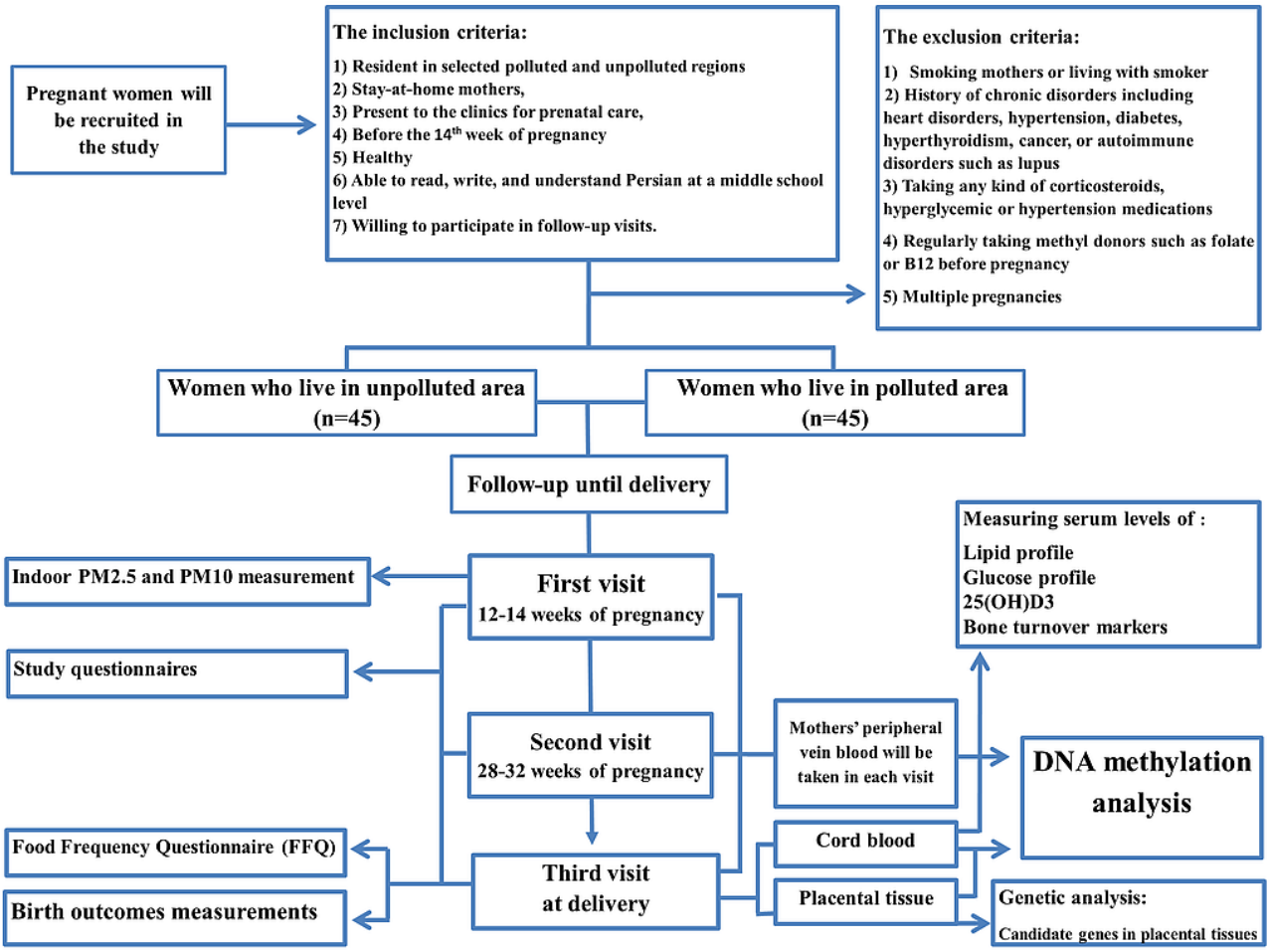
This is a birth cohort study designed by the Endocrinology and Metabolism Research Institute of Tehran University of Medical Sciences. The research has been supported by the National Institute for Medical Research Development of Iran (grant no. 940173).

Study Population

In our birth cohort study, we will enroll pregnant women attending prenatal care clinics in two regions in Tehran, Iran: the most polluted and the least polluted. The study population is the group of eligible mothers living in these two regions who agree to participate in this study. The inclusion criteria are as follows: (1) resident in the selected polluted and unpolluted regions, (2) stay-at-home mothers (3) presenting to the clinics for prenatal care (4) before the 14th week of pregnancy who are (5) healthy, (6) able to read, write, and understand Persian at a middle school level and (7) willing to participate in follow-up visits. The exclusion criteria are as follows: (1) smoking mothers or living with a smoker, (2) having a history of chronic disorders, including heart disorders, hypertension, diabetes, hyperthyroidism, cancer, or autoimmune disorders such as lupus, (3) taking any kind of corticosteroids, or hyperglycemia or hypertension medications, (4) regularly taking methyl donors such as folate or vitamin B_{12} before pregnancy, or (5) having a multiple pregnancy. If a mother moves out the selected region, is employed, or travels between polluted and unpolluted regions regularly, she will be excluded from the study. The participants in the two regions (polluted and unpolluted) will be matched by age, pregestational body mass index, and parity.

Written informed consent will be obtained from all study participants in accordance with procedures approved by the Ethical Committee of the National Institute for Medical Research Development (IR.NIMAD.REC.1394.018) of Iran. Consent is attained by a research midwife or a doctor who is not directly involved in the routine perinatal care of the women. A participant may subsequently decide to withdraw from the study at any time without prejudice to their future care. In this study, 40 participants would be required in each group to have 90% power to detect a difference of 4% at global DNA methylation levels between the 2 groups. We anticipate recruiting 80 participants to investigate the role of indoor and outdoor air pollution on global DNA methylation levels of maternal and cord blood and placental tissue. We estimate that the dropout rate during the study will be 10%, so a total of 90 pregnant women will be needed for the duration of the study with a minimum of 45 participants in each subgroup (Figure 1).

Figure 1. Study design. Flow diagram of selection of pregnant women living in polluted and unpolluted regions of Tehran. PM2.5: particulate matter with particle diameter 2.5 μm; PM10: particulate matter with particle diameter 10 μm.



Exposure Measurement

We will calculate the regional background levels of PM10, PM2.5, and nitrogen dioxide for each mother's home address. The values of air pollutants will be obtained from the Tehran Air Quality Control Company in 4×4 km grids.

To explore the potential effect of exposures during pregnancy, we will calculate regional PM10 and PM2.5 concentrations (micrograms per cubic meter) during various times: the mean levels at 1 week before delivery, during the last month of pregnancy, and for each of the 3 trimesters of pregnancy. We will also calculate the exposure during the whole pregnancy.

To reduce bias due to exposure misclassification, we plan to measure the PM2.5 and PM10, as individual levels, manually by using Dylos DC1100 air quality monitors (Dylos Corporation, Riverside, CA, USA) in each participant's address (indoor). Also, we will collect drinking water to measure contaminants including hardness, nitrite, and nitrate.

Data Collection in Each Area

First and Second Visits

At the first visit (12-14 weeks of pregnancy), we will complete study questionnaires with the participants to provide detailed information on place of residence, socioeconomic status, sleep habits, smoking status, health status, medical history, and previous pregnancy history. At the second visit (28-32 weeks of pregnancy), a maternal health history questionnaire will be completed to record what medicines, herbs, or vitamins the mother is taking and any adverse events and health problems experienced. We will take the mothers' peripheral venous blood after an overnight fast of 10-14 hours for biochemical, DNA methylation, and gene expression analyses at the first and second visits.

Third Visit (Delivery Time)

We will follow-up participants monthly until delivery. A food frequency questionnaire will be completed to calculate nutrient elements taken in. At the delivery time, we will collect maternal and cord blood for biochemical, gene expression, and DNA methylation analyses. We will also obtain samples of placental tissue for gene expression and DNA methylation analyses.

Perinatal Outcomes

After delivery, we will record neonatal birth parameters such as the newborn's sex, birth date, birth weight and length, gestational age, Apgar score, and level of neonatal care required (normal newborn nursery, level 2 or level 3 intensive care). All neonates will be assessed for congenital anomalies immediately after birth. We will condense birth dates into a seasonal scale, classified as cold periods (October to March) and warm periods (April to September).

Biochemical and Genetic Analyses

Blood Sampling

At each visit, we will collect blood samples for epigenetic and genetic analyses and for biochemical analysis. The serum will be divided into 2 aliquots: for routine prenatal tests (fetal blood sampling, cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, and insulin), and for measuring 25-hydroxyvitamin D_3 and bone markers (procollagen I aminoterminal propeptide, osteocalcin, and C-terminal cross-linked telopeptide of type I collagen). The separated sera will be kept at –80°C until analysis.

Tissue Biopsy

The tissue biopsy will be taken from the fetal side, 1-1.5 cm below the chorioamniotic membrane at a fixed location in relation to the umbilical cord.

Global DNA Methylation Analysis

Genomic DNA will be isolated from placental tissue and the mother's peripheral venous blood using the standard method.

Briefly, DNA is extracted by the phenol method from whole blood and homogenized placental tissues. We will determine global DNA methylation as previously published [41,42]. Global DNA methylation will be expressed as the percentage of 5-methyldeoxycytidine (5-mdC) versus the sum of 5-mdC and deoxycytidine (dC): [5-mdC/(5-mdC + dC)]%.

Gene Expression Analysis

We will extract RNA from peripheral venous blood using a Qiagen kit (QIAGEN NV, Venlo, the Netherlands). Gene expression will be analyzed by using real time polymerase chain reaction after complementary DNA synthesis. Candidate genes include GSH, DNA (cytosine-5)-methyltransferase-1-alpha, SAMe, brain-derived neurotrophic factor, synapsin I, AKT serine/threonine kinase 2, SOS Ras/Rac guanine nucleotide exchange factor 1, SOS Ras/Rac guanine nucleotide exchange factor 2, and phospholipase C gamma 2) in maternal and placental tissues.

Statistical Analysis

We will present categorical data as frequencies (%) and numbers, and continuous data as mean and standard deviation. We will use chi-square test to compare the prevalence of adverse birth outcomes in the two regions. Student *t* test will compare the differences in global DNA methylation levels in pregnant women in the two regions (polluted and unpolluted) at each trimester.

We will use Spearman correlation coefficients and linear regression to assess the association of global DNA methylation from blood and placental tissue with nitrogen dioxide, PM10, and PM2.5 (data will be obtained from the Air Quality Control Company).

We will construct a stepwise logistic regression model to determine the independent effect sizes of nitrogen dioxide, PM10, and PM2.5 exposures during pregnancy on global methylation. An appropriate cutoff point will be determined for DNA methylation levels, and then the levels will be defined as a dichotomous variable. We will consider covariates for entry into the model, including the newborn's sex, maternal age (years), gestational age (weeks), parity (1, 2, or 3), sleep duration, dietary intakes of vitamin B_{12} and folate, regional temperature, and season at conception.

The $2^{(\Delta\Delta Ct)}$ formula will be used to calculate relative transcript abundance. Student *t* test will be used to compare gene expression differences of all included genes in blood and placental tissue between the two groups, that is, pregnant women who live in polluted and unpolluted regions. For multiple testing corrections, we will use the false discovery rate [43,44]. We will consider 2-tailed *P* values <.05 as statistically significant. The same analyses will be performed in 2 subgroups from each polluted region: participants with and without classroom education.

Results

The project was funded in March 2016 and enrollment will be completed in August 2017. Data analysis is under way, and the first results are expected to be submitted for publication in November 2017.

Discussion

To our knowledge, this is the first birth cohort study in Tehran, which is rated as one of the world's most polluted cities, to measure global DNA methylation in pregnant women who live in polluted and unpolluted regions and to investigate the interaction between adverse pregnancy outcomes and air pollution as an environmental factor. In addition, we plan to improve women's knowledge about how to reduce prenatal exposure to air pollution and prevent adverse pregnancy outcomes attributable to air pollutants.

Developmental adaptations due to epigenetic modification may permanently "program" the fetus and may lead to adverse pregnancy outcomes that form the origin of diseases that may arise in adult life.

Based on the evidence, we supposed that prenatal exposures to air pollutants can influence fetal reprogramming by epigenetic modifications such as DNA methylation. This could explain the association between air pollution and adverse pregnancy outcomes.

Of note, there are some potential problems and limitations in our study. Primarily, some confounding factors could have a possible effect on blood and tissue DNA methylation, such as some lifestyle-related factors, environmental tobacco smoke, the season, and environmental temperature. To minimize the impact of lifestyle and regional differences in methylation patterns, we will adjust for the mother's socioeconomic status, maternal diet, and maternal sleep habits in our analysis. Also, we will consider exposures to other air pollutants such as second-hand smoke and indoor air pollution. We will exclude mothers who smoke or live with a smoker. We will obtain the temperature of each region from Air Quality Control Company data. In addition, the differences in effect estimates of air pollutants on DNA methylation could be further related to

differences in maternal nutritional status. To control for the impact of nutritional status, a food frequency questionnaire will be filled out for all participants to measure special nutrients associated with DNA methylation, such as folate and vitamin B_{12}. However, we can't control for some unknown factors that are associated with blood and tissue DNA methylation, as well as levels of air pollutants.

Acknowledgments

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Authors' Contributions

ZM, AH, MR, and SM conceived the study design; ZM and AH contributed to design data collection tools and wrote the statistical analysis plan. ZM and AH will monitor data collection for the whole trial and analysis of the data. ZM and AH drafted the manuscript, and all authors reviewed the draft of the manuscript and revised it. All authors approved the final manuscript to be published.

Conflicts of Interest

None declared.

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Abbreviations

GSH: γ-glutamyl-cysteinyl-glycine
PM2.5: particulate matter with particle diameter 2.5 μm
PM10: particulate matter with particle diameter 10 μm
SAMe: S-adenosylmethionine
WHO: World Health Organization

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Protocol

Delirium After Mechanical Ventilation in Intensive Care Units: The Cognitive and Psychosocial Assessment (CAPA) Study Protocol

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Abstract

Background: In the intensive care unit (ICU), critical illness delirium occurs in the context of multiple comorbidities, multi-organ failure, and invasive management techniques, such as mechanical ventilation, sedation, and lack of sleep. Delirium is characterized by an acute confusional state defined by fluctuating mental status, inattention, and either disorganized thinking or an altered level of consciousness. The long-term cognitive and psychosocial function of patients that experience delirium in the ICU is of crucial interest because preliminary data suggest a strong association between ICU-related delirium and long-term cognitive impairment.

Objective: The aim of this study is to explore the relationship between delirium in the ICU and adverse outcomes by following mechanically ventilated patients for one year following their discharge from the ICU and collecting data on their long-term cognition and psychosocial function.

Methods: This study will be conducted by enrolling patients in two tertiary ICUs in Australia. We aim to recruit 200 patients who have been mechanically ventilated for more than 24 hours. Data will be collected at the following three time points: (1) at discharge where they will be administered the Mini-Mental State Examination (MMSE); (2) at 6 months after discharge from the ICU discharge where the Impact of Events Scale Revised (IES-R) and the Telephone Inventory for Cognitive Status (TICS) tests will be administered; and (3) at 12 months after discharge from the ICU where the patients will be administered the TICS and IES-R tests, as well as the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE). The IQCODE will be administered to their “person responsible” or the significant other of the patient.

Results: Long-term cognition and psychosocial function will be the primary outcome of this study. Mortality will also be investigated as a secondary outcome. Active enrollment will take place until the end of September 2016 and data collection will conclude at the end of September 2017. The analysis and results are expected to be available by March 2018.

Conclusion: Delirium during mechanical ventilation has been linked to longer ICU and hospital stays, higher financial burdens, increased risks of long-term cognitive impairment (ie, dementia), poor functional outcomes and quality of life, and decreased

survival. However, delirium during mechanical ventilation in the ICU is not well understood. This study will advance our knowledge of the comprehensive, long-term effects of delirium on cognitive and psychosocial function.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12616001116415; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=371216 (Archived by WebCite at http://www.webcitation.org/6nfDkGTcW)

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KEYWORDS

intensive care; delirium; mechanical ventilation; cognition; psychosocial outcomes

Introduction

Delirium is a disturbance of consciousness, developed over a short period of time, where inattention is accompanied by a change in cognition and/or perceptual disturbance [1]. Delirium occurs in a variety of health care settings [2] and affects between 15% to 20% of general hospital patients [3,4], including as many as 80% of critically ill, intensive care unit (ICU) patients receiving mechanical ventilation [5].

In the ICU, delirium is associated with critical illness itself, particularly with multiple comorbidities and multi-organ failure, as well as management-related factors such as mechanical ventilation, sedation, and lack of sleep [2,6,7]. Delirium is also associated with adverse outcomes including death and long-term cognitive impairments [7-9], and potentially traumatic stress symptomatology. Several studies suggest delirium-related risks are cumulative and may foster the development of cognitive dysfunction, poorer functional status, and impair quality of life [7-23]. Despite literature reports of a reduced quality of life for survivors of critical illness and delirium in the ICU, the long-term follow-up of cognitive and psychosocial function still remains relatively unexplored. This study will address this by following up with patients for one year after discharge from the ICU. We will employ a set of tests that complement each other [24] in order to create a comprehensive view of a patient's cognition and psychosocial well-being at 12 months after leaving the ICU. These tests assess cognition and evidence of post-traumatic stress disorder (PTSD) [25], while also using each patients "person responsible" to assess their relative's and/or friend's psychosocial function at 12 months after their discharge from the ICU in comparison to their pre-ICU psychosocial abilities. This study is expected to provide novel insight into the cognitive and psychosocial impact of ICU mechanical ventilation-related delirium and to assist in improving the care of critically ill intensive care patients by highlighting the importance of the need to monitor for the development of delirium.

Methods

We are conducting a prospective case-control study in two ICUs in Australia: the Canberra Hospital in the Australian Capital Territory and the Prince of Wales Hospital in Sydney, New South Wales. The study was approved by the ACT Health Human Research Ethics Committee (ETH.6.12.130) and the Southern Health Human Research Committee (12/242 (HREC/I2/POWH/460). Since eligible participants are not able to give informed consent on enrolment due to their health status (ICU treatment), their substitute decision maker or "person responsible" will be identified. This person is approached to provisionally consent to participation on behalf of the patient. The "person responsible" is given a full explanation of the study and is provided with the Cognitive and Psychosocial Assessment (CAPA) study information sheet. They are then asked to consent to participate in the study on behalf of themselves and the patient. If the patient is not sedated or delirious, the study is explained to them; however, the "person responsible" is still required to complete and sign the consent form on behalf of themselves and the patient whilst the patient is ventilated. Further, consent from the "person responsible" authorizes their later involved in the assessment of patients' overall function at the 12-month follow-up.

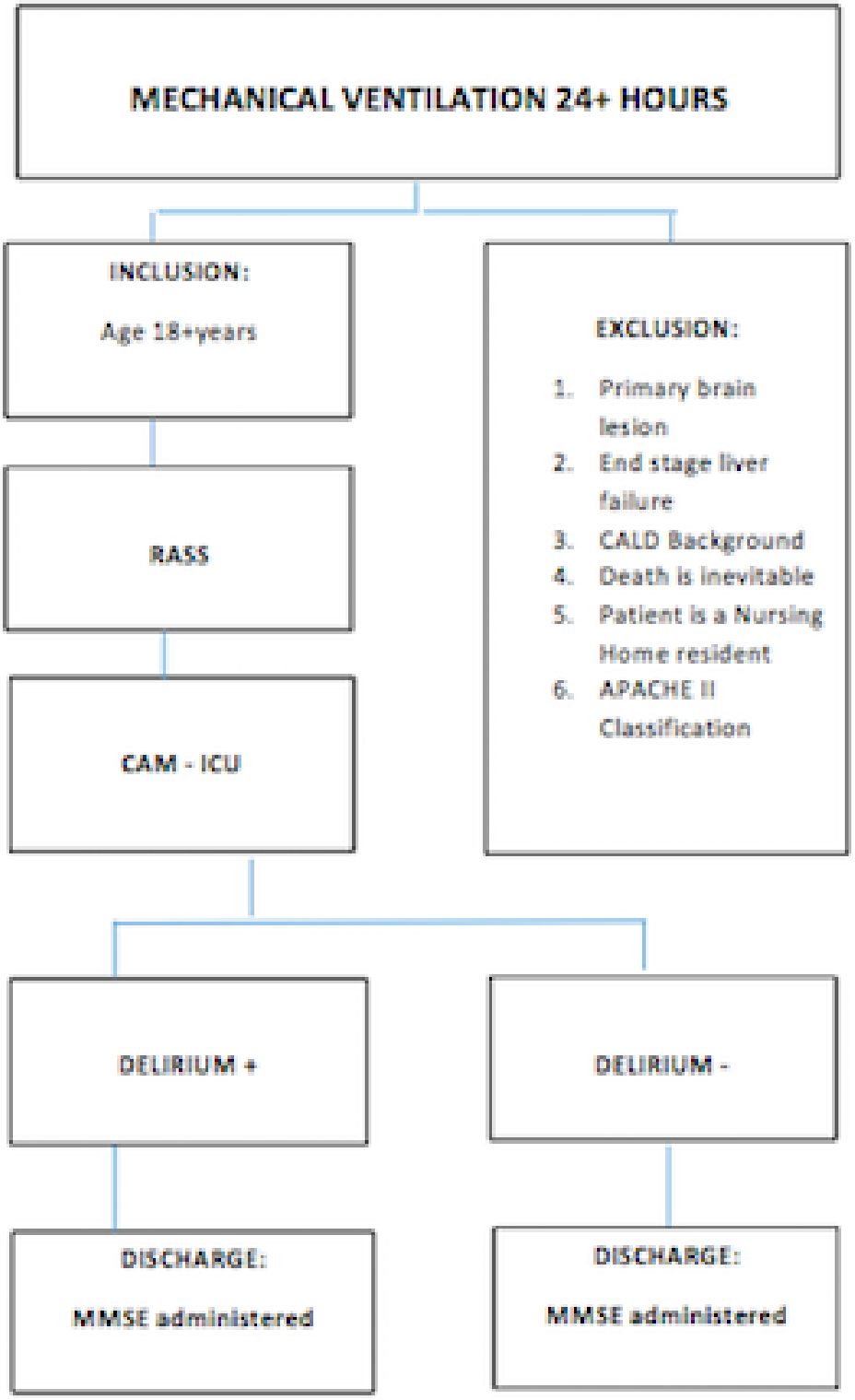
Despite being recruited to the study through their "person responsible," the patients receive no other intervention other than standard protocol care during their ICU stay. The standard care in both recruiting sites involves administering the following during mechanical ventilation: (1) the Richmond Agitation and Sedation Score (RASS) [26,27], and (2) the Confusion Assessment Method for the ICU (CAM-ICU) [28].

After being recruited to the study, the patients have their sedation level assessed by the RASS [26,27] every 4 hours. The RASS is a scale that indicates the patient's level of sedation and ranges from +4 to –5. A RASS score of 0 represents a patient who is alert and calm, while positive scores indicate different levels of agitation from restless (+1) to combative (+4). Negative scores indicate different levels of drowsiness from drowsy (–1) to unarousable (–5).

Patients with a RASS score between –2 and +3 will be administered the CAM-ICU [28]. The CAM-ICU is an adaptation of the Confusion Assessment Method and is widely used for diagnosing delirium with yes and no questions for use with non-speaking, mechanically ventilated patients in the ICU. The study participants are not exposed to any additional testing during their time in the ICU.

Patients assessed as suffering delirium via the CAM-ICU at any time are allocated into the delirium positive study group, while delirium-negative patients are re-tested on a daily basis during the time they remain mechanically ventilated. Those patients who never test positive for delirium are allocated to the delirium-negative group (Figure 1).

Figure 1. a. CALD Culturally and Linguistically Diverse Background; b. APACHE II Acute Physiology and Chronic Health Enquiry II; c. RASS Richmond Agitation Sedation Scale; d. CAM-ICU Confusion Assessment Method for the Intensive Care Unit; e. MMSE Mini Mental State Examination.



Participants

Patients participating in this study are critically ill, mechanically ventilated, and may require immediate administration of sedative medications by infusion. As a consequence of the immediacy of the situation and the urgent need for sedation, we obtain provisional consent from the patient's "person responsible" prior to enrolling patients in the study. Adult patients greater

than 18 years of age are approached for recruitment after being mechanically ventilated for more than 24 hours. The exclusion criteria are (1) suspected acute primary brain lesion; (2) end stage liver failure or acute hepatic failure; (3) culturally and linguistically diverse (CALD) background—literature suggests that in times of crisis people automatically revert to their own language and our psychosocial questionnaires are not specifically designed for CALD [29,30]; (4) death is deemed imminent and inevitable; (5) patient is a nursing home resident and/or physical/cognitive decline is evident [31,32]; and (6) the Acute Physiology and Chronic Evaluation (APACHE II) [33] classification indicates underlying terminal illness.

Procedure and Enrolment

Patients are asked to sign formal consent to participate upon discharge from the ICU. If they confirm their enrolment, they are administered the MMSE [34], the first cognitive assessment (Multimedia Appendix 1). At 6 months, the patients are contacted and administered the telephone-modified version of the MMSE called the Telephone Interview for Cognitive Status (TICS) [35,36] (Multimedia Appendix 2). They also receive the Impact of Events-Revised (IES-R) questionnaire [37,38] (Multimedia Appendix 3) by mail to assess for early symptoms of PTSD [25]. At 12 months after discharge, the patients are contacted, the TICS is administered, and they are mailed the IES-R. The Informant Questionnaire on Cognitive Decline (IQCODE) [37] (Multimedia Appendix 4) is also mailed to their "person responsible" who was identified at the time study recruitment. The hospital outcome assessments are recorded up to one year after discharge from the ICU (Figure 2).

For a pilot study that we conducted in 2011, we followed 8 patients (4 delirium-positive and 4 delirium-negative) for 3 months after their discharge from the ICU. During this time, the design and choice of measurement tools for this investigation were informed.

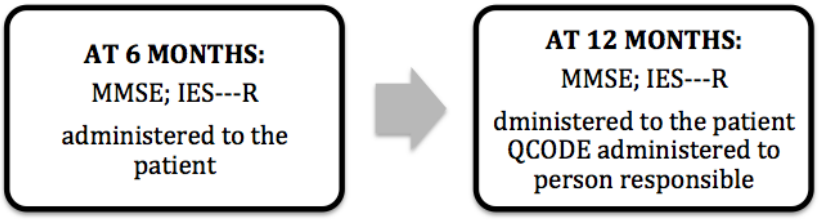
The questionnaires we employ in this study are well-established and validated in measuring cognition and psychosocial well-being. The MMSE, the most commonly used measure of cognitive function in hospitalized patients [34], is scored from 0 to 30, with lower scores indicating poorer performance. We administer the MMSE for the first time after patients formally consent and at the time of their discharge from the ICU. The TICS is a modified and validated version of MMSE and is administered to the patient over the phone at the 6- and 12-month follow-ups.

The IES-R is a non-diagnostic, self-report measure designed to assess subjective distress for any specific life event. The IES-R consists of the three subscales: hyper arousal, intrusion, and avoidance. These subscales parallel the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for PTSD. This questionnaire is administered to the patient at the 6- and 12-month follow-ups.

The IQCODE is a tool used to assess cognitive impairment in older people. It is widely used in conjunction with other cognitive tests and with no age limitations (personal communication DB and JL, August 2011). The IQCODE was found to correlate highly with conventional cognitive screening tests [25], such as the MMSE, and moderately with a range of neuropsychological tests, such as the Wechsler Adult Memory Scale (WAMS) and the Wechsler Adult Intelligence Scale (WAIS). Since the IQCODE provides information complementary to other brief cognitive tests, such as the MMSE [38], we supplemented the MMSE with the IQCODE to improve the study's cognition screening accuracy, as well as gain a retrospective assessment of the patient's cognitive function.

We have obtained permission to use the above tools through direct contact with authors (Multimedia Appendix 5), and email correspondence (DB with DSW and AFJ, August 2011). All of the questionnaires have been validated, are found to be reliable and specific to psychosocial assessment [34-39], and are less time-consuming than other conventional cognitive and neuropsychological tests.

Figure 2. Assessments after hospital discharge. TICS: Telephone Interview for Cognitive Decline; IES-R: Impact of Events Scale Revised; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly.



Measures

This study aims to test the hypothesis that delirium during mechanical ventilation in the ICU promotes long-term cognitive and psychosocial decline and impacts one's health-related quality of life when compared with non-delirium patients [8-23]. The data recorded at study enrolment, during their stay in the ICU, and at discharge are shown in Textbox 1.

Textbox 1. Data recorded at the time of patient enrolment in the study, during their stay in the intensive care unit, and at discharge

Collected data

- At enrolment
  - Demographic data
    - Name
    - Mailing address
    - Contact number
    - Date of birth
    - Age
    - Indigenous status
    - Sex
  - Date and time of admission to the intensive care unit (ICU)
  - ICU admission diagnosis—Acute Physiology and Chronic Evaluation (APACHE II)
  - Date and time of first intubation
- Daily
  - Richmond Assessment Sedation Scale (RASS)
  - Confusion Assessment Method for the ICU (CAM-ICU)
- At discharge from the ICU
  - Delirium positive or negative
  - Date and time of discharge from the ICU
  - Survival status at discharge from the ICU
  - Mini-Mental State Examination (MMSE)
- After discharge from the ICU (episode outcome at 6 and 12 months)
  - Survival status
  - Dependency status
  - Cognitive status

Sample Size

The primary outcome of this study is the relative decrement in MMSE at 6 months after discharge from the ICU. We used the most relevant clinical trial employing MMSE to quantify cognitive function of both delirium-positive and delirium-negative patients to estimate the expected outcomes for our patients at 6 months after discharge from the ICU in order to make a sample size calculation. We estimated the clinically important reductions expected in MMSE and calculated that, at a type 1 error rate of 5% (alpha .05), we can find the clinically significant difference of 2 points on the MMSE between groups with 80% power if we include a minimum of 81 patients in each group (delirious and not delirious). To allow for potential dropouts following recruitment, we plan to enroll 200 patients.

Safety Monitoring

Both internal and external monitoring is utilized through this study. The principal investigator has on-site assessment through monthly meetings with the supervisors at both hospitals. An external person is also appointed at each research site to independently monitor the research process.

Statistical Analysis

All statistical analysis will be done using Statistical Package for the Social Sciences (SPSS) Research Engine, Version 22.0 IBM SPSS Statistics (2015). We plan to employ the Student *t* test to compare mean outcomes in each group when assuming a normal underlying distribution can be justified and the Mann-Whitney U test to compare medians when this assumption fails. We will compare differences in proportionate outcomes using a Chi-square analysis. When calculating multiple time points for the purpose of comparing groups over time, we will apply appropriate correction for multiple testing using the Bonferroni correction. For all of these methods, we will determine if there is a statistically significant difference between the groups (*P* values less than .05). Results will be presented as differences between groups with 95% confidence intervals. We will also consider both analysis of covariance (parametric)

or Kruskal-Wallis (non-parametric) testing as appropriate and will investigate the influence of potential confounders and correlations by logistic or multiple regression techniques. Further, we will randomly select two groups of patients (30 delirium-positive and 30 delirium-negative) to cross validate our results and assess whether they are stable for both samples.

Results

The primary outcome of this study is the assessment of long-term cognition and psychosocial function. Patient mortality will be the study's secondary outcome. Active enrollment will take place until the end of September 2016 and data collection will conclude at the end of September 2017. The analysis and results are expected to be available by March 2018.

Discussion

The use of sedation and multiple psychoactive medications in the ICU, combined with patients' metabolic disturbances, underlying infections, and multi-organ failure, may promote delirium and create new or exacerbate existing cognitive impairments [10-23]. Burgeoning evidence has emerged in support of the association between the ICU experience of delirium and adverse patient outcomes, including longer hospital stays and poor functional recovery [40-43]. We hope this study, with its design and comprehensive data collection, will deliver novel insights into the impact of intensive care delirium on patients' long-term cognitive and psychosocial outcomes, further informing the care of critically ill ICU patients.

Acknowledgments

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Authors' Contributions

DB conceived the study and drafted the manuscript. MB provided important mentoring in designing the study in relation to clinical processes, safety monitoring, statistical analysis plan, and ethics submissions to both research sites. JCLL helped select research instruments. FVH assisted in acquiring funding and was vital in getting the study operational at Canberra Hospital. HR assisted in acquiring funding, and together with MN, was instrumental in enrolling the patients at Canberra Hospital. PR assisted in recruiting patients in the Prince of Wales Hospital. All authors critically revised the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Mini-Mental State Examination.

[PDF File (Adobe PDF File), 184KB - resprot_v6i2e31_app1.pdf]

Multimedia Appendix 2

Telephone Interview for Cognitive Status (TICS).

[PDF File (Adobe PDF File), 1MB - resprot_v6i2e31_app2.pdf]

Multimedia Appendix 3

Impact of Events Scale-Revised (IES-R).

[PDF File (Adobe PDF File), 94KB - resprot_v6i2e31_app3.pdf]

Multimedia Appendix 4

Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).

[PDF File (Adobe PDF File), 21KB - resprot_v6i2e31_app4.pdf]

Multimedia Appendix 5

MMSE:TICS permission.

[PDF File (Adobe PDF File), 1MB - resprot_v6i2e31_app5.pdf]

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Abbreviations

APACHE II: Acute Physiology and Chronic Evaluation
CALD: culturally and linguistically diverse background
CAM-ICU: Confusion Assessment Method for ICU
ICU: intensive care unit
IES-R: Impact of Events Scale Revised
IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly
MMSE: Mini-Mental State Examination
PTSD: post-traumatic stress disorder
TICS: Telephone Interview for Cognitive Status

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Original Paper

Feasibility of Ecological Momentary Assessment of Daily Sexting and Substance Use Among Young Adult African American Gay and Bisexual Men: A Pilot Study

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Abstract

Background: Recent evidence suggests that sexualized text communication (“sexting”) is associated with substance use and sexual risk behaviors among young adults, yet little is known about this relationship among young adult African American gay and bisexual men, a population disproportionately impacted by HIV in the United States. Rapid advances in mobile phone technology indicate a clear need for research using mobile health (mHealth) methods such as ecological momentary assessment (EMA) to serve as a viable counterpart to retrospective evaluation methods by using real-time data collection to assess sexting and substance use among this population.

Objective: The objective of this pilot study was to (1) describe the EMA study design and protocol, (2) characterize the study population, and (3) assess the feasibility of a random prompt text message-based thrice-daily EMA over 14 days, as a means of prospectively studying sexting, marijuana, and alcohol use among a sample of young adult African American gay and bisexual men ages 21 to 25.

Methods: Participants were recruited through flyers and snowball sampling during spring and summer 2015 at a community-based HIV/AIDS prevention, care, and support organization in Washington, DC. Eligible participants were enrolled in a one-time in-person study visit that consisted of informed written consent to participate in the study, a self-administered survey, a semi-structured interview, and enrollment and training in EMA data collection. Commencing the day after the study visit, a random prompt survey was texted to participants on their personal mobile phones 3 times a day over a 14-day data collection period assessing mood, texts sent, texts received, sexts sent, sexts received, marijuana want, marijuana use, and alcohol use.

Results: EMA feasibility was tested with 25 self-identified African American gay (n=16) and bisexual (n=9) men (mean age of 23.48 years, SD 1.5). Each random prompt survey had 8 questions with responses including yes/no and Likert scale options. There were 104 total days of EMA observation, and the retention rate was 72% (18 out of 25 participants). Participants responded to the random prompt surveys with a 57.3% compliance rate providing a total of 544 completed surveys out of 949 surveys. The overall mean response time to complete a survey was 6.1 minutes. There were significant positive associations between EMA texts sent and received questions (ρ 0.84, $P<.001$) as well as sexts sent and received queries (ρ 0.72, $P<.001$).

Conclusions: The use of an EMA protocol has the potential to be a very useful research tool for understanding episodic behaviors such as sexting and substance use in this relatively understudied and underserved population, and has implications for practice. Additional research is needed on how to maximize survey compliance.

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KEYWORDS

ecological momentary assessment; mobile phone; text messaging; sexting; marijuana; alcohol; young adult; gay and bisexual; African American men

Introduction

Despite an overall reduction in new HIV infections in the United States, young African American gay and bisexual men continue to experience a disproportionate burden of HIV [1]. In 2014, among all African American gay and bisexual men diagnosed with HIV in the United States, an estimated 39% (4321) were aged 13-24 [1]. Young adulthood is a critical period of vulnerability for HIV-related risk behaviors including uptake in consumption of mood-altering substances before and during sexual encounters [2,3]. Among young adult African American gay and bisexual men, the most commonly used substances are alcohol and marijuana [4].

In recent years, researchers have begun to investigate an emerging mobile phone technology trend—sexualized text communication known as “sexting” [5-7]. Sexting describes sending and receiving sexually suggestive photos or text messages via mobile phone [5-7]. Benotsch et al found that sexting among young adults was associated with substance use (eg, alcohol, marijuana, ecstasy, cocaine), multiple sexual partners, unprotected sexual encounters, and sexually transmitted infections [5]. Bauermeister et al found that sexting was more prevalent among young adult gay and bisexual men compared to their heterosexual peers [7]. Although valuable contributions to the literature, both studies [5,7] were limited either by a predominately white, heterosexual or non-heterosexual sample, making it difficult to generalize to young adult African American gay and bisexual men.

Retrospective self-reports are the dominant method of data collection for assessing sexting and substance use among young adults [5-7]. However, collecting data through self-reporting methods can threaten the reliability and validity of measurement, particularly if individuals under- or overreport their behavior [8-10]. Ecological momentary assessment (EMA), a mobile health (mHealth) method that involves repeated sampling of an individual's behavior in real-time, is an innovative counterpart to traditional research methods that have heavily relied on retrospective self-reported measures [9,10]. EMA can increase the accuracy of self-disclosed, episodic behaviors such as sexting and substance use, and offers an observational longitudinal approach for collecting multiple, real-time assessments of these behaviors over time, and in an individual's environment [9,10]. The use of EMA also offers unique advantages, as it is designed to minimize recall bias, capture time-stamped data, and increase validity in daily life settings [9,10]. Additionally, EMA employs mobile technology data collection tools, including PDAs, Palm Pilots, and mobile phones [9,10]. Rapid advances in mobile phone technology and text messaging have vastly impacted communication and offer a promising approach to developing EMA methods for understanding how mobile phone technology trends, such as sexting, are associated with HIV-related risk behaviors.

Building on existing literature that has used EMA methods with young adult African American gay and bisexual men, the objective of this pilot study was to (1) describe the EMA study design and protocol, (2) characterize the study population, and (3) assess the feasibility of a text message–based thrice-daily EMA over 14 days, as a means of prospectively studying sexting, marijuana, and alcohol use among a sample of young adult African American gay and bisexual men aged 21 to 25. Feasibility was assessed in terms of random prompt text message survey response compliance, question response compliance, and response times. Retention was also assessed, and recommendations for future EMA research and implications for practice are presented.

Methods

Study Participants

Participants were recruited through flyers and snowball sampling during spring and summer 2015 at a community-based HIV/AIDS prevention, care, and support organization in Washington, DC. Prospective participants were screened by phone by a trained study coordinator to determine whether they met the study’s eligibility criteria, which included self-identifying as black/African American, self-identifying as gay or bisexual, being between the ages of 21 and 25, residing in the Washington, DC, metro area, being English-speaking, having a personal mobile phone and using it daily, having a mobile phone plan with unlimited text messages, and being able to travel to the designated study site.

Study Procedures

All eligible participants were screened and enrolled until the target sample size of 25 was met, which is characteristic of EMA pilot studies [11-13]. Participants completed a one-time study visit that consisted of informed written consent, a self-administered survey, a semi-structured interview, and training in EMA data collection. The self-administered survey assessed sociodemographic characteristics (eg, age, education, annual income, and current employment status), social networking application behavior (eg, self-reported use of the social networking applications Facebook and Jack’d), text messaging behavior (eg, self-reported daily texting frequency, sending and receiving sexts), sexual history (eg, self-reported number of male partners in the past 12 months), substance use (alcohol, combustible and noncombustible tobacco products,

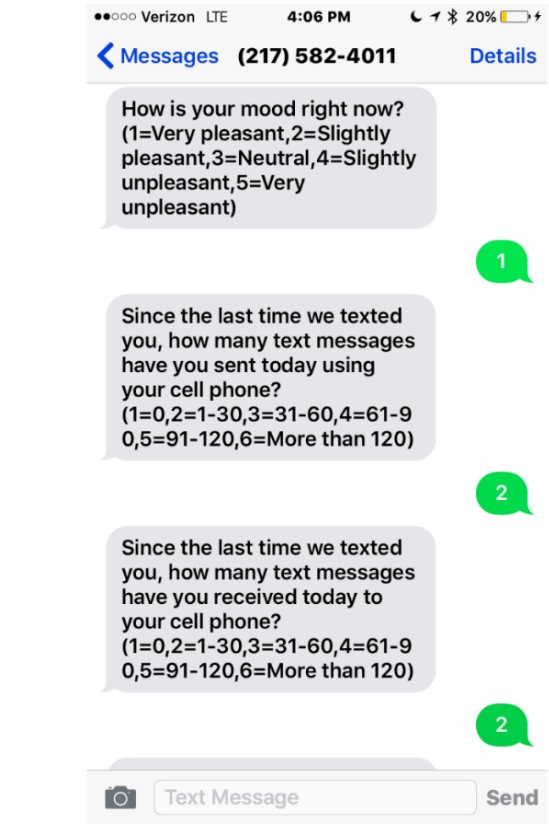
and marijuana), and psychological state (eg, self-reported anxiety and depression symptoms using the Patient Health Questionnaire for Depression and Anxiety [PHQ-4]) [14].

Ecological Momentary Assessment Data Collection

After participants completed the self-administered survey, the primary author registered their phones to receive the random prompt surveys, and participants were trained on how to respond to them via dummy surveys triggered to their phones. The EMA data collection system at the primary author's institution initiated random prompt surveys 3 times a day for 14 days. On weekdays, surveys were delivered between 6:00 AM and 23:59 PM. On weekends, surveys were delivered between 9:00 AM and 23:59 PM. The EMA data collection system recorded the date and time it took the participant to respond to and complete a random prompt survey, and the date and time a survey expired. The survey expired after 15 minutes of inactivity. The EMA data collection system returned an error message to prevent skipping items or entering out-of-range values. Text messages reminding participants to complete the random prompt surveys were delivered to participants' phones each day at 8:00 PM, and the primary author was available by office phone, work cell, and email to respond to participants' inquiries and concerns.

The random prompt survey consisted of 8 questions with responses including yes/no and Likert scale options. Questions were adapted from similar EMA questionnaires combined with current literature on sexting and substance use [7,15-17]. Figure 1 presents a screenshot of 3 of the 8 questions of the EMA random prompt text message survey. Questions included "How is your mood right now?" (1=very pleasant, 5=very unpleasant), "Since the last time we texted you, how many text messages have you sent today using your cell phone?" (1=0, 6=more than 120), "Since the last time we texted you, how many text messages have you received today to your cell phone?" (1=0, 6=more than 120), "Since the last time we texted you, did you send a sexually explicit message or photo of yourself using your cell phone today?" (1=yes, 2=no), "Since the last time we texted you, did you receive a sexually explicit message or photo of someone by way of cell phone today?" (1=yes, 2=no), "Right now, how much do you want to use marijuana?" (1=not at all, 4=to a great extent), "Since the last time we texted you, have you used marijuana?" (1=yes, 2=no), and "Since the last time we texted you, did you use alcohol, including sips of someone's drink or your own drink?" (1=yes, 2=no).

Figure 1. Screenshot of 3 of the 8 ecological momentary assessment (EMA) random prompt text message survey questions.



Participants received a US $25 Visa gift card at the one-time study visit. Following 14 days of EMA data collection, participants who completed less than 50% (0-20) of the random prompt surveys received a US $25 Visa gift card for their time and cell phone usage. To maximize response compliance, participants who completed 50% or more (21-42) of the random prompt surveys received a US $50 Visa gift card. Additionally, during data collection, the primary author contacted participants via phone call, text message, or email and informed them of their progress toward earning the US $50 Visa gift card. The Chesapeake Institutional Review Board approved all study procedures (Pro00012060) and a Certificate of Confidentiality was obtained through the National Institute on Drug Abuse.

Ecological Momentary Assessment Compliance Measures

Retention was defined as the percentage of participants who completed surveys on at least 10 of the possible 14 days of EMA data collection. Survey compliance reflects the proportion of complete surveys out of all surveys texted to the participant's phone. To count as a complete survey, all 8 survey questions were required to be answered by the participant. Partial survey compliance includes abandoned surveys, where at least 1 survey question was answered but not all 8 survey questions. Question compliance is the proportion of questions answered out of all questions sent. Time to complete a survey reflects the time between the first survey prompt and when participants completed their responses. Participants were prompted 3 times at 5 minute intervals; as such, time to complete a survey reflects not only the actual time to answer all 8 survey questions but also the number of prompts sent before a response was received.

Data Analysis

Descriptive statistics were used to characterize the study population in terms of sociodemographic characteristics, childhood experiences (parental smoking status, perceived introduction to adult responsibilities), self-reported health, personal financial status, use of social networks, sexualized text communication, sexual history, substance use, and compliance measures. Differences in survey compliance on baseline characteristics were examined using linear regression. Comparisons between week 1 and week 2 compliance measures were evaluated using paired *t* tests. Pairwise correlations were assessed for all 8 daily measures (mood, text sent, text received, sext sent, sext received, marijuana want, marijuana use, and alcohol use) using Pearson correlation. Cronbach alpha was also produced for the following related measures: (1) text sent, text received, sext sent, sext received and (2) marijuana want, marijuana use, alcohol use. All statistical analyses were completed in SAS version 9.4 (SAS Institute Inc) and Stata version 13 (StataCorp LP) with figures created in both SAS and JMP version 10.0.02 (SAS Institute Inc).

Results

Baseline Characteristics of Participants

Participants (n=25) were self-identified black/African American gay (n=16) and bisexual (n=9) men who ranged in age from 21 to 25 (mean 23.48, SD 1.5) years. More than half (15/25, 60%) reported annual incomes below US $35,000. The majority of the sample reported full or part-time employment (21/25, 84%) and at least some college education (21/25, 84%). When asked to describe their overall personal financial situation, 48% (12/25) of the sample reported just meeting basic expenses or not meeting expenses. In regard to childhood experiences, 64% (16/25) of the sample reported that one of their parents or guardians smoked cigarettes during their childhood. In terms of taking on adult responsibilities, 76% (19/25) of the sample reported growing up faster than other people their age. Most of the sample (19/25, 76%) reported using their phone multiple times per day to access social networking sites such as Facebook, Twitter, and Instagram. Nearly all (24/25, 96%) reported that they have received a sexually explicit photo of someone to their phone, and most of them (21/25, 84%) reported that they have sent a sexually explicit photo to someone using their phone. Over two-thirds (17/25, 68%) of the sample reported using marijuana every day or some days, and 56% (14/25) reported using little cigars/cigarillos/bidis at least 1 time in the past month. Additionally, 48% (12/25) reported drinking alcohol at least 2 to 3 times per week in the past month, and 36% (9/25) reported no condom use the last time they had anal sex with a man. According to the PHQ-4 [14], 52% (13/25) reported mild, moderate or severe psychological distress. Table 1 summarizes participants' characteristics.

Table 1. Participant characteristics.

		Survey compliance	
		β	*P* value[a]
Sociodemographics			
Race, n (%)			
African American	21 (84)	5.72	.65
More than 1 race (ref[b])	4 (16)	—	—
Age, mean (SD)	23.5 (1.5)	1.28	.68
Education, n (%)			
High school or less (ref)	4 (16)	—	—
Some college or more	21 (84)	8.33	.51
Employment, n (%)			
Working, paid or unpaid	21 (84)	4.11	.75
Not working (ref)	4 (16)	—	—
Childhood			
Parent/guardian smoked cigarettes, n (%)			
Yes	16 (64)	−14.53	.12
No (ref)	9 (36)	—	—
Grew up compared to peers, n (%)			
Faster	19 (76)	−18.2	.08
Slower/same rate (ref)	6 (24)	—	—
Self-reported health			
Health, n (%)			
Excellent or very good	17 (68)	11.66	.24
Good or fair (ref)	8 (32)	—	—
Psychological distress, n (%)			
None (ref)	12 (48)	—	—
Mild, moderate, or severe	13 (52)	−0.84	.93
Personal financial status			
Income, n (%)			
<US $35,000	15 (60)	—	—
US $35,000+	8 (32)	—	—
Unsure	2 (8)	—	—
Financial status, n (%)			
Live comfortably or meet needs with a little left	13 (52)	−8.11	.38
Just meet basic needs or don't meet basic needs (ref)	12 (48)	—	—
Financial satisfaction, n (%)			
Pretty well satisfied or more or less satisfied	16 (64)	−12.46	.19
Not satisfied at all (ref)	9 (36)	—	—
Social networking technologies			
Social networking on cell phone, n (%)			
Multiple times per day	19 (76)	−1.01	.93
Daily, weekly, or never (ref)	6 (24)	—	—

		Survey compliance	
		β	*P* value[a]
Use Jack'd application, n (%)			
Multiple times per day or daily (ref)	6 (25)	—	—
Weekly or monthly	12 (50)	4.78	.67
Never	6 (25)	0.81	.95
Sexting			
Received sexually explicit text, n (%)			
Yes	24 (96)	—	—
No (ref)	1 (4)	—	—
Received sexually explicit photo through text, n (%)			
Yes	24 (96)	—	—
No (ref)	1 (4)	—	—
Sent sexually explicit text, n (%)			
Yes	23 (92)	—	—
No (ref)	2 (8)	—	—
Sent sexually explicit photo through text, n (%)			
Yes	21 (84)	−8.90	.48
No (ref)	4 (16)	—	—
Sexual history			
Used condom in most recent sexual encounter, n (%)			
Yes	15 (62.5)	22.71	.02
No (ref)	9 (37.5)	—	—
Substance use			
Alcohol use past 30 days, n (%)			
2-4 times per month (ref)	13 (52)	—	—
2-3 times per week	12 (48)	0.06	>.99
Marijuana use, n (%)			
Every day or some days	17 (68)	−6.30	.53
Not at all (ref)	8 (32)	—	—
Little cigar/cigarillo use, n (%)			
Yes	14 (56)	−6.95	.46
No (ref)	11 (44)	—	—

[a]*P* value for linear regression; regression analyses were not performed for variables with small cell sizes (n≤2).

[b]ref: referent.

Feasibility Assessment

The EMA data collection period was programmed to last 14 days. There were 25 participants who provided 104 days of observation (April 17, 2015, through July 30, 2015). Average number of days of observation was 10.64 (SD 3.2, range 0-14). Due to a system scheduling error, 5 participants responded to the EMA random prompt text message surveys less than 14 days. Additionally, 1 participant's phone was lost during the data collection period resulting in missing data. Another participant did not complete any surveys during the 14-day EMA data collection period but was included in the final sample since surveys were still sent to his phone. The total retention rate was 72% (n=18). Table 2 summarizes EMA compliance data.

Table 2. Ecological momentary assessment compliance data.

	Totals	Ranges
Number of participants, n (%)	25 (100)	
Total days of observation[a], n	104	
Average days of observation per person, mean (SD)	10.64 (3.2)	Range: 0-14, interquartile range: 10-12
Retention[b], n (%)	18 (72.0)	

[a]First entry 4/17/15, last entry 8/6/15 (when cut off at 2 weeks last day was 7/30/15, so 104 days).

[b]One participant lost phone and was unable to complete the study; retention defined as percentage of participants who completed surveys on at least 10 of 14 days.

Table 3 summarizes EMA compliance data overall and by week. A total of 949 random prompt surveys were texted to the sample's phones and a total of 544 surveys were completed, resulting in an overall compliance rate of 57.3%. Due to the aforementioned system error, fewer surveys were sent out in week 2 compared to week 1. A total of 277/484 (57.2%) surveys were completed over week 1, and 267/465 (57.4%) surveys were completed over week 2. There were 41 surveys that were partially completed resulting in an overall partial survey compliance rate of 4.3%. Over week 1, 22/484 (4.5%) surveys were partial, and over week 2, 19/465 (3.9%) surveys were partial. Overall, 364 (36%) surveys expired due to nonresponse. A total of 4496 survey questions were completed resulting in an overall question compliance rate of 59.22%. Over week 1, 2290 (59.14%) questions were completed, and over week 2, 2206 (59.30%) were completed. Completion time was evaluated as the number of minutes elapsed from initiation of each survey to synchronization with the server. The overall mean response time was 6.06 (SD 4.99) minutes. The mean response time over the first week was 6.1 (SD 5.2) minutes, and over the second week it was 6.0 (SD 4.8) minutes.

Figure 2 shows the time, in minutes, participants took to complete the survey for each individual response on weekdays versus weekends across study days. Response time did not vary significantly between weekdays and weekends ($M_{weekday}$: 6.1 [SD 5.0] minutes; $M_{weekend}$: 6.0 [SD 5.0] minutes). Most points on weekdays and weekends lie beneath the 10-minute mark which indicates it took 2 or fewer system prompts to solicit a complete response from participants.

There were significant positive associations between EMA text sent and received questions (ρ: 0.84, P<.001) as well sexting sent and received queries (ρ: 0.72, P<.001). For text-focused EMA questions (text sent, text received, sext sent, sext received), the resulting Cronbach alpha was 0.68, suggesting acceptable internal consistency.

Table 3. Ecological momentary assessment compliance data overall and by week (data restricted to weeks 1 and 2 only).

	Overall	Week 1	Week 2
Response/compliance rate, n (%)			
By survey[a]	544 (57.3)	277 (57.2)	267 (57.4)
Partial surveys	41 (4.3)	22 (4.5)	19 (4.1)
By question[b]	4496 (59.2)	2290 (59.1)	2206 (59.3)
Status, n (%)			
Complete	544 (57.3)	277 (57.2)	267 (57.4)
Expired	364 (38.4)	185 (38.2)	179 (38.5)
Abandoned	41 (4.3)	22 (4.5)	19 (4.1)
Time to complete EMA[c]random survey[d], mean (SD)	6.1 (5.0)	6.1 (5.2)	6.0 (4.8)

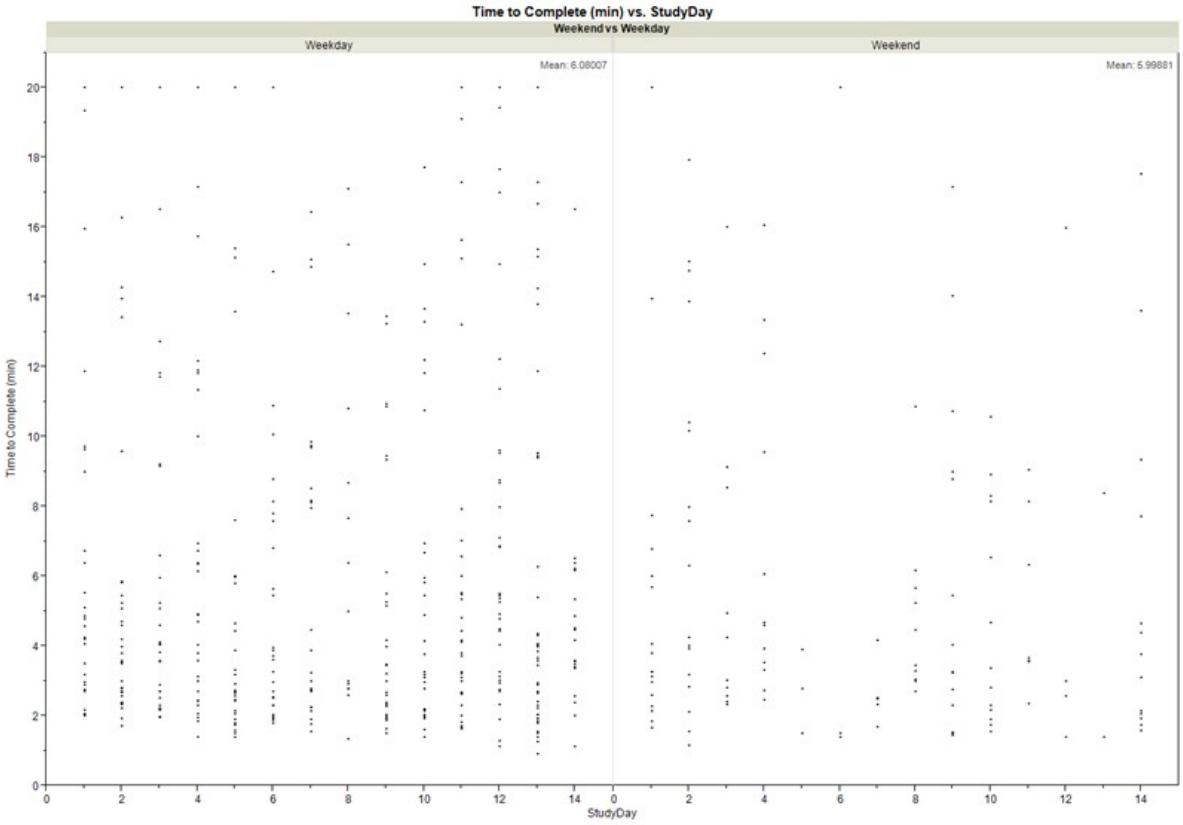
[a]Total number of random prompts completed/total number of random prompts possible (14 days × 25 participants × 3 surveys per day); excludes status code "initiating" from denominator.

[b]Total number of questions completed/total number of questions possible.

[c]EMA: ecological momentary assessment.

[d]Number of minutes elapsed from initiation of each random survey to synchronization with server; restricted to only complete responses and winsorized anyone who took over 20 minutes at 20 minutes.

Figure 2. Time-to-complete survey from first prompt by system to last response by participant on weekdays versus weekends across study days.



Discussion

Principal Findings

To our knowledge, this is one of the first pilot studies to examine the feasibility of mobile phone-based text message EMA to prospectively capture sexting and marijuana and alcohol use among a sample of young adult African American gay and bisexual men. Study findings suggest that completing random prompt text message surveys 3 times per day across 14 days is a feasible approach. This study also underscores the importance of partnering with community-based HIV/AIDS prevention, care, and support organizations, as findings demonstrate the feasibility of recruiting, enrolling, and retaining young adult African American gay and bisexual men in an intensive, longitudinal pilot study.

This study found an overall survey compliance rate of 57.3% (544/949), with a rate of 57.2% (277/484) across the first week and a rate of 57.4% (267/465) across the second week. Previous EMA studies have reported compliance rates from 50% to 90% [12,18,19]. Compared to these studies, an overall survey compliance rate of 57.3% is promising, given that compliance was impacted by 8 days of observation due to the participant whose phone was lost during the data collection period. Additionally, data for the participant who did not complete any surveys—suggesting that he dropped out the day after his study visit—was included since random prompt surveys were still texted to his phone across the 14-day course of the study. Future studies will involve repeated testing of the system software and EMA protocol and procedures, to ensure quality assurance. Particular attention should be given to a lower-burden EMA protocol and procedures that better meet the needs of young adult African American gay and bisexual men. For example, each random prompt survey contained 8 questions. Since most participants (21/25) reported working either full-time or part-time, it is possible that they were less likely to complete a survey when they were engaged in the active duties of their employment. Future research will explore prompting participants to answer fewer than 8 questions in a survey.

There were also similar response rates in question compliance in the first week (2290/4496, 59.14%) compared to the second week (2206/4496, 59.30%). Future research will include conducting individual interviews or focus groups with members of the study population. These methods of formative research may provide an opportunity to explore why a participant may or may not complete a random prompt survey, thereby informing acceptability and strategies to maximize compliance.

Similar to other studies [15,20], participants were provided up to 15 minutes to complete a random prompt survey, and the mean time to complete across the 14-day assessment was 6.1 minutes. Findings demonstrate that participants completed surveys in a very timely manner. Additionally, mean response time on weekdays (6.1 minutes) and weekends (6.0 minutes) were all under 10 minutes, indicating that it took 2 or fewer system prompts to solicit a complete response (eg, answered all 8 questions in a survey) from participants. This suggests a high level of comfort with text messaging among participants. Mean time to complete a survey was slightly but not significantly faster on weekends, suggesting that participants

may not have been as engaged in the active duties of their employment compared to weekdays.

Implications for Practice and Future Research

In this study, nearly all participants reported having received a sexually explicit photo of someone to their phone (24/25, 96%) and having sent a sexually explicit photo to someone using their phone (21/25, 84%). Additionally, 68% (17/25) reported using marijuana every day or some days, 48% (12/25) reported drinking alcohol at least 2 to 3 times a week in the past month, and 36% (9/25) reported no condom use the last time they had anal sex with a man. The sexting, substance use, and sexual risk behavior among this sample of young adult African American gay and bisexual men suggests that EMA data collection tools, including mobile phones and text messaging, have the potential to address mobile phone technology trends such as sexting and reinforce substance use treatment and HIV prevention, care, and support services available through community-based HIV/AIDS organizations serving this population. Future research involves (1) repeated testing of the EMA protocol and data collection system, (2) limiting the number of questions asked in a random prompt text message survey, (3) soliciting buy-in to the study during orientation, (4) increasing study visits, (5) retraining participants during study visits, (6) providing feedback on response compliance, (7) providing a higher bar for incentives, (8) including both random prompts and self-reports to capture events and assess level of substance use, and (9) evaluating protocol acceptability by participants.

Limitations

There are limitations to consider when interpreting study findings. While the sample size (n=25) was appropriate for pilot study research [21], the study is limited in generalizability, in that it uses a convenience sample of young adult African American gay and bisexual men who reported full or part-time employment, some college education, access to mobile phones with unlimited data plans, and residence in the Washington, DC, metro area. Although 15/25 participants (60%) reported annual incomes below US $35,000 and 9/25 participants (36%) reported that they just meet basic expenses, this study is unlikely to capture the diversity of viewpoints of all young adult African American gay and bisexual men. Additionally, in an effort to not overburden participants, EMA data collection was limited to 2 weeks. Future research should extend data collection to 3 or 4 weeks to provide more “in the moment” data.

Conclusions

Compared to their white and Latino peers, young adult African American gay and bisexual men are arguably at an increased risk for HIV infection [1,22,23]. Mobile phone technology and text messaging present opportunities for novel, innovative research and HIV prevention strategies. This feasibility study highlighted the utility of an EMA approach for advancing knowledge about episodic behaviors, such as sexting and marijuana and alcohol use, to inform research and prevention strategies for this relatively understudied and underserved population. Additional research is needed to customize a fully effective EMA platform.

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Authors' Contributions

SLS conceived the study design and manuscript topic, led and conducted data collection and data analysis, and wrote the first draft of the paper. HE conducted data analysis and contributed to manuscript writing. MWH, RSN, ABH, and NGM contributed to interpretation of results and manuscript writing.

Conflicts of Interest

None declared.

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Abbreviations

EMA: ecologic momentary assessment
PHQ-4: Patient Health Questionnaire for Depression and Anxiety

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Protocol

Co-creating and Evaluating a Web-app Mapping Real-World Health Care Services for Students: The servi-Share Protocol

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Abstract

Background: University students aged 18-30 years are a population group reporting low access to health care services, with high rates of avoidance and delay of medical care. This group also reports not having appropriate information about available health care services. However, university students are at risk for several health problems, and regular medical consultations are recommended in this period of life. New digital devices are popular among the young, and Web-apps can be used to facilitate easy access to information regarding health care services. A small number of electronic health (eHealth) tools have been developed with the purpose of displaying real-world health care services, and little is known about how such eHealth tools can improve access to care.

Objective: This paper describes the processes of co-creating and evaluating the beta version of a Web-app aimed at mapping and describing free or low-cost real-world health care services available in the Bordeaux area of France, which is specifically targeted to university students.

Methods: The co-creation process involves: (1) exploring the needs of students to know and access real-world health care services; (2) identifying the real-world health care services of interest for students; and (3) deciding on a user interface, and developing the beta version of the Web-app. Finally, the evaluation process involves: (1) testing the beta version of the Web-app with the target audience (university students aged 18-30 years); (2) collecting their feedback via a satisfaction survey; and (3) planning a long-term evaluation.

Results: The co-creation process of the beta version of the Web-app was completed in August 2016 and is described in this paper. The evaluation process started on September 7, 2016. The project was completed in December 2016 and implementation of the Web-app is ongoing.

Conclusions: Web-apps are an innovative way to increase the health literacy of young people in terms of delivery of and access to health care. The creation of Web-apps benefits from the involvement of stakeholders (eg, students and health care providers) to correctly identify the real-world health care services to be displayed.

(JMIR Res Protoc 2017;6(2):e24) doi:10.2196/resprot.6801

KEYWORDS

mapping of services; real-world health care services; Web-app; access to care; university students

Introduction

Overview

The years spent in university are a time of increasing independence and growth for young people. During this period, students actively make decisions about their health care and the healthy (or unhealthy) behaviors that they wish to adopt [1]. To prevent the risk of several diseases, young people aged 18-30 years are encouraged to regularly consult a general practitioner (and a gynecologist for females) in addition to consultants for particular health conditions (eg, dentists or ophthalmologists) [2]. Notwithstanding national recommendations and health promotion programs, French university students underuse health care services, with 20% not consulting a health professional (general practitioner or specialist) during their university years [3]. A small number of international studies have examined why young people avoid and delay medical care [4], providing a conceptual categorization of three main barriers: low perceived need to seek medical care; traditional barriers to medical care such as high cost, absence of health insurance, and time constraints; and lack of knowledge concerning the organization of the health care system and its services [5]. A study conducted on 41,000 French university students reported that: 23% of the participants did not feel the need to seek medical care, 13% did not have time for medical consultations, and 12% had economic difficulties to access and pay for health care services [3]. Another study examining 2000 French young adults (not all students) aged 15-30 years reported that lack of knowledge concerning the organization of the health care system and its services is a significant factor hindering utilization of health care services for 30% of young participants [6]. Our study took these three barriers into account with a specific focus on lack of knowledge as one component of students' *health literacy*, namely the lack of acquired and assimilated information on how to access health care [7]. Usually supported and guided by their parents in the management of their health consultations, young people moving away from home to start their university studies face, for the first time, the need to find a health care service, contact it, and access it on their own.

In parallel, university students are a technologically capable generation, having been born and raised in the age of home computers and portable electronic devices [8]. Using new technologies for obtaining information on the availability of health care services could represent an appealing solution for increasing students' health literacy.

However, notwithstanding their high use of new technological devices [9], young people have expressed their concerns about the quality and utility of existing electronic health (eHealth) tools [10]. Similarly, professionals coming from real-world health care services sometimes perceive eHealth solutions as complicating the health care provider-patient relationship [11], and being an unreliable source for medical advice [12].

A small number of eHealth devices have been evaluated to date [13]. Most of these devices have been produced by Web-developers that have little experience of health care, and have not taken stakeholders' opinions into consideration. More specifically, eHealth devices proposed as a bridge between eHealth and real-world health care are still scarce. Very little is known about the possible association between the use of eHealth tools and the use of real-world health care services, especially among young people [14].

We embarked on co-creating and evaluating a Web-app available on laptops, personal computers, smartphones, and tablets to show university students of the Bordeaux area of France low-cost or free health care services at their disposal, and where these services are exactly located. This is the local Bordeaux example of Web-app that could be extended at the national level in other French universities. The iterative processes of co-creating and evaluating the Web-app called the *services for the Internet-Based Students Health Research Enterprise (i-Share) students' cohort* (servi-Share) are described in this paper.

The servi-Share Project

The servi-Share project is nested in the larger i-Share cohort study, which is a nationwide online survey on the health and well-being of French-speaking university students. The i-Share cohort study started in 2013 from the collaboration of the University of Bordeaux and the University of Versailles Saint-Quentin (France), and is still ongoing across France. To be eligible to participate, students must be officially registered at a university or higher education institute, be at least 18 years of age, be able to read and understand French, and provide online consent for participation. The i-Share study was approved by the Commission Nationale de l'Informatique et des Libertés (CNIL; National Commission of Informatics and Liberties; DR-2013-019).

Preliminary analyses were conducted in the third year of the cohort study, on a total of 8770 students, 6578 of whom were females (75.01%). Results showed relatively high percentages of avoidance and delay of medical care: 3251 students (37.07%) declared having gone without recommended care, notwithstanding the need to see a doctor (general physician, consultant, eye-specialist); 1316 students (15.01%) declared having not seen a dentist, notwithstanding the need for a consultation; and 1325 students (15.11%) reported having gone without complementary health exams (ie, blood sample, radiography) prescribed by a doctor. Given these high rates, we explored the opportunity to put into practice a Web-based intervention aimed at facilitating students' access to real-world health care services. The servi-Share project was then implemented. First, a beta version of the servi-Share Web-app was developed and tested by students. Second, considering the results of the beta version tests, the Web-app will be corrected and implemented to be openly and largely diffused to university students within the Bordeaux area.

The two main hypotheses underlying the servi-Share project are that: (1) co-creating and evaluating a health Web-app with stakeholders may contribute to the production of an effective quality eHealth device, and (2) a better-quality eHealth device mapping real-world health care services should increase young people's health literacy in terms of knowledge of and access to health care.

Methods

The production of the Web-app consisted of two main processes: (1) co-creation, and (2) evaluation. Each process consisted of further operational stages involving academic staff and industry Web-developers, together with two target stakeholder groups (university students and real-world health care service providers). The two processes used both qualitative and quantitative methods. We opted for the co-creation process to involve stakeholders from the very beginning of the project, and not as mere testers of the finished Web-app [15]. The goal of this approach was to produce a Web-app that met the real needs of students, and corresponded to the precise choices of real-world health care service providers.

Process 1: The Co-creation

Exploring the Need of Students to Know and Access Real-World Health Care Services

A mixed-method field survey was conducted on the campuses of the University of Bordeaux. Participants were selected randomly following a quota sampling for the quantitative phase (paper questionnaire), and a snow-balling approach for the qualitative phase (semistructured face-to-face interviews). Our sampling strategy and rationale for the number of participants were based on previous project experience with university students, who declared that they were often unavailable, given their workload. At least 100 respondents to the questionnaire and 15 participants in the qualitative phase were considered sufficient to obtain a saturated sample. Finally, 126 students (72 females, 57.1%; mean age 22.1 years) answered the paper questionnaire and 16 students (11 females, 69%; mean age 22.3 years) underwent the semistructured face-to-face interview. The survey was coordinated by a junior full-time researcher and conducted by a group of four public health students (1 male and 3 females; mean age 23.7 years), constituting the stakeholder group of university students for the project. The results of this survey showed that students had the feeling that accessing real-world health care services is an expensive practice (59/126, 46.8%) which takes time (49/126, 38.9%). The qualitative phase allowed for the identification of a third overarching reason for students not to access to care: lack of knowledge of the health insurance system and the services offered. Two thirds of the students from both phases of the survey reported a strong interest in receiving a list of free or low-cost health care services available near their home and campus. The French health insurance system reimburses a large portion of medical consultations [16], but students expressed the need to be informed of the presence of totally free health care services adapted to their young age. Furthermore, receiving this list from a trusted source, such as a university research team, was felt to be reassuring. Complete results of the mixed-method field survey are available elsewhere (personal communication by Montagni et al, 2016).

Identifying the Real-World Health Care Services of Interest for Students

Based on the results of the survey described above, we established the following inclusion criteria for the real-world health care services to be displayed in the Web-app: being located in the Bordeaux metropolitan area (surface area 579,27 km^2; 28 municipalities in the Aquitaine-Limousin-Poitou-Charentes region, France); being free or low-cost (ie, costing a maximum of €15 per consultation); being addressed, either exclusively or among other population groups, to young people aged 18-30 years; and being outpatient. All health domains were taken into consideration without any exception (from general health to sexual health, gynecology, and dentistry). Emergency services were excluded, because the focus of the Web-app related to recommended general consultations.

At this stage, both target stakeholder groups selected by the servi-Share project were involved. For university students, the four public health students of the first stage performed a qualitative search consisting of a preliminary revision of existing documents (fliers, informative booklets), and the consultation of official Websites of the University of Bordeaux and local health services. These students produced an initial list of services in a prestructured Excel table and contacted each one by email and/or phone service. This phase served to produce a final list of 95 services distinguished according to their field of expertise (eg, addictions, contraception), their offer (eg, consultations, delivery of information, medical activities), and the type of professionals (eg, medical doctors, nurses, social carers). For each service, contact information and addresses were provided.

The target stakeholder group of real-world health care service providers was composed of seven health care professionals based in Bordeaux (1 health center director, 1 health center codirector, 1 psychiatrist, 1 general practitioner, 1 social worker, 1 administrative secretary, and 1 nurse). The stakeholder group of real-world health care service providers verified the list and counter-checked the details with respect to the inclusion criteria. After face-to-face meetings between the two target stakeholder groups, a final list of 88 health care services was established. Assuming that the Web-app will be maintained on the long term, we plan to contact the panel of seven health care professionals based in Bordeaux once per year to review and keep the list of health care services up-to-date. These professionals are also meant to inform our research group anytime new health care services are created or old health care services are closed.

Deciding on User Interface, and Developing the Beta Version of the Web-App

Academic staff and industry Web-developers involved in the project engaged the stakeholder group of four university students in the development of the Web-app. The four students participated in three 2-hour meetings with the industry Web-developers. Sessions were documented and students were encouraged to write on material provided, comment on the color templates, and suggest design decorations. Subsequent exchanges were facilitated by emails and phone calls.

For the stakeholder group of real-world health care service providers, their intervention at this stage was limited to the verification of information to be displayed in the Web-app. The stakeholder group of real-world health care service providers checked the information for clarity and comprehension, and

corrected the descriptions of the real-world health care services. The correct contents were sent by email to the Web-developers. Figure 1 shows how description of the services is provided in the beta version of the servi-Share Web-app.

We finally opted for a youth-friendly approach [17], balancing trusted informative content and a fresh design. Feedback at this stage was specifically sought regarding the colors, size, readability, and comprehension of the text and design elements (eg, logo, symbols). Students primarily had suggestions regarding specific design constructs, recommending graphic design to be gender neutral, with positive images and a simple interface. The beta version of the servi-Share Web-app was then produced. A detailed view of the beta design is shown in Figure 2.

Figure 1. Example of description of a service displayed in the servi-Share Web-app.

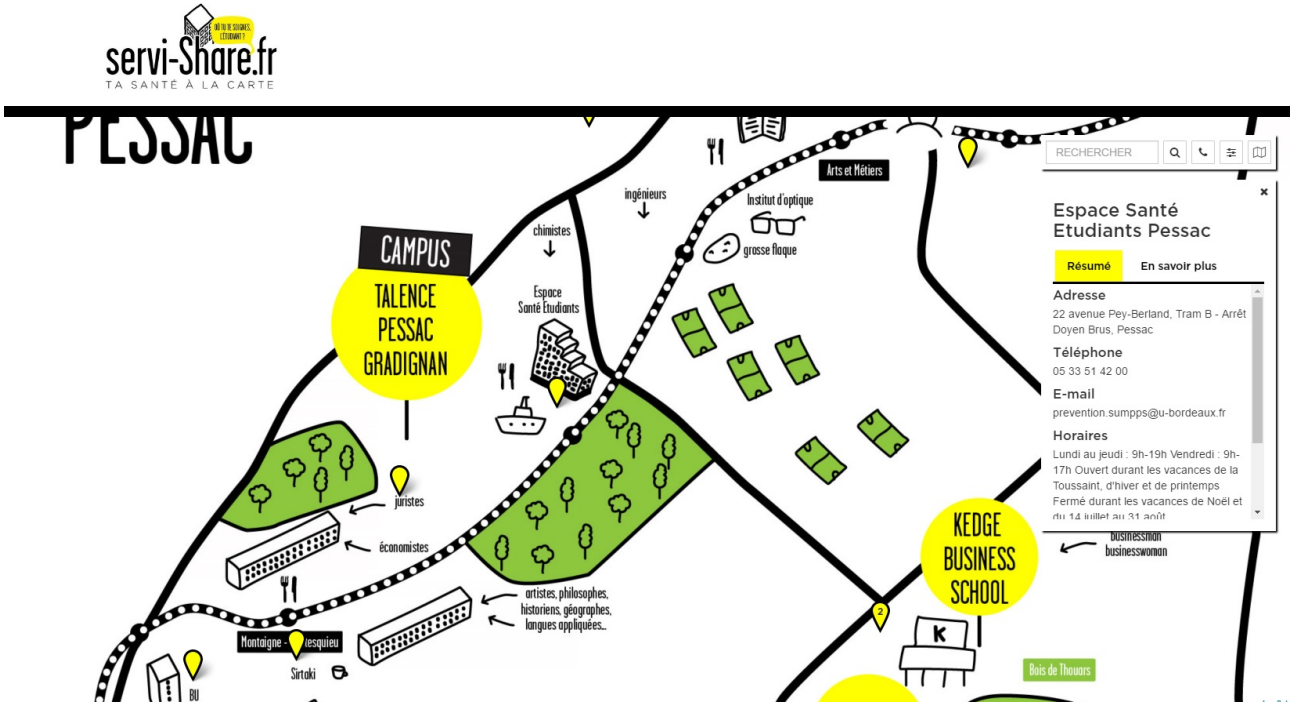
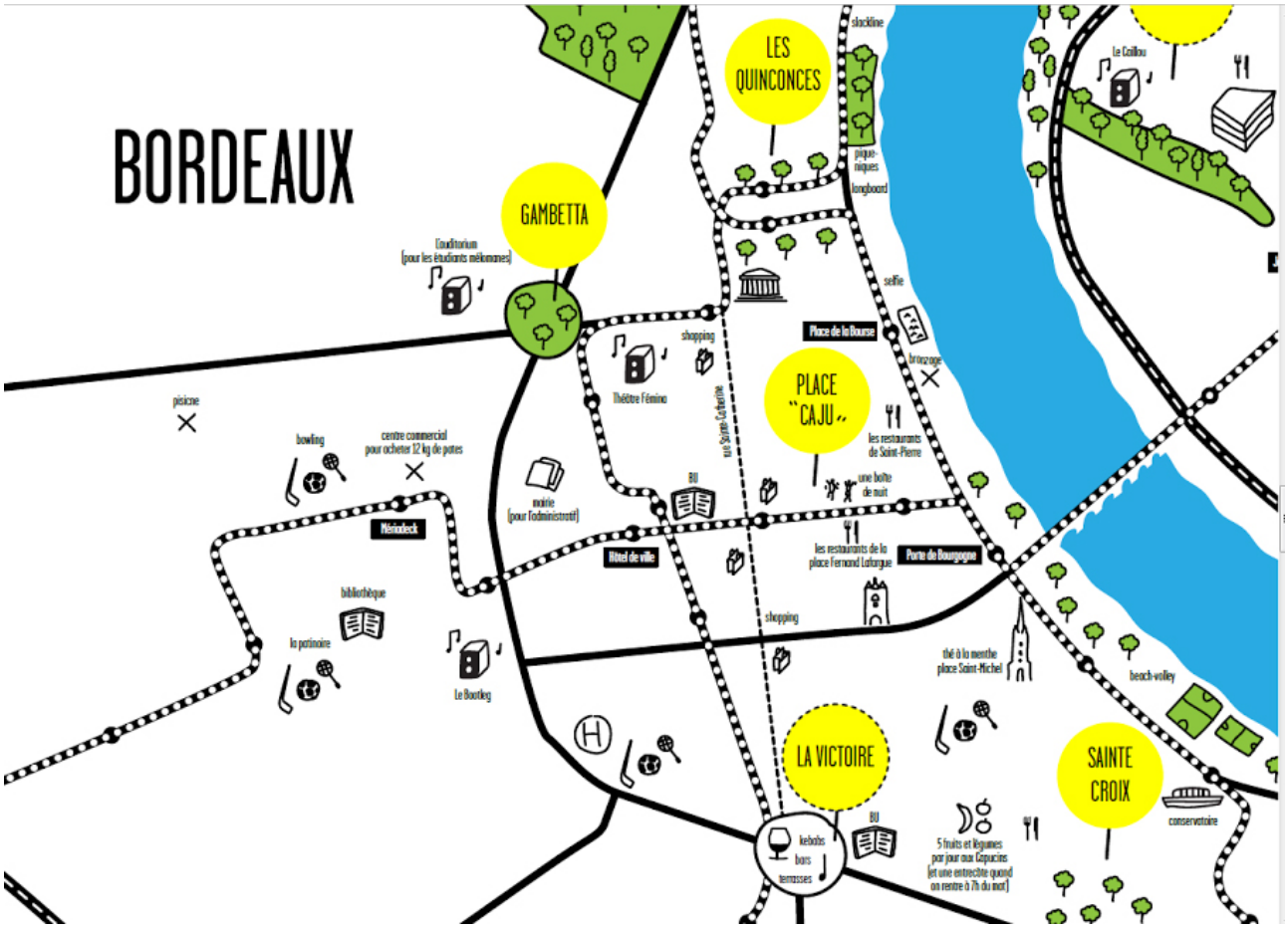


Figure 2. Detail of the map layout in the servi-Share Web-app.



Process 2: The Evaluation

Testing the Beta Version of the Web-App with Target Audience

An initial one-week test was performed by research staff from the i-Share study: 7 people tested the Web-app to report technical problems (eg, slow page loading), misspellings, and display issues. The second test of the beta version of the Web-app took two months and consisted of emailing the Web-app link to a sample of students belonging to the i-Share cohort study, in which the servi-Share project is nested. Students participating in the i-Share cohort study had voluntarily given their email addresses, and consented to be contacted following the regulations of the national board CNIL (DR-2013-019). We chose a convenience sample of 1300 students based on the following criteria: being a student in one of the universities or post-secondary schools of the Bordeaux area, being aged 18-30 years, and having completed both the i-Share baseline questionnaire and first follow-up questionnaire. Students responding to the follow-up questionnaire were thought to be actively involved in research, thus increasing the possibility of having their rapid feedback. According to the general response rate of i-Share participants to other substudy surveys (approximately 20%), we expected at least 300 students to use the Web-app and answer a 7-item questionnaire on the access to real-world health care services (see Multimedia Appendix 1). This sample did not include students from the co-creation process, to avoid bias in the answers and have new feedback on the Web-app.

The beta test was intended to develop a better understanding of how the Web-app was being used, and what issues arose during implementation. Student testers were asked to independently interact with the interface and search for real-world health care services on the Web-app. For ethical reasons, participants' usage of the Web-app could not be registered and health care services that were searched could not be tracked. The beta version of the Web-app is secured and password protected for students having received the link in the invitation email. Of the 1300 invited students, a final sample of 319 students tested the Web-app (24.54%).

Collecting Testers' Feedback Via a Satisfaction Survey

At the end of the test of the beta version (early November 2016), a satisfaction survey was sent by email to all 319 student testers. The survey was carried out using a Google form and included 10 items on six thematic issues: feasibility (item 1, "Have you encountered any difficulties in using this Web-app?"); appreciation of the Web-app (item 2, "Do you like the Web-app design?", and item 10, "How would you rate this Web-app?"); increased knowledge and perceived benefits (item 3, "Have you discovered through this Web-app some health care services you had never heard about before?", and item 4, "Have you found in the Web-app some new health care services you will have access to for the future?"); general interest (item 5, "Will you use this Web-app in the future instead of other geolocalization

search engines if you need to contact a health care service?", and item 8, "Will you recommend this Web-app to your friends?"); diffusion channels (item 6, "Where would you like to see this Web-app being promoted and diffused?", and item 7, "Through which channels do you think that students should be informed of the existence of this Web-app?"), and suggestions for improvement (item 9, "What would you like to add to this Web-app?").

The satisfaction survey represented the first step of the evaluation of the servi-Share Web-app. Using a participatory research methodology consisting of an iterative approach, we involved stakeholders in the short-term evaluation of the Web-app. In total, 73 of 319 students (22.9%, no missing values) answered the satisfaction questionnaire. Results are shown in Table 1.

Table 1. Results of the satisfaction questionnaire (n=126).

Thematic issue	Items	Yes	No
1. Feasibility	Item 1 - Have you encountered any difficulties in using this Web-app?	6 (8%)	67 (92%)
2. Appreciation	Item 2 - Do you like the Web-app design?	55 (75%)	18 (25%)
3. Increased knowledge and perceived benefits			
	Item 3 - Have you discovered through this Web-app some health care services you had never heard about before?	62 (85%)	11 (15%)
	Item 4 - Have you found in the Web-app some new health care services you will have access to for the future?	61 (84%)	12 (16%)
4. General interest			
	Item 5 - Will you use this Web-app in the future instead of other geolocalization search engines if you need to contact a health care service?	50 (68%)	23 (32%)
	Item 8 - Will you recommend this Web-app to your friends?	51 (70%)	22 (30%)

Concerning the diffusion channels (items 6 and 7), 54 of 73 students (74%) answered that they would like the Web-app to be displayed on the official website and social network pages of their university, 40 students (40/73, 55%) would not mind finding the Web-app on GooglePlay and/or AppStore, and 70 students (70/73, 96%) underlined the importance of diffusing the Web-app via the support of official institutions (eg, university and town hall).

Concerning suggestions for improvement (item 9), 65 of 73 students (89%) said the Web-app should display supplementary health care services, such as general practitioners and pharmacies, and 55 students (55/73, 75%) also reported that they would like to make an appointment online using the Web-app. Finally, when asked to rate the Web-app (item 10) on a scale from 0 to 10 points, 61 students (61/73, 84%) attributed a score of >7 points.

Results confirmed the interest of developing and diffusing a Web-based support informing students on the availability of free or low-cost health care services. Particularly positive results on items 3 and 4 confirmed students' acquired knowledge (health literacy) of the real-world health care services in the Bordeaux area, providing a proximal outcome of the utilization of our Web-app.

Planning a Long-Term Evaluation

For the second step of the evaluation, the real impact of the Web-app on users' health behaviors and practices in the long-term will be measured via the analysis of the i-Share cohort data. Each year, participants in the i-Share cohort must respond to a new yearly follow-up questionnaire. We plan to insert ad hoc items on at least two upcoming questionnaires to verify whether students have ever used the servi-Share Web-app and what impact it has had on their consultations and hospitalizations. Statistics on the number of participants accessing the Web-app will also be available and will give an approximative indication of the popularity of the Web-app. To corroborate our results, in the two years following the launch of the Web-app, the providers of the real-world health care services displayed in the Web-app will be asked (by means of a questionnaire) whether young people accessing their services have used our interactive map before consultations. All measures coming directly from stakeholders should provide a complete evaluation of the utility and quality of the servi-Share Web-app.

Results

The co-creation process took a total of 8 months (January-August 2016). The first step of the evaluation process has taken 4 months (September-December 2016). The second step of the evaluation (ie, long-term impact) is planned to take two years. Results are expected to contribute to the evidence-based development of a strategy of cooperation and collaboration among researchers, stakeholders (students and health care providers), and industry to produce eHealth tools of good and certified quality. The project was financed from January-December 2016 by the National Alliance for Life and Health Sciences (Alliance Nationale pour les Sciences de la Vie et de la Santé, AVIESAN) through two research financing Thematic Multi-Organisms Institutes (Instituts thématiques multi-organismes, ITMO) for Public Health (ITMO Santé Publique) and Health Technologies (ITMO Technologies pour la Santé).

Discussion

Here we have outlined the co-creation and evaluation processes used during the development of a Web-app mapping real-world health care services. The methodologies of the singular stages of these two processes have also been described, and we have underlined the utility of including stakeholders in both processes. The philosophy underpinning the servi-Share project is one of collaboration, empowerment, and participation, moving towards research *with* rather than *on* stakeholders.

For co-creation, the participatory approach with stakeholders was effective for informing design and development processes to help ensure our project is relevant, connects with young people, is grounded in the real-world, and can respond to the new social realities in which students live [18].

For evaluation, the two steps of this process permit us to assess: (1) in the short-term, if the Web-app is of interest to students and increases their health literacy in terms of knowledge of real-world health care services (proximal outcomes); and (2) in the long-term, if the Web-app will imply behavioral changes that make students more frequently contact and access real-world health care services (distal outcomes). The second step of the evaluation process will allow us to test whether the servi-Share Web-app represents a valid bridge between eHealth and real-world services, and whether other functions (eg, making appointments online) should be added to the Web-app.

Existing literature on health literacy strongly suggests that young people's health empowerment is induced by knowledge improvement [19,20]. However, the transition from knowledge to action is a debatable question. The longitudinal results issued from the i-Share cohort will help us understand whether the use of the geolocalizing Web-app servi-Share is positively related to the access to real-world health care services (ie, an increased number of accesses to real-world health care services). Using our Web-app, we hypothesize that students will better understand the organizational structure and offerings of real-world health care services, thus identifying the health care services to promptly contact and attend. Avoidance and delay of medical care could then be reduced.

Strengths and Limitations

The servi-Share Web-app is different from other Web-mapping tools (eg, Google Map, Waze Map, Bing Map) that display any type of service without specific quality criteria, as it maps and describes preselected real-world health care services. This preselection should facilitate the choice by users, who can feel reassured by the fact that the health care services that are displayed are specifically addressed to them, are free or low-cost, and are advised by an expert scientific team.

However, a limitation of this study is that one may argue that a Web-app showing real-world health care services could increase the workload of these services, and overwhelm them with contacts that do not correspond to legitimate health needs. The aim of the servi-Share Web-app is not to increase undue consultations, but to guide students to a well-conceived selection of the services to access. Conversely, the servi-Share Web-app has not been conceived as a substitute for real-world health care services. The young population we are addressing is at risk for medical care avoidance. Most students do not know who to contact when they fall ill, and consequently do not seek care and tend to self-medicate, thus worsening their health conditions [21].

Conclusions

We have described a novel approach using a Web-app linking real-world health care services and eHealth. Our preliminary findings concerning the co-creation process suggest that this participatory approach was both feasible and welcomed by both groups of stakeholders (university students and real-world health care service providers). Findings from the evaluation process will assess the long-term impact of the Web-app on real-world health care access by university students. Our Web-app is expected to be beneficial to young people, health care providers, policymakers, and health system managers.

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Authors' Contributions

IM drafted the manuscript. EL, JW, and CT revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

The web-application 7 item questionnaire on the access to real-world healthcare services .

[PDF File (Adobe PDF File), 589KB - resprot_v6i2e24_app1.pdf]

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Abbreviations

CNIL: National Commission of Informatics and Liberties
eHealth: electronic health
i-Share: Internet-Based Students Health Research Enterprise
ITMO: Thematic Multi-Organisms Institute
servi-Share: services for the Internet-Based Students Health Research Enterprise students' cohort

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Protocol

Dance for Adults With Fibromyalgia—What Do We Know About It? Protocol for a Scoping Review

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Abstract

Background: Fibromyalgia is a chronic disorder characterized by widespread muscular tenderness, pain, fatigue, and cognitive difficulties. Nonpharmacological treatment options, such as physical activity, are important for people with fibromyalgia. There are strong recommendations to support engagement in physical activity for symptom management among adults with fibromyalgia. Dance is a mode of physical activity that may allow individuals with fibromyalgia to improve their physical function, health, and well-being. Dance has the potential to promote improved pain processing while simultaneously providing the health and social benefits of engaging in physical activity that contributes to symptom management. However, we are unaware of current evidence on dance as a nonpharmacological/physical activity intervention for adults with fibromyalgia.

Objective: The aims of the study are to provide an overview of the extant evidence to understand how dance is used for individuals with fibromyalgia; to examine the extent, range, and nature of research activity in the area; and to determine the value of undertaking a full systematic review.

Methods: Scoping reviews are useful to comprehensively and systematically map the literature and identify key evidence, or research gaps. The search strategy will involve electronic databases including Medline, Embase, Cochrane Library, PsycInfo, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Literature in the Health Sciences in Latin America and the Caribbean (LILACS), Allied and Complementary Medicine (AMED), International Bibliography of Theatre and Dance, Physiotherapy Evidence Database (PEDro), Trip, Proquest Theses/Dissertations, Web of Science, World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov. The study will be mapped in seven stages: (1) identifying the research questions, (2) identifying relevant studies, (3) selecting the studies, (4) charting the data, (5) collating, summarizing and reporting the results, (6) consulting, and (7) disseminating the knowledge.

Results: The search, title, and abstract are now completed; full text screening was carried out and authors are awaiting interlibrary loans and translations. Data extraction will start shortly after full text 'screening' is completed. Completion is expected in Fall 2017.

Conclusions: To our knowledge this will be the first attempt to systematically identify knowledge of dance as a potential intervention for adults with fibromyalgia. This scoping review offers a feasible means for describing the evidence specific to dance and fibromyalgia; results will provide unique insights concerning the breadth and depth of literature in the area. An analysis

of this body of literature as a whole may reveal new research directions or unknown ways this intervention could strengthen current management approaches of the disease.

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KEYWORDS

fibromyalgia; dance; scoping review; physical activity; adults; protocol

Introduction

Description of the Condition

Fibromyalgia is a chronic disorder characterized by widespread muscular tenderness, pain, fatigue, and cognitive difficulties [1,2]. Individuals with fibromyalgia may experience sleep disturbances, anxiety, depression [3,4], and difficulty with attention and concentration, as well as a range of gastrointestinal (eg, irritable bowel syndrome) and somatosensory (eg, hyperalgesia, allodynia, paresthesia) symptoms. These symptoms can affect an individual's quality of life, often negatively impacting family dynamics, capacity and productivity at work, and independence [2]. The diagnosis is often complex requiring a history of typical symptoms over time and the exclusion of somatic diseases by medical examination [1].

Fibromyalgia is common worldwide with the prevalence reported to be 2% to 4% of the general population, with diagnosis in females outnumbering diagnosis in males [1,5]. Insights gained from research in the past several decades implicate numerous factors in its pathophysiology including changes in brain and neural structure and function, muscular physiology, hormonal factors, inflammatory markers, and genetic influences [6]. Mounting evidence shows that individuals with fibromyalgia experience pain differently from the general population because of dysfunctional pain processing in the central nervous system [7].

Description of the Intervention and How It Might Work

There is vast evidence supporting exercise interventions for individuals with fibromyalgia; in the most recent European League Against Rheumatism guidelines, Macfarlane et al [8] concluded there is a strong recommendation to support both aerobic and resistance training in symptom management for individuals with fibromyalgia. This is in part due to the pain management achieved through physical activity and the low cost and ease of access to physical activity opportunities. Physical activity is defined as any bodily movement produced by skeletal muscles resulting in energy expenditure [9]. Dance, a genre of physical activity, can be a social experience, an artistic expression, or a leisure activity as well as rigorous physical activity. Building on perspectives shared by Beardsley [10], we operationalize dance as a purposeful, deliberate, and expressive motion of the body caused by contraction of the skeletal muscles. Dance may or may not include music; although dance movements could be called "functional" (eg, bending, walking, reaching), the goal of dance movement is the deliberate and purposeful expression of the body itself through movement [11].

There is evidence describing benefits of dance for chronic disease conditions. Dance among individuals with heart failure has demonstrated increased functional and cardiovascular benefits as well as increased motivation for participation [12], quality of life [13], and a reduction in cardiovascular mortality [14] when compared to traditional exercise training. Research shows exercise capacity and quality of life improved with dance in individuals with Parkinson disease [15]. Emotional benefits were seen after dance-based exercise participation in older individuals with or without chronic depression or depressive symptoms [16]. Also, dance enhanced the locomotor ability (ie, movement from one place to another) of individuals with severe rheumatoid arthritis [17]. Other dance genres such as jazz dance [18], Argentine tango [19,20], Turkish folklore [21], Korean traditional dance [22], social dance [23], ballroom dance [24], modern dance [25], waltz [26], and specific designed-exercise dance programs [27] have shown benefits for individuals with a myriad of clinical conditions.

One specific dance-based therapeutic approach common in the literature of individuals with chronic conditions is dance movement therapy (DMT). The American Dance Therapy Association defines DMT as a psychotherapeutic use of movement that furthers the emotional, social, cognitive, and physical integration of the individual. This form of dance has a systematic treatment approach, is goal-oriented, and may include a variety of dance movement methods [28]. Chronic conditions DMT has been used for include cancer [28], schizophrenia [29,30], depression [31], dementia [32,33], and Parkinson disease [15]. We are aware of 3 publications including adults with fibromyalgia [34-36].

Dance contributes to the physical training of balance, coordination, strength, flexibility, aerobic capacity, bone health, and proprioception (ie, knowing where the body is in space). Additionally, dance promotes increased motivation to exercise [37], increased attention and cognitive capacity through increased neural connections and blood flow [38], increased vitality [39], and positive effects on mood [22], everyday competencies, and social life [40]. Dance can also offer auditory, visual and sensory stimulation; motor learning; emotional perception; expression; and interaction. All these features make dance an "enriched environment" which stimulates the brain's plasticity [40]. Characteristics of dance suggest that it is worth evaluating as a means of relieving fibromyalgia symptoms.

Pain Processing

Widespread pain and fatigue are hallmark symptoms of fibromyalgia and are known factors limiting an individual's participation in treatment [41]. During physical activity, the muscular and physiological stress on the body stimulates the release of endorphins, which contributes to the sensation of an

activity high and, potentially, a "social high" [42]. Evidence supports that both physical pain (the unpleasant experience that is associated with actual or potential damage to tissue) and social pain (the unpleasant experience that is associated with actual or potential damage to one's sense of social connection or value) are processed with shared neural circuitry [43]. This supports the hypothesis that experiences in social and physical pain may be similar for the individual, such that individuals experiencing chronic physical pain are more likely to avoid activities for fear of inducing both social and physical pain [43,44]. Therefore, a social activity intervention may lead to improved treatment outcomes for adults with fibromyalgia by improving pain processing.

Social Bonding and Pain

Dance is an engaging and enjoyable form of physical activity. Group or social dance facilitates social bonds through working in synchrony (performing the same movements at the same time) [42,45]. Synchronization and physical exertion, such as through dance, independently elevate the pain threshold [42]. Moreover, dance can increase self-control, which impacts psychological health and therefore the experience of chronic pain [34]. Dance has the potential to promote improved pain processing while simultaneously providing the health and social benefits of engaging in physical activity that contribute to symptom management for adults with fibromyalgia.

Why It Is Important to Do This Scoping Review

The authors of this scoping review have worked extensively on synthesizing the evidence of exercise training for adults with fibromyalgia [46-48]. To date, we do not know what evidence exists examining dance for adults with fibromyalgia. As there is a continuous need to offer appropriate nonpharmacological options to people with fibromyalgia, and after contemplating various systematic approaches available for reviewing the literature, we chose to undertake a scoping review as the best method to understand the evidence around dance for adults with fibromyalgia. We wish to examine the extent, range, and nature of research activity in the area and determine the value of undertaking a full systematic review.

Methods

Overview

Scoping review methodology is particularly useful for examining the breadth of the research in a specific topic area. Also, scoping reviews are useful to comprehensively and systematically map the literature and identify key evidence or research gaps. Unlike most synthesis reviews, scoping reviews do not narrow the review to specific research designs. Nonetheless, this type of review is rigorous and methodical in its approach to examining the extent, range, and nature of research activity in a particular field [49-52] while encompassing both empirical and conceptual research with openly framed questions.

In designing the protocol for this scoping review, we drew primarily upon Arksey and O'Malley's seminal work [49] on a 6-stage scoping review framework. Adaptations (including the addition of a seventh step) were driven by an intention to develop a feasible approach for reviewing the body of literature.

Stage 1. Identifying the Research Questions

Following Arksey and O'Malley's suggestion, we followed an iterative process for developing the research questions. We continued doing this as we became increasingly familiar with the literature. We realized the need for an iterative process and first ran a trial search.

Our intention to comprehensively examine and map the evidence on dance in adults (ie, 18 years or older) with fibromyalgia prompted us to develop the following initial questions:

What is known from the literature about dance for adults with fibromyalgia (eg, definition of dance, participant characteristics)?

What type of dance is commonly used (eg, traditional mainstream, adapted, dance to music) and what are the characteristics of dances reported (frequency, time, length, etc)? Who is in charge of the instruction, and what is the setting in which dance occurs?

What type of publications are reporting dance, what is the quality of the publications, and what are the main outcomes measured and reported?

Do studies report the acceptability, feasibility, and applicability of dance for clinical practice?

Have studies reported any challenges or limitations upon implementation of a dance class/intervention?

Stage 2: Identifying Relevant Studies

The aim of this scoping review will be to comprehensively address 'the above' broad research questions; however, parameters are required to guide the search strategy.

Eligibility Criteria

The following inclusion criteria will be used to guide the search and review the articles:

- Published in any language (for publications that are not in a language mastered by the review team [English, Norwegian, Swedish, Icelandic, Spanish, German, Portuguese, French] individuals proficient in the language or translation software will be used)
- Human subjects
- Adults aged 18 years and older with fibromyalgia
- Publications that target adults with fibromyalgia of any gender or ethnicity in any setting (private practice, clubs, community association) and type of dance
- Publications including research projects, pilot experience, and protocols
- Scope limited to include published literature (ie, peer-reviewed journals, books or book chapters, dissertations, guidelines) and grey literature
- Concepts of dance/therapy/movement and fibromyalgia evident either in title or abstract during screening phase

Explicit exclusion criteria identified:

- Publications with a population that is not exclusively adults with fibromyalgia or we cannot isolate the results for adults with fibromyalgia

- Publications in which individuals are nonactive participants (ie, they are observers only)

The nature of a scoping review is to include multiple forms of evidence and not exclusively randomized controlled trials. Our inclusion criteria were established to identify and include research reports of participation in dance and exclude research reports of observation of dance. Therefore, self-report data, such as published case studies or reports in the grey literature, of participants engaging in dance as related to fibromyalgia symptoms would meet inclusion criteria.

Databases

An experienced information specialist will establish and test the search strategy. Based on her expertise and the outline of this project, she will select keywords and controlled vocabulary terms to maximize sensitivity and specificity within the search. She will be instrumental in choosing and applying search terms to comply with databases in the health and social sciences. The complete and final search strategy will be provided in a follow-up publication. Upon completion, the results from each database will be documented, and the references will be imported into a bibliographic management software to eliminate duplicates. References will be imported to a review software for screening.

Databases used:

- Medline in-process and other nonindexed citations (Ovid)—1946 to present
- Embase and Embase Classic (Ovid)—1947 to present
- Cochrane Library (Wiley)
- PsycINFO (Ovid)—1806 to present
- Cumulative Index of Nursing and Allied Health Literature (CINAHL) (EBSCO)—1937 to present
- Literature in the Health Sciences in Latin America and the Caribbean (Literatura Latino Americana em Ciências da Saúde, LILACS)
- Allied and Complementary Medicine (AMED) (Ovid)—1985 to present
- International Bibliography of Theatre and Dance (EBSCO)—1984 to present
- Physiotherapy Evidence Database (PEDro)
- Trip
- ProQuest Theses and Dissertations—1997 to present
- Web of Science Core Collection (Thomson Reuters)—1900 to present
- World Health Organization International Trial Registry Portal
- ClinicalTrials.gov

Searching other resources:

- We will search the bibliographies of relevant studies and reviews.
- Corresponding authors of previously found dance randomized controlled trials will be contacted regarding their knowledge of ongoing studies or groups involved in the area.
- An a priori set of fibromyalgia associations will be selected and their associations' webpages will be screened for annual reports or findings that these associations produce based on their own research, which will be retrieved.

Stage 3. Selecting the Studies

We will use a 2-stage selection process. In the first instance, 2 reviewers will independently screen citations and abstracts for inclusion. At this stage, uncertainties from the reviewers will not automatically eliminate the record. We will determine final inclusion at the second level (full text screening). A third reviewer will arbitrate in cases where there is disagreement at the final stage. All authors will be trained in software use, and a predetermined and piloted criteria will be followed at both stages.

The full text of all papers identified as having potential for inclusion will be requested. Non- English articles will be translated. Data will be extracted from papers included by independent review authors. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [53] will be used to report final numbers upon completion of the scoping review.

Stage 4. Charting the Data

We will collect and sort information from the selected full text articles (see Table 1). We will use standardized data extraction forms created and piloted by the team for this purpose. Team members will train in data extraction to standardize the process and ensure consistency of the data extraction process. We will examine the charting consistency with the questions and purpose. Additional categories may emerge during the data collection process, in which case, in consultation with the team, we will adapt and restructure the forms.

Table 1. Data to be extracted

Data	Details to be extracted (if available)
Publication summary	Author, year, title, publication type, inclusion/exclusion, country, language of publication
Population	Total sample size, age, gender, diagnosis, years since diagnosis, baseline characteristics, comorbidities, medication, diagnostic criteria
Intervention	Objective/type (ie, leisure, training, complementary)
	Descriptor such as: frequency, intensity, length, mode, setting, instructor qualifications, follow-up, use of music, dance alone, in-group, with partner
Setting	Community, hospital, club, university, etc.
	Cost and equipment
Outcomes	Any outcomes: symptoms (eg, pain, fatigue, sleep), psychosocial (eg, depression, self-awareness, mood, self-esteem), physical function (eg, physical health, range of motion, cardiovascular, strength, flexibility), health-related quality of life, relationships, and communication (isolation, verbalization, family support), withdrawals. Adverse events, harms, or related terms: challenges, limitations, barriers, injuries, exacerbations
Other	Effectiveness
	Adherence to intervention such as acceptability, feasibility, applicability for clinical practice

Given the authors' backgrounds in systematic review of interventions for adults with fibromyalgia, the appraisal of included studies will be restricted (if found) to those scientific publications explicitly addressing intervention effectiveness. This may provide direction for future research.

Stage 5. Collating, Summarizing, and Reporting the Results

The unique purpose of a scoping review is to aggregate the findings and present an overview.

We plan to do the following:

- Map results (main sources, quantity, and quality of evidence available) from the literature.
- Provide a descriptive summary: extracted data from all included publications will be summarized to describe the use of dance in adults with fibromyalgia. Because this is a scoping review, there is no principal summary measure. However, if possible, the following analyses will be completed:
  - Descriptive statistics will be used to summarize the data. Frequencies and percentages will be used to describe nominal data.
  - Conceptual definitions will be subject to a comparative analysis where verbatim 'extracts' will be coded by review authors. The purpose will be to identify the dimensions and properties of each definition as well as their relationships with other components. This analysis will involve identification of dimensions of the concept of dance, recurrent themes, variations, contradictions, and connections.
  - If possible, we will use computer-assisted clustering techniques to present the information in graphical form (eg, bubble plot, word cloud) [54,55].
- A glossary of terms will be created to clarify definitions found in the literature.

We will follow and adapt PRISMA reporting guidelines for systematic reviews [53], PRISMA equity [56], and a PRISMA harms checklist [57] to accurately report the results and analysis summary.

Step 6: Consulting

With the aim to ensure applicability and usability of results, the findings of this scoping review will be shared throughout the protocol writing, collating, and summarizing phases with the consumers associated with the team. They will provide their comments and thoughts throughout the scoping review's duration. We will also engage research experts in dance, fibromyalgia, and synthesis methods to review the project protocol and provide objective feedback in findings and final reporting. The fibromyalgia and physical activity team (led by AJB) will be asked to validate our findings and provide feedback and guidance on the completion of the final manuscript. All responses and opinions will be integrated into the study.

Step 7: Disseminating the Knowledge

Although not part of Arksey's framework, we believe it is important to make the content of this scoping review available to clinicians and consumers with the goal of increasing awareness of the literature and helping to make evidence-informed choices for clinical management of fibromyalgia. Some of the steps we plan to take include writing a scientific publication, presenting the results at a conference, distributing a plain language summary report to self-help groups and organizations working with individuals with fibromyalgia, posting a summary of the results to the fibromyalgia and exercise team website, and exploring the dance4healing app as a venue to distribute our results. Additionally, we plan to develop teaching material from this scoping review (eg, case study) to be used in chronic disease management courses in health and rehabilitation programs involving undergraduate and graduate students.

Results

The search, title, and abstract are now completed; full text screening was carried out and authors are awaiting interlibrary loans and translations. Data extraction will start shortly after

full text 'screening' is completed Completion is expected in Fall 2017.

Discussion

A large body of evidence from the past decades supports the use of physical activity as one of the main nonpharmacological interventions for adults with fibromyalgia. Exercise training (eg, aquatic, resistance, aerobic) is often part of the overall management of fibromyalgia, decreasing peoples's symptoms and improving their quality of life. However, our understanding of dance use in this population is limited. To our knowledge this will be the first attempt to systematically identify knowledge of dance as a potential intervention for adults with fibromyalgia.

This scoping review offers a feasible means for synthesizing the evidence specific to dance and fibromyalgia; results will provide unique insights concerning the breadth and depth of literature in the area. We anticipate we will be able to identify research trends and potential gaps specific to our research questions as well as novel ideas for primary research concerning this intervention. An analysis of this body of literature as a whole may reveal new research directions or unknown ways this intervention could strengthen current management approaches of the disease.

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Authors' Contributions

JB and CB conceptualized the initial review protocol. The entire team (JB, CB, AB, SMG, SK, and EK) collaboratively drafted the manuscript, with numerous iterations and substantial input and appraisal from all authors. All authors have approved the final version of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AMED: Allied and Complementary Medicine
CINAHL: Cumulative Index of Nursing and Allied Health Literature
DMT: dance movement therapy
LILACS: Literature in the Health Sciences in Latin America and the Caribbean
PEDro: Physiotherapy Evidence Database
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Short Paper

Online Dissemination Strategies of a Canada Research Chair: Overview and Lessons Learned

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Abstract

Background: Little is known about the use of online dissemination strategies, such as websites and social media, to increase the visibility and uptake of research.

Objective: To describe two online dissemination strategies of the Canada Research Chair in Implementation of Shared Decision Making in Primary Care over an eight-year period.

Methods: Our two sources of online dissemination data were the website of the Canada Research Chair in Implementation of Shared Decision Making in Primary Care and the Chair's Twitter account. We conducted a content analysis of the news section of the website. We extracted website usage statistics using Google Analytics and analyzed indicators such as total number of visits, new and returning visitors, page views per visit, time spent onsite per visit, visitors' country of origin, and most popular pages. From the Chair's Twitter account, we collected the number of tweets, followers, and follows. We consulted Google Scholar to chart the trend in citations of the Chair's articles over the same period.

Results: From the website's inception in January 2008 to December 2015, we recorded an average of 7906 visits per year (3809 in 2008; 8874 in 2015), 65.85% of which involved new visitors (5206/7906). The average number of pages viewed per visit was 3.2 and average bounce rate was 57.87% (4575/7906). Visitors spent an average of two minutes and 12 seconds per visit. We computed visits from 162 countries, with the majority from Canada (5910/7906, 74.75%). In order of frequency, the seven most visited pages were: (1) home page with news of publications and grants (24,787 visits), (2) profile of Chairholder (8041 visits), (3) profiles of research team members (6272 visits), (4) list of research team members (4593 visits), (5) inventory of shared decision making (SDM) programs (1856 visits), (6) interprofessional approaches to SDM (1689 visits), and (7) description of Chair activities (1350 visits). From the inception of the Twitter account in April 2011 to November 30, 2016 we recorded 5831 tweets in French and English, 1679 followers, and 1112 follows. The total number of visits and visitors to the website increased during the first three years, stabilized, and then dropped slightly, while the number of returning visitors rose slightly. In comparison, citations of the Chair's articles increased steadily over the same period, rising more sharply as visits to the website declined.

Conclusions: Over an eight-year period, visitors to the website increased in the first three years before levelling off. Meanwhile, the Chair's citations rose continuously. There was no observable association between website visits or Twitter activity and rising citations. Our results suggest that online dissemination may not yet be a major determinant of research uptake or visibility in the scientific community.

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KEYWORDS

social media; knowledge translation; shared decision making; online dissemination; knowledge dissemination

Introduction

Knowledge dissemination strategies are essential for moving health services research into practice [1-4]. Traditional strategies include peer reviewed publications and conferences. Newer online methods [5,6] include passive platforms (eg, websites) as well as more active social media platforms (eg, Twitter) that allow the creation and exchange of user-generated content [7]. While research teams are increasing their use of online dissemination strategies, little is known about their influence on the visibility and uptake of research results [8-12].

The Canada Research Chair in Implementation of Shared Decision Making in Primary Care, based in Quebec City, was created in June 2006 (evolving into the Canada Research Chair in Shared Decision Making and Knowledge Translation in 2016) [13]. The mission of the Chair is to provide health professionals and their patients with the necessary skills to engage in shared decision making (SDM) throughout the healthcare continuum, and it aspires to be a world-class training and support center for the implementation of SDM in Canada and abroad. In March 2008, the Chair began to invest in online dissemination in both French and English, and has been doing so ever since. We sought to describe the use of two of the Chair's online dissemination strategies over an eight-year period.

Methods

Sources of Data

Our three sources of retrospective data were: (1) the website of the Chair [14] and site statistics obtained from Google Analytics; (2) the Chair's Twitter account (SDM_ULAVAL); and, for comparison purposes, (3) Google Scholar citations data on the Chair's articles [15]. The website was created in March 2008 at Laval University and is managed by a French speaking webmaster who spends approximately four hours per week populating, translating, and updating it. English pages are reviewed by an English editor. The Twitter account was created in 2011 by the Chairholder, who is solely responsible for its content.

Data Collection

From the website's inception in March 2008 to December 31, 2015, we collected data on the news section and classified it into five categories: (1) publications; (2) honors, awards, and scholarships; (3) grants; (4) congress and conference announcements; and (5) others. We extracted usage statistics from Google Analytics from January 1, 2008 to December 31, 2015, including: (1) number of visits, (2) number of visitors, (3) new visitors, (4) returning visitors, (5) page views per visit, (6) bounce rate, (7) time spent on the site per visit, (8) country of origin of visitors, and (9) most popular pages. The bounce rate represents the percentage of visitors who enter the site and then leave, rather than continuing to view other pages. We collected data from the Chair's Twitter account on November 30, 2016 on number of tweets, number of followers, and follows since its inception in April 2011. We collected the average number of tweets per month over 21 months using TweetStats [16]. We also collected data from Google Scholar on citations of the Chair's research articles from March 2008 to December 2015.

Data Analysis

We performed content analysis of the website based on the five categories of the news section. Descriptive statistics such as frequency distributions, means, and standard deviations were calculated to summarize indicators of the website usage from Google Analytics. We charted citations of the Chair's articles over the same period.

Results

Website

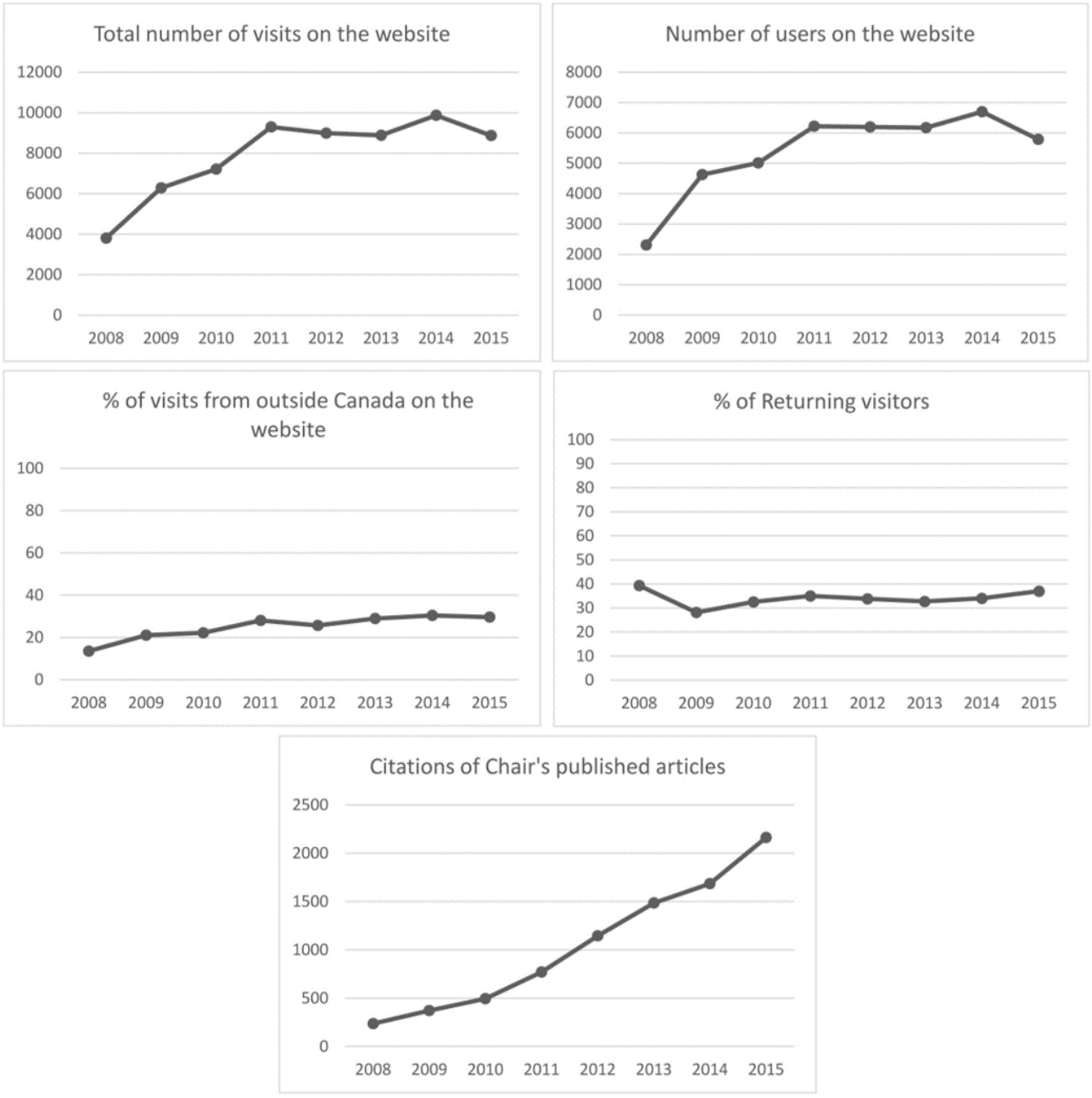
As of December 31, 2015, we recorded 184 news items: 79 regarding publications; 35 regarding honors, awards, and scholarships; 22 regarding grants; 45 regarding conference announcements, and 3 regarding various other topics. We recorded an average of 7906 visits and 5382 users per year (See Table 1 and Figure 1), and 65.85% (5206/7906) of visits were from new visitors. The average number of pages viewed per visit was 3.2, and the average bounce rate was 57.87% (4575/7906). Visitors spent an average of 2 minutes and 12 seconds per visit. The number of visits and visitors increased during the first three years (from 3809 visits and 2311 visitors in 2008 to 9301 visits and 6224 visitors in 2011), remained stable from 2011 to 2014, and then dropped slightly to 8874 visits and 5789 visitors in 2015. We computed visits from 162 countries over the eight years, with the majority from Canada (5910/7906, 74.75%). The seven most visited pages were: (1) home page with news of new publications, awards, and grants, as well as the Chair's Twitter feed (24,787 visits); (2) profile of the Chairholder (8041 visits); (3) profiles of team members (6272 visits); (4) list of team members (4593 visits); (5) inventory of SDM programs for healthcare professionals (1856 visits); (6) interprofessional approaches to SDM (1689 visits); and (7) description of Chair activities (1350 visits). All other pages were consulted fewer than 1000 times.

Table 1. Indicators of the website usage from Google Analytics and citation of Chair's published articles

Year	Total number of visits (n)	Number of users (n)	New visitors (%)	Returning visitors (%)	Page views per visit (n)	Bounce rate (%)	Time spent on site per visit (minutes)	Visits from outside Canada (%)	Citations of Chair's published articles
2008	3809	2311	60.6	39.4	4.70	40.12	3:19	13.60	238
2009	6289	4634	71.8	28.2	3.42	56.32	2:18	21.18	372
2010	7215	5014	67.4	32.6	3.14	58.28	2:01	22.27	495
2011	9301	6224	64.9	35.1	3.07	61.35	2:04	28.09	773
2012	8992	6203	66.1	33.9	2.90	63.21	1:43	25.78	1147
2013	8891	6178	67.2	32.8	2.69	60.72	1:55	28.96	1486
2014	9877	6702	65.9	34.1	3.09	61.88	2:45	30.45	1685
2015	8874	5789	62.9	37.1	2.85	61.07	2:15	29.70	2164
Average over 8 years	7906	5382	65.9	34.2	3.23	57.87	2:12	25.00	1045

We observed an increase in the total number of visits and visitors to the website in the first three years, then a stabilization until 2015 when the numbers dropped slightly. In the final year, the percentage of returning visitors increased slightly, but this finding was not statistically significant. There was a slight downward trend for visits to the home page, with an increasing bounce rate.

Figure 1. Graphic representation of indicators of the website usage from Google Analytics and citation of Chair's published articles over eight years.



Citations

Citations of the Chairholder's articles increased from 238 to 2164 (800%) over the eight years.

Twitter

We recorded an average of 100 tweets per month on SDM_ULAVAL, the Chair's Twitter account, from April 2014 (as far back as the tool permitted) to December 2015. As of November 30, 2016, the account had 5831 tweets, 1679 followers, and 1112 follows.

Discussion

This study retrospectively describes the implementation of two online dissemination strategies of a Canada Research Chair, namely a website and a Twitter account. We observed that over an eight-year period visitors to the website increased most in the first three years, levelled off, and then dropped slightly in the final year. The percentage of visitors from outside Canada dropped less in the final year, and the percentage of returning visitors rose slightly. Meanwhile, citations of the Chair's research articles rose steadily.

The early rise in visits to the Chair's website followed by stabilization may reflect the fact that online strategies are ephemeral tools that may have immediate, rather than lasting, impact [14]. The high bounce rate and recent downward trend in visits to the website may reflect the increasingly stiff competition in research visibility. It appears that for these knowledge translation tools to be effective, they require an increasingly aggressive and time-consuming online presence. Conversely, webmetrics cannot compute time spent on bounced pages, and as the home page contains regularly updated news

about publications and a live feed of the Chair's Twitter account, visitors may have felt that they needed to look no further. The slight rise in percentage of returning visitors and the high number of Twitter followers suggest that the Chair's online dissemination strategies may have attracted a faithful following.

Our results showed no direct correlation between the Chair's citations and usage of the website and Twitter account. While some authors have shown significant correlation between social media mentions and download and citation counts [14,15], they also note the difficulty of collecting appropriate data, and warn that citation levels of manuscripts are just as likely to reflect their scientific quality or popular appeal. Many scientists consider the value of Twitter to be, first, "a constant live literature alert service crowdsourced from peers," and second, its social impact, which complement (rather than increase) citations [15]. Our results show that our website may perform a similar complementary function: visitors' second main interest after the home page showing news of the Chair (24,787 visits) was in lists and profiles of team members (18,906 visits). This finding suggests that an online presence may be as important for scientific networking as it is for direct uptake of results.

Limitations

The Chair website was not launched until March 2008, meaning that data for the complete year was missing and total traffic was therefore underrepresented. In addition, we did not chart the evolution of Twitter data for the entire study period.

Conclusions

We could not determine a direct link between our online dissemination strategies with increased research uptake or visibility over time. This finding suggests that online dissemination may not yet be a major determinant of research uptake or visibility in the scientific community. However, appropriate metrics (including measures of social impact) and high-quality data are needed to understand the full impact of these tools and discover the most effective ways to use the various platforms.

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As of June 1, 2016, FL is Tier 1 Canada Research Chair in Shared Decision Making and Knowledge Translation. We thank Louisa Blair for editing the manuscript.

Conflicts of Interest

FL was the Chairholder of the Canada Research Chair in Implementation of Shared Decision Making in Primary Care.

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Abbreviations

SDM: shared decision making

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Original Paper

Involving Children With Cancer in Health Promotive Research: A Case Study Describing Why, What, and How

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Abstract

Background: Participatory research approaches have been introduced to meet end-users' needs in the development of health promotion interventions among children. However, whereas children are increasingly involved as passive informants in particular parts of research, they are rarely involved as partners, equal to adult researchers, throughout the research process. This is especially prominent in the context of child health where the child is commonly considered to be vulnerable or when the research concerns sensitive situations. In these cases, researchers and gatekeepers to children's involvement base their resistance to active involvement of children on potential adverse effects on the accuracy or quality of the research or on ethical or moral principles that participation might harm the child. Thus most research aimed at developing health promotion interventions for children in health care is primarily based on the involvement of parents, caregivers, and other stakeholders.

Objective: The objective of this paper is to discuss reasons for involving children in health promotive research and to explore models for children's participation in research as a basis for describing how researchers can use design methodology and participatory approaches to support the participation and contribution of children in a vulnerable context.

Methods: We developed and applied a model for children's participation in research to the development of a digital peer support service for children cancer survivors. This guided the selection of appropriate research and design methodologies (such as interviews, focus groups, design sessions, and usability evaluation) for involving the children cancer survivors (8-12 years) in the design of a digital peer support service.

Results: We present a model for what children's participation in research means and describe how we practically implemented this model in a research project on children with cancer. This paper can inform researchers in their planning of strategies for children's participation and ensure future development of health promotion interventions for children is based on their perspectives.

Conclusions: Challenges in reaching a suitable degree of participation during a research project involve both creating opportunities for children to have genuine influence on the research process and organizing this involvement so that they feel they understand what they are involved in and why. To achieve this, it is essential to enable children to be involved in research over time to gain confidence in the researchers and to develop children's abilities to make decisions throughout the research processes.

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KEYWORDS

children; participation; involvement; research

Introduction

Overview

In Sweden, approximately 300 children are diagnosed with cancer each year [1], but advances in diagnosis, risk stratification, and treatment protocols have resulted in most children surviving the disease. Increased survival rates have created new needs for treatment and support associated with physical and psychological late effects of the treatment—effects that may not manifest themselves until years later [2]. Managing these late effects as well as social challenges that are associated with the experiences and consequences of the disease can be facilitated by social support from peers who share similar experiences [3]. This notion is supported by observations that those who experience more social support within this target group report fewer symptoms of depression and anxiety [4]. The availability of peer support is, however, limited, and resources are often offered sporadically and at a limited number of geographically confined locations [5]. Digital peer support built on accessible and asynchronous technologies could potentially solve the feasibility limitations of face-to-face peer support. Designing such digital services is dependent on knowing the preferences and requirements of the target group [6]. Based on this, we set out to involve children cancer survivors in the design of a digital peer support service for children between the ages of 8 and 12 years who have been cured from cancer. Involving this user group in the design and evaluation of a digital peer support service is particularly challenging due to the built-in complexity of the context, coupled with vulnerability, gatekeeping, and availability. Children are often viewed as vulnerable due to their dependence on adults. It is therefore essential to protect children from harm associated with involvement in research and carefully handle consent to participation, confidentiality, research context, and activities [7]. The vulnerability of children is even more pronounced when it comes to children with illnesses, and it is common that their participation is restricted by various gatekeepers such as ethical boards, health care professionals, or parents [8]. The characteristics of the intended user group (eg, age span, medical history, geographic spread, and clinical restrictions) make it difficult to recruit, meet, and engage the children on a regular basis. Research processes and methods that take all these considerations into account could be powerful ways to involve children in the context of health promotive research such as that outlined above.

In recent years, there has been a growing body of academic articles describing involvement of children in research projects [8-11]. A few of these address methodological issues especially from the perspective of children with cancer. Different participatory research approaches have been introduced in order to meet children's needs in the development of health promotive research. Even though all approaches have an end-user focus in common, they differ in regard to whether the children are passive partners in separate parts of the research project or if the children are active partners throughout the research process with real influence over the project. Thus, children are often involved as subjects in research but do not commonly participate as research partners in the development of interventions [9]. The competence and ability of children to participate in research is generally undervalued [10] and their involvement in research is therefore mainly passive [9,11]. This is even more apparent when research concerns children in sensitive contexts such as children survivors of cancer. Involvement of children in research in sensitive contexts is, however, important to ensure that developed resources meet needs based on the cognitive and emotional developmental stages of the children and their requirements on usability and experiential quality [12-14]. Children's involvement in research is nonetheless disputed and treated with reluctance by some, especially when researchers base their resistance on the notion that involving children might adversely affect the accuracy or quality of the research or on ethical principles that participation might harm the child [8,14-16]. Most research with the purpose of developing health promotion interventions for children in health care is consequently primarily based on the involvement of parents, caregivers, and other stakeholders. However, adults' views and experiences cannot replace the qualities that come with genuine involvement and partnership with children regarding their perspectives on health promotion and development of resources based on their own perspectives [9,11,17]. Thus, we still have some way to go before children's participation in research is seen as a precondition for and a hallmark of quality and validity of research.

The objectives in this paper are twofold. First, we discuss the reasons for involving children in health promotive research and explore models for children's participation in research. Second, we present how we involved children in the development of a digital peer support service and describe how different methodologies tackled challenges with involving children in a vulnerable context and how the methodologies corresponded to different levels of participation.

Why Is It Essential to Involve Vulnerable Children in Health Promotive Research?

Increasing focus on the significance of involving children in research concerning themselves has contributed to less research being performed *on* children or from the parents' or caregivers' perspectives. Instead, studies with a child focus are increasingly being performed *with* and *for* children, with the children seen as social actors who are treated as experts on their own lives [17]. How children are viewed is essential to the discussion about children's involvement in research. Children as social actors was emphasized by the Convention on the Rights of Children [18] in 1989 in what it described as the right of children to participate in and influence all matters that relate to them. This right includes both research and development that directly or indirectly affect children. Central principles state that all children have equal dignity and rights (Article 2), that children's best interests shall be a primary consideration in all actions concerning them (Article 3), and that children have the right to shape and express their opinions and have them taken into account in all matters affecting them (Article 12). These principles are relevant for how researchers relate to children's participation and serve as a standard for how integration and assessment of children's participation in research should be planned and estimated.

Children's participation in research is increasingly seen as essential for providing new knowledge and developing health promotion interventions that are credible from a child perspective [10]. This has led to the development of new methodological approaches that involve children throughout the research process instead of limiting their involvement to distinct parts of the research and to single methodological approaches such as observations, interviews, and questionnaires [19]. For example, an emerging field of participatory design methodology with children has been used to bring researchers and children together in a systematic process of collaboration for the design of health promoting interventions [12,13,20]. The participation of children in research can be achieved through involvement in different stages of the research process and for different purposes such as defining the need for research in a particular area, formulating research questions, planning and designing methodology, assembling and analyzing data, designing the proposed interventions, and giving recommendations for dissemination of findings [15]. However, the degree of children's participation in stages of the research process depends on adults' perceptions of their capabilities to participate and the importance of their participation for the quality and credibility of the research [8,15,16]. It is also affected by the trust between the researcher and the child [21] and the capability of the researcher to minimize the social differences between them. The researcher needs to reflect on research values, purpose, and methodological traditions [9] and be aware that children are representatives of a younger generation that in many aspects have other experiences, values, and goals than that of the adult researcher [17]. The researcher also needs to reflect that children's involvement appears to evolve and progress over time [22]. It is essential that the level of children's participation in research depends on the attitudes of adults around them [15] but also on the conditions and experiences associated with each child and her/his parents [8,23]. The notion of risk and the trust in the researcher and the institutions represented are vital for parents to give their permission for their children's involvement in health research [21]. Perceptions among researchers that child participation can have a negative influence on the quality and credibility of the research are associated with participation that is limited to involvement without any real influence or relevance. Many researchers are dedicated to participative methods giving children opportunities to express views and share experiences. It is less common, however, that children are given the opportunity to have a significant role in the research design, data gathering, analysis, interpretation, and implementation of the outcomes of the research [9]. This article suggests that children need to be involved in research in its true sense in order for the researcher to be able to understand the context of the research area.

Children's Participation in Research: What Is It About?

Overview

Models that describe levels of participation are valuable as benchmarks in the planning of research and as guidance for evaluation of participation. There are a number of models available, some of which have been disseminated and are widely practiced (Table 1). Based on similarities and overlaps between these models, we have categorized different levels of children's involvement into nonparticipation, consultative participation, and collaborative participation. These 3 categories represent condensations that we have made based on the different levels of participation that are described in these models. Nonparticipation can be described as situations where adults avoid involving children or involve them in ways that have no real impact on the research and even in ways that give a false semblance of partnership and real influence over the implementation of the research and the findings resulting from the research. Consultative participation means that adults seek children's views in order to build knowledge and understanding of their lives and experiences. This is primarily done by inviting children to express their views and to provide data to the researcher. The children's opinions are treated seriously, and the researcher gains knowledge and an understanding about their lives through this process. However, at this level of participation, children are not equal to the adult researchers and have no impact or control over the focus of the research and the outcomes and interpretations. At the collaborative level there is a greater degree of partnership between adults and children, where children have the opportunity to be actively involved and influence all stages of the research process. The partnership between the child and the researcher includes consultation, mutual trust, and shared decisions. Not only are children's views taken into account at this level, the children are also involved in making decisions.

Table 1. Descriptions of levels of participation in various models of child participation in research.

Models	Nonparticipation	Consultative participation		Collaborative participation		
				Adult-initiated	Child-initiated	Jointly initiated
Hart [24]	Manipulation, decoration and tokenism	Assigned but informed	Consulted and informed	Shared decision with children	Directed by children (adults facilitate); shared decision with adults	
Treseder [25]		Assigned but informed	Consulted and informed	Shared decision with children	Directed by children (adults available); shared decision with adults	
Shier [26]		Listened to and encouraged to share views	Children's views are taken into account	Involved in decision making; given power and responsibility		
Chawla [27]		Prescribed participation; assigned participation	Invited participation	Negotiated participation	Self-initiated negotiated participation; graduated participation	Collaborative participation
Reddy and Ratna [28]	Active resistance, hindrance, manipulation, decoration and tokenism, tolerance, indulgence	Assigned but informed	Consulted and informed	Shared decision with children	Shared decision with adults; directed by children (adults invited)	Jointly directed
Lansdown [29]			Children consulted and invited	Children collaborate with adults	Led or managed by children (adults support)	

The collaborative level includes different approaches regarding who initiates and directs the research process—adult-initiated, child-initiated, or jointly initiated. Even though the children have a decisive role in the collaborative participation, their participation is dependent on adults who support and facilitate their involvement. The goal of the collaborative participation level is to empower children to influence both the process and outcomes for any given research activity. According to the definitions outlined in the Convention on the Rights of Children [18], the minimum level for children's participation in research dealing with themselves is collaborative participation [26]. This means that researchers should always strive toward integrating collaborative levels of participation in their research process where appropriate. For example, approaches that are normally used for consultative participation, such as interviews and questionnaires, can achieve the collaborative level of participation by giving children the opportunity to influence the content of the questions asked and the conditions under which the data collection is done. This influence gives them control over what the research is going to be about and how the research is going to be carried out.

The most widely referred model for child participation in research is that described by Hart [24], who uses a ladder to present different levels of participation. Hart's model, as well as all the other models we have included, comprises 2 levels where children are informed at a consultative level and a third level where the child and adult collaborate through an adult-initiated process. Few models [24,25,27-29] include child-initiated collaboration, and only 2 models [27,28] describe jointly initiated collaboration in which adults and children work together to reach common goals. In the partnership of jointly initiated collaboration, both children and adults are empowered to play different roles and both share ownership of the process.

Some of the models are linear (starting with nonparticipation and continuing hierarchically with levels of gradually increased involvement) and imply that there is a goal to reach the highest level of participation [24]. Other models are circular (nonhierarchical) [25,27,29] indicating that each level has the potential to be the most appropriate for a given circumstance and therefore do not include a progressive hierarchy between the levels. The model by Chawla [27] urges that it is important to understand which degree of participation already occurs in formal and informal settings as well as taking the children's existing life experiences into account. The model by Lansdown [29] emphasizes that the child's participation should be introduced as early as possible in the process and with as much control as possible. The models by Chawla [27] and Treseder [25] also highlight that children can go from 1 level of participation to another when they progress in competence and ability to participate. All models describe assessment of when and how to involve children in the process, but 2 models [26,29] have a stronger focus on practical planning and evaluation of situations where adults work with children. All the models are based on the identification of the appropriateness of different levels of participation based on the conditions and experiences of the children involved and that forms and levels of participation should be adapted to the various activities taking place in the research process. The models should thus not be used as tools to focus participation toward the highest level of involvement but as supports for researchers on involving children in each phase of the research process at a level that is possible and appropriate for the best interest of the child.

However, it is important to be aware of how the power relationship between the researcher and the participating child could be balanced so that children have a genuine possibility of influencing the research process. If not, there is a risk of tokenism where the children are given a voice and opinion but have little if any real influence on discussions and decision making. The authors of the models state that the outcome of children's participation in research is active citizenship and democracy.

As outlined above, these models for children's participation in research describe different levels of participation from nonparticipation to consultative and finally collaborative participation. But none of the models alone describes the content in all these levels, and there are ambiguities as to how the different levels relate to the requirements on participation that are declared in the Convention on the Rights of Children and on what grounds a certain level of participation is desirable in a certain situation. This shortcoming complicates the application of the principles of child participation in planning, implementation, and dissemination of research and knowledge that relate to children and that are based on their participation. We therefore propose another more practically concrete model that is inspired by the work of the International Association for Public Participation and includes both the consultative (inform and consult) and collaborative (involve, collaborate, and empower) levels of participation. Below we describe the 5 levels of participation in this model and why these can be used to reach certain goals for the research, what promises that are made to the children involved, and how the children are practically included in the research process (Table 2). An important point with this model is that although the highest levels of participation are found among the collaborative types of participation, it also shows how and why to optimize children's participation to the most appropriate and feasible level of participation. This can help researchers in increasing children's participation in areas of research where they have primarily been involved as informants and consultants.

Table 2. Levels of participation in the research process.

	Consultative participation		Collaborative participation		
	Inform	Consult	Involve	Collaborate	Empower
The goal with child participation	Respecting children while keeping them informed	Preparing and performing research based on children's views	Involving children throughout the research process	Making decisions with children throughout the research process	Enabling children to be involved in making final decisions throughout the research process
The promise to the child	You have access to all information and have been informed equally as much as anybody else in the project.	You will be important for information-seeking and feedback throughout the research process.	You will work together with us to help and contribute with your perspective on the research.	You will be an equal partner in finding and developing solutions in line with the purpose and aims of the research.	Your efforts and contributions will be visible and implemented in the outcomes of research.
Activities to involve the child	Explain to the child what is to be done, how and why, as well as the consequences of participation.	Study the child's experiences through interviews, observations, and questionnaires.	Work with the child in workshops and other activities in which they are allowed to contribute with their perspectives.	Involve the child in workshops and other activities in which they are allowed to ideate, create, contribute, test, and evaluate.	Present to the child which contributions they have made to allow them to elaborate and confirm.

Consultative Participation: Inform

Children have fundamental rights to be informed of everything that involves them—including research [18]. In participatory research, the goal should be to provide the children with information on a level commensurable with their age and cognitive skills and having in mind their potential vulnerability as children and end-users [12,13]. This means that efforts have to be made to adapt information both regarding the format of the information and the appropriateness of its content. It is equally important to make it clear for the child that he or she has access to all information and has received as much information as everybody else who is involved in the research: other children, their parents, stakeholders, or others [29]. The children also have the right to know what their involvement will be and the consequences of participation.

Consultative Participation: Consult

An important aspect and value with child participation is their contribution to the identification of the purpose and aims of research and in obtaining feedback on plans, data collection, and interpretations [30]. There are sometimes concerns that the increased involvement of children in research can compromise the quality and credibility of the data. However, our stance is that the involvement of the target group in the formulation of purpose and research questions is essential for the validity of the research approach. It not only provides justification that the research is relevant and important but also contributes important input to formulating the purpose of the research, which methodological choices should be made, which participants are most appropriate to recruit, and when and how they should be involved. The consultation of children from the start of the research process thus sends a signal that children have an important role in defining what the research should be about and how it should be performed. This is valuable for the researcher-child relationship, the continued communication with stakeholders during the research process and when disseminating the results to the participating children, and the intended target group and stakeholders who are involved in the research process or are the beneficiaries of the research outcomes.

Collaborative Participation: Involve

Using tangible ways to ensure that children's goals, concerns, attitudes, and preferences are understood and reflected in the outcomes of a project also promotes the participating children's development of skills and confidence in how to contribute toward the purpose and aims of research. The aims of such activities are for the children to work together with the researchers to help and contribute with their perspectives on the research. This could be done by using a playful and creative approach during interviews and workshops, for example, through storytelling, photography, and drawing activities. In order to ensure that the children's involvement will be valuable and significant for the outcomes and progression of research, it is important that the planning of when, where, and how children are involved is carefully considered in relation to their age and abilities, not least to ensure that their participation is not of a decorative or manipulative nature and to avoid their rights or integrity being violated through their participation [24,29].

Collaborative Participation: Collaborate

To ensure that child involvement does not finish with being consultative and limited to informing or merely supporting researchers in the research process, the researchers need to find ways to involve children in decision making throughout the research process. At this level, the adult researchers share ownership of the research with the children and ensure that the children have real opportunities to influence the research process and outcome [31]. This requires a different mind-set from the adult researcher and requires that the children be invited to play a significant role in the codesign of research [9]. Having children involved in actual decision making indicates that they are viewed as important and equal partners in finding and developing solutions in line with the purpose and aims of the research [24,26].

Collaborative Participation: Empower

Empowering children through participation means allowing children to take an active role and have influence when making final decisions in both process and outcomes in any given research activity [26]. In order to achieve this, adults interacting with the children have to be credible and trustworthy so that the children's efforts and contributions become visible and implemented in the outcomes of the research. At this level, an increase of self-directed actions and final decision making lies predominantly in the hands of the children. The overall goal with empowered children is that they can become active advocates for the realization of their own rights and can play a useful citizenship role in their community. Final decision making does not necessarily mean that children make decisions that adults commit to follow. Taking part in final decision making can also mean helping adults to make decisions by participating in analysis and interpretation or to be given the opportunity to provide feedback on or confirm decision made by adults.

Methods

Case Description and How We Involved Children Cancer Survivors in Research

We applied our model for children's participation in research to our development of a digital peer support service for children cancer survivors. The model helped us in guiding selection of the most appropriate methodologies for each step of the design and research process to ensure both feasibility of the process and involvement of the target group. The design and research process resulted in a digital peer support service adapted to the needs and preferences of the target group. The service was in the form of a mobile app called *Give Me a Break*. The app provides an interactive platform for play and social interaction that is a safe meeting place where cancer survivors (8-12 years) can interact with peers, find new friends, and build long-lasting friendships. The platform is composed of a virtual playground that connects users and provides creative playful activities facilitated by an online youth worker with the objective of stimulating interaction and integration of social media applications and thereby encouraging continued interaction using other social media channels or other venues. The service is introduced at discharge from intensive care or during clinical check-ups at the hospital following completion of treatment. In this section, we describe how we worked to involve the children in this process and how their involvement made it possible for us to focus on the children's perspectives in the design of a digital service that relates to their goals, attitudes, problems, and frustrations and that meets their worldview, their cognitive and emotional developmental stage, age, and gender. More detailed descriptions of the methodology used and evaluation of the validity of the methodology for supporting different levels of children's participation in the research have been presented elsewhere [5,20,32-35].

Results

Inform: Respecting Children While Keeping Them Informed

Before we could inform and ask the children about their willingness to participate in our research, we asked the adults around the children. A key factor for having children participate and interact with adult researchers is that gatekeepers give them the possibility and permission to do so. Most important for this is that parents give permission for their children's involvement, and this is strongly dependent on trust they have in the researcher and the associated institutions [21]. Research that addresses child health and how this can be promoted can be legally, ethically, and morally complex and therefore requires a dialogue with stakeholders and gatekeepers in order to establish a suitable level of involvement of the children. In our case, we first had discussions with representatives from the pediatric health care services, and they confirmed the need for the proposed research and the planned approach. These health care professionals surveyed parents and children concerning whether they wanted to participate. The parents' positive attitude to allow their children to participate in our study was based on

trust in our roles as scientists and trust in health care professionals in terms of their approval of our research.

We made efforts to provide information in formats that were appreciated by the children. During project initiation, this meant that information was available to the participating child in age-appropriate fact sheets, illustrations, and websites. An important aspect of the information during project initiation was that the information letter and consent form were designed and formulated in a way that made it clear to the child the aims and activities they agreed to participate in. The children and parents were first given an invitation to participate through their nurse and then through age-appropriate written information and consent forms. This increased the likelihood that the information was appreciated and that the message was understood. It also showed the children that we were interested and committed to reaching the child in a way that was appropriate for them. The children were also given the opportunity to sign the consent form even if it was not needed in a legal sense. This was important to convey our ambition that the children were to be active participants in the research and that they had the right to decide on their participation. This way of recruiting participants to the study resulted in that several eligible participants opted out of participating in the study either indirectly as the result of judgments made by representatives from the pediatric health care services or directly based on considerations or decisions made by the parents or by the children themselves.

The researcher responsible for collecting data in the form of questionnaires, interviews, or workshops carefully planned (through review of the literature and several workshops with the research group) how to provide information in a child-friendly way and which type of data was to be collected and why and how. For example, we have seen the importance of using schedules that can be placed on the table in front of the children or posted on the wall of the premises in which the activities take place so the children can keep track of what they are doing and where they are in the time plan. The children appreciated these schedules because it made clear what should be done during the meeting and invited the child to resume with previous questions or ask new questions as work progressed.

Another example relates to data collection; it can be important for the child to feel in control of what information is documented and how. This affects, for example, how scientists can document with field notes without the child feeling studied and manipulated by the adult. It also affects how to suitably use the recording of sound and images and explain how this type of data is stored and who has access to the recorded material. These are important details for children, who are increasingly aware of the risks in relation to how information about them is documented and shared among others. To ensure that the children in our study felt that they had control over the documentation, we started the data collection with an explanation about underlying principles of their participation and how we planned to document the process and that only members of the research team had access to the data. All our methods used at this level of participation are summarized in Table 3.

Table 3. Consultative participation: inform.

	Invitation			Data collection		
The methods used at this level	We gave information to and collected permission from parents and representatives from pediatric health care.	Children and their parents were given verbal invitation to participate by their nurse.	We designed and formulated information letter and consent form in a child-friendly way.	We gave verbal explanation of what data will be collected, why, and how.	We gave verbal explanation about underlying principles of their participation and how we planned to document the process.	Schedules of activities were used so that the child could keep track of what is to be done.

Consult: Preparing and Performing Research Based on Children's Views

From a participatory design approach, the users should also have impact on the purpose and design of the project [13]. Our research project was prepared and initiated based on needs of peer support formulated from national cohort data of young adult cancer survivors [33], as well as a blog observation made on the Swedish Childhood Cancer Foundation website. Based on the observed blog post, we documented how an adolescent girl described that she really wanted a cancer friend and a peer to talk to. We then used pilot studies with individual interviews with young adult cancer survivors, parents, and clinicians in order to gain insight into the problem and get an understanding of which research question should be used to provide more information and create an understanding of the phenomenon. By presenting these research-driven objectives and ambitions in a very preliminary form to the potential user group, we were able to redefine our initial plans based on key input from the potential users. This ensured that we from the beginning framed the research in line with the needs and preferences of the target group.

For data collection there is a need to establish a strategy for how children's perspectives are to be taken into account. This can be done together with representatives of the target group or be influenced by other children from the same age group. The main thing is that researchers choose a data collection strategy that gives children the best opportunities to participate with their opinions and share information while safeguarding their interests and rights. The difference in the power relationship that exists between children and adults cannot be overestimated [36]. Since the experience of this power imbalance differs between individuals, research should be designed to safeguard that children are treated with respect and to prevent them from feeling subordinated or exploited. Such feelings, even if they are caused unintentionally, hamper the children's ability and motivation to participate in the research. In planning our research interviews, we have been careful to choose premises familiar to the children in order to give them a safe environment to work in. We have also been careful with how we dress, the

language we use, and how we behave in order to avoid using or strengthening markers of power that the children recognize from school, health care, or society. We planned the timeframe for data collection and for working together in workshops adapted to the children's life world, such as school hours and holidays and hours of the day that best suited the children. This meant that the planning was done based on when the children had the opportunity to participate and when they had optimal capability to mobilize the most energy and commitment for their participation. All these considerations were important to ensure that the children could participate in the research as equal partners and also felt that they were seen as equal partners by the adult researchers. At the beginning of each interview and workshop sessions a range of icebreaking activities, such as exercises to get to know each other by talking about things we like to do or movies or music we like, were used in order to build trust and a relationship between adults and children. We were also careful to find a balance between how many adults and children were involved simultaneously and made sure the adults involved did not vary over time so it was possible for children and researchers to establish a rapport and relationship.

As outlined above, the information given to the child during consultation is crucial for the child's ability to be involved. Similarly, the methodological setup for how the consultation is carried out should be adapted to the needs and existing life experiences of the participating children. When we organized focus groups and design workshops we evaluated our design through piloting to assess the feasibility and relevance of the outlined activities and content related to the preferences and experiences of the target group.

In order to gain an understanding of children's views of the defined phenomenon, we started with focus groups and interviews divided into 2 separate sessions with children between the ages of 8 and 12 years with experiences of cancer treatment. The interviews focused on the children's own experiences of friendship and peer support in the context of everyday life following cancer treatment. The focus groups had a semistructured approach and were divided into 3 phases: (1) an icebreaking phase with "get to know" exercises, (2) a discussion phase centered on friendship, and (3) a closure phase where the session was summarized and where both the children and researchers had the opportunity to reflect on their participation. At the end of the first session, the children had the opportunity to suggest discussion themes for the upcoming session. Data analysis was done by the researcher and was based on children's views during the interviews. The methods used at this level of participation are summarized in Table 4.

Table 4. Consultative participation: consult.

	Establishing the idea, purpose, and design		Data collection		
The methods used at this level	We based our purpose on needs formulated from national cohort data of young adult cancer survivors and from empirical data collected from blog observations of users.	Individual pilot interviews were done with young adult cancer survivors, parents, and clinicians.	We designed approaches to avoid power imbalance and to support motivation to participate.	Pilot interviews were done with children to validate the interview techniques.	Semistructured focus group interviews were done with the purpose of getting children's views on the phenomenon.

Involve: Involving Children Throughout the Research Process

In our project, we have seen that a combination of involvement of different parties may be the best solution to achieve as high a degree of participation as possible. There can, for instance, be occasions when children are not expected to understand the problem or context as a whole, such as a complicated treatment process, but where the researcher still wants to take measure of their perspectives, perceptions, and experiences. In such contexts, we designed plans and methods for how to involve the children as much as possible, for example, by interviewing children along with their parents to supplement the children's experiences with their parents' experiences in those respects which the children are not able or willing to participate. Another solution that we used was to strategically select areas of research in which children legally, ethically, or morally are not considered to be mature enough or able to participate and in these cases use stakeholders as proxy informants to complement these areas in which children cannot participate. An example of this could be to use stakeholders as informants about possible causes of ill health in the target group and to use children from the target group as informants around what can promote their health. For both of these strategies, the interpretation of the knowledge obtained must be carefully balanced so that the results reflect a reasonably accurate picture of the children's reality. Thus, the researcher has to ensure that the stakeholders' contributions are not excessive or contribute things that are not supported or appreciated by the children, identify any misinterpretations or errors, and improve or add details that have been missed.

A further aspect of what promotes a consultative participation of children in research is how we as adults create conditions for meeting the children on a level that is appropriate based on their daily lives and their abilities and interests. The importance of choosing a playful and creative approach during interviews and workshops cannot be overstated [37]. For example, we used photography and drawing as a complement to common interview questions for data collection in order to encourage the children to express their views and experiences. We also used design-oriented iterative workshops to include children from the target group in the analysis and processing of quantitative or qualitative information obtained. These workshops helped to include the children's perspectives when interpreting the data and base further development on contributions from the children themselves. In order for this to work, we used methods to support children's participation (eg, brainstorming and sketching) where children came with ideas and suggestions for solutions that the researchers together with designers elaborated

on and embodied in sketches or low-fidelity prototypes that were then iteratively refined together with the children. In the first workshop each child-adult pair created a character that was presented to the rest of the group. This work visualized basic demographic information, personal values, and motivational aspects of the user group. After the workshop, the characters were compiled into proxy personas by the researchers and these were used for creating storyboards. Each storyboard illustrated a redemption scenario based on the characters the children created during the first workshop and that was used as working material in the subsequent workshops to obtain the children's perspectives on solutions to challenges and problems of the proxy personas highlighted in the scenario descriptions. This approach made the children's contribution to the research and design process concrete and tangible and helped us in making the children's participation visible in the final material. This iterative (4 workshops) collaboration with the target group also made it possible for us to continually get feedback on the focus of the research and the results and ensure that the design process was appropriate. Children could, through their role as both informants and consultants, help us with deciding to continue on a path or if alternative directions or strategies needed to be taken.

To evaluate the prototype we developed based on the compiled empirical data, we involved children in usability tests, a user diary study, and a follow-up focus group interview. During the usability test sessions, children were individually given tasks to perform to evaluate functionality. A facilitator guided them throughout the tasks. The second part of the evaluations consisted of a 2-week use study where the children who tested the prototype were given diaries with questionnaires to fill out each day. After the use study was complete, children were invited to participate in a focus group interview around their experiences of the use of the prototype. All the methods we used at this level of participation are summarized in Table 5.

Table 5. Collaborative participation: involve.

	Optimizing children's participation		Evaluation of the prototype		
The methods used at this level	We combined participation of children and proxy informants during the research process.	We created playful and creative material and approach during data collection.	We used usability tests.	We used a 2-week use study with diary documentation.	We used a follow-up focus group interview.

Collaborate: Making Decisions With Children Throughout the Research Process

We have used a collaborative approach for data collection to involve children not only as informants but also as important and equal partners in decision making and design. Through the use of iterative design workshops, we were able to collaborate with children, starting with very general contribution to defining the user group, continuing with defining goals, problems, and frustrations of this group and, finally, identifying and designing solutions for how to support or help the user group in the best way. By making this into an iterative process, we as researchers were able to summarize and prepare outputs from each workshop until the next session. Cooperation with the children from the target group in several iterative steps allowed for the children to initially take a fairly simple role that did not entail a high degree of independence but rather a dependence on the support from a collaboration with other participants, both adults and children. As the children became experienced and confident in the role as co-creators and increasingly familiar with the complexity of the challenges of the research topic, they developed an increasingly independent role and were able to take more responsibility to contribute to the process going forward toward the purpose of the research. During this development of the child's ability and independence as co-creator, it is important that the support from and collaboration with adults is adapted and changed as the work moves forward. One should not underestimate the importance of support from adults to initially help the child with understanding the meaning of the activities and with assisting the child in the informative or creative activities. The support from adults must thus initially be quite extensive and thereafter gradually reduced as the child develops confidence and experience [20]. One should, for example, not be afraid of initially pairing each child with an adult, as they might not be able to participate without such support. Such a high degree of adult involvement and support can thereafter be reduced to finally be at a minimum level. In order to support this, we used a co-creation process where the first session dealt with defining and describing the target group and the aim of the research and where outcomes were the result of the work from pairs of a child and an adult. The outcomes of several such pairs were then summarized and formed the basis for the next session where the children could take a more independent role.

In projects where the children have a high degree of participation during data collection, it is common that this participation is interrupted when the data analysis phase begins. In our project we have, during analysis and implementation, used summaries and abstractions of qualitative data, compilations of statistical data, or sketches and prototypes and invited the children who participated in the data collection to comment and provide feedback on these outputs. This interaction has been designed in the form of joint workshops, individual follow-up interviews, or written or digital demonstration of summations, models, sketches, or prototypes. Activities have been arranged either as single events or as repeated short interactions with children. The main purpose of this iteration is to offer children the opportunity to provide feedback on the conclusions and implications that have been made based on the data they participated in gathering, contribute with essential information for the continuation of the research and design process, and finally assess the research and design outputs through prototype usability evaluation. The opportunity to provide feedback and to continually evaluate the outcomes in the research process ensures that the results of the research are credible and based on the objectives that the children have with their participation. All the methods we used at this level of participation are summarized in Table 6.

Table 6. Collaborative participation: collaborate.

	Iterative design workshops			Follow-up and feedback workshops with children
The methods used at this level	We performed workshops to build familiarity and create proxy personas.	We used workshops to co-create redemption scenarios.	We used workshops for feedback and prototyping.	We used workshops to verify and further develop ideas. The children worked in teams and moved between stations with low-fidelity prototypes on which they gave verbal and drawn feedback.

Empower: Enabling Children to Make Final Decisions Throughout the Research Process

In order to connect the empirical findings from the previous steps into a coherent model that could effectively and efficiently drive the design of a health promoting service for the children in the target group, we used summaries of key traits of the user group to construct personas to capture the human-centered values in the project. The persona is a model of a user archetype that is based on empirical data and focuses on behaviors and goals of the users in the target group [38]. The activity of generating personas is both analytical and creative. The children were involved in this work by the shaping of characters describing demographic information, values, and motivational aspects that were used as a foundation for proxy-personas used in redemption scenarios [20]. The final personas were created based on the documentation of children's reflections and discussions of the scenarios. Supported by our personas and accompanying context and key path scenarios describing the use of the digital service that we wanted to develop, we were able to keep the interests of the user group in focus during prototyping by aligning all design ideas with the goals, preferences, attitudes, and frustrations described for our personas. In doing so we sought to ensure that the interests of the user group were integrated into the scenarios that were used during the prototyping and implementation phases of the project. The use of personas, co-created with the children, indirectly involved the children in decision making during the design process and prevented ideas, conclusions, or initiatives that were based on the empirical data and appreciated by the researchers and designers but were not in line with the developed personas.

At the end of both the design and prototyping phases of the project, outcomes such as descriptions, visualizations, sketches, mock-ups, and prototypes were presented to be verified by the involved children for feedback and confirmation or identification of further design directions. For example, following the focus group sessions and design workshops, all summarized data, the completed personas, and the first design directions of the prototype were presented to the participants and their parents at a workshop. The feedback and responses at this session were documented and used for continuing the research and design process. Similarly, at the end of the prototype development, a printed outline of the purpose and functionality of the service was presented to the participants, and the aesthetics of the design were presented on a website with illustrations, screenshots, and movie clips. All participants were given the opportunity to evaluate the prototype design and relevance in accordance with the purpose of the project and their individual experiences and preferences. These final iterations were important not only to ascertain quality and relevance of outcomes but also to consolidate the participant's role as partners in the research and design and to show the importance of their contribution for the outcomes of the project. All our methods used in this phase are summarized in Table 7.

Table 7. Collaborative participation: empower.

	Personas	Validation workshop with children and parents	
The methods used at this level	We co-created personas that throughout the process kept the interests of the children in the focus of the researchers.	We performed a workshop to verify that the outcomes of the research were in line with the goals and concerns of the target group. Children and their parents gave verbal feedback on confirmation or identification of further design directions for the ideas and prototypes presented at each station.	The participants involved in the initial focus groups evaluated the outcomes of the research in the form of a printed outline of the purpose and functionality of the service; a website presenting the aesthetics of the design with illustrations, screenshots, and movie clips; and a form evaluating the prototype design and relevance to the purpose of the project and individual experiences and preferences.

Discussion

Lessons Learned

The benefit of our research was the combination of a variety of methods to reach the most appropriate level of participation for the children in relation to the purpose of each part of the project. We believe that the combined approach in our study demonstrated that children's participation in research is an important quality indicator for the research process and for the outcome of the research. Our intention with this paper was not to evaluate the validity of our model as such but rather to practically show how we implemented the model and our experiences of how this supported us in incorporating the children's perspectives to our research process. The methodologies described in this paper have been evaluated in several studies describing the different phases of the research project. These studies have evaluated the feasibility of involving the children in the research process as well as the importance of their involvement for the research outcomes [5,20,32-34]. Evaluation of implementation of this model in projects with other objectives in other contexts is needed to keep it up to date and to further prove its validity. Some experiences from our work on the project are worth mentioning.

One practical challenge when including children in research is that gatekeepers have a role in limiting researcher access to participants [8]. In our case, we believed it was crucial for

children's participation that we convincingly could describe the forms of participation to parents and stakeholders in the health care system and support them and the children themselves to participate. We achieved this primarily by being clear in the information we shared with parents, stakeholders, and children by adapting this information to each target audience. We also put effort into involving health care professionals, who had responsibility for the children's care process, early in the planning of the research in order to establish trust with the health care professionals and the children's parents.

Children's right to refuse participation is another area of significant challenge. There could be riskiness to health care professionals or parents using their influence to convince the child to participate in a project if they support the idea of the project [9]. There could also be a risk that the children choose to participate only because they want to please their parents. To counteract this, we made efforts to give every child age-appropriate written and verbal information and give them the opportunity to sign the formal informed consent in order to display that they themselves have the right to decide if they wanted to participate or not. In some cases, the children wanted to participate but not the parents, and in some cases, the parents wanted to participate but not the children. In both these cases, it ended up that these children were not included in the study. The children who chose to participate expressed that their motivation to participate was that it could be fun and they wanted to contribute to the improvement for other children who share their experiences.

One major challenge when working together with children in research is the power imbalance that exists between the adult researchers and the children. In our case, we made up a strategy for ensuring that we treated the children as equal partners in the different stages in the project. To work toward achieving this, we had several discussions in the research group at the beginning and throughout the project in order to be aware of our own assumptions and behaviors. We made efforts, in the way we were dressed, the language we used, and the way we behaved in the group of adults and children, to minimize any experience of power imbalance between us. We also put efforts into allowing all parts of the project to take the time that was needed for the children to feel they had the opportunity to contribute and that there would be enough room for the children to iteratively verify the outcomes of the decisions taken together with them. This meant that the project went on for a longer time period than first anticipated (3 years instead of 2) and involved more interactions than if the children's participation would have been only consultative. The extensive time spent on interaction between the children and the researchers and designers posed a challenge to the project in several ways. For example, we as researchers had to adapt our traditional research process to a work process that took into account that all parts of the project would be iterated with the children and timed with their life world. Research funders and stakeholders had to be continuously informed of the progress of our work and the value of using substantial time for interaction with the children in the research. Finally, the children's interest in participating depended on their feeling that it had a significant impact on the outcomes. A further difficulty with running a project over a long period of time (3 years) was that the oldest children eventually aged out of the intended target group for the project and their interest in working with the younger children changed as they reached adolescence.

Implications

The model described in this paper and the experiences from our case can inform researchers in their planning of strategies for children's participation in research. Increasing the level of children's participation is a valuable asset in the development of digital health promotion interventions for children since it brings in user perspectives that are essential for the design of relevant and functioning services that meet user needs and are adapted to user preferences. Furthermore, being able to implement a model-based structure for the why, what, and how of children's participation facilitates connecting with stakeholders and gatekeepers for child participation in the initiation of a project.

In our project we have involved children in all phases of the research process in order to understand their motivations, behaviors, and preferences and to ensure the outcome of the research is in line with the goals and needs of the children. There are some significant challenges in involving children in the research process that are valuable to pay attention to [10,24]. The challenges include how to achieve an appropriate level of participation during a research project and how to create opportunities for children to feel that they understand and have genuine possibilities to influence the research process [8,14]. One important issue for children's participation in research is to assure that they understand what they are involved in. It is important to not only provide information to their parents but to also inform the children in an age-appropriate format and in a way that makes it clear to the child what purposes and activities they agreed to participate in. Similarly, even if formal informed consent from the children is not needed in a legal sense for them to be involved in research, this requirement signals an intention from the researchers that the children are active participants in the research and that they have the right to decide on their participation. Another issue that needs consideration is that the goal with involving children in research is not necessarily to reach the highest but rather the most appropriate level of participation. The linear composition of many of the models described in Table 1 does not capture the complexity of children's abilities and prerequisites for participation. The opportunities for children to achieve the empowerment level (described in Table 2) during the research process is a matter of time and trust. Through a process of iterative meetings with the researchers during a prolonged time period where the children can see in what ways their contribution has meaning for the outcomes, they gradually progress in capacity to contribute toward the objectives of the research. This means children need possibilities for participation in research over time to build trust in the researchers and to develop abilities to make decisions along the research process.

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Conflicts of Interest

None declared.

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