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Protocol

Reducing Sedentary Time for Obese Older Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: Older adults have high rates of obesity and are prone to chronic health conditions. These conditions are in part due to high rates of sedentary time (ST). As such, reducing ST could be an innovative strategy for improving health outcomes among obese older adults. To test this theory, we developed a novel, technology-enhanced intervention to reduce sitting time (I-STAND) and pilot tested it to assess the feasibility, acceptability, and preliminary effects of the intervention on ST and biometric outcomes.

Objective: The current paper aims to describe the rationale, design, and methods of the I-STAND sitting reduction pilot trial.

Methods: Older adults with obesity (n=60) were recruited from a large health care system and randomized to receive I-STAND or a healthy living intervention. I-STAND combined personal coaching with a technology-enhanced intervention (Jawbone UP band) to cue breaks from sitting. Participants completed self-report and biometric assessments at baseline and 3 months. Additional qualitative results were collected from a subset of I-STAND participants (n=22) to further inform the feasibility and acceptability of the interventions. The primary outcome was total hours of daily sitting time measured by the activPAL device. Secondary outcomes included sit-to-stand transitions, bouts of sitting longer than 30 minutes, physical function, blood pressure, fasting glucose, cholesterol, and depressive symptoms.

Results: Study enrollment has ended and data processing is underway.

Conclusions: Data from randomized trials on sitting reduction are needed to inform novel approaches to health promotion among older adults with obesity. Our trial will help fill this gap. The methods used in our study can guide future research on using technology-based devices to assess or prompt sedentary behavior reduction, or those interested in behavioral interventions targeting obese older adults with novel approaches

Trial Registration: ClinicalTrials.gov: NCT02692560; https://clinicaltrials.gov/ct2/show/NCT02692560 (Archived by WebCite at http://www.webcitation.org/6wppLTWAl)

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KEYWORDS

Sedentary lifestyle; exercise; aging; chronic conditions; medical informatics

Introduction

Currently, one-third of adults over the age of 60 are affected by obesity [1], and rates are projected to double between 2000 and 2030 among those 65 and older [2]. The consequences of obesity in older adulthood include poor physical function, increased disability, elevated risk of morbidity (arthritis, diabetes) and mortality, decreased quality of life, and higher healthcare costs

[3-5]. Novel behavioral interventions are needed to reduce these problems and those associated with other aging-related chronic conditions.

Increased physical activity, particularly at moderate-to-vigorous levels, promotes healthy weight and has a plethora of positive health effects [6,7]. Yet, of all age groups, older adults are the least likely to meet physical activity guidelines (2.4% of adults aged 65 and older by objective measures) [8]. Many older adults may be unable or unwilling to increase their level of physical activity, and reducing sedentary behavior could be a more feasible goal.

Sedentary behavior has been defined as "any waking behavior characterized by an energy expenditure <1.5 metabolic equivalents while in a sitting or reclining posture" [9-11]. Common sedentary activities among older adults include watching television, doing seated activities (eg, knitting, reading, attending seated events), and riding in an automobile [10,12,13]. Lab studies suggest that sitting adversely impacts cardiometabolic health markers such as triglycerides, glucose, and insulin sensitivity [14]. Sedentary time (ST) is high among older adults at 8 to 10 hours per day or 65% to 70% of waking hours [15-17]. Older adults with obesity tend to have an even higher ST at 10 to 11 hours per day [16,18].

Reducing sitting behaviors among older adults with obesity could promote health benefits. Randomized trials of sitting reduction have been promising in adult populations, particularly those based in the workplace [19,20]. However, data from randomized studies are lacking among older populations. The majority of studies are small pretest posttest studies. These studies indicate preliminary feasibility of reducing ST, achieving around 30 to 50 minute reductions in sitting time per day [21-27]. Only one of these studies, conducted by our team, focused on older adults with obesity and found reductions in sitting were feasible and consistent with reductions in non-obese older adults [22]. Building on our preliminary work, we developed the I-STAND intervention which combines our prior cognitive behavioral intervention with new elements such as prompts to stand delivered by a wrist-worn activity sensor (Jawbone UP band) and biomarker assessments. To determine the feasibility, acceptability, and preliminary behavioral and health effects of the I-STAND intervention, we conducted a randomized controlled pilot trial. The current paper details the rationale, design, and methods of this trial.

Methods

Trial Design

A 12-week single-blind, randomized two-arm trial design was employed to evaluate the efficacy of the I-STAND intervention for decreasing sitting time compared to a healthy living control group. Enrollment began in February 2016 and data collection finished in February 2017.

Setting

The study is being conducted by the Kaiser Permanente Washington Health Research Institute (formerly, Group Health Research Institute). All activities were reviewed and approved by the Kaiser Permanente Washington (KPWA) Institutional Review Board.

Recruitment

Potential participants were identified using electronic health records from members of Kaiser Permanente Washington. Participants were limited to members whose primary care clinics were located in King County, WA to facilitate in-person appointments. Individuals were deemed potentially eligible if their: electronic medical records indicated they were aged 60-89, body mass index was ≥30 (to select for a group at risk for chronic conditions who may benefit the most from ST reduction), and enrollment in the health plan was continuous for the prior 12 months. Individuals were excluded if they resided in long-term care or a skilled nursing facility in the prior 12 months, had a new cancer or heart failure diagnosis, or had a new diagnosis of dementia or serious mental health disorder.

Study invitation letters were mailed to a random selection of potentially eligible individuals who met the criteria above. Those who were interested in learning more were asked to call study staff for more information. Up to three mailings were sent to potential participants if they did not respond to the initial invitation or opt out of further contact. Interested responders were screened for eligibility by phone. Additional eligibility requirements were: self-report of sitting ≥ 7 hours per day, able to stand, and able to walk one block with or without an assistive device.

Contacts and Procedures

Persons screened as potentially eligible by phone provided oral consent to participate and were scheduled for an in-person appointment. They were then mailed an activPAL device. activPAL is currently considered the most valid and objective measure of sitting time [28]. This small lightweight device was worn on the front-middle part of the thigh with a waterproof dressing. Participants were provided with clear instructions and photos showing them how to adhere the device to their leg. The device was worn on the leg 24 hours a day to assess active and sitting time. Participants wore the device for at least 7 days prior to coming to an in-person baseline assessment. Participants completed a log to record their sleeping hours.

At the in-person baseline visit, participants met with a study staff member who collected written informed consent, downloaded their activPAL data, and collected other baseline assessment data (including a questionnaire, biometric assessments, and a fasting blood draw). A separate study health coach then randomized individuals and met with them to inform participants of their randomization group. Participants then completed their first health coach visit in person. Participants randomized to receive the I-STAND intervention arm were also provided a Jawbone UP band and trained on how to use it. The baseline visit lasted 1.5 to 2 hours.

Participants also completed an in-person assessment at 3 months post-randomization. Similar to baseline, each person wore an activPAL device for 7 days prior to the visit to assess active and sedentary behavior. During the 3-month visit, the biometric assessments and blood draw were repeated by a blinded study staff member, and a follow-up questionnaire was also

administered. Participants received $50 each for completing the baseline and 3-month visit. A subsample of I-STAND participants (n=22) were invited to participate in a separate qualitative exit-interview following study completion. Interviews were conducted by phone within 10 days of the final session. Additional study contacts are outlined as part of the descriptions of the intervention and control conditions (below).

Randomization & Blinding

Randomization occurred during the in-person baseline visit. The health coach used an automated macro, developed and overseen by the study statistician in Stata, to process the participant's downloaded baseline activPAL data. The macro computed preliminary estimates of activity metrics such as average daily sitting and standing time. Participants were randomized in a 1:1 allocation to I-STAND or the healthy living control. Randomization was stratified by baseline average daily sitting time (≥9 hours vs <9 hours), in permuted blocks of randomly varying size (2 or 4). Staff responsible for collecting baseline and follow-up data were blinded to participants' treatment arm. Participants and health coaches were aware of treatment assignment, since individuals received a different intervention depending on their assignment.

I-STAND Intervention

Theoretical framework

The experimental I-STAND intervention was based on relevant behavioral theories including social cognitive theory, the ecological model, and habit formation. Social cognitive theory posits that the interaction of individual, social, and environmental influences impact behavior. Specifically, constructs such as self-efficacy, social support, goal-setting and action planning, and cues were deemed important for inducing changes in sitting behavior. The ecological model specifies the importance of considering influences at the built environment level including the home and neighborhood environment which could shape sitting behaviors [29]. Principles of habit formation suggest that unconscious and automatic processes typically underlie decisions to sit. Bringing these decisions into conscious awareness will help make decisions to stand (instead of sit) more automatic over time [30].

Intervention Development

In our prior work, we developed a theory-based ST reduction intervention (using the theories above) and tested it over 8 weeks among older adults with obesity [22]. We then conducted in-depth qualitative interviews to refine and improve the program [27]. The program resulted in a 30-minute reduction in sitting time, comparable to other preliminary studies in older adult populations. The interviews suggested that sitting is a highly ingrained habit often performed unconsciously and additional prompts were suggested to help constantly remind participants to bring their sitting habits into conscious awareness. These findings further informed the design of the I-STAND intervention.

Format

I-STAND consisted of 2 in-person health coaching sessions (the first immediately following their baseline measurement visit and the second 1 week later), 4 follow-up health coaching phone calls (every 2 weeks after the first 2 in-person sessions), and written materials. Participants were also offered email reminders to work on their individual goals on the off-weeks of the biweekly calls.

Key Components

I-STAND combined the behavioral theories into an approach that focused on using inner, outward, and habit reminder strategies to enhance awareness of sitting behavior and enabled participants to make simple changes that would enhance self-efficacy and reduce sitting time (see Table 1). One of the main tools provided to participants was a Jawbone UP band (Jawbone®, San Francisco, CA) to provide gentle vibrations every 15 minutes of inactivity to remind participants to take breaks from sitting regularly throughout the day (serving as an outward reminder) [31]. In addition to reminder strategies, key components included: 1) a workbook with biweekly content focusing on the various types of reminder strategies, which was used with each health coaching session; 2) feedback charts were provided to participants based on their activPAL wear at baseline and wearing the device at 2 additional check-in points 1 week following the baseline week and at the study mid-point (around week 6). The feedback charts included both numeric and graphic depictions of average daily waking time spent sitting, standing, and stepping, as well as their total breaks from sitting, sitting bouts lasting longer than 30 minutes, and step count; and 3) health coaching sessions as described below. Table 1 provides an overview and descriptions of the I-STAND intervention components.

Health Coaching Sessions

Sessions focused on using different types of reminders, building self-efficacy through motivational interviewing strategies, problem-solving barriers, and setting an action plan consisting of graded individualized goals using the workbook which contained action planning and goal-tracking worksheets. At the first in-person intervention visit, health coaches met with participants for 1 hour to develop rapport, learn more about their daily activities, elicit motivations for joining the study, provide an intervention overview, and introduce and review study tools, including the workbook, feedback chart, and Jawbone UP wristband. They also reviewed safety information to ensure that participants would not injure themselves by standing more (eg, stand on a cushioned surface, gradually build the amount of standing time). Health coaches then worked with the participants to set an action plan with obtainable goals, using tailored reminder strategies. During the week following the baseline week, participants wore another activPAL monitoring device and returned in person to meet with the health coach. The second in-person visit, which lasted about 45 minutes, focused on reviewing participant progress on their goals and problem-solving barriers with the assistance of a second feedback chart from wearing the activPAL the prior week; learning about additional reminder strategies; and setting goals for the next 2 weeks.

Table 1. Overview of I-STAND Intervention Components.

Component description	Examples of content
Health coaching sessions: 2 in-person and 4 phone calls	• Motivational interviewing to identify values and support goal attainment • Learning about reminder strategies and selecting personalized reminders to help achieve goals • Enhancing self-efficacy for sitting reduction • Problem-solving identified barriers to achieving goals • Reviewing feedback charts at in-person sessions and at mid-point • Action planning including setting stepped goals building towards a 1-hour reduction in sitting time
Feedback charts: Provided 3 times during the intervention	• Color graphs and tables showing sitting time, standing time, breaks from sitting, steps, number of sitting bouts lasting longer than 30 minutes • Reviewed during health coach sessions at baseline, 1 week, and 6 weeks
Workbook: Provided at first in-person session	• Written educational materials • Action-planning pages • Goal-tracking forms • Home environment audit form
Reminder strategies	
Inner: Internal or bodily cues	• Using mindfulness to be more aware of how body feels when sitting • Standing up anytime you notice your body feeling uncomfortable
Outward: Cues in the environment	• Using the Jawbone UP band, a kitchen timer, or another identified environmental cue • Making environmental changes to the home based on audit results (e.g. setting up a standing work space, finding a counter on which to read the newspaper, moving furniture to create room to stand)
Habit: Ingrained daily habits that can be used as cues	• Standing for 5 minutes while engaging in daily habits such as drinking coffee, reading the newspaper, talking on the phone • Standing for 5 minutes after doing a daily habit like taking medication or going to the bathroom

Thereafter, health coaches met with participants by phone every 2 weeks (for approximately 20 to 40 minutes for each session) to review progress on goals, problem-solve barriers, use the workbook to guide participants on different types of reminders, and set new action plans at the end of the visit. Additional topics covered in the workbook and health coaching sessions included social support, social environment and norms, conducting a home environment audit, and making home and/or work environment changes based on the audit results.

Healthy Living Control Condition

Participants in the control condition received 1 in-person health coaching session (after the baseline measurements were completed) followed by 5 mailed contacts. The program was based on usual care that is available to members of KPWA. At the in-person session, participants were provided with a workbook consisting of health education on a variety of topics relevant to aging including depression, advance directives, nutrition, sleep, pain, and bladder control. Participants were instructed to select 1 topic to work on every 2 weeks. Content was derived from online educational information available to KPWA members, which was approved by Kaiser Permanente physicians. During the in-person health coaching session, participants then worked through a goal-setting worksheet with the health coach to help get them oriented to their program. Every 2 weeks, participants received a check-in letter and were asked to complete a form to mail back regarding their progress with their goals.

Health Coach Training and Fidelity

The I-STAND and Healthy Living conditions were delivered by 2 health coaches who had relevant degrees but no prior experience with health coaching. They were trained by the study principal investigator who is a licensed clinical psychologist (DER) to use motivational interviewing strategies (eg, reflective listening, open-ended questions, affirmations, and summaries) and problem-solving techniques to support behavior change. Fidelity was enhanced by using structured scripts for each session and materials in a study workbook specific to the intervention and control group. Initial sessions were audio-recorded and reviewed to support health coach training. All intervention contacts were tracked in a Microsoft Access tracking database.

Assessment Measures

The primary outcome was total daily waking hours spent sitting measured by the activPAL micro device (PAL Technologies Ltd, Glasgow, UK). The activPAL was used because it has been feasible in other studies with older adults [22,24,32], is sensitive to change,[22,33] and has high validity in comparison to direct observations [28,34,35]. The device was initialized, sealed in a waterproof casing and then adhered to the front- center thigh with a waterproof medical adhesive (Tegaderm). Participants were instructed not to remove the device but they were given additional materials for affixing the device in the event that the adhesive became compromised or if they developed any irritation. They were provided with logs to track their sleep time

each day they wore the device. The data were downloaded and processed using proprietary activPAL software and programs developed for Stata and R statistical software packages. The processing programs removed logged sleep time from the data to calculate waking hours spent sitting. Similar to standard procedures for accelerometer processing, data were considered valid if wear time was greater than 10 hours per day with a minimum of 4 valid days of data for each assessment period [8,36,37]. To account for variations in wear time, activPAL outcomes will be adjusted for wear time. In addition to sitting time, activPAL will be used to assess secondary outcomes including average daily sit-to-stand transitions, standing time, steps, and bouts of sitting longer than 30 minutes.

Other secondary outcomes included physiologic measures and a battery of physical measures thought to be sensitive to changes in ST and relevant for chronic disease. Physical function was measured by the Short Physical Performance Battery, which objectively evaluated lower extremity function with tasks for balance, gait speed, and lower-extremity strength (chair rise) [38,39]. Cardiometabolic outcomes (fasting glucose and a cholesterol panel) were assessed by finger prick using an Alere Cholestech LDX System machine and Lipid + Glucose cassettes. This device has shown very good agreement with established laboratory methods [40-42]. Blood pressure was measured on the left arm using an Omron HEM-907XL digital monitor. Blood pressure was assessed 3 times and the average of the latter 2 measures used.

Exploratory outcomes included cognitive function as measured by the Trail Making Test Parts A and B (to assess psychomotor speed and fluid cognitive abilities) [43,44]. Time to complete each task as a raw score will be used in analyses weight which was measured with a calibrated portable digital scale (Tanita HD-351) and height with a stadiometer (Seca 213). Waist circumference was measured twice at the superior border of the iliac crest. The average of 2 measurements will be used in our analyses [45]. Additional exploratory outcomes were self-reported and included benefits and barriers of sitting reduction [46], self-efficacy for reducing sitting time [46-49], habit formation (Self-Report Habit Index) [50], quality of life with the Patient-Reported Outcomes Measurement Information System global scale [51], and depressive symptoms with the Patient Health Questionnaire-8 [52,53].

Qualitative Assessment

Qualitative exit-interviews lasted about 45 minutes and followed a semi-structured interview guide. The semi-structured interview guide was intended to capture feedback on the acceptability of the intervention, barriers and facilitators to sitting reduction, and perceived health impacts of sitting reduction. Only I-STAND participants were interviewed. Due to scheduling and other logistics, 22 of the 29 intervention participants were interviewed. The interviews were audio-recorded and transcribed. A formal qualitative analysis using thematic analysis and a group of coders will be undertaken to identify barriers and facilitators to sitting reduction and guide future refinements to the I-STAND intervention.

Statistical Analysis

The primary outcome will be defined as the change between baseline and 12 weeks in daily sitting time during waking hours, adjusted for wear time. Sitting time adjusted for wear time is a percentage calculated per day as: 100*(sitting time/hours device was worn during waking hours). This measure is averaged across valid wear days within an assessment period. Linear regression models will estimate the difference in mean change in adjusted daily sitting time from baseline to 12 weeks between the healthy living and I-STAND intervention groups. We will adjust for baseline sitting time and important potential confounders. Our primary analysis will include participants with valid sitting time outcome data at both baseline and 3-months data (complete case approach). We will conduct sensitivity analyses including all randomized participants and assuming no change (baseline value carried forward) for participants lost to follow-up. Similar analyses will assess the impact of the intervention at 3 months on secondary outcomes. If linear regression normality assumptions are violated, we will consider transformation of the outcome measures.

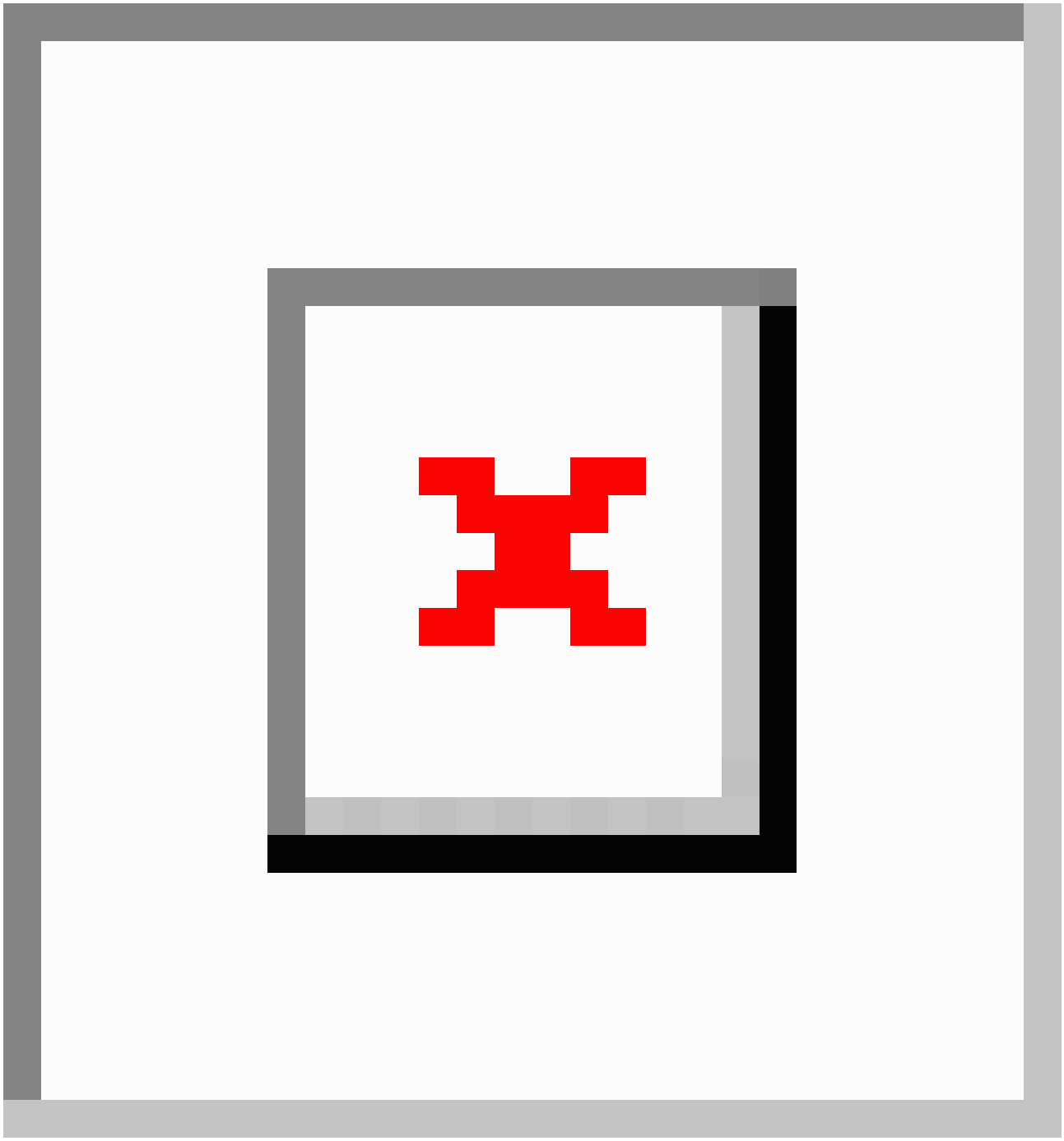
Power

Based on preliminary data from our prior work [22], we estimated the change from baseline in sitting time adjusted for wear time would have a standard deviation of 8.3%. Assuming an 80% follow-up rate, a sample of 60 (30 in each arm) was estimated to provide 80% power to detect a between-group difference in sitting time adjusted for wear time of about 60 minutes per day.

Results

Study enrollment was completed. As Figure 1 depicts, 111 (14.6%) of those mailed a study invitation letter responded by calling the study phone line. Of these, 60 were randomized (7.9% recruitment rate). A total of 29 participants received the I-STAND intervention with no drop-outs over 3 months. Thirty-one participants were randomized to the Healthy Living control condition and 6 (19%) dropped out. Data processing and analysis is currently underway.

Figure 1. Consolidated Standards of Reporting Trials flow diagram.



Discussion

Study Rationale

Given the high levels of ST and low physical activity among older populations at risk for chronic conditions, alternative health-promoting approaches are needed. We were able to easily recruit a sample of older adults with a high level of ST to test our intervention. The research base currently lacks evidence from randomized controlled trials to reduce ST among older adults and the current study will be an important contribution to the field. Published trials from adult populations have used standing desks and motivational enhancement to reduce sitting time [19,54]. More recent interventions have incorporated wearable technologies to help provide reminders to take frequent breaks from sitting [55,56]. Only a few studies to date have targeted older adults [21,24-26,56] and the majority were pre-post test studies. While standing desks are effective, [19] they are not as applicable to populations that are largely not working like older adults. Therefore, our approach combined various strategies, including cues from a wearable technology, to remind participants to frequently take breaks from sitting and provide environmental supports for standing. Our findings will elucidate the effectiveness of such approaches.

Strengths and Limitations

The main limitations of the study included our inability to study outcomes longer than the 12-week study period. Future studies would benefit from longer term follow-up. Another limitation

is that there was differential drop-out by condition. The reduced interaction with healthy living participants may have contributed to greater drop-out in this group. Analyzing the study results will help determine the characteristics of completers and non-completers so we can better understand whether our results will be externally valid. Strengths include the use of mixed methods, objective measures of our primary outcomes, inclusion of cardiometabolic outcomes, and the high-risk target population.

Conclusions

The findings from our study will inform approaches to reducing sitting among a high-risk population. Furthermore, the outcomes will provide novel information on whether sitting reduction results in meaningful changes in health. Data from randomized trials are needed to inform public health guidelines on sedentary behavior.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

CONSORT-EHEALTH checklist (V 1.6.1).

[PDF File (Adobe PDF File), 535KB - resprot_v7i2e23_app1.pdf]

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Abbreviations

KPWA: Kaiser Permanente Washington
ST: sedentary time

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Protocol

mHealth Technology and Nurse Health Coaching to Improve Health in Diabetes: Protocol for a Randomized Controlled Trial

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Abstract

Background: Chronic diseases, including diabetes mellitus, are the leading cause of mortality and disability in the United States. Current solutions focus primarily on diagnosis and pharmacological treatment, yet there is increasing evidence that patient-centered models of care are more successful in improving and addressing chronic disease outcomes.

Objective: The objective of this clinical trial is to evaluate the impact of a mobile health (mHealth) enabled nurse health coaching intervention on self-efficacy among adults with type-2 diabetes mellitus.

Methods: A randomized controlled trial was conducted at an academic health system in Northern California. A total of 300 participants with type-2 diabetes were scheduled to be enrolled through three primary care clinics. Participants were randomized to either usual care or intervention. All participants received training on use of the health system patient portal. Participants in the intervention arm received six scheduled health-coaching telephone calls with a registered nurse and were provided with an activity tracker and mobile application that integrated data into the electronic health record (EHR) to track their daily activity and health behavior decisions. All participants completed a baseline survey and follow-up surveys at 3 and 9 months. Primary and secondary outcomes include diabetes self-efficacy, hemoglobin A_{1c} (HbA_{1c}), and quality of life measures.

Results: Data collection for this trial, funded by the Patient-Centered Outcomes Research Institute, will be completed by December 2017. Results from the trial will be available mid-2018.

Conclusions: This protocol details a patient-centered intervention using nurse health coaching, mHealth technologies, and integration of patient-generated data into the EHR. The aim of the intervention is to enhance self-efficacy and health outcomes by providing participants with a mechanism to track daily activity by offering coaching support to set reasonable and attainable health goals, and by creating a complete feedback loop by bringing patient-generated data into the EHR.

Trial Registration: ClinicalTrials.gov NCT02672176; https://clinicaltrials.gov/ct2/show/NCT02672176 (Archived by WebCite at http://www.webcitation.org/6xEQXe1M5)

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KEYWORDS

randomized controlled trial; study protocol; mobile health; health coaching; motivational interviewing; type 2 diabetes mellitus; patient generated health data; electronic health record; patient engagement; person-centered outcomes research

Introduction

Diabetes mellitus is a global epidemic highly amenable to health promotion interventions. Over 29 million Americans are currently living with diabetes. Since 2000, approximately 1 million new cases are diagnosed each year, with type-2 diabetes accounting for 80-95% of cases [1,2]. Uncontrolled diabetes can lead to major vascular complications including heart disease and stroke, hypertension, blindness, lower limb amputations, peripheral neuropathy, lipid abnormalities, and kidney disease [3-6] and can have a profound impact on quality of life and functional ability. Promotion of self-management strategies such as healthy eating, being physically active, monitoring blood glucose, medication adherence, stress management, and healthy coping are essential for preventing adverse consequences of diabetes [7].

Health interventions that involve active patient engagement have sustained and improved clinical and psychosocial outcomes over didactic interventions with limited patient input [8-12]. Traditional offerings for diabetes management typically emphasize education and do not address patient-centered goals and personal motivations [9]. Diabetes management in the electronic health record (EHR) is episodic and provider-centered, focused on diagnostic, clinical, and pharmaceutical records, with no process to capture and review patient-centered goals or patient-generated health data (PGHD). A vital shift is needed to actively involve patients in developing their care plan and to effectively highlight patient-centered priority areas in the EHR with the health care team.

In the Patient and Provider Engagement and Empowerment through Technology ($P^2E^2T^2$) to Improve Health in Diabetes study, we sought to design and test an intervention to enhance self-efficacy of diabetes self-management for persons living with type-2 diabetes mellitus. In collaboration with persons living with diabetes, healthcare providers, and technology stakeholders, we created a patient-centered intervention with the following components: 1) A wearable mobile activity tracker and nutrition apps; 2) Nurse health coaching sessions; and 3) Integration of patient-generated daily activity data into the EHR. This protocol describes the randomized controlled trial designed to test the impact of the $P^2E^2T^2$ Program to Improve Health in Diabetes intervention on self-efficacy compared to those who receive usual care.

Intervention Design: Pilot Data and Key Stakeholder Partnership

Several previous studies established the basis for the current protocol, exploring design features and testing feasibility and efficacy of elements of the intervention.

Nurse Health Coaching and Sustained Self-Efficacy

Our team has studied the effect of nurse health coaching in a population of people living with type-2 diabetes. In a previous randomized experimental study comparing nurse health coaching to usual care, we offered the intervention group 6 nurse health coaching sessions, occurring approximately every 2 weeks, over a 3-month period. The nurses based coaching sessions on the principles of motivational interviewing, a patient-centered counseling technique used in many disciplines to support behavior change and enhance self-efficacy [13,14]. A total of 121 participants were enrolled in the study. Of those, 101 completed all 3 measurements of self-efficacy at baseline, 3 months, and 9 months and were included in the analysis. Results demonstrated sustained effects of the intervention with a significant difference in self-efficacy scores at 9 months among those who received nurse health coaching relative to the control group [15]. A limitation of this study was the lack of objective patient-generated data about goal attainment, including physical activity and nutritional outcomes.

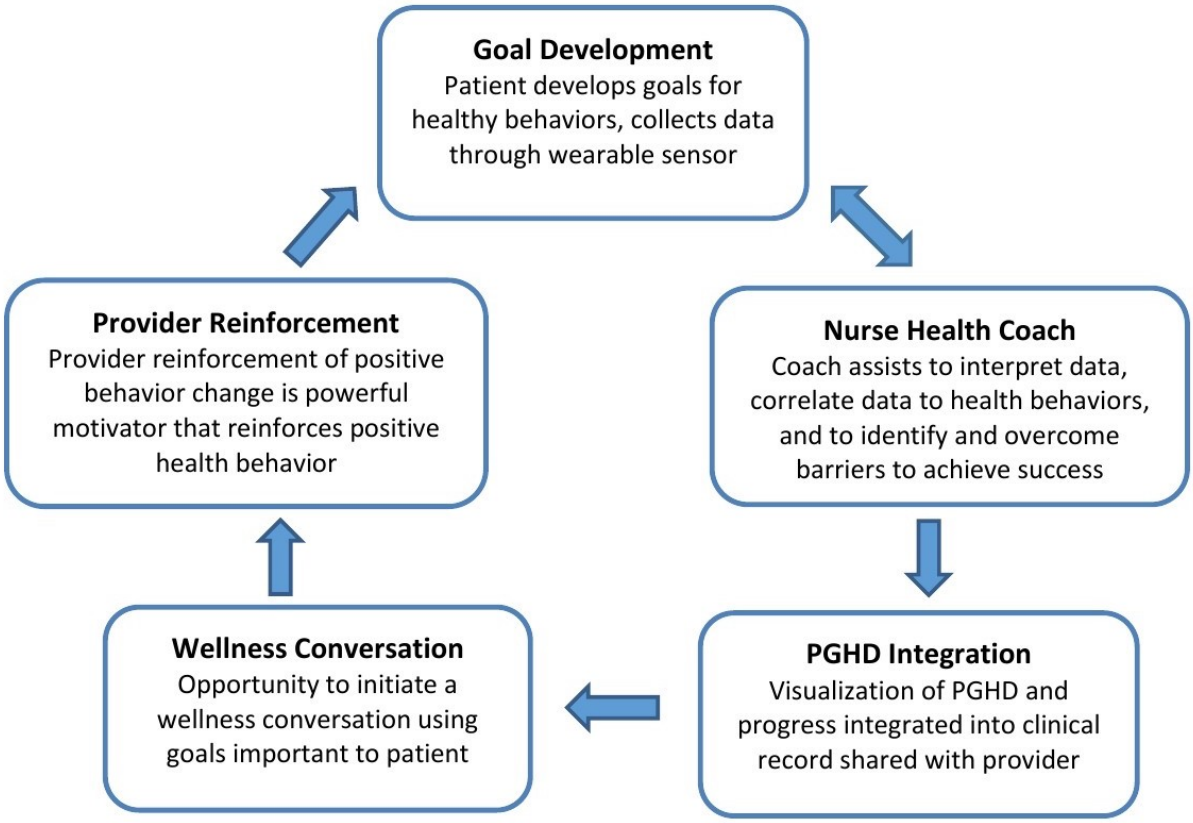
Tracking Health Data is not Enough

Prior to conducting an intervention study focused on improving exercise health and self-efficacy within an employee wellness program, our team conducted focus groups to understand potential users' beliefs about the role of fitness trackers and nurse health coaching in supporting people to attain improved health behaviors. We conducted 4 focus groups with 30 employees of a large health system. Principal findings from this qualitative study elicited participant views that to create effective behavior change interventions, technology tools must go beyond tracking of PGHD. Participants identified the need for a health expert (nurse coach and/or primary care provider) to collaborate with them to create context and meaning from the data collected through an mHealth device. The following pathways to create meaning were identified: synthesizing data; helping to generate incremental, attainable goals; providing data-informed, tailored, and timely feedback; and provider investment in patient-centered behavior change work. A resulting model of how these design elements could ultimately change patient and provider engagement in health behavior change emerged from this work (Figure 1).

Engagement of Key Stakeholders in Intervention Design

This intervention program was developed with extensive input from patient, provider, and technology and informatics experts about key elements and considerations essential to build a program aimed at enhancing self-management success of persons living with diabetes. We invited the participation of three advisory boards: The Patient Advisory Board comprised of seven persons living with diabetes; the Provider Advisory Board comprised of 13 health care providers (primary care physicians, specialists, diabetes educators, and leaders from other health systems in the region); and the Technology Advisory Board comprised of 15 technology and informatics experts. Stakeholders met regularly with the research team. We brought data, prototype iterative designs, and results to our advisors to confirm relevancy of the findings, and to understand how to build an interface allowing for meaningful, right-sized, bidirectional data elements that complement and enhance current health system workflows.

Figure 1. Changing the conversation about health. PGHD: patient-generated health data.



Essential Intervention Components

The $P^2E^2T^2$ intervention design was finalized based on pilot study findings and input from key stakeholders. It is important to note that while all stakeholders discussed the value of blood glucose as a PGHD element, the decision was made to not include actionable data (requiring timely monitoring and provider intervention) in this initial demonstration to bring PGHD into the EHR. The core components of the intervention are: 1) the provision of a commercial sensor fitness tracking watch; 2) access to an existing mobile nutrition application; 3) regular nurse health coaching sessions over a period of three months; and 4) integration of PGHD and nurse coaching summaries into the EHR for provider, patient, and nurse coach reflection and tracking of progress.

Methods

Design

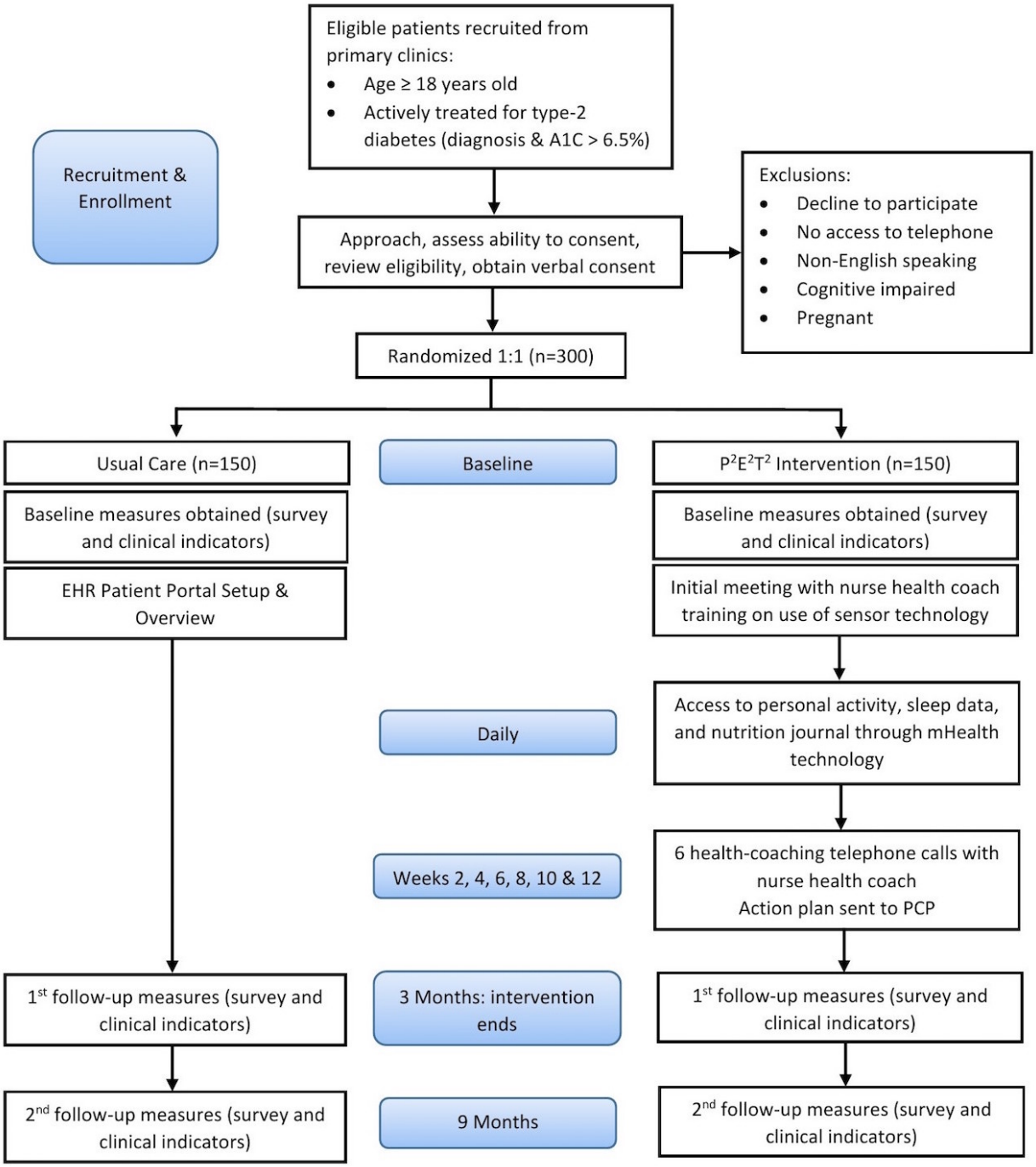
The $P^2E^2T^2$ Program to Improve Health in Diabetes study is a prospective, randomized controlled trial conducted at an academic health system in California with 2 arms: 1) usual care offered through existing chronic disease management resources at the health system, and 2) the $P^2E^2T^2$ Program. We planned to enroll 300 patients with type-2 diabetes from the health system's primary care network, randomizing half to usual care and half to the $P^2E^2T^2$ Program's mHealth enabled nurse health coaching intervention. The study was approved by the University's Institutional Review Board and was registered at ClinicalTrials.gov (NCT 02672176).

Recruitment

Participants were recruited from three academic primary care clinics, 2 suburban and 1 hospital-based primary care clinic. Settings were purposely selected in an effort to enroll a diverse group of individuals living with diabetes. Eligibility criteria included: aged 18 years or older, living with diabetes mellitus (defined as diagnosis of diabetes mellitus type-2 and most recent HbA_{1c} lab test result of 6.5% or higher), enrollment at one of the participating primary care clinics, and able to speak English. Individuals were excluded if they did not have access to a telephone, did not speak English, were pregnant, or could not consent due to cognitive impairment (see Figure 2).

A query of the EHR using criteria for age, diagnosis, and clinic site generated a list of potentially eligible patients. Study information packets were mailed to individuals, including a brochure describing the study and an opt-out card. In the mailing, individuals were informed that a research team member would contact them by phone if they did not return the opt-out card to the study office within two weeks. To maintain confidentiality, the opt-out card identified participants only by an anonymous study identification number, did not include any personal information, and did not mention diabetes to ensure privacy of personal health information. Research staff made telephone calls to those who did not return an opt-out card 3 weeks after the mailing. With successful contact, a standardized script was used to describe the study, discuss expectations of participation, review eligibility, and answer any questions. Individuals who were interested in participating and met eligibility criteria were verbally consented and then randomized to a group.

Figure 2. Diagram of Patient and Provider Engagement and Empowerment through Technology (P2E2T2) patient enrollment, randomization, intervention, and timeline. EHR: electronic health record; PCP: primary care provider.



Group Allocation, Blinding, and Enrollment

Following verbal consent, block randomization to either usual care or intervention with a 1:1 ratio stratified by clinic site was accomplished using the Research Electronic Data Capture (REDCap), a secure Web research application designed to support data for research studies [16].

Participants were blind to their study group assignment as all participants received training in the use of health system technology offerings. Participants were assigned a unique personal identifier and a group identifier allowing for blinding at the point of analysis. Once randomized, participants were invited to attend an in-person group onboarding session according to their group allocation. At both control and intervention group sessions, participation expectations for the study were outlined, questions were answered, signed informed consent was obtained, and the baseline survey was completed on paper or tablet according to preference. All participants were informed of expectations for survey completion at baseline, 3 months, and 6 months.

Control Group

During the onboarding session, participants received information and training on currently available technology (existing electronic patient portal) and diabetes related resources available

at the health system. MyChart, a personal patient portal to the health system's EHR system, was introduced and accounts were created for participants who did not already have an active account. Participants were shown how to access and use the MyChart portal through a smartphone, tablet, and/or personal computer. The features of MyChart, including making appointments, viewing labs, contacting providers, and accessing diabetes resources were reviewed. Usual care resources highlighted on the health system's website and accessible to all patients living with diabetes at the health system (online educational tutorials, diabetes group classes, private messaging with a diabetes educator, and links to diabetes related websites), were reviewed with the participants. After the onboarding session, participants in the usual care group had no further contact with the study team other than reminders and prompting to complete survey measures at relevant intervals.

Intervention Group

Participants randomized to the intervention arm received all elements of the orientation created for the control group, plus had an extended orientation to prepare them for the mHealth technology and nurse coaching components of the $P^2E^2T^2$ intervention.

The $P^2E^2T^2$ intervention consists of 3 components: 1) regularly scheduled telephone nurse health coaching sessions; 2) provision of a wireless sensor and mHealth application to capture physical activity, sleep, and nutrition data; and 3) integration of daily PGHD into the EHR.

Nurse Health Coaching

Participants in the intervention group were paired with a nurse health coach who collaborated with them to support health behavior changes. The goal of coaching is to promote mutual goal setting, track relevant health behavior data, and derive meaning from the data to reinforce and improve healthy choices (see Figure 1). An initial face-to-face meeting occurred during the onboarding session where participants met their assigned coach and learned about the coaching aspect of the intervention. Following the in-person meeting, telephone-coaching sessions were scheduled every 2 weeks for 3 months (6 contacts total) at times that were convenient for the participant. The initial coaching session elicited goals and motivations for improved health and established agreed upon metrics (eg, daily steps, calories, and carbohydrates) that the patient and nurse would track and discuss at subsequent telephone sessions. Nurses planned for 30-45 minutes for initial calls and 15-30 minutes for subsequent calls. With consent of participants, the coaching conversations were audio-recorded and uploaded to the study's secure drive to monitor nurse health coach performance for quality assurance and intervention fidelity.

mHealth Technology

Each participant received a Garmin VivofitHR activity tracker watch. The watch captures real-time activity data, including steps taken, distance travelled, active calories burned each day, active minutes per week, heart rate, and hours of sleep at night. Participants can personalize goals and receive visual acknowledgement on the watch when they reach their goal for the day. MyFitnessPal, the nutrition tracking application, was an optional component installed on the iPhone or iPod to allow participants to log food and beverage consumption. Participants are able to view trends in activity level, sleep, and nutrition on their smartphone or computer. Participants were encouraged to wear and use the activity tracker for the entire 9-month duration of study participation. The study team made available technical support to participants by telephone throughout the intervention.

Patient-Generated Health Data Integration Into the Electronic Health Record

The data collected by the sensors synchronizes to either an iPhone or an iPod touch. Participants who did not have a compatible iPhone were given an iPod touch for use during the study. Apple HealthKit and MyChart were connectors that allowed PGHD to be automatically transmitted into the EHR for review by nurse coaches and the patient's healthcare providers.

In order to facilitate the passive transfer of PGHD to the EHR, participants were encouraged to synchronize the activity tracker to their iPhone or iPod each day. Passive data transfer of PGHD between the mHealth technology and the EHR occurred for steps and calories burned. Calories and macronutrient information consumed by the participant and logged into the application were also transmitted into the EHR. At the time this study was initiated, it was not possible to passively transmit active minutes per week, sleep, weight, or nutrition data into the EHR, so participants were instructed to enter this data manually using MyChart if they wanted their coach or provider to have access to it.

EPIC is the EHR provider for the health system. We used an EPIC feature called Synopsis to design a single screen page to graphically display key PGHD elements in the EHR. Weight, activity, nutrition, and sleep PGHD can be individually selected and displayed in concert with clinically relevant data elements such as laboratory values, medications, and vital signs. Multiple authentication protocols were enacted by the patient and provider to authorize the collection and integration of sensor data into the EHR. The PGHD visualization dashboard within the EHR allowed the nurse and healthcare team the ability to view patient data collected by participants in their daily lives.

Summary documentation of coaching activities was also integrated in the EHR. After the final coaching call, the nurse coach sent a summary of each participant's goals and achievements to his or her primary care provider. Participants were encouraged to continue goal setting and attainment to improve their health, to wear the fitness tracker, and to synchronize their PGHD with MyChart for an additional six months, coinciding with the study end date.

Table 1. Study outcome measure. Data for all variables collected at baseline, 3 months, and 9 months.

Variable	Source/Instrument
Self-efficacy	Survey, Diabetes Empowerment Scale – Short Form
Readiness to Change	Survey, Readiness to Change
HbA_{1c}	Electronic health record abstraction
Quality of Life	Survey, Patient Health Questionnaire depression scale-9, Perceived Stress Scale, PROMIS (emotional distress, physical function and sleep disturbance)
Provider Satisfaction	Survey, Consultation and Relational Empathy Measure, Consumer Assessment of Healthcare Providers and Systems

Sample size

Sample size goals were based on our previous randomized controlled trial of nurse coaching to improve disease self-management in which we found significantly higher self-efficacy scores in the nurse coaching intervention group compared to the control group [15]. A recruitment goal of 300 (150 for each arm) was established for this study based on both power and projected attrition. Attrition was 16% in the previous study using a similar intervention design with comparable demands on participants for time and response. Even under the conservative assumption that design effects and dropout rates could result in a reduced sample size of 100 per treatment group, the $P^2E^2T^2$ study has at least 80% power to detect the specified clinically important effect size.

Study Measures and Outcomes

The primary outcome of interest is self-efficacy, measured using the Diabetes Empowerment Scale–Short Form, a validated eight-item instrument designed to assess the psychosocial self-efficacy of people living with diabetes [17]. The Diabetes Empowerment Scale–Short Form includes items that address managing the psychosocial aspects of the diabetes, assessing dissatisfaction and readiness to change, and setting and achieving goals. Secondary outcomes of interest include changes in HbA_{1c}, readiness to change, provider satisfaction [18,19], and quality of life measures [20-22]. Table 1 provides a complete list of variables collected and timing of collection.

Data Collection

All measures were collected in both the intervention and usual care groups at three time points: baseline, three months (coinciding with intervention completion), and six months (selected to assess sustained effects of the intervention). At baseline, participants completed a demographic survey to assess age, gender, race, education level, income level, and health history. Participants received a $50 gift card for completion of each survey.

Surveys were emailed to study participants using REDCap. Paper surveys were available if preferred. Clinical data required to measure study outcomes were abstracted from the EHR and recorded in the REDCap study database by the nurse health coach at each data collection time point.

Statistical analysis

Our analytic approach uses multivariate regression modeling for all hypothesis testing to estimate population trends and individual differences in change, such as those due to treatment effects. The mixed effects models include a main independent variable, a binary indicator for intervention assignment, and a parsimonious set of covariates to reduce the potential for confounding. Model fit will be based on deviance tests for nested models, the Akaike Information Criterion and the Bayesian Information Criterion for non-nested models. The estimates for the fixed effects will be assessed using a predetermined significance level (.05) on two-tailed tests and 95% confidence intervals. Intent-to-treat analysis will be used to assess the effect of the intervention by treating all eligible patients enrolled in the $P^2E^2T^2$ program, regardless of intervention completion.

Data Monitoring

All study personnel involved received Human Subjects Protection and Health Insurance Portability and Accountability Act compliance training. All data were managed and analyzed at the institution and maintained on secure servers accessible by individual login and password. In order to utilize commercially available mHealth devices it was necessary for the participants to share private and personal information with commercial technology vendors according to their privacy disclosures and terms of service.

Results

The development phase of the study was completed and successful integration of PGHD into the EHR was in place prior to participant enrollment. The clinical trial was conducted between February 2016 and May 2017, with final data collected by December 2017 and final analyses and results anticipated by mid-2018.

Discussion

This study combines evidence-based solutions for successful health improvement by offering nurse health coaching sessions paired with objective personal activity data collected through mHealth technology. We believe this is the first clinical trial to directly integrate and synchronize PGHD into the existing EHR of a large academic health system.

While type-2 diabetes is a progressive disease with a genetic component that in not modifiable, diabetes and associated comorbidities share common risk factors influenced by unhealthy behaviors. By focusing on health behavior goals identified by patients, the $P^2E^2T^2$ program has the potential to improve both general health and quality of life. When

individuals have the opportunity to take control of their health and make better behavioral decisions, they can directly prevent or mitigate the impact of chronic conditions. We hypothesize that greater personal and health outcomes can be achieved when the focus is on health goals prioritized and generated by the individual. The $P^2E^2T^2$ program builds on traditional approaches to chronic disease management by providing tools and supports for individuals to accomplish patient-determined goals and bringing objective PGHD to the EHR to provide a more complete picture of efforts to improve and manage health. These data complement laboratory values and other clinical indicators and give a more complete and time-related summary of behavioral changes, such as physical activity, nutrition, and sleep. Together with clinical data, they offer an opportunity for a more comprehensive discussion about wellness.

There are several challenges in this approach. While there is growing consumer interest in personal technology devices and desire to integrate PGHD into chronic disease management, adoption is challenging for both patients and systems. This intervention depends on willingness and capacity to adopt technology as well as access to the technological tools. Technology use is on the rise across all age and socioeconomic groups, yet the digital divide persists, especially pertaining to readiness [23]. To address these challenges, we provided the necessary technology to individuals and developed extensive technology training and support materials. These materials were tested in advance with our patient advisory group for feedback and design improvement prior to dissemination. Lastly, the telephone support line staffed by research assistants to troubleshoot any technology or use issues by participants enhanced adoption of the technology.

The integration and use of PGHD into the secure and closed system of the EHR was a significant challenge. We believe this integration to be essential since technology that does not integrate with health systems' EHR was unlikely to be used by clinicians and providers. Given clinical time constraints, easy access and alignment with workflow is essential. Even though we have successfully integrated PGHD into the institution's EHR, it will be important to identify barriers to integration into practice workflow during primary care visits.

Conclusion

The $P^2E^2T^2$ Program to Improve Health in Diabetes will serve as a resource to understand if the combination of objective mHealth gathered PGHD and nurse health coaching helps individuals with type-2 diabetes improve self-efficacy to manage their health. Integrating data generated by patients in their daily lives into the EHR allows for meaningful analysis of behavior choices and encourages patient-centered models of care to support and motivate patients to reach personal goals. It is imperative to the long-range plan of building systems and programs that, if found to be beneficial, this intervention can be designed to scale and translated to achieve outcomes in a larger population with various health challenges.

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Authors' Contributions

HMY, SM, MD & YTF designed, developed core elements of the intervention, and oversaw implementation of the study. SF managed implementation and was a nurse health coach on the study. All authors contributed to development of the manuscript, read, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

EHR: electronic health record
HbA_{1c}: hemoglobin A_{1c}
mHEALTH: mobile Health
$P^2E^2T^2$: Patient and Provider Engagement and Empowerment through Technology
PCP: primary care provider
PGHD: patient-generated health data
REDCap: Research Electronic Data Capture

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Protocol

Telegerontology as a Novel Approach to Address Health and Safety by Supporting Community-Based Rural Dementia Care Triads: Randomized Controlled Trial Protocol

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Abstract

Background: Telegerontology is an approach using videoconferencing to connect an interdisciplinary team in a regional specialty center to patients in rural communities, which is becoming increasingly practical for addressing current limitations in rural community-based dementia care.

Objective: Using the remotely-delivered expertise of the Telegerontology dementia care team, we aim to enhance the caregiver/patient/physician triad and thereby provide the necessary support for the person with dementia to "age in place."

Methods: This is a cluster randomized feasibility trial with four rural regions in the province of Newfoundland and Labrador, Canada (2 regions randomly assigned to "intervention" and 2 to "control"). The study population includes 22 "dementia triads" that consist of a community-dwelling older Canadian with moderate to late dementia, their family caregivers, and their Primary Care Physician (PCP). Over the 6-month active study period, all participants will be provided an iPad. The intervention is intended as an adjunct to existing PCP care, consisting of weekly Skype-based videoconferencing calls with the Telegerontology physician, and other team members as needed (occupational therapist, physical therapist etc). Control participants receive usual community-based dementia care with their PCP. A baseline (pre-) assessment will be performed during a home visit with the study team. Post intervention, 6- and 12-month follow-up assessments will be collected remotely using specialized dementia monitoring applications and Skype calls. Primary outcomes include admission to long-term care, falls, emergency room visits, hospital stays, and caregiver burden.

Results: Results will be available in March of 2018.

Conclusions: Results from this study will demonstrate a novel approach to dementia care that has the potential to impact both rural PCPs, family caregivers, and people with dementia, as well as provide evidence for the utility of Telegerontology in models of eHealth-based care.

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KEYWORDS

Aging; Remote Assessment; Monitoring

Introduction

In 2011 the estimated prevalence of dementia in Canada was 340,000 with just under one-third (109,500) living at home [1]. Community-based dementia care relies heavily on family caregivers, with 92% of surveyed Canadians with dementia reporting friends or family members managing care and transportation. A further 58%-92% report family caregivers assisting with personal care, medical care, activities of daily living, meal preparation, and emotional support [1]. With such high demands on family caregivers of people with dementia, they are at increased risk of stress and burden [2], medical and psychiatric comorbidities [3,4], and social isolation [5]. Rates of dementia [6] and mortality [7] are also higher among caregivers, perpetuating and compounding the issue into a cycle of caregiving that leads to early disability, cognitive decline, and death. These detrimental effects of caregiving can also translate to negative consequences for people with dementia, including earlier institutionalization [8] and increased mortality [9]. Approaches that support the caregiver as well as the patient are therefore fundamental to community-based dementia care.

The health care triad model of dementia care proposes management of dementia that is both family and patient centered, while acknowledging that the primary care physicians (PCPs) are usually the first contact in the health care system for persons with dementia and their family caregivers [10]. This integrative approach values symptom diagnosis and management, medication management, and emotional support with a focus on comprehensive care coordination [10] and has been employed in both rural and urban settings [11]. And while this is a favorable approach, PCPs in rural Canada can face challenges when attempting to provide adequate community-based care for dementia patients and their families. Although rural Canadian PCPs are more accessible than specialist services, some research suggest that they may have limited training in dementia specific management [12]. Rural PCPs also report a need for better collaboration, partnerships, and integration of services [13] in order to provide the very best care for people with dementia and their families. How best to support the dementia triad in rural areas of Canada is still poorly understood, and few studies have explored the utility of the health care triad model of dementia care as a theoretical basis for an intervention [11]. Taken together, this evidence demonstrates a clear need to design and deliver evidence-based services to support people living with dementia in the community, their family caregivers, and PCPs [14].

Technology-based intervention is one line of inquiry aiming to address support for rural dementia care triads. There is some evidence to suggest that people with dementia and their family caregivers are already using the Internet to access Internet-based health resources [15]. Internet interventions for family caregivers of people with dementia have shown promise addressing caregiver well-being [16-18]. Less is known about how the Internet can be used to manage dementia at home. Some research suggests that videoconferencing is a valid method to assess dementia [19,20]. Telemedicine has been used to accurately diagnose dementia [21] and telehealth has effectively supported pre-assessment and follow-up when used in combination with an in-person interdisciplinary memory clinic assessment [22].

This paper describes a novel approach to rural community-based dementia care that combines the health care triad model of dementia care (patient, caregiver, and PCP) with an innovative Telegerontology intervention. Telegerontology is an approach using videoconferencing to connect an interdisciplinary team in a regional specialty center to people in rural communities. The aim of this study is to use Telegerontology in order to systematically detect and address care needs of people with dementia and their family caregivers, while augmenting PCP relationships with dementia patients and their families. The overall objective is to assist people with dementia to age successfully "in place." Furthermore, findings from this study will be used to identify feasibility issues that will inform the design of a full-scale randomized control trial (RCT).

Methods

Aim

Using the remotely delivered expertise of the Telegerontology dementia care team, we aim to enhance the caregiver/patient/physician triad and thereby improve rural community-based care for people with dementia.

Objectives

The objectives will be as follows:

1. Test Telegerontology's ability to enhance the caregiver/patient/ PCP triad and thereby improve care "in place" (ie, health care utilization) for people with dementia.
2. Assess and optimize a remote monitoring method for managing care of people with moderate- to late-stage dementia living at home in rural Canada in order to inform the design of a full-scale RCT.
3. Explore issues related to care of people with dementia from the caregivers' and PCPs' perspectives.

Study Design

Overview

The study was approved by the local research ethics authority. This is a cluster randomized feasibility trial assessing 4 rural regions (2 per study arm) comparing usual rural community-based dementia care to Telegerontology plus usual rural community-based dementia care. Using the opaque envelope method, the rural regions will be randomized to control or intervention after baseline assessment. The intervention will last 6 months with the measurement of outcomes taking place at baseline, after 6 months (post), with follow-up occurring 6 months (6-month follow-up) and 12 months (12-month follow-up) after cessation of the intervention.

The study population will include 22 "dementia triads" that consist of a community-dwelling older Canadian with moderate to late dementia, their family caregivers, and their PCP. The study will be carried out in communities located in rural areas of Newfoundland and Labrador, Canada but will be monitored remotely from the metropolitan city of St John's, Newfoundland and Labrador. We define *rural* in this study to mean a

community with less than 10,000 residents and a location that is greater than two hours' drive from the metropolitan city, where specialist health services are located. Before randomization, recruitment will begin by enrolling PCPs from rural communities who will make initial contact with potential participants. Written informed consent will be obtained for every individual agreeing to participate in the study except in the case for an individual with advanced dementia who lacks capacity, in which case consent will be obtained from the substitute decision maker. Consent will be reviewed without the presence of the PCP in order to limit undue influence for participation in the study.

Inclusion Criteria

Dementia Patient/Caregiver Dyad

Community-dwelling adults aged ≥60 years will be screened by PCP for having a score of 4 or greater on the Global Deterioration Scale [23], and have a formal diagnosis of dementia based on the Diagnostic and Statistical Manual of Mental Disorders IV. Caregiver is defined as an individual who self-identifies as providing support with instrumental activities of daily living in an informal (friend or family) capacity and who was referred to the study by the PCP.

PCPs

PCPs located in a rural area of Newfoundland and Labrador must be willing to participate in a 1 hour focus group, and must refer at least 1 community-dwelling patient with moderate/late-stage dementia who agrees to participate in the study.

Exclusion Criteria

Dementia Patient/Caregiver Dyad

Patients with a diagnosed comorbid psychiatric condition (eg, schizophrenia, bipolar disorder, psychoses not yet determined) will be excluded. In addition, those who are currently participating in other studies or experimental therapies will be excluded.

Dropout

Dropout is defined as any participant who voluntarily withdraws or who cannot be successfully contacted within a month of the defined follow-up times. The impact of dropouts on statistical analysis, including intention to treat, will be discussed subsequently.

Control and Intervention Group

Over the 6-month active study period, all participants will continue usual community-based dementia care with their PCPs. All participants will also be given new iPads by the study team with Skype and the specialized dementia monitoring applications installed. In addition, all participants will be referred to the Canadian Alzheimer Society's FirstLink Program [24,25] which includes a 10-week education session for caregivers that can be accessed remotely by Skype, and provided links to Internet-based health resources for dementia caregivers. Because FirstLink is already available in the target communities, all participants were referred in order to standardize exposure across groups.

PCPs of all participants will also receive a written report of the initial home assessment at the beginning of the 6-month active study period to implement at their discretion. Study flow is described in detail in Figure 1.

Intervention Group

The intervention works as an adjunct to existing PCP care and consists of scheduled weekly Skype-based videoconferencing calls (additional calls available as needed) with the Telegerontology physician, who is a family practice geriatrician. The program's development was based on principals of the health care triad model of dementia care [10]. Calls will focus on symptom diagnosis and management, medication management, comprehensive care coordination, and emotional support. During the 6-month intervention, the Telegerontology physician will liaise via telephone and email correspondence with the PCP and specialized geriatric team as required. The team will include a geriatrician, geriatric psychiatrist, nurse, physiotherapist and occupational therapist. Access to other allied health professionals (social worker, speech language pathologist, and recreational therapist) will also be available when deemed necessary. During this time, participant families will also have access to specialized dementia monitoring iPad applications that may be used by the Telegerontology physician in clinical decision making. Any potential changes to patient's treatment plans will be managed by the participant's PCP in consultation with the Telegerontology physician and acting in collaboration with the specialist gerontology health care team.

iPad Application Development

Three standardized scales to assess dementia and caregiver burden were developed into specialized monitoring apps for the iPad through Memorial University's Distance Education, Learning and Teaching Support. The Cohen Mansfield Agitation Inventory [26], the Cornell Scale for Depression in Dementia [27] and the Caregiving Hassles Scale [28] were selected because they were designed to be completed by caregivers, and were appropriate to evaluate caregiver burden or domains of function for targeted management of moderate to late stage dementia. The scales are validated tools to assess agitation, depression and daily hassles associated with dementia care [28-30] and will be discussed in detail subsequently.

The apps will be pre-loaded onto iPads. The main screen of the app displays a list of questions (Figure 2, panel A). An error message appears if participants miss questions and a list of missed questions appears to direct participants (Figure 2, panel B). Login is managed by the Telegerontology team, so participants will not be required to enter username, password or server information when opening the apps (Figure 2, panel C). Permission to reproduce these scales was granted by the authors and acknowledgements were included on the administrative page of the app (Figure 2, panel C). Each participant will be assigned a unique anonymous ID linked to the study number, which will allow the Telegerontology physician to access information remotely from a secure web portal (Figure 3).

Telegerontology Measurement Framework

A measurement framework was designed to include domains from The International Classification of Functioning, Disability and Health [31] and the Wilson-Cleary Conceptual Model of Patient Outcomes [32]. Assessments encompass the following domains: personal, environment, impairment, disability, participation, quality of life, and health care use. Outcome measures, clinical assessment tools, remote monitoring tools and circle of care measures to be administered at each time point in relation to the study objectives are described in Table 1.

Outcome Measures

Primary and secondary outcomes will be collected at baseline (pre-), during the intervention, after the intervention (post), and 6- and 12-month follow up. Assessments will be completed by trained clinical personnel who are also members of the research team. First assessments will be completed during the home visit, with subsequent measures collected remotely. All data will be manually entered into SPSS for analysis. The study outcomes will be used to answer the primary research question regarding Telegerontology's ability to enhance the caregiver/patient/PCP triad and thereby improve care "in place" for people with dementia.

Figure 1. Study flow. After PCP recruitment, participant referrals and home assessment, the rural regions will be randomized to control or intervention.

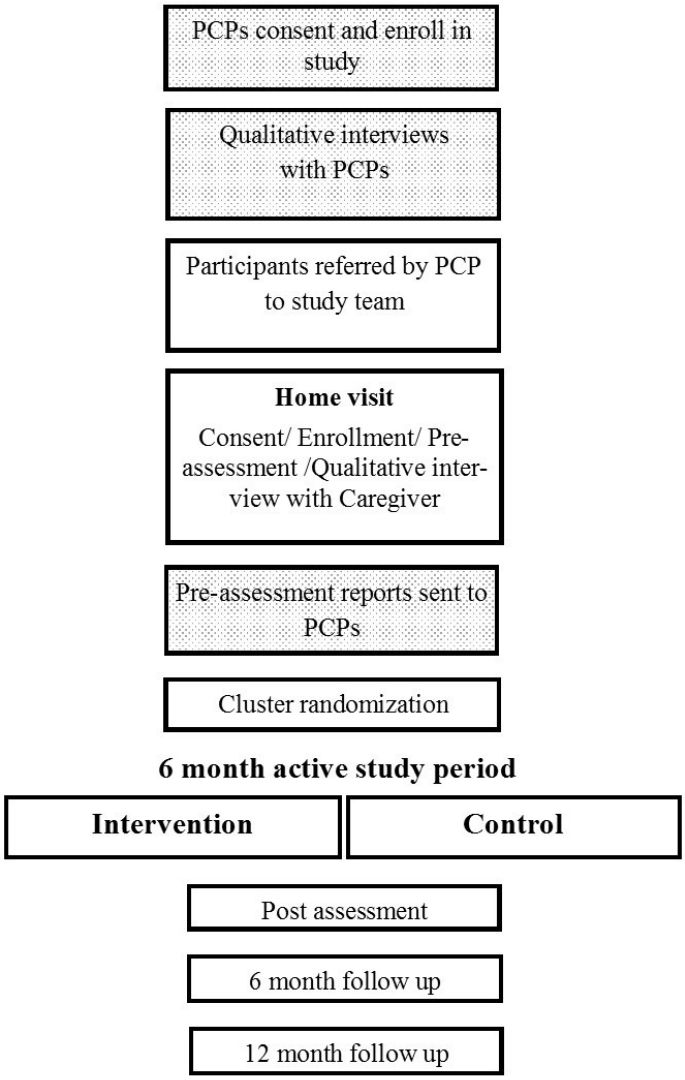


Figure 2. (A) Main screen display, (B) Error message for missing responses, (C) Administrative login page.

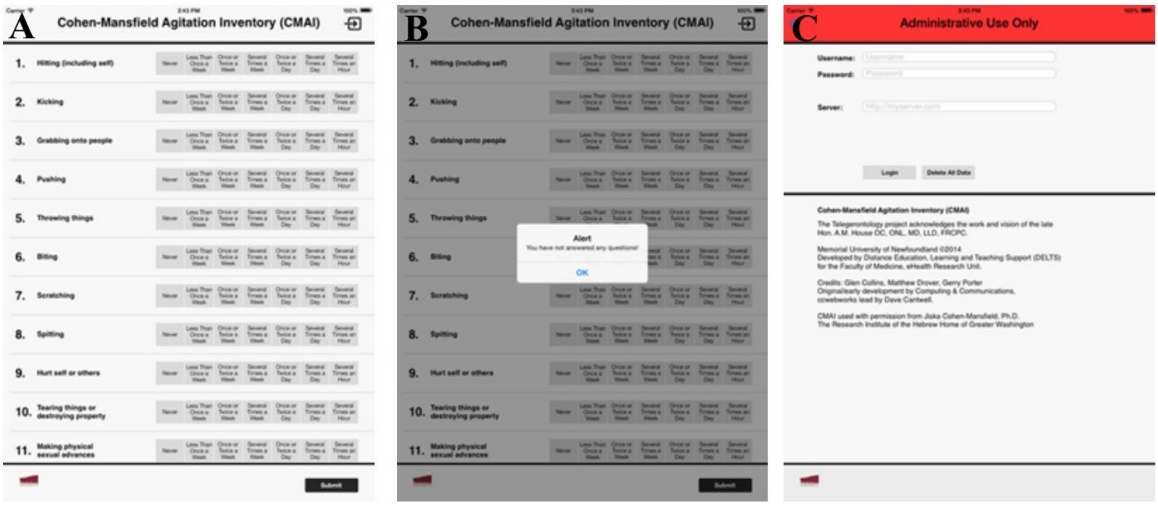
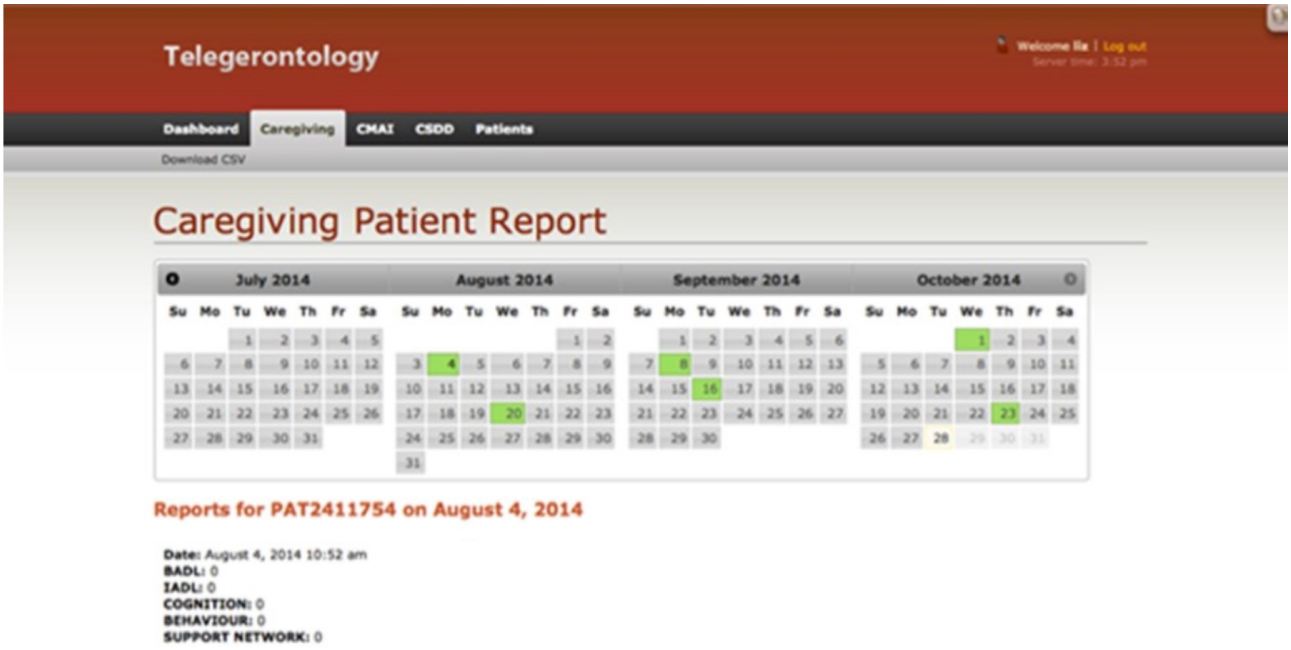


Figure 3. Screenshot of secure web portal. Colored calendar blocks indicate days when app is completed by caregiver. Scores from reports are displayed by clicking on a colored block.



Primary Outcomes

Primary outcomes will be reported by caregivers and confirmed through medical records and chart reviews (schedule of assessment described in Table 1). Based on Canadian incidence rates, we anticipate these outcomes will be detectable during the 18-month study period [33-35]. The primary outcomes will be as follows:

1. Admission to long-term care (LTC): Date that participant is admitted to LTC.
2. Emergency room (ER) visits: Total number of ER visits over 6 months.
3. Falls: Total number of falls over 6 months.
4. Hospital stays: Total number of hospital stays over 6 months.
5. Caregiving Hassles Scale: This 42-item scale assesses the daily burden of caring for a family member with dementia. Caregivers are asked to rate patient requirements and behaviors on a 5-point scale of frequency, ranging from "Did not occur" to "A lot." High scores indicate higher level of caregiver burden. Assessment takes 20 minutes to complete [28]. Administered by iPad, at pre, post, 6- and 12-month measures, in addition to an outcome measure, this scale will be used as a monitoring tool during the intervention at the discretion of the Telegeronology physician.

Secondary Outcomes

The secondary outcomes will be as follows:

1. Referrals: Total number of referrals to specialist care over 6 months.
2. PCP visits: Total number of PCP visits over 6 months.

Clinical Assessment Tools

These tools will be used to help characterize the progression of dementia throughout the study and to inform clinical decision making (schedule of assessment described in Table 1). These assessments will also be used to address feasibility issues and to inform remote monitoring practices. All assessments will be administered by the physician or physiotherapist.

Demographics and Medical History

Demographic information including age, sex, marital status, educational background, and living situation will be collected along with information about the patient's circle of care. Medical information including allergies, comorbid diagnoses, medications, consultations, laboratory reports, details of the dementia diagnosis, and results of previous tests and assessments will be collected by chart review.

Table 1. Measures mapped to study objectives and schedule of assessment.

Measure	Schedule (Stage)				
	Baseline	During intervention	Post assessment	6-month follow-up	12-month follow-up
Outcome Measures					
Emergency room visits[a]			✓[b]	✓	✓
Hospital stays[a]			✓	✓	✓
Admission to LTC[a,c]			✓	✓	✓
Falls[a]			✓	✓	✓
Referrals[a]			✓	✓	✓
PCP visits[a,d]			✓	✓	✓
Caregiving Hassles Scale[a,e]	✓	✓	✓	✓	✓
Clinical Assessment Tools					
Demographics and medical history[e]	✓				
Barthel Index of Activities of Daily Living[e]	✓				
Timed Up and Go test[e]	✓				
Kettle test[e]	✓				
Face washing functional task[e]	✓				
Custom Caregiver Quality of Life Index[e]	✓				
Global Deterioration Scale[e]	✓		✓	✓	✓
Mini Mental Status Exam[e]	✓		✓	✓	✓
Montreal Cognitive Assessment[e]	✓		✓	✓	✓
Occupational therapy home video assessment[e]	✓				
Cohen Mansfield Agitation Inventory[e]	✓	✓	✓	✓	✓
Cornell Scale for Depression in Dementia[e]	✓	✓	✓	✓	✓
Telegerontology time tracking[e]		✓			
Qualitative interviews (caregivers and PCPs)[f]	✓				

[a]Test Telegerontology's ability to enhance the caregiver/patient/ PCP triad and thereby improve care 'in place' (ie, health care utilization) for people with dementia.

[b]✓=Performed at time point.

[c]LTC: Long-term care.

[d]PCP: Primary care physician.

[e]Assess and optimize a remote monitoring method for managing care of people with moderate- to late- stage dementia living at home in rural Canada in order to inform the design of a full-scale randomized control trial.

[f]Explore issues related to care of people with dementia from the caregivers' and primary care physicians' perspectives.

Barthel Index of Activities of Daily Living

The Barthel Index assesses self-care, mobility, and activities of daily living. It is widely used in geriatric assessment settings. Information is collected from observation, self-report or informant report. It takes approximately 5-10 minutes to complete. Maximum score is 100, indicating complete independence. Low scores on individual items highlight areas of need [36].

Timed Up and Go Test

The Timed Up and Go test assesses mobility, balance, walking ability, and fall risk in older adults [37]. When the assessment begins, the patient sits in the chair with his/her back against the chair back. On the command “go”, the patient rises from the chair, walks 3 meters at a comfortable and safe pace, turns, walks back to the chair, and sits down. Timing begins at the instruction “go” and stops when the patient is seated. The time (sec) between the command to start and when the buttocks touch the chair is collected. The patient should have one practice trial that is not included in the score and must use the same assistive device each time he/she is tested to be able to compare scores. The Timed Up and Go takes less than 5 minutes to administer [37]. Minimal detectable change in Alzheimer’s disease has been reported as 4.09 seconds [38].

Kettle Test

The Kettle Test was developed as a brief performance-based measure to assess cognitive skills in a functional context. The test uses a standard set of items including an electric kettle (empty and disassembled parts); ingredients for beverages, presented on a tray together with other ingredients as distracters; and necessary dishes and utensils together with distracters. The task of preparing two hot beverages is broken down into 13 discrete steps that can be evaluated. All 13 steps of the task are scored on a 4-point scale. The total score ranges from 0 to 52 with higher scores indicating the need for greater assistance [39].

Face Washing Functional Task

The face washing task is not based on a standard scale. Participants will be asked to demonstrate for the observer the personal care activity of face washing. Qualitative observations will be noted, focusing on aspects of safety and independence.

Global Deterioration Scale

This scale assesses the stages of cognitive function in primary degenerative dementia. It is broken down into 7 different stages. Stages 1-3 are the mild stages of dementia. Stages 4-5 are the moderate stages of dementia. Beginning in stage 6, an individual can no longer maintain independence without assistance. Within the Global Deterioration Scale , each stage is numbered (1-7), given a short title (Mild, Moderate, etc), and followed by a brief listing of the characteristics for that stage. Caregivers can estimate the stage of an individual in the disease process by observing that individual's behavioral characteristics and comparing them to the Global Deterioration Scale [23].

Mini Mental Status Exam

The Mini Mental Status Exam (MMSE) is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score of less than 24 is indicative of cognitive impairment. The MMSE takes about 5-10 minutes to administer and is therefore practical to use repeatedly and routinely. The instrument relies heavily on verbal response and reading and writing. Therefore, patients that are hearing and visually impaired, intubated, have low English literacy, or those with other communication disorders may perform poorly even when cognitively intact [40].

Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) test is a one-page 30-point test administered in approximately 10 minutes [41]. The MoCA assesses several cognitive domains including short-term memory, visuospatial abilities, executive functions verbal fluency and abstraction, attention, concentration and working memory, and orientation to time and place. The MoCA is more sensitive to mild cognitive impairment compared to the MMSE, and has also been used to assess cognitive impairment in Alzheimer’s disease [42], frontotemporal [43], and vascular dementia [44].

Custom Caregiver Quality of Life Index

The custom caregiver quality of life index includes 10 questions about the impact of caring for a person with dementia, aspects of the caregiver’s life, and the caregiver’s mental well-being. Areas include alteration in daily routine, sleep, financial train, outlook, mental stain, guilt, frustration, impact of illness on family, and feeling well informed about dementia. Scores range from 1 (not at all) to 5 (very much) with higher scores indicating greater impact of caregiving on quality of life.

Remote Assessment Tools

The remote assessment tools will be used by the Telegerontology team for clinical decision making through the intervention period (schedule of assessment described in Table 1). We anticipate some variation in the frequency of their administration, dependent on the individual.

Cohen Mansfield Agitation Inventory

The Cohen Mansfield Agitation Inventory is a caregiver’s rating questionnaire consisting of a list of 29 agitated behaviors, each rated on a 7-point scale of frequency. Ratings pertain to the two weeks preceding the administration of the Cohen Mansfield Agitation Inventory [26] and takes approximately 20 minutes to complete.

Cornell Scale for Depression in Dementia

The Cornell Scale for Depression and Dementia was developed to assess signs and symptoms of major depression in patients with dementia and measure caregivers’ rating of 19 items. Ratings are based on symptoms present in the past week. Each question is scored as: 0=absent; 1=mild or intermittent; 2=severe; and n/a=unable to evaluate. High scores indicate more symptoms of depression [27].

Caregiving Hassles Scale

The Caregiving Hassles Scale has been described above under primary outcomes.

Occupational Therapy Home Video Assessment

The research assistant will collect a detailed video of the home and living space based on a standard checklist developed by the specialized gerontology health care team's Occupational Therapist (Table 2). The Occupational Therapist will then assess the video recordings and compile a detailed report of home safety recommendations for the PCP to review with the patient/caregiver (schedule of assessment described in Table 1).

Time Tracking

Telegerontology Time Tracking

Telegerontology team members will log the time spent delivering support to families during the intervention period as well as all other related tasks such as chart review and report writing. This measure will be used to help address feasibility issues, to inform remote monitoring practices, and may also inform future cost-benefit analyses based on the study findings.

Circle of Care Measures

Circle of care is defined as anyone who is involved in patient care and can include formal care providers and informal caregivers [45,46]. These measures will not be used as outcome measures, but rather to address the research objective to identify existing issues in rural areas when caring for people with dementia from the caregivers' and primary care physicians' perspectives (schedule of assessment described in Table 1).

Baseline Interviews

Baseline interviews will be completed in person by the research assistant who will visit participants, caregivers and PCPs in their respective communities. All interviews will be audio recorded and transcribed for analysis. The interviewer will be experienced with qualitative research methods and will attempt to elicit detail using reflexive probes based on the participants' answers.

PCP Interview

Prior to the active study phase, all recruited PCPs will be asked to take part in a qualitative focus group. The interview will center around 3 main questions (Textbox 1).

Caregivers Interview

All caregivers will be asked to take part in a qualitative interview at baseline. The interview will center around two main questions (Textbox 1).

Sample Size Calculation

Sample size was calculated based on regional population statistics rather than for statistical power, targeting 2.5% of the population of community-dwelling dementia patients in the target region. Based on prevalence estimates, 98.5/1000 Canadians over 40 years of age have dementia with 34% living at home. The total population for the entire recruitment region of the present study is approximately 38,490 suggesting that the total population of community-dwelling dementia patents is approximately 1,289. Therefore, we aim to recruit 42 participants for inclusion in this study accounting for a 30% dropout rate.

Table 2. Occupational Therapy Home Safety Video checklist.

Video	Description
1	A short video walking from the driveway outside, going into the house through the usual entry door, straight through the kitchen/living area into the person's bedroom and then into the bathroom.
2	Kitchen (short video)
3	Bedroom (short video)
4	Bathroom (short video)
5	Living room (short video)
6	Stairs (short video)
7	Laundry (short video)

Textbox 1. Qualitative interview questions.

PCP Interview Questions

- Describe the care required to manage people with dementia in their homes.
- From your point of view, how well are your patients being managed at home?
- How would you envision an ideal circle of care to maintain people with dementia in their homes?

Caregivers Interview Questions

- From your point of view, how well are you managing the health of your loved one at home?
- In an ideal world, how could things be improved? What are the main challenges you experience? Have you had successes caring for your loved one?

Statistical Analysis

Data entry, consistency check, and cleaning will be performed prior to analysis. Mean and standard deviation will be used for continuous variables, while frequency and percentages will be used to describe categorical variables. We do not anticipate this study will detect statistically significant findings however, as part of a secondary analysis, unpaired *t* tests will be used. Differences between intervention and control groups with respect to outcomes will be compared using repeated measures ANOVA or independent *t* test split by group. Data analysis will be conducted using SPSS statistical software. A $P<0.05$ will be used to determine potential significance. The 95% CI for differences will also be calculated. With respect to dropout, every person who is randomized regardless or subsequent fall, death, or admission to LTC will be included in the final analysis. If participants drop out before the intervention or voluntarily withdraw they will not be included in the final analysis. For analysis of the clinical assessments tracked over the course of the study (schedule of assessment described in Table 1), intention-to-treat analysis will be used by carrying the last observation forward.

Qualitative analysis will follow the Framework Method [47]. This method helps build rigor and trustworthiness in qualitative analysis by providing a clear audit trail from the original data to the final themes including illustrative quotations.

Results

Recruitment began in January of 2014. Data collection was completed in April 2017. Results will be available in March of 2018.

Discussion

Significance of Study

The proposed study is the first study, to our knowledge, to use Telegerontology together with Skype and specialized remote monitoring apps for the iPad to optimize health and safety among rural community-dwelling Canadians with dementia. The results could have particular importance given the international increase in prevalence of dementia [48], and the shift away from institutional-based models of care in Canada and other countries [49].

Study Strengths and Limitations

The proposed study has several notable methodological strengths. The initial home visit is designed to help build rapport between the Telegerontology physician and participants. This method is also in keeping with previous research, which suggests that telehealth has effectively supported assessment and follow-up when used in combination with an in-person interdisciplinary memory clinic assessment [12].

Next, the Telegerontology measurement framework, based on the ICF and Wilson-Cleary models provides in-depth, multi-factor profiles of participants contributing to a methodology that acknowledges the broad range of factors that can impact health planning and management of community dwelling people with dementia. Likewise, the inclusion of caregivers and PCPs as participants adds further depth to both characterizing and assessing participants with dementia by acknowledging and building on the role of the caregiver and PCP in the health care triad. The development of remote monitoring apps from existing validated scales to assess dementia and caregiver burden is also a methodological strength of this study.

There are also several limitations in the protocol. The relatively small sample size can be seen as a drawback, however, based on regional prevalence estimates, the sample size is realistic for the target population. There may also be considerable variability between participants within a group, further complicating statistical analysis. Next, the Telegerontology physician serves as both an interventionist and assessor. This has the potential to create bias, however the primary outcome measures were selected partially to address this issue since they are based on participant self-report/chart review rather than clinical assessment.

Conclusion

This proposed study will provide an evaluation of Telegerontology together with Skype and specialized remote monitoring apps for the iPad to optimize health and safety among rural community-dwelling Canadians with dementia. Results from this study will demonstrate a novel approach to dementia care that has the potential to impact both rural PCPs, family caregivers, and people with dementia, as well as provide evidence for the utility of Telegerontology in a full scale RCT.

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Conflicts of Interest

None declared.

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Protocol

Testing Behavior Change Techniques to Encourage Primary Care Physicians to Access Cancer Screening Audit and Feedback Reports: Protocol for a Factorial Randomized Experiment of Email Content

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Abstract

Background: Cancer Care Ontario's Screening Activity Report (SAR) is an online audit and feedback tool designed to help primary care physicians in Ontario, Canada, identify patients who are overdue for cancer screening or have abnormal results requiring follow-up. Use of the SAR is associated with increased screening rates. To encourage SAR use, Cancer Care Ontario sends monthly emails to registered primary care physicians announcing that updated data are available. However, analytics reveal that 50% of email recipients do not open the email and less than 7% click the embedded link to log in to their report.

Objective: The goal of the study is to determine whether rewritten emails result in increased log-ins. This manuscript describes how different user- and theory-informed messages intended to improve the impact of the monthly emails will be experimentally tested and how a process evaluation will explore why and how any effects observed were (or were not) achieved.

Methods: A user-centered approach was used to rewrite the content of the monthly email, including messages operationalizing 3 behavior change techniques: anticipated regret, material incentive (behavior), and problem solving. A pragmatic, 2x2x2 factorial experiment within a multiphase optimization strategy will test the redesigned emails with an embedded qualitative process evaluation to understand how and why the emails may or may not have worked. Trial outcomes will be ascertained using routinely collected administrative data. Physicians will be recruited for semistructured interviews using convenience and snowball sampling.

Results: As of April 2017, 5576 primary care physicians across the province of Ontario, Canada, had voluntarily registered for the SAR, and in so doing, signed up to receive the monthly email updates. From May to August 2017 participants received the redesigned monthly emails with content specific to their allocated experimental condition prompting use of the SAR. We have not yet begun analyses.

Conclusions: This study will inform how to communicate effectively with primary care providers by email and identify which behavior change techniques tested are most effective at encouraging engagement with an audit and feedback report.

Trial Registration: ClinicalTrials.gov NCT03124316; https://clinicaltrials.gov/ct2/show/NCT03124316 (Archived by WebCite at http://www.webcitation.org/6w2MqDWGu)

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KEYWORDS

early detection of cancer; primary health care; feedback; electronic mail; persuasive communication; clinical trials as topic; behavior change techniques; process evaluation; implementation science

Introduction

Health care provider behavior is an important determinant of patients' use of screening services [1-5]. A number of knowledge translation strategies intended to target provider behavior already exist , including audit and feedback [6], reminder/recall systems [7], and incentives [8]. The effectiveness of these strategies varies considerably and may be partly explained by variation in the features of the interventions [6,7], the differing clinical contexts in which the interventions are used, and the extent to which clinicians actually engage with the interventions [9,10]. For example, physicians may not access feedback reports regularly if they lack trust in data quality, if they are not motivated to improve on the indicators measured, or if they encounter organizational or other constraints that interfere with quality improvement [11].

In 2012, the global burden of cancer amounted to 8.2 million deaths, representing 13% of all deaths globally [12,13]. Screening can reduce cancer-related mortality [14] if appropriate tests are used [15] and if a sufficient number of patients from the target population participate [16]. Despite the availability of organized screening programs for colon, breast, and cervical cancer in Ontario, Canada [17], more than one-third of the eligible population in the province are not up to date with screening tests for these cancers [18].

Cancer Care Ontario (CCO) is the agency that oversees population-based cancer screening programs in Ontario. It currently uses a multifaceted strategy to increase cancer screening rates, including public media campaigns, letters mailed to patients overdue for screening, and an audit and feedback tool available to primary care physicians. The online audit and feedback tool, known as the Screening Activity Report (SAR), is updated monthly to help primary care providers identify specific patients who are overdue for screening and/or who have screening results that require follow-up in addition to comparing their performance to the regional average. Use of the SAR by primary care physicians is associated with higher rates of colorectal, breast and cervical screening [19]. However, most primary care physicians in the province do not regularly use the SAR. To encourage use, CCO sends a monthly email to primary care physicians who have registered for the SAR (see Multimedia Appendix 1); however, internal CCO data extracted in 2016 revealed that 50% of email recipients did not open the email, and less than 7% of recipients clicked the enclosed link to log in to their SAR. Therefore, we worked with CCO to develop a study to test theory- and user-informed content to improve the salience and impact of emails, with the objective of increasing SAR access and, ultimately, aligning cancer screening rates with guidelines. In this manuscript, we describe the design of a pragmatic, factorial randomized experiment using the Multiphase Optimization Strategy (MOST) [20] to evaluate the impact of different components in the monthly SAR delivered by email to primary care physicians across Ontario and an accompanying process evaluation.

Methods

Intervention Design: Monthly Emails Prompting Use of the Screening Activity Report

The team first employed a user-centered design approach informed by principles of behavior change theory to rewrite the monthly emails and identify email components, or behavior change techniques (BCTs), to test in an experiment . BCTs are defined as "active components of an intervention designed to change behavior" [21]. We identified BCTs from the Behavior Change Technique Taxonomy (v1) [22] that could influence primary care physician behavior [23].

The rewriting process emphasized content development and involved focus groups with adopters (physicians who already access and use the SAR) and nonadopters (physicians who have not accessed the SAR for at least 1 year). CB and DL, both qualitative experts at Cancer Care Ontario, led the groups of discussion. Through this process, we identified 3 modifiable components that could be prioritized for testing in a trial. Specifically, we hypothesized that the following BCTs could

help increase the effectiveness of the emails: anticipated regret (ie, induce or raise awareness of expectations of future regret about not logging in to the SAR), material incentive (behavior) (ie, Identify opportunity for using SAR to access available monetary bonus for achieving high cancer screening rates), and problem solving (ie, generate or select strategies that include overcoming barriers and/or increasing facilitators to accessing the SAR) (see Multimedia Appendix 2). The details of this process and the iterative changes made based on adopter input will be reported separately.

The BCTs tested are presumed to target 1 or more determinants of behavior (ie, the potential mechanism of action) as described in the theoretical domains framework (Table 1).

We verified the importance of the selected BCTs with adopters and nonadopters. We used the theoretical domains framework terminology to describe the potentially relevant determinants because mapping between BCTs and theoretical domains framework is already established [21,24]. For example, "anticipated regret" targets emotion and beliefs about consequences, which may drive primary care physicians to access their SAR (Figure 1).

Study Design

This approach follows the MOST framework to optimize and evaluate multicomponent behavioral interventions [20,25]. Factorial experiments allow for the estimation of main effects of multiple factors in a single experiment by combining experimental conditions [26,27]. Thus, such designs are useful options in health behavior research to efficiently compare more than 1 intervention, particularly, as in our case, when there is no expectation that the factors being tested will substantially interact [28,29]. The trial itself is a 2×2×2 factorial randomized experiment with 8 experimental conditions (Figure 2).

Table 1. Content and hypothesized mechanism of change for each behavior change technique.

Items	Behavior change techniques/factors tested		
	Material incentive (behavior)	Anticipated regret	Problem solving
General description[a]	Explicitly link SAR[b] use to a monetary bonus[c] (awarded only if achieving high cancer screening rates)	Induce or raise awareness of expectations of future regret about not logging in to the SAR	Provide strategies that aim to overcome identified barriers to accessing the SAR
Operationalization	Logging into the SAR can help you maximize your screening rates and save time when calculating your preventive care bonus.	How would you feel if a patient had a poor outcome because you missed an abnormal test result?	We know accessing the SAR involves work for you and your staff. Here are 3 tips from other Ontario primary care doctors on how to fit using the SAR into your schedule: • Email ONE ID at ONEIDBusinessSupport@ehealthontario.on.ca to register a delegate with eHealth Ontario so they can check your report • Book calendar time right now to check your report • Tackle a few patients at a time
Theoretical domains framework-based determinants	Reinforcement, intention	Emotions, beliefs about consequences, intention	Behavioral regulation, environmental context and resources

[a]The descriptions of the behavior change techniques are in line with the Behavior Change Techniques Taxonomy (v1) [22].

[b]SAR: Screening Activity Report.

[c]The financial incentive was already available from the Ministry of Health for achieving screening thresholds; the communication emphasizes how use of the SAR can help in attaining the bonus funds associated with these thresholds.

Figure 1. Logic model of the content and hypothesised mechanism of change.

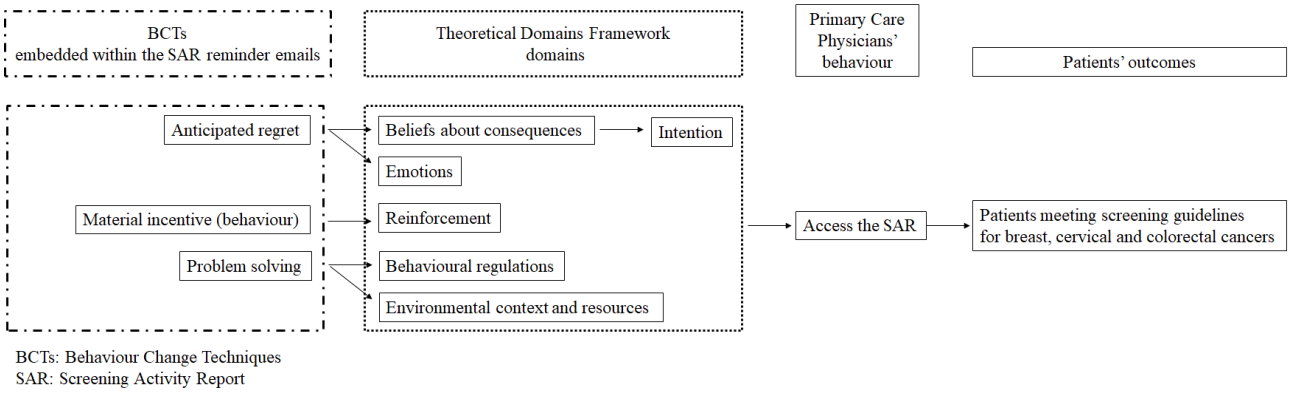
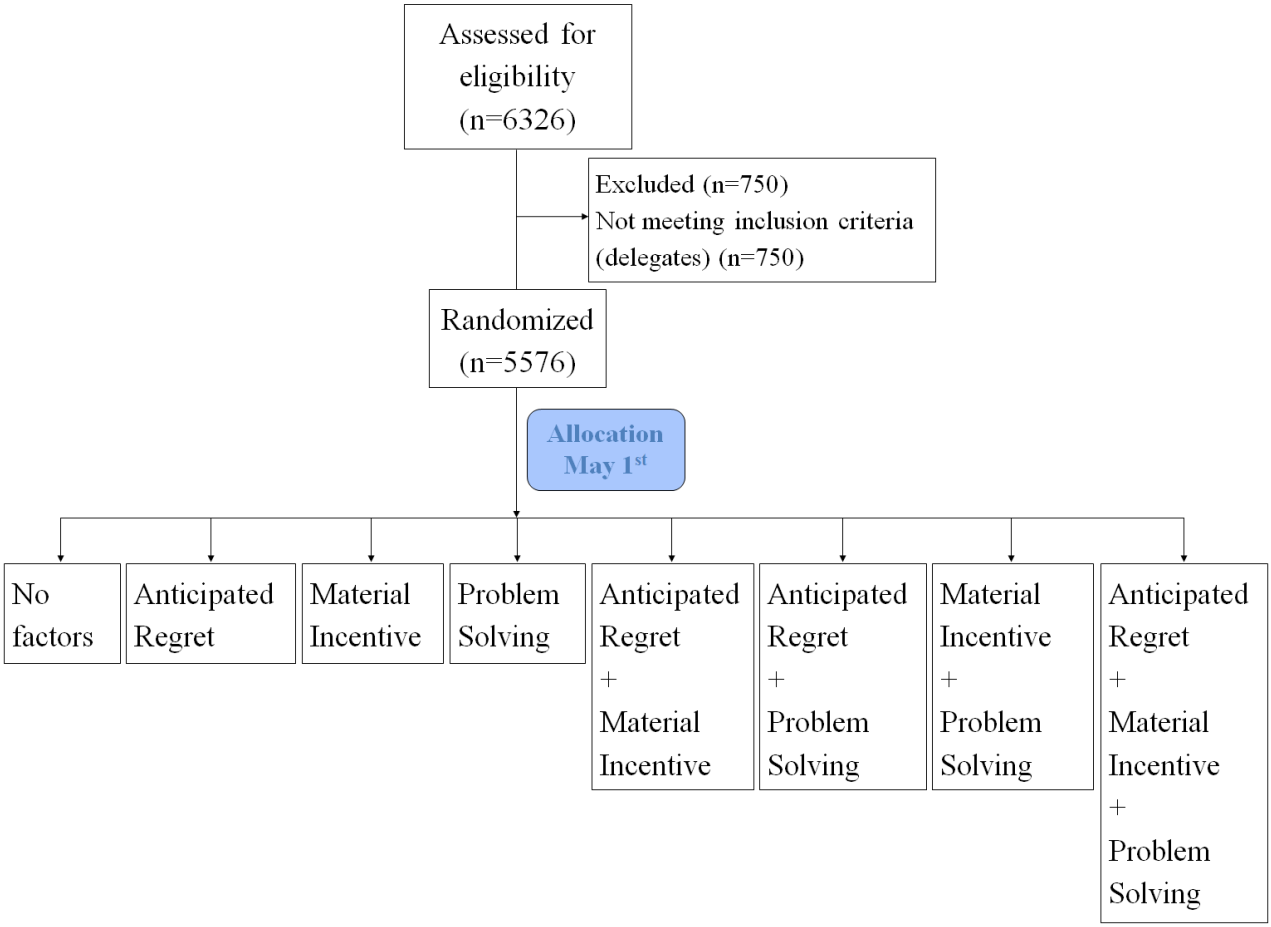


Figure 2. Allocation flow diagram.



Three components in the redesigned SAR email will be tested. Each of these 3 factors in the trial will either be turned on or turned off in the email (Table 2).

The trial received approval from the Research Ethics Board at Women's College Hospital and is registered on ClinicalTrials.gov [NCT03124316].

Setting

The setting for this study will be primary care because this is the main point of entry to the health care system for Ontarians. In Ontario, the vast majority of primary care is delivered by primary care physicians, and patient visits to physicians are covered under the provincial health plan. According to Statistics Canada, 92.5% of Ontarians aged 12 years and over have a regular medical doctor, usually a primary care physician [30]. Almost three-quarters (73%) of Ontarians are associated with a primary care physician working in a physician enrollment model, meaning the primary care physician has an identifiable list of patients [31]. Primary care physicians working in physician enrollment models can register for the SAR and thus automatically receive the monthly email update from CCO.

Participants and Recruitment

Eligible participants will be primary care physicians already registered to access the SAR and receive monthly emails from CCO. In Ontario, as of May 1, 2017, 8462 primary care physicians were working in a patient enrollment model. Of these, 5576 eligible physicians had signed up for the SAR. These 5576 physicians will be automatically enrolled in our study. We received a waiver of consent for providers' participation because the intervention (email receipt) was considered to pose minimal risk (as primary care physicians were already receiving an email), individual primary care physician recruitment was not feasible, and there were concerns that informing providers about the trial might prime participants to act in a certain manner. Participating physicians can opt out of receiving the SAR emails as usual.

Allocation and Blinding

A deidentified list of eligible participants will be exported from CCO to an independent statistician who will allocate participants to receive 1 of the 8 experimental conditions via simple randomization using computer-generated random numbers.

The different email versions (featuring the different BCTs to be tested) (see Multimedia Appendix 3) will be sent out in 45-minute intervals starting from 9 AM on the 10th day of each month (or if the day falls on the weekend, on the next business day) for 4 months between May and August 2017. The emails could not be sent at the same time since the Cancer Care Ontario's outgoing mail server could not handle sending out all of the emails at the same time. That is why a delivery schedule made up of 9 intervals (each 45 minutes long) was devised. To address the concern raised regarding sending time, we randomized the order in which the email versions would be sent (ie, 1 version sent per interval) per month. Delivery order will be determined via block randomization.

Table 2. Experimental conditions. + refers to the presence of the factor and – refers to the absence of the factor.

Experimental condition	Factor 1: anticipated regret	Factor 2: material incentive	Factor 3: problem solving
1	–	–	–
2	+	–	–
3	–	+	–
4	–	–	+
5	+	+	–
6	+	–	+
7	–	+	+
8	+	+	+

All randomization procedures will be conducted in SAS version 9.4 (SAS Institute Inc). Treatment allocation will be concealed from the research team and CCO collaborators. It is not possible to blind participants as they must receive the intervention and may notice differences in email content and design; however, they are unlikely to be aware of the different components of the email being tested.

Data Collection and Outcomes

In this experiment, all data will be routinely collected from CCO administrative databases. Table 3 details the variables to be collected and used in analysis.

All outcomes will be measured at the level of the physician-participant. The primary outcome will be a dichotomous variable indicating whether or not the primary care physician accessed the SAR at least once between May and August 2017. Secondary outcomes measured at the end of the 4-month trial via CCO database sources will be the total number of times the SAR was accessed (between May and August 2017) and physician adherence to screening guidelines for breast, colon, and cervical cancer for their practice (as of August 31). Process measures will include the number of participants opting out of emails or with emails that bounce back (ie, inactive email address) and the number of calls to CCO and/or eHealth Ontario contact center during the trial regarding the SAR (eg, password retrieval queries).

Statistical Analyses

Physician baseline characteristics (sex, years of practice), their history of SAR use (previous use/no previous use), their baseline cancer screening rates (breast, cervical, and colon), and their practice characteristics (size of group, rurality, payment model) will be described across experimental conditions.

The unit of analysis for all outcomes will be the primary care physician. The effect of each intervention factor on the primary outcome (accessing the SAR at least once during the 4-month trial) will be analyzed using logistic regression. Indicator variables will be specified for each of the experimental factors using effect coding where +1 indicates the presence and –1 the absence of each factor. With effect coding, the regression coefficient represents the difference in the mean response across all experimental conditions with that factor turned on against the mean for all experimental conditions with that factor turned off. For example, the regression coefficient for “anticipated regret” will represent the difference in the log-odds of accessing the SAR for providers allocated to conditions where this factor is turned on (study arms 2+5+6+8) versus providers allocated conditions where the factor is turned off (study arms 1+3+4+7) (Table 2). The effect of each intervention factor will be expressed as an odds ratio with 95% confidence interval. The model will adjust for history of SAR use as a fixed covariate.

Dichotomous secondary outcomes (participants opting out of emails or with emails that bounce back) will be analyzed as described for the primary outcome. Total number of times the SAR was accessed and number of calls to CCO will be analyzed using Poisson regression with the natural log of the number of person-months as an offset term. For these models, the effect of each intervention factor will be expressed as a rate ratio with 95% confidence interval. In the event of significant overdispersion as assessed by a Lagrange multiplier test, a negative binomial distribution will be specified. For physician adherence to cancer screening guidelines, the dependent variable will be the number of eligible patients who meet a set of cancer-specific guidelines out of the total number of eligible patients listed to that provider and analyzed using logistic regression.

We had no a priori hypotheses about the interactions between the BCTs tested (anticipated regret, material incentive [behavior], and problem solving). Secondary analyses will include all 2-way interaction terms between experimental factors as well as comparison across the 8 experimental conditions. Secondary analyses will examine differences across subgroups defined by physician characteristics (eg, sex, years in practice, baseline screening rates, practice size, history of SAR use) and practice characteristics (eg, size of group, rurality, payment model). The length of the emails will also be explored as a potential effect modifier.

All analyses will be conducted in SAS version 9.4 (SAS Institute Inc) with statistical significance assessed at the 5% level.

Power Calculation

In this experiment, sample size is predetermined by the number of eligible physicians signed up for the SAR (5576 eligible physicians at the time of randomization).

Table 3. Data collection.

Variable	Definition
Primary outcome	
SAR[a] access	Whether or not eligible physicians accessed the SAR at least once during the 4-month trial (May to August 2017)
Secondary outcomes	
Number of times SAR accessed	A count of the number of times the physician logged in to the SAR in the 4-month period (May to August 2017) prior to the data cutoff date. Multiple log-ins within a single day will only be counted as 1 log-in.
Adherence to cancer screening: breast (posttrial)	Proportion of enrolled, eligible patients who are up to date with breast screening at the physician level Numerator: screen-eligible, enrolled patients who had a mammogram in the 24 months before the report cut off date per PEM[b] physician Denominator: breast screening–eligible, enrolled patients per PEM physician
Adherence to cancer screening: cervical	Proportion of enrolled, eligible patients who are up to date with cervical screening at the physician level Numerator: screen-eligible, enrolled patients who had a Pap test in the 36 months before the report cutoff date per PEM physician Denominator: Cervical screening–eligible, enrolled patients per PEM physician
Adherence to cancer screening: colon	Proportion of enrolled, eligible patients who are up to date with colorectal tests intended for screening at the physician level Numerator: screen-eligible, enrolled patients who had either a colonoscopy in the 120 months and/or flexible sigmoidoscopy in the 60 months and/or FOBT[c] in the 24 months before the report cutoff date per PEM physician Denominator: screen-eligible, enrolled patients per PEM physician
Process measures	
Number of calls to CCO[d]	Number of calls to CCO contact center regarding the SAR (May-August)
Number of calls to ehealth Ontario	Number of calls to ehealth Ontario contact center regarding a ONEID-related issue (May-August)
Number of participants opting out	Proportion of participants deciding to opt out of receiving the email during the 4-month trial
Number of participants with emails that bounced back	Proportion of participants with emails that bounced back (ie, inactive email address)
Subgroup analyses	
History of SAR use	PEM physicians who have never logged in, those who have not logged in for 1 year but did previously, and those with 1 or >1 log-ins in the year prior to the trial
Baseline cancer screening rate: breast (pretrial)	Proportion of enrolled, eligible patients who are up to date with breast screening at the physician level as of March 31, 2017
Baseline cancer screening rate: cervical (pretrial)	Proportion of enrolled, eligible patients who are up to date with cervical screening at the physician level as of March 31, 2017
Baseline cancer screening rate: colon (pretrial)	Proportion of enrolled, eligible patients who are up to date with colorectal tests intended for screening at the physician level as of March 31, 2017
Sex	Sex of physician
Years in practice	From the year of graduation
Practice size	Number of patients enrolled to the physician's practice
Size of group	The total number of physicians belonging to the group and practicing within the LHIN[e] Note: physicians who are part of the physician enrollment model group but practicing in another LHIN will not be included in this count
Payment model	Identifies the specific type (ie, fee-for-service or capitation)
Rurality	According to postal code of the PEM physician's primary practice

[a]SAR: Screening Activity Report.

[b]PEM: physician enrollment model.

[c]FOBT: fecal occult blood test.

[d]CCO: Cancer Care Ontario.

[e]LHIN: Local Health Integration Network.

For testing each experimental factor, a sample size of 5576 physicians achieves 95% power to detect an absolute difference of 4% in SAR use (between those with the factor present versus those with the factor absent) using a 2-sided test at the 5% level of significance assuming a control arm proportion of 0.20 (estimated based on prior CCO data). We would consider small differences in proportions of primary care providers accessing the SAR to be clinically important. For example, if an intervention component resulted in only 4% more primary care providers accessing the SAR (ie, 223 more primary care providers) and if each of those primary care providers identified only a few patients overdue for screening, this would result in cancer screening for an additional 500 to 600 Ontarians.

Screening 500 to 600 more people in over 4 months could be expected to lead to cancer diagnosis and appropriate treatment in less than 1 patient [32]. This positive potential outcome should be placed in context, as screening also has potential harms including false positives and complications at a rate dependent on the nature of the test and the risk of the underlying population. For example, if 1000 people are screened for colon cancer, 1 to 2 people will get extra years of life and 35 people will be falsely diagnosed when taking using fecal occult blood test while 2 people will get extra years of life, 5 people will have cancer prevented and less than 1 person will have complications when using flexible sigmoidoscopy [33]. Patients and family physicians should consider the balance of risks and benefits when considering a given screening test, especially as people age [34]. False positives and overdiagnosis can lead to overtreatment and may have negative psychological impacts on patients [35].

Embedded Process Evaluation

The process evaluation aims to complement the results of the factorial randomized experiment by exploring how and why the email interventions may (or may not) have resulted in changes in accessing and using the SAR [36]. In semistructured interviews (see Multimedia Appendix 4) with primary care physicians, we will explore how the operationalized BCTs target (or fail to target) determinants of their SAR access (Figure 1).

Recruitment

Invitation emails will be sent to primary care physicians participating in the experiment, and a Can $150 (US $121) gift card will be offered as an honorarium. Purposive sampling will be used to ensure both primary care physicians who have not logged in to the SAR and those who have logged at least once are included in the sample. We will use convenience sampling (physicians within study investigators' professional and personal networks) and snowball sampling (asking participants to forward the recruitment email to potential participants in their own networks of physician colleagues). We will seek recruitment of both SAR users and those who have not used the SAR, with sampling continuing until saturation. To the greatest extent possible within feasibility constraints, we will attempt to recruit physicians exposed to each of the 3 factors during the trial. Interviews and recruitment will continue until no new themes emerge and saturation is apparent regarding the information given for both groups of physicians (those who have and have not accessed the SAR).

Data Collection

Telephone-based semistructured interviews will be conducted with eligible primary care physicians who received a rewritten email as part of the trial. It is anticipated that interviews will last about 30 minutes. All interviews will be audio-recorded. If participants are unable to retrieve an email they received, we will send them the email with all operationalized BCTs immediately prior to the interview. The interview guide will be pilot-tested prior to use and refined as needed throughout the interview process (see Multimedia Appendix 4). The guide includes specific questions developed for each physician group (ie, those who accessed the SAR and those who did not access the SAR at least once during the trial). The questions are also tailored to the email they received to inform about the potential mechanisms of action by which the included BCTs produced change or not regarding SAR access and use [21]. The interview will also explore general impressions of the redesigned emails and about the SAR more generally.

Data Analysis

All audio-recorded interviews will be transcribed. Qualitative data will be analyzed using the framework method which involves the organization and summary of qualitative data by both cases (rows) and themes (columns) [37]. Included BCTs and targeted determinants corresponding to the theoretical domains framework will be applied as deductive codes (beliefs about consequences, emotions, intention, reinforcement, and behavioral regulation). A second level of inductive coding will capture mechanisms of action and will seek to link these mechanisms to specific intervention components (BCTs) whenever possible. Open coding will be applied when emerging themes do not align with theoretical domains framework constructs or when participants highlight the intervention's failure to activate a potential mechanism of action. All data will be coded by 2 independent analysts using NVivo (QSR International Pty Ltd) (GV and 1 member of the research team). A third analyst will be consulted if discrepancies arise and no consensus can be reached. Once common themes are established across all interviews, the analytical framework will be applied and data will be charted in the framework matrix [37]. We will continue interviews until no new themes emerge and then conduct 3 additional interviews to verify saturation of themes.

Quantitative data from the trial (including exploratory subgroup analyses) and qualitative data from the pretrial focus groups and the posttrial semistructured interviews will be integrated and interpreted by 2 members of the team. In keeping with recommendations for triangulation [38,39], findings regarding barriers and facilitators of logging in and using the SAR and regarding primary and secondary trial outcomes will be summarized in 1 table, known as a convergence coding matrix.

Convergence of findings across all data sets will be assessed: full agreement (data convergence), partial agreement (complementarity between data), conflicting findings (discord) or silence (finding identified in only 1 data source and no additional sources) [40]. We will examine points of divergence to better understand the relationship between theory and outcomes, find out how an intervention may work or not in particular conditions, and identify areas of opportunity for future research on how interventions could be improved.

Results

The trial was launched in May 2017 and stopped in August 2017. At the time of submission of this article, data cleaning and analysis have not yet begun. Recruitment for the embedded process evaluation has paused with 11 physicians having completed semistructured interviews, as saturation of themes seemed to have been reached according to preliminary impressions formed during the interviews.

Discussion

Our partnership with CCO allows for a province-wide trial of BCTs operationalized within emails that will simultaneously address applied questions of relevance to the organization and explore issues of interest to the broader implementation science literature. As such, it is an example of what we have previously described as an implementation science laboratory [41]. This kind of partnership enables low-cost trials by leveraging routinely collected administrative data, while improving research translation by ensuring that findings can be implemented in a sustainable way to improve health service performance [42]. This project will support CCO in its aim to ensure the continuous improvement and delivery of care to patients by "implementing provincial cancer prevention and screening programs, conducting research, and rapidly transferring knowledge of new research into improvements and innovations in clinical practice and cancer service delivery" [43]. From a scientific perspective, the lessons learned may provide insights regarding how to stimulate primary care physician engagement with audit and feedback tools, which may be generalizable to other contexts in Ontario and to other health care systems.

This work is not without limitations. First, generalizations drawn from focus group data are known to be problematic in that they are not usually indicative of participants' individual opinions [44]. It could have been beneficial to get feedback from individual family physicians in a nongroup setting away from group of peers (eg, online survey, informal interviews) to verify that this matches the takeaways from the focus group. However, in our case, because we were using methods of cocreation, a group activity was required. More discussion relative to the intervention design phase will be reported further by our team. Second, inferences made from interviews in the qualitative process evaluation could be subject to a potential selection bias or volunteer bias. It is hard to recruit family physicians and therefore the ones agreeing to participate could have a specific pattern regarding SAR use and opinions. For example, they could be physicians who may be performing better and/or are more invested in understanding and improving their practice. For this reason, our interview findings may also lack generalizability to other family physicians—for example, the ones performing lower regarding cancer screening or/and less using the SAR.

The experiment also has limitations. Historically, according to internal CCO data, half of physicians receiving the SAR notification emails do not even open them. This suggests that features of the email such as subject line and sender may be important predictors of the user behavior we will be using as our primary and secondary outcomes. In our design phase, we worked with users and nonusers to choose sender and subject lines that we expect will optimize opening rates across all experimental conditions. It is possible that the sender or subject line may interact with our independent variables (BCTs) but the design of our trial does not allow us to identify such interactions. We plan to explore any potential such interaction in the process evaluation and anticipate that new hypotheses will be generated for testing in future trials. In addition, while we can assess whether emails were opened, we cannot know if emails were filtered to spam folders (in which case content redesign is unlikely to help). Finally, other physician sociodemographics such as ethnicity may also have been important covariates to examine but those data were not available at CCO.

A key strength of this study is its opportunistic and pragmatic design, which is likely to enhance external validity. We anticipate that the lessons learned may be applicable not only for CCO but for other health system organizations that need to support physicians in engaging with available tools to provide high-quality care.

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Conflicts of Interest

During the course of this project, authors CAB, DL, SU, and JT were employed at CCO.

Multimedia Appendix 1

Current version of the monthly email sent by Cancer Care Ontario.

[JPG File, 141KB - resprot_v7i2e11_app1.jpg]

Multimedia Appendix 2

Rewritten email containing the 3 behavior change techniques.

[PNG File, 70KB - resprot_v7i2e11_app2.png]

Multimedia Appendix 3

The 8 email interventions.

[PDF File (Adobe PDF File), 736KB - resprot_v7i2e11_app3.pdf]

Multimedia Appendix 4

Semistructured interview guide.

[PDF File (Adobe PDF File), 45KB - resprot_v7i2e11_app4.pdf]

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Abbreviations

BCT: behavior change technique
CCO: Cancer Care Ontario
FOBT: fecal occult blood test
LHIN: Local Health Integration Network
MOST: Multiphase Optimization Strategy
PEM: physician enrollment model
SAR: Screening Activity Report

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Protocol

Motivational Interviewing and Medication Review in Coronary Heart Disease (MIMeRiC): Protocol for a Randomized Controlled Trial Investigating Effects on Clinical Outcomes, Adherence, and Quality of Life

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Abstract

Background: Preventive treatment goals for blood pressure and cholesterol levels continue to be unmet for many coronary patients. The effect of drug treatment depends on both its appropriateness and the patients' adherence to the treatment regimen. There is a need for adherence interventions that have a measurable effect on clinical outcomes.

Objective: This study aims to evaluate the effects on treatment goals of an intervention designed to improve patient adherence and treatment quality in secondary prevention of coronary heart disease. A protocol for the prespecified process evaluation of the trial is published separately.

Methods: The Motivational Interviewing and Medication Review in Coronary heart disease (MIMeRiC) trial is a prospective, randomized, outcomes-blinded trial designed to compare individualized follow-up by a clinical pharmacist using motivational interviewing (MI) and medication review with standard follow-up. Patients were randomized to 2 groups after stratification according to their beliefs about medicines. After standard follow-up at the cardiology clinic, patients in the intervention group are seen individually by a clinical pharmacist 2 to 5 times as required over 7 months, at the clinic. The pharmacist reviews each patient's medication and uses MI to manage any problems with prescribing and adherence. The primary study outcome is the proportion of patients who have reached the treatment goal for low-density lipoprotein cholesterol by 12 months after discharge. Secondary outcomes are the effects on patient adherence, systolic blood pressure, disease-specific quality of life, and health care use.

Results: The protocol for this study was approved by the Regional Ethics Committee, Linköping, in 2013. Enrollment started in October 2013 and ended in December 2016 when 417 patients had been included. Follow-up data collection will conclude in March 2018. Publication of the primary and secondary outcome results from the MIMeRiC trial is anticipated in 2019.

Conclusions: The MIMeRiC trial will assess the effectiveness of an intervention involving medication reviews and individualized support. The results will inform the continued development of support for this large group of patients who use preventive medicines for lifelong treatment. The design of this adherence intervention is based on a theoretical framework and is the first trial of an intervention that uses beliefs about medicines to individualize the intervention protocol.

Trial Registration: ClinicalTrials.gov NCT02102503; https://clinicaltrials.gov/ct2/show/NCT02102503 (Archived by WebCite at http://www.webcitation.org/6x7iUDohy)

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KEYWORDS

medication adherence; medication therapy management; pharmacist; coronary artery disease; randomized controlled trial

Introduction

Coronary heart disease (CHD) is the leading cause of death worldwide, and an aging population means that the number of people affected by the disease is increasing [1]. The acute treatment of CHD has been revolutionized in the last two decades, and mortality and morbidity have been more than halved [2,3]. This means that more patients are now treated with secondary prevention measures to minimize the risk of new CHD events. Pharmacological treatment for secondary prevention of CHD reduces morbidity and mortality through a direct thromboprophylactic effect and through effects on hypertension, hyperlipidemia, and high blood glucose, with resultant reductions in the progression of atherosclerotic plaque and stabilization of plaques. The effect of the drug treatment depends on both its appropriateness to the individual and the patient's adherence to the dosage regimen. Suboptimal prescribing and poor adherence increase morbidity and mortality [4]. Despite established guidelines and widespread access to effective and inexpensive medicines, preventive treatment goals for blood pressure and cholesterol continue to be unmet for many coronary patients [5-7]. The reasons for this include suboptimal prescribing and the 20% to 30% of patients who stop taking their preventive medicines, that is, whose adherence worsens, at some point after the initiation of treatment [4,8]. In a report on the burden of nonadherence, the World Health Organization concluded that "Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments" [9].

The reasons for nonadherence are multiple and individual, and therefore, any attempted intervention must have a broad approach to inventorying problems and must allow for individualized problem solving to be effective in a wide group of patients [9]. Interventions that are effective for both adherence and clinical outcomes are usually complex in nature, according to a Cochrane review [10]; however, overall, there is little evidence that adherence interventions can enhance clinical outcomes [11]. This is in part because the studies often lack the power to detect differences in clinical outcomes and sometimes also in the adherence outcome [11]. Another large review and meta-analysis of 771 adherence interventions, which did not include clinical outcomes, suggests that interventions may have a small effect on adherence and that this effect is higher for interventions delivered face-to-face, by pharmacists, and with a behavioral rather than a cognitive approach [12]. A Cochrane review of adherence interventions for lipid-lowering drugs also suggests that team-based intensification of patient care can improve cholesterol management through better adherence in both short and long term [13].

A recent review of interventions for patients with CHD suggests that simple adherence interventions might be as effective as complex ones, but this review only studied effects on adherence, and in half of the included studies, patients were followed up only for 6 months or less [14]. Adherence to the right medicines must increase for the intervention to be effective, and pharmacist interventions (including patient education, feedback to the physician, and medicine management) can improve risk factor management in patients with cardiovascular disease [15-18]. Motivational interviewing (MI) has been used with some effect in medication adherence interventions [19-21] and also specifically when administered by nurses in cardiac care [22].

The theoretical framework for the intervention evaluated in this study is described in detail in a separate manuscript, which also describes the development from pilot study and the study protocol for evaluation of the intervention process [23].

The primary objective of this trial was to evaluate the effects of MI and a medication review, as part of a secondary prevention program in patients with CHD, on achieving goal levels of low-density lipoprotein cholesterol (LDL-C) by 12 months after discharge, compared with standard care.

The secondary objectives were to evaluate the effects of the intervention on systolic blood pressure, adherence to secondary prevention drugs, health-related quality of life (general and disease-related), and secondary care use. A health economic assessment will also be conducted, but this is not described in detail in this study protocol.

Methods

Trial Design

Motivational Interviewing and Medication Review in Coronary heart disease (MIMeRiC) is a randomized, controlled, outcomes-blinded, superiority trial with two parallel groups. Patients have been randomized to standard care (control) or standard care plus a follow-up program that includes medication review and MI (intervention). Ethical approval has been obtained from the Regional Ethics Committee, Linköping, Sweden (Dnr-2013/236-31). The trial is registered in clinicaltrials.gov (NCT02102503).

Study Setting and Population

Patients with CHD (International Classification of Diseases-10 I20-I21) were recruited from the cardiology unit at the County Hospital in Kalmar, Sweden. This is a 400-bed teaching hospital in rural Sweden; the cardiology unit has 30 beds and performs around 1300 angiographies and 600 percutaneous coronary interventions a year, but no open-heart surgery. All patients with coronary artery disease, regardless of how acute it was, were chosen because they all undergo the same standard follow-up at the outpatient clinic. See Textbox 1 for inclusion and exclusion criteria.

Textbox 1. List of inclusion and exclusion criteria.

Inclusion criteria:

Patients must:

- speak Swedish
- have an angiography during their hospital stay
- be scheduled for follow-up at the out-patient clinic in Kalmar
- have verified coronary artery disease (International Classification of Diseases-10 I20-I21)

Exclusion criteria:

Patients are excluded if any of the following conditions apply:

- cognitive impairment or any other condition making interviews or phone calls difficult
- nonparticipation in the standard follow-up at the outpatient clinic
- prior participation in this study

Recruitment

The recruitment of patients was changed during the study because of practical problems with screening. This change was judged not to affect the generalizability of the result, and it was verified by the Regional Ethics Committee.

October 2013-May 2014, November 2014-September 2015

Patients admitted to the coronary angiography unit were screened for eligibility, and eligible patients were given written and verbal information about the trial by a nurse or a study pharmacist and were invited to take part. Patients who agreed to participate were contacted within 2 weeks by a pharmacist who explained the implications of the research and asked for informed consent (documented by the pharmacist during the phone call).

October 2015-December 2016

Patients scheduled for a follow-up visit to a cardiology nurse 2 weeks after discharge were screened for eligibility. Eligible patients were given written information to read in the waiting room, and verbal information was given by the nurse. The nurse explained the implications of the research and asked for written informed consent.

Randomization

The patients were randomized in blocks of 10, stratified according to their attitudes toward their heart medicines, as measured by the Beliefs about Medicines Questionnaire-Specific (BMQ-S) [24,25] after their standard care follow-up with the physician (see Figure 1). Patients may be accepting (A), ambivalent (B), or neutral or skeptical (C), which can affect their likelihood of being adherent [26,27]. An accepting patient has a strong belief in the necessity for drugs and minimal concerns about the drug, an ambivalent patient has a strong belief in the necessity for drugs and is highly concerned about the drug, and a skeptical patient does not believe in the necessity for drugs and is highly concerned about the drug. We chose to stratify the patients according to their attitude toward medication because a patient's beliefs about medication are partly affected by their previous medical history and type of CHD, and we believe that the patient's attitude toward medication has a greater effect on adherence and the need for intervention than these underlying factors. Data on patient beliefs and other baseline measures were collected directly after the physician visit. The randomization sequence for each stratum was computer-generated by a statistician who is not involved in data collection. An intervention to control allocation ratio of 1:1.14 was chosen to account for an expected greater loss to follow-up in the control arm. For each patient, a folded sheet of paper with the group allocation and unique study identification number written on it was kept in a sealed opaque envelope marked with a serial number; it was impossible to read the information without opening the envelope. A study administrator collected baseline questionnaires and defined the stratum of each patient before assigning the patient to the intervention or control groups according to the serial number.

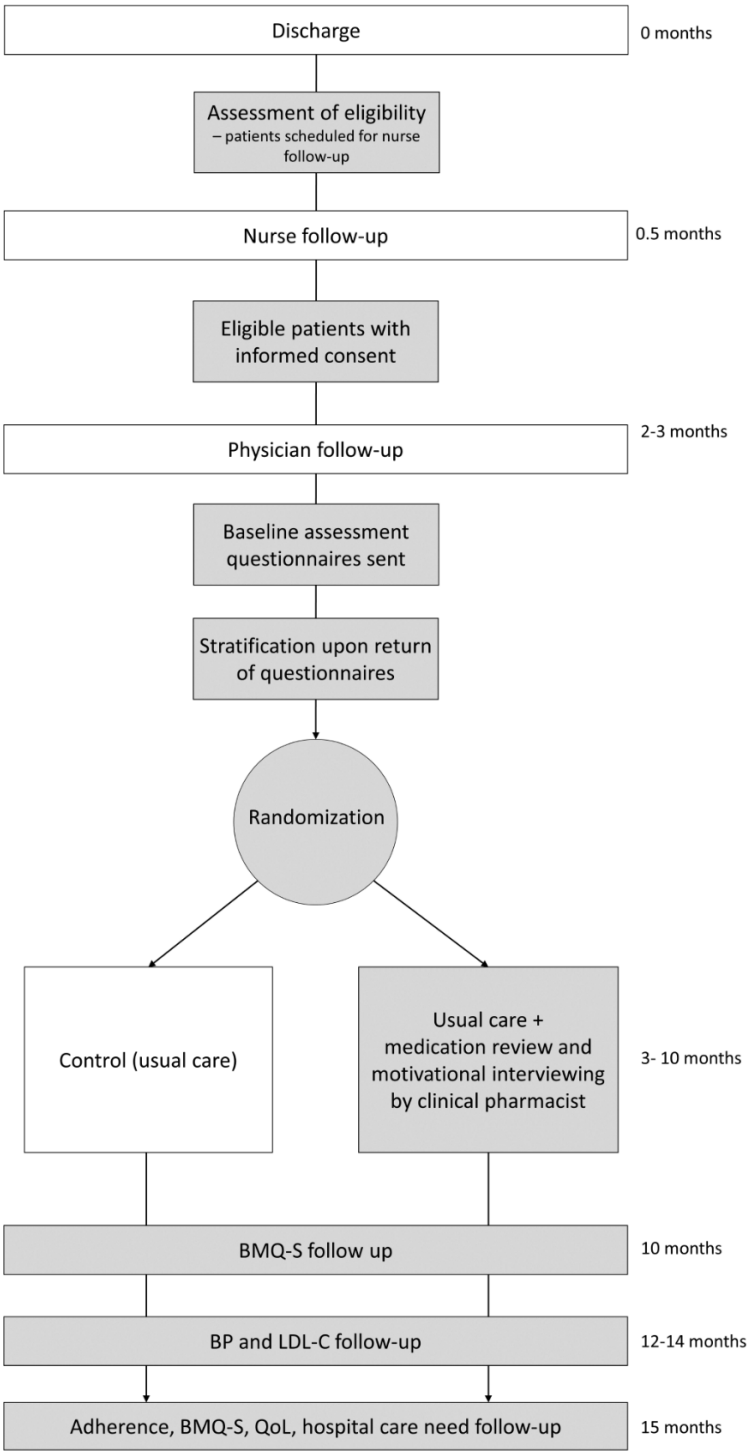
Intervention Group Protocol

The intervention is a follow-up program run by a clinical pharmacist, which is carried out in addition to the standard care. The clinical pharmacist carries out MI and reviews the patient's medication. The mainstay of the intervention consists of two appointments at the cardiac outpatient clinic, but this is adjusted according to the patient's needs. For a full list of study events, see Table 1.

First Visit, 3 Months After Discharge

Intervention participants are scheduled for a 60-min appointment with the clinical pharmacist, following their standard follow-up appointments at the clinic, around 3 months after discharge. The pharmacist prepares an advanced medication review [28] based on documentation in the electronic health record (EHR) that is shared between the hospital and primary care facility, applying national and European guidelines to assess the quality of prescribing [29,30]. The baseline data on the patient's beliefs about medicines are also recorded.

Figure 1. Study flow chart. Each box represents a separate event. White boxes are standard care events, light gray boxes are study events; BMQ-S: Beliefs about Medicines Questionnaire-Specific; BP: blood pressure; LDL-C: low density lipoprotein cholesterol; QoL: quality of life.



The clinical pharmacist uses MI when seeing the patient. An agenda is set to focus the interview on how the medication works for the patient, what it means in terms of side effects, the patient's worries, their understanding of the purpose of the medicines, and their thoughts about risks and benefits. The goal is that the patient should feel safe and secure with their medication, and that any problems affecting adherence or quality of life will be found and solved together. If the medication review indicates a need for intensifying the treatment, this is first discussed with the patient to assess their readiness for change. At the end of the consultation, the pharmacist prepares a written summary of the discussed issues and the agreed next steps. The summary is given to the patient together with the next scheduled appointment time.

Any drug-related problems that cannot be solved by the pharmacist and patient together are discussed with the cardiologist after the visit either in person or via the EHR, and the pharmacist then contacts the patient by phone if prescription changes are made. The pharmacist documents the assessment and findings in the EHR.

Table 1. Schedule of events by treatment arm.

Study event (including standard care)	Control	Intervention
Discharge	Always	Always
Nurse visit (2 weeks after discharge)	Always	Always
Physical training in cardiac rehabilitation is offered	Always	Always
Referral to welfare officer	If needed	If needed
Physician visit (around 2 months after discharge)	Always	Always
Extended follow-up in cardiac clinic or primary-care facility	If needed	If needed
Referral to primary-care facility	Always	Always
First pharmacist visit (around 3 months after discharge)		
Medication review and MI[a]		Always
Written summary of discussion		Always
Discussion with cardiologist if problems with cardiac drugs or treatment goals		If needed
Referral to primary-care facility if problems with other drugs		If needed
Follow-up phone call		Always
Intensified intervention only		
Up to four extra contacts by phone or in person		If there are negative attitudes or drug-related problems[b]
Follow-up pharmacist visit (10 months after discharge)		
Medication review and MI		Always
Written summary of discussion		If needed
Follow-up phone call		If needed
Referral to primary-care facility if problem with any drug or treatment goal		If needed

[a]MI: motivational interviewing.

[b]Intensified intervention is not a randomized treatment arm.

The pharmacist makes a follow-up phone call 2 weeks after the visit to enquire about the agreed changes, to see if there are new questions, and to strengthen the message from the interview.

Follow-Up Visit, 10 Months After Discharge

The pharmacist reviews the EHR for any changes in health and prescribing, and monitors the lipid profile (the patient receives a referral for a laboratory test along with the scheduled appointment), before seeing the patient. The patient's beliefs about medicines are reassessed, and MI is used to elicit the patient's thoughts and problems. The consultation, which lasts approximately 20-30 min, aims to support the patient for their coming lifelong (supposedly) medicine use and to guide them to obtain follow-up at a primary care facility if they have no established primary care contact. Any problems found at this stage are communicated to the primary care physician, either through referral or with a personal message in the EHR. A written summary is provided and a follow-up phone call is made only if new problems are encountered.

Adjusting the Intervention According to the Patient's Need

The intervention protocol is adjusted according to the patient's beliefs about medicines or need for support. If the patient is assessed as accepting at baseline, the pharmacist can shorten the initial consultation to 30-40 min if appropriate. If the patient has negative beliefs, that is, ambivalent, skeptical or neutral, the pharmacist arranges a more thorough interview and offers the patient more visits or continued contact by phone. This more intensive intervention protocol offers the patient up to four extra contacts, either in person or by phone, as an extension of the first visit. During the first visit, the pharmacist and the patient decide together whether the patient's worries or drug-related problems require more contacts.

Intervention Pharmacists

The intervention is performed by two clinical pharmacists (LH and MJÖ) with training in both medication review and MI. One of the pharmacists has formal specialist training in clinical pharmacy, focusing on cardiovascular medicine (60-credit Master's program in clinical pharmacy at Uppsala University, Sweden) and has completed a 15-credit course in MI from Linnaeus University, Sweden. The other has completed a 12-credit course in clinical pharmacy and pharmacotherapy from Lund University, Sweden, 2 days of internal training in MI, and a 3-day course run by a member of Motivational Interviewing Network of Trainers. Both pharmacists have carried out 5 consultations coded by Motivational Interviewing Treatment Integrity 3.1 with feedback and, in at least one of

these, have been evaluated as "beginning proficiency" (≥3.5) in the global rating of MI-spirit.

Standard Care

Participants in the control group receive standard care only. Standard care at the cardiology unit of the County Hospital in Kalmar comprises a 60-min appointment with a cardiac specialist nurse 2 weeks after discharge and a 60-min appointment with an assistant physician or cardiologist about 2 months after discharge. Unless the patient requires specialist follow-up or more treatment at the cardiac clinic, referral is made to the primary care facility for continuing follow-up. All patients are also offered cardiac rehabilitation such as physical training in a group at the hospital or at a primary care facility closer to home. See Table 1 for details.

Study Parameters and Data Collection

Baseline assessment data, including demographics, level of education, civil status, CHD presentation type, previous CHD history, comorbidities, smoking status, type of cardiovascular intervention, and prescribed medicines, were collected from the EHR by a member of the research staff before randomization. Further baseline data were obtained from questionnaires sent to the participants by mail after their physician visit at the cardiology clinic with instructions to return them within 10 days; these questionnaires covered medication adherence, beliefs about medicines, and health-related quality of life. Baseline data on lipid status and blood pressure were collected from the EHR. See Table 2 for a full list of the collected data and Figure 1 for an outline of study assessments.

To promote participant retention, control group patients receive a postal card stating the appreciation of the research team for their return of questionnaires at baseline and 10 months. Intervention group patients do not receive a card as they are instead summoned for a visit.

Lipid status and blood pressure are assessed 12-14 months after discharge. Patients who have had a myocardial infarction are followed-up at 12-14 months by the national quality register SEPHIA (Secondary prevention after Heart Intensive care Admission), and assessments of lipids and blood pressure are therefore recorded in the EHR. We use these data so that participants do not need an extra assessment because of the study. For noninfarction patients, the research team arranges for the assessment of lipids and blood pressure. All patients contacted by either SEPHIA or the research team receive a referral for a laboratory test and blood pressure measurement, which they can choose to do at the drop-in clinic at the hospital or at their primary care facility.

At 15 months postdischarge, participants complete all questionnaires for the outcomes assessment: Morisky 8-item adherence scale (MMAS-8), BMQ-S, EuroQoL 5 Dimensions 5 Levels, and HeartQoL questionnaire. A time of 15 months was chosen to relate the answers on the MMAS-8 to the pharmacy refill date 12-16 months after discharge. Data are collected from the Swedish Drug Prescription Register (adherence), the Health Care Register of Kalmar County (hospital admissions), and, for deceased participants, the registry of Causes of Death administered by the National Board of Health and Welfare.

Control for Bias

Because randomization took place after the standard care process, the doctors and nurses involved in these standard visits did not know whether their patients would be in the control or the intervention group. This introduced a control for bias during the standard care period. However, this control is lost for doctors with whom the pharmacist discusses treatment during subsequent periods of the study, as it will be obvious that they are discussing intervention patients, and for doctors and nurses involved in the care of those intervention patients who have further contact with the clinic after the standard follow-up. Pharmacists are not involved in any care of patients at the cardiology clinic outside of this study.

All the outcomes data (returned questionnaires, prescription fill data, and health care use) for each patient are collected in an individual, coded, clinical research form (CRF). Data from registers and the EHR are collected by a blinded research assistant who is not involved with the care of the study patients. Researchers will enter the data from the coded CRFs into the database.

To assess selection bias, all participants will be compared with eligible patients who declined to participate, in terms of age, sex, type of CHD, new or recurrent CHD, and marital status.

Statistical Methods

The primary analysis will take place 16 months after inclusion of the last patient, according to the intention-to-treat principle. The primary outcome will be analyzed using logistic regression models. Secondary outcomes will be analyzed with appropriate statistical methods based on the type of data. Primary and secondary regression analyses will be adjusted for baseline variables. Per protocol analyses will also be performed. All tests will be two-sided and a P value of <.05 will be considered significant.

Sample Size

Initial Assumptions and Calculations

In quality registry data from 2012, the proportion of patients achieving the LDL-C treatment goal in Kalmar was less than 0.3 [33]. To detect a shift in proportion from 0.3 to 0.5 in goal achievement for LDL-C, our initial sample size calculation resulted in a group size of 93 patients, for 80% power at a significance level of P=.05 (two-sided).

Table 2. Study assessment schedule indicating when data is collected.

Collection of data	Discharge	Nurse visit at 2 weeks	Physician visit at 2 months	Baseline questionnaire[a]	10 months	12 months	15 months
Patient eligibility		✓					
Patient informed consent		✓					
Retrospectively after consent (EHR [b])							
Patient medical history	✓						
Demographics	✓						
Medications	✓						✓
Lipid panel	✓		✓			✓	
Systolic blood pressure (EHR)			✓			✓	
BMQ-S[c]				✓	✓		✓
QoL [d] , health-related							
Heart-QoL				✓			✓
EQ-5D-5L[e]				✓			✓
Medication adherence							
Self-reported				✓			✓
Pharmacy refill							✓
Hospital admissions							✓

[a]Sent after the physician visit.

[b]EHR: electronic health record.

[c]BMQ-S: Beliefs about Medicines Questionnaire-Specific.

[d]QoL: quality of life.

[e]EQ-5D-5L: EuroQoL questionnaire [31,32].

Another registry, the national "Öppna Jämförelser" (Open Comparisons), measures the proportion of patients who have had a myocardial infarction and who fill a prescription for a statin 12-16 months later. The report from 2012 stated that 80% of myocardial infarction patients from Kalmar County Hospital filled a statin prescription [34]. To detect a difference of 10% in the proportion of patients with refill adherence, with 80% power at a significance level of P=.05 (two-sided), 195 patients would be required in each group.

We assumed an attrition rate of 40% in the intervention group and 60% in the control group, because the protocol for the latter can be regarded as an extended questionnaire study. Because patients were enrolled about 2 months before they were asked to fill in the first set of questionnaires, we assumed a high attrition rate at this stage, and because they are volunteers, we wanted withdrawal from the study at this stage to be a simple process. Patients who did not answer these first questionnaires will not be included in the outcome analyses.

On the basis of our primary outcome (LDL-C goal achievement) and expected attrition rate, a sample size of 130+140 patients (intervention plus control) would be required. However, this would not have the power to detect a meaningful difference in adherence (one of the secondary outcomes). As one of the problems encountered in prior intervention studies has been the lack of power to detect differences in both adherence and clinical outcomes, we based our sample size calculation on the number required to show a difference in adherence, that is, 195 patients at follow-up.

We therefore aimed to include 273+312 (=585) patients in the intervention and control groups, with an allocation ratio of 1:1.14.

Amended Sample Size Calculation in 2016

During the study, we learned two things that greatly impacted our sample size: (1) the goal achievement in standard care improved significantly and (2) our assumed attrition rate was too high. As described earlier, problems with recruitment also delayed the study, and this was another incentive to look at the required sample size.

The goal achievement for LDL-C in 2012 did not reflect the circumstances during our follow up in 2014-2017 because treatment possibilities changed the likelihood of reaching the target (the atorvastatin patent expired in 2013 and local guidelines successively changed, based on this). In 2015, the proportion of patients reaching the target was 0.5 nationally and 0.45 at Kalmar Hospital [35]. This reduced the power of the study to reject the null hypothesis unless the sample size was increased. On the other hand, our estimated attrition rate of 40-60% was shown to be too high, as only 16.9% (71/418) patients failed to return their baseline questionnaires, and with exclusions for other reasons (after obtaining patient consent), our attrition rate was 23% up to baseline assessment. We

calculate the attrition based on this because all patients who filled in the baseline questionnaires, who do not later contact us to withdraw their consent, can be assessed for the primary outcome (LDL-C) as well as the pharmacy fill adherence and hospital admission outcomes, even if they drop off and fail to return follow-up questionnaires. As the assumptions behind the sample size calculation for the adherence measure are very uncertain and our funding would not permit recruitment after the end of 2016, we prioritized power for the primary outcome, and it was decided to end recruitment when at least 400 patients had consented or in December 2016 at the latest. The new calculation was based on the goal achievement of 0.45 at Kalmar Hospital and our expectation to reach 0.6 in the intervention group. This would mean 170 patients needed in each group for a power of 80% to reject the null hypothesis, or 134 needed for 70% power.

Outcomes

Primary Outcome

The primary outcome parameter of the MIMeRiC trial is the proportion of patients who reach the treatment goal for LDL-C levels. The treatment goal, as assessed by SEPHIA, is an LDL-C of <1.8 mmol/L, or a reduction of 50% from baseline.

LDL-C was chosen as the primary outcome because it is an objective measure of a variable related to the risk of recurrent disease. The national quality registry data indicate that it is more difficult to reach treatment goals for LDL-C than for systolic blood pressure [33], and we also regarded the measurement of LDL-C at a single laboratory to be more reliable than blood pressure measurements at several different health care facilities.

The assessment of LDL-C is part of the follow-up process in SEPHIA, and the test is administered by the cardiology outpatient clinic for all patients with acute myocardial infarction. Patients with other forms of CHD will be followed by the research team for this assessment and asked to go to their primary care facility or the cardiology outpatient clinic for assessment, whichever is most convenient for them. LDL-C values are calculated from the serum concentrations of cholesterol and fasting triglycerides, using the Friedewald formula.

Secondary Outcomes

Patient Adherence

The proportion of patients who adhere to the treatment regimen will be assessed using self-reporting and refill data. The phases of adherence under study are implementation and persistence, as defined by the ABC-taxonomy [36]. Because self-reporting and refill data have their individual disadvantages, they will be combined [37]; thus, the patient is considered nonadherent if either they are nonpersistent according to refill data or they are nonadherent according to self-report. However, as self-reporting is only possible for one medication per questionnaire [38], we will use this combined measure only for cholesterol-lowering drugs, as they relate to our primary outcome.

Self-reported adherence to cholesterol-lowering drug regimens will be measured with the MMAS-8 [38-40]. Although this has been validated in hypertension, studies have validated the earlier version (MMAS-4) in statin treatment [41,42]. Self-reporting with different methods or instruments has been used in adherence trials using MI [20] and in many studies of adherence interventions in general [11]. For the combined adherence measure, patients will be regarded as nonadherent in the implementation phase if they score <6 points on the MMAS-8 [37,39]. However, to further investigate the relationship between different adherence measures and the outcome, we will tabulate the results from the MMAS-8, refill adherence, and LDL-C assessments and perform statistical analyses, using the 3 categories of high (8), medium (6 to 7.75), and low (<6) adherence in MMAS-8 [38].

Refill adherence will be assessed using the Swedish Prescribed Drug Register. Patients will be defined as nonpersistent if they have not purchased the drug at least once during the 12- to 16-month period after discharge. The 4-month period is based on the Swedish reimbursement system [43]. The proportion of patients who are persistent to dosage regimens for cholesterol-lowering drugs, aspirin, platelet aggregation inhibitors, beta-blocking agents, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers will be assessed using refill data compared with prescription data, as recorded in the EHR. For cholesterol-lowering drugs, a third adherence estimate will be used, the percentage of days covered adherence measure. A cutoff point of 80% has been set for the percentage of days covered measure [44]. This means that if a patient has collected medicines during the follow-up period, but has not collected enough to cover 80% of the doses prescribed in the EHR, the patient is considered either nonadherent during implementation or as having discontinued treatment.

Systolic Blood Pressure

We will also measure the proportion of patients with systolic blood pressure <140 mm Hg 12 months after discharge. As for LDL-C, this is part of the second follow-up in SEPHIA. Patients not included in the SEPHIA registry will be followed by the research team and asked to attend their primary care facility or the cardiology outpatient clinic for assessment, whichever is most convenient for them.

Quality of Life

Changes in quality of life will be measured with the HeartQoL [45] questionnaire. This questionnaire was developed for use in patients with ischemic heart disease; it measures both physical and emotional items. Mean changes between baseline and follow-up will be calculated for each group, as well as the proportion of patients with increased, maintained, or decreased quality of life. Our rationale for measuring this is that the items of HeartQoL would be affected partly if the treatment is better but possibly more by reducing side effects. It might be that increased treatment or adherence has a negative impact or that a more individual treatment leads to improved quality of life because of fewer side effects. However, there could also be negative consequences on the preventive effect for CHD. Although quality of life is challenging to evaluate, and multiple instruments can be used, there is reason to believe that this could be an important outcome in adherence interventions [46].

Secondary Care Use

Information about the patients' unscheduled secondary care use will be collected from the health care register in the County of Kalmar. The number of emergency visits or hospitalizations due to cardiovascular disease and the time to first contact will be recorded for each group. Data will also be collected retrospectively for the 10-year period before the index date so that adjustments can be made as required.

Results

A total of 417 patients were included in the study before recruitment stopped in December 2016, see Figure 2. Unmet inclusion criteria were later identified for 12 patients, standard follow-up was delayed by more than 3 months for 10 patients, 5 patients were excluded for other reasons, 1 was deceased, and 3 were missed in administration, which resulted in 386 patients being sent baseline questionnaires. By April 2017, all had been approached and given baseline questionnaires and 317 patients had answered the questionnaires; 69 patients have withdrawn their participation by failing to return their baseline questionnaires.

Baseline characteristics have been registered in our database for the 234 subjects with baseline data collected before September 2016; these are described in Table 3. The mean (SD) age of the subjects is 68 (10.3) years and 73.9% (173/234) are male. About 70% (161/234) of the participants have had a myocardial infarction or other acute event, and about 30% (66/234) of participants have an earlier history of CHD. Medicines prescribed at discharge to these subjects can be seen in Table 4.

Figure 2. Flow diagram of study participants, status as of April 2017. For those excluded, (i) indicates cognitive impairment or any other condition making interviews or phone calls difficult; (ii) indicates nonparticipation in the standard follow-up at the out-patient clinic; and (iii) indicates prior participation in this study. LDL-C: low-density lipoprotein cholesterol; BP: blood pressure.

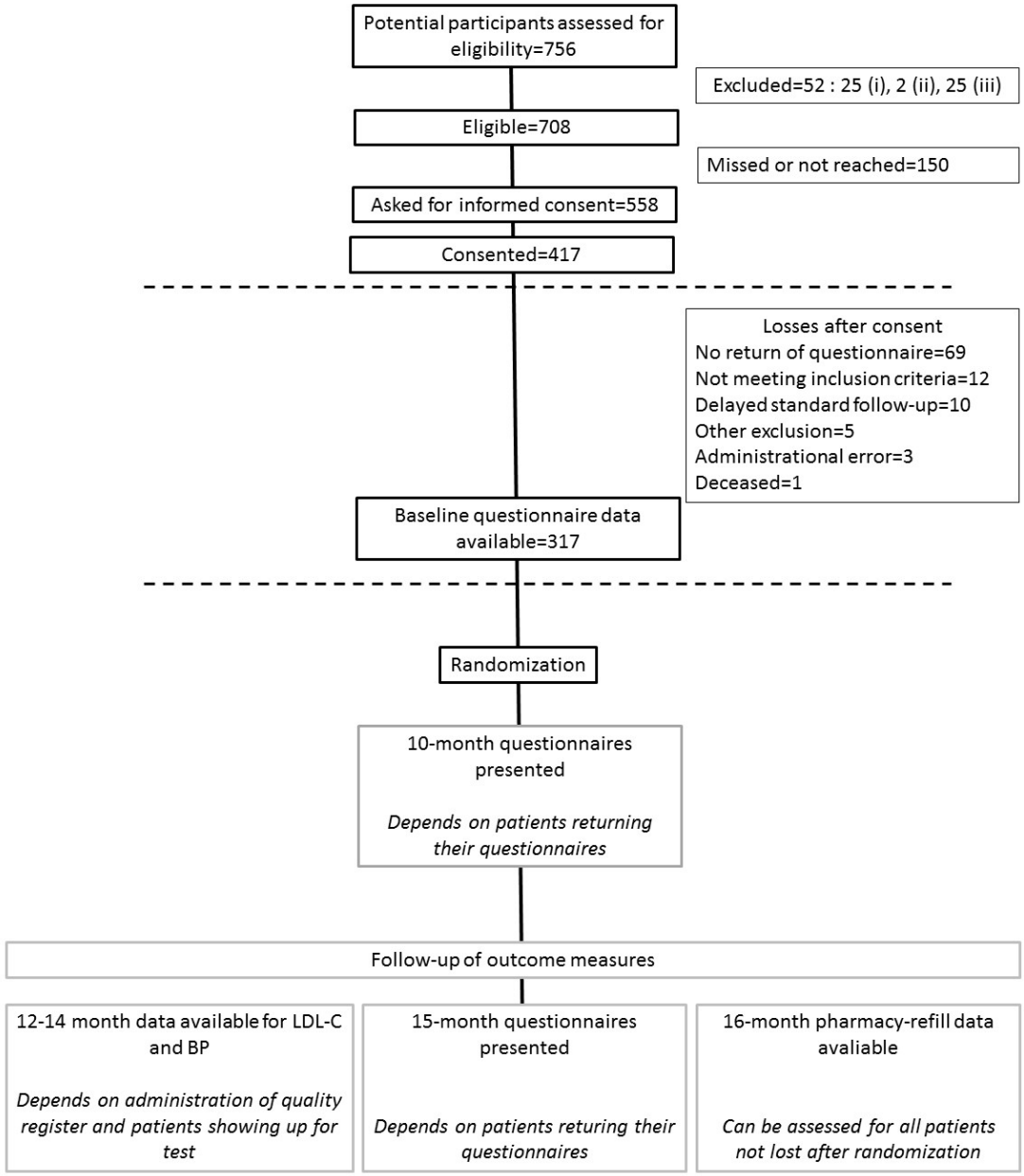


Table 3. Baseline characteristics of the first 234 subjects enrolled into the Motivational Interviewing and Medication Review in Coronary heart disease (MIMeRiC) study for whom complete baseline data are available.

Variable	All subjects
Demographics	
Age (y), mean (SD)	68 (10.3)
Male, n (%)	173 (73.9)
Clinical history	
STEMI[a], n (%)	68 (29.1)
non-STEMI, n (%)	63 (26.9)
Unstable angina, n (%)	30 (12.8)
Chronic angina, n (%)	50 (21.4)
Other reason for PCI[b], n (%)	15 (6.4)
History of CHD[c], n (%)	66 (28.2)
Beliefs about medicines	
Necessity score, mean (SD)	18.5 (3.8)
Concern score, mean (SD)	12.9 (5.1)
Accepting, n (%)	113 (48.3)
Ambivalent, n (%)	75 (32.1)
Neutral, n (%)	24 (10.3)
Skeptical, n (%)	21 (8.9)

[a]STEMI: ST-elevation myocardial infarction.

[b]PCI: percutaneous coronary intervention.

[c]CHD: coronary heart disease.

Table 4. Medicines prescribed at discharge to the first 234 patients enrolled in the Motivational Interviewing and Medication Review in Coronary heart disease (MIMeRiC) study.

Medicine prescribed	At discharge, n (%)	New prescription[a], n (%)
ASA[b]	202 (85.6)	126 (53.4)
Clopidogrel	81 (34.3)	69 (29.2)
Ticagrelor	119 (50.4)	118 (50.0)
Warfarin	20 (8.5)	8 (3.4)
ACEi[c]	119 (50.4)	80 (33.9)
ARB[d]	86 (36.4)	36 (12.7)
BB[e]	206 (87.3)	132 (55.9)
Statin	217 (91.9)	139 (58.9)

[a]Patients who have received a medicine for the first time.

[b]ASA: acetylsalicylic acid.

[c]ACEi: angiotensin converting enzyme inhibitor.

[d]ARB: angiotensin receptor II blocker.

[e]BB: beta-blocker.

Discussion

This protocol describes the methodology for a study assessing the effectiveness of an intervention involving extended follow-up of the pharmacological treatment of patients with CHD using MI and medication review. Our randomized controlled trial acknowledges that optimal prescribing and monitoring of medications as well as high patient adherence is a prerequisite for adequate secondary prevention.

The aim of the intervention is to improve secondary prevention of CHD, and the effectiveness will be measured by assessing patient adherence as well as intermediate biological outcomes such as relevant treatment outcomes, perceived quality of life, and number of hospital admissions. We use two complementary adherence measures: self-report and pharmacy refill for the cholesterol drugs, which are directly linked to the primary outcome: LDL-C.

The design of this adherence intervention is based on a theoretical framework and it is the first trial of an intervention that uses beliefs about medicines to individualize the intervention protocol. Many adherence interventions have failed to assess or find long-term effects. Because this intervention follows the patient throughout the year after hospitalization for CHD and targets all patients regardless of adherence, we hope that it can prevent patients from discontinuing their medicines in the long term. It has been shown that the greatest loss in adherence (persistence) is during the first year and that patients who are persistent at 2 years continue to be adherent [47].

Strengths and Limitations

Patients were recruited directly after their acute event or treatment for chronic CHD and were invited to participate regardless of age and comorbidities as long as they underwent the standard follow-up procedure at the clinic. However, because the intervention involves extra contacts with the hospital, some patients will decline participation; this could create a selection bias, especially among patients who live far from the hospital or patients with multi-morbidity or greater age. A limitation of this study is that it is conducted in one single hospital clinic. The findings may thus be generalizable to other clinics only in a limited manner.

The duration of follow-up is 12 months from the start of the intervention (ie, 15 months after discharge) for the outcomes measured by the study itself: adherence, quality of life, and hospital admissions. However, for practical reasons, we chose to use the follow-up at 12 months after discharge for measuring lipids and blood pressure, because these tests are already in place for the quality register for secondary prevention of myocardial infarctions. We acknowledge that 12 months' follow-up might be too short to assess the effect on hospital admissions due to cardiovascular disease if the intervention primarily affects how patients manage their drugs in the longer perspective, and therefore, we aim to assess this outcome again after 3, 5, and 10 years.

The broad inclusion criteria and few exclusion criteria strengthen the generalizability of the study. The many outcomes of the study, from adherence and LDL-C to quality of life and hospital admissions, is another strength. Few adherence studies have used two adherence measures and are also designed to analyze a relevant clinical outcome, with follow-up of 1 year [11]. We also expect to have more than 80% of participants analyzed at follow-up [11].

Protocol Amendments During Trial

After initiation of the study, we faced obstacles with our recruitment process, mainly due to patients not being identified for eligibility testing before discharge. We tried to remedy this by increasing the input from the research team, but after several months, without much difference in recruitment, we decided to change the procedure. This required the omission of a medication reconciliation that was initially part of the protocol for both study groups, as it was done at the inclusion phone contact before randomization. The reconciliation was appreciated by the nurses involved in the follow-up, but changing this meant little in the actual care of patients because the nurses were able to carry out a reconciliation during their consultation. After including the specialist nurses in the recruitment process, the enrollment rate increased markedly.

As described in the Methods section, the patent for atorvastatin expired during the study period, which resulted in more patients being treated with this drug as first-line treatment. This meant that more patients reached their treatment target without need of treatment assessment or changes in prescribing. We therefore recalculated our needed sample size based on more relevant presumptions. Another change affecting treatment was the release of the new American guidelines on treatment of blood cholesterol late in 2013 [48]. These guidelines no longer recommended a specific LDL-C treatment target for patients with CHD, but instead advocated high- or moderate-intensity statin treatment. This has affected how the cardiologists and pharmacists in Kalmar evaluate their patients' treatment, even though national and European guidelines were not changed accordingly. We cannot assess how much this has affected the treatment of the study patients, but we assume that it lowers the motivation to reach an LDL-C target level.

During the study, we also learned that patients undergoing a coronary artery bypass graft operation were sometimes recruited into the study up to 6 months before their treatment actually took place. Because these are only a minority of the study participants, we will conduct a sensitivity analysis with this group excluded in the outcomes analysis.

Clinical Implications

Patients today have concerns about their drugs because of what they read in the papers [49,50], what they hear from others, and the limited time for follow-up in their health care facility. They are left with no one to talk to about their concerns. Many patients suffer from adverse drug effects but do not contact their health care facility [51]. This results in a burden of health problems affecting their daily lives and causing worries, which possibly affect their quality of life. We propose that our model for extended follow-up will counteract this problem, but none of our outcome measures actually measure the impact of the intervention on an individual patient's day-to-day living [52]. However, we believe that querying the patients on their beliefs about medicines possibly comes closest to providing information on how patients live with their medicines. We will therefore assess this and other measures of how the patients perceive the intervention in a process evaluation for which we publish a separate protocol [23].

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Authors' Contributions

MJO contributed to the study design, data collection, and first draft of the manuscript. TE contributed to the study design and review of manuscript. GP contributed to the study design and review of manuscript. LH contributed to the study design, data collection, and review of manuscript. All authors have approved the final paper.

Conflicts of Interest

None declared.

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Abbreviations

BMQ-S: Beliefs about Medicines Questionnaire-Specific
CHD: coronary heart disease
CRF: clinical research form
EHR: electronic health record
LDL-C: low-density lipoprotein cholesterol
MI: Motivational Interviewing
MiMeRiC: Motivational Interviewing and Medication Review in Coronary heart disease
SEPHIA: secondary prevention after heart intensive care admission

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Protocol

Effect of Impulsive Compression Treatment on Postoperative Complications After Open Peripheral Vascular Revascularization (In Situ): Protocol for a Randomized Control Trial

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Abstract

Background: In patients with critical leg ischemia (CLI), the standard operative choice is an in situ bypass to the lower extremity to improve the patients´ prognosis and quality of life. Postoperative complications after surgery occur in 18 % of the patients, prolonging hospitalization and convalescence. The main operative complication is edema. This can be prevented by early mobilization or stimulation of the natural venous pump in the leg.

Objective: To investigate whether compression therapy with foot pump reduces postoperative edema, facilitates wound healing of the operation wounds, promotes healing of ischemic ulcers, and shortens hospitalization, increasing and improving the patient's subjective quality of life faster.

Methods: The protocol is designed as a randomized, unblinded prospective study with 50 patients in each group. Standard postoperative routines after bypass surgery, including short-stretch bandaging of the operated legs, are compared to supportive stimulation of the venous pump by an impulsive compression foot pump. The postoperative edema of the leg is measured 10 cm below the patella and 8 cm proximal to the medial malleolus. Measurements are performed preoperatively, 1 and 4 days postoperatively and at discharge.

Results: The primary endpoint is reduction of leg edema by at least 50%. The secondary endpoint includes earlier mobilization in the pump group and decreased length of stay in hospital. Quality of life is evaluated through the European Health Related Quality of Life Questionnaire 5 Dimensions (EQ-5D) and Vascular Quality of Life Questionnaire-6 (VascuQol-6) questionnaires. The start of the study is February 1, 2018, and the end of the study is February 1, 2020. First results will be available April 2020.

Conclusions: In orthopedic surgery of the lower extremities, the use of foot pumps has shown a reduction of edema and thrombosis in risk patients. Although important positive effects may be expected after vein bypass surgery, no reports have yet investigated the use of the device in vascular-operated patients and no analysis or meta Cochrane reviews are available in this field.

Trial Registration: ClinicalTrials.gov NCT03192982; https://clinicaltrials.gov/ct2/show/NCT03192982 (Archived by WebCite at http://www.webcitation.org/6xMZJ06dw)

(JMIR Res Protoc 2018;7(2):e58) doi:10.2196/resprot.8799

KEYWORDS

Critical leg ischemia; postoperative edema; Foot pump

Introduction

Critical leg ischemia (CLI) is a predominant cause of poor wound healing, leg amputation [1], and has a significant, negative impact on quality of life [2]. In patients with CLI, the standard operative choice is an in situ bypass to the lower extremity to improve the patient's prognosis and quality of life. However, postoperative complications after an in situ bypass occur in 18% of patients, prolonging their hospitalization and convalescence. The main postoperative complication is edema. Measured 10 cm below the patella, edema is developed among approximately 6%-8% during the first day, increasing to 8%-10% at the fourth day (nonpublished). Postoperative edema can be prevented by early mobilization which stimulates the natural venous pump in the leg, but mobilization is often difficult in patients with CLI due to wound problems prior to surgery. In addition, CLI is associated with age and limited walking distance and coexists with other manifest diseases, which might also make mobilization difficult. Supportive stimulation of the venous pump by an impulsive compression foot pump may be an effective solution. Patient's stimulation of the venous plexus in the arch of the foot has shown to reduce leg edema and thrombosis risk in patients undergoing orthopedic surgery on the lower extremities [3-10]. However, in the literature, there is no description of treatment of vascular surgical patients treated with foot pump. Thus, the primary objective of this study is to investigate whether a foot pump is effective in reducing postoperative edema in patients undergoing an in situ bypass.

Background and Rationale

In situ bypass to the lower extremity is the standard operation choice on patients with critical leg ischemia, accounting for approximately 18% of patients' wound problems [11], prolonging their hospitalization time and convalescence. One of the reasons for wound problems is postoperative edemaThe edema is expected after open vascular reconstruction (in situ bypass surgery). Early mobilization can prevent development of the postoperative edema. Through mobilization, the patient stimulates the natural venous pump in the leg. However, patients are often hard to mobilize in an early stage due to the wound and age. Stimulation of the venous plexus in the arch of the foot has, in other categories of patients, shown to reduce postoperative edema of leg and thrombosis risk in patients undergoing orthopedic surgery on the lower extremities. The subjective quality of life is often impaired in relation to the above mentioned surgical treatment. Through a quicker recovery, the patient can rapidly regain mobility and walking capability.

There is no analysis or meta Cochrane reviews in this field.

Objectives

The objectives will be as follows:

1. To investigate whether compression therapy with foot pump reduces postoperative edema.
2. Through reducing edema, facilitate wound healing of the operation wounds, promote healing of ischemic ulcers, and decrease major amputation rate.
3. Shorten hospitalization.
4. Increase and improve the patient's subjective quality of life faster.

Methods

The trial design is a 1:1 randomized prospective study. All surgical procedures will be performed by vascular surgeons. The postoperative care will be performed by special nurses in cooperation with vascular surgeons at the Department of Vascular Surgery, Lillebaelt Hospital, Denmark.

Participants, Interventions, and Outcomes

Eligibility criteria

Inclusion:

The study will include patients who have undergone in situ from common femoral artery to a popliteal artery above knee/below knee or crural artery.

Exclusion:

The study will exclude patients with former deep vein thrombosis, symptomatic postthrombotic syndrome, or ischemic wounds that are in such manner that compression of the foot is not possible.

Age of Subjects:

Subjects will be between the ages of 18 and 99 years.

Interventions

Post operation, the foot pump will be placed on the foot, according to randomization. The pump must be placed on the foot immediately after the operation is finished. The foot pump will be left on the foot until full mobilization is reached. The pump should not harm or hurt the patient when it is placed on the foot in the correct position.

The control group will follow the department's ordinary postoperative routines for inset bypass short-stretch bandaging. The short-stretch bandage is a padded bandage that stretches from the toes and up to the upper thigh with a 40 mmHg pressure.

Outcomes

End points

The end points are as follows:

1. Reduction of leg edema by 50%, 10 cm below the patella and 8 cm proximal of the medial malleolus on the operated leg three days post operation in patients treated with impulsive compression in comparison to nontreated.
2. "Wound complications" are defined according to the national Danish vascular registry "karbase", including infections, hematoma, and lymph excretion over two days. The pump is expected to have influence on the wounds on the thigh/crus and not in the groin. We therefore separate on wound complications in the groin and the other part of the leg.
3. Time to mobilization in pump treated patients (ie, patient can get out of bed and go to the toilet).
4. Length of stay in hospital.

Participant timeline

Trial baseline

The start of patient inclusion is February 1, 2018, and the study will be finished February 28, 2020. The first results are expected by April 30, 2020.

Time Schedule for Measuring Assessing Symptoms As Edema

The time schedule will be as follows:

1. In the open clinic when the patient is included.
2. The day after the operation.
3. Day 4 and the day of patient discharge.
4. Day 42 (control in our open clinic for control of the operation results).

The measure procedure will be as follows:

1. The circumference of the leg will be measured at 10 cm below the distal part of the patellae and 8 cm above medial malleolus.
2. In the same procedure, we will evaluate pain by the Visual Analogue Scale (VAS).
3. Randomization when the patient is on the operation table.
4. Operation performed.
5. Post operation.
6. The control group follows the department's ordinary postoperative routines for inset bypass — short-stretch bandage. A short-stretch bandage is a padded bandage that stretches from the toes and up to the upper thigh with a 40 mmHg pressure.
7. Time for full mobilization is recorded in all patients.
8. Reoperations is noted.
9. Toe pressure is measured at inclusion, immediately post operation and at discharge.
10. Time for discharge is noted.
11. Paraclinical factors to be examined: confusion, pneumonia, infection of the urinary tract.
12. Duplex study at Day 42 of reverse flow in the deep veins associated with standard duplex study of AV fistulas postoperatively.
13. Quality of life questionnaire (VascuQol-6) baseline + 42 days + 6-month + 12-month, (Appendix 1).
14. EQ-5D baseline + 42 days + 6-month + 12-month, (Appendix 2).

Sample size

The sample will comprise of 50 patients in each group with a total of 100 patients.

Statistical Analysis and Structural Analysis

Through decreasing the postoperative edema by 50 %, we can reduce the wound complication rate for patients from 18% to 12%, given a sigma of 10 and the two-sided test, with an alpha value of 0.05 and beta of 0.80 involving 44 patients in each group. Assuming a dropout rate of 6 patients in each group, the "sample size" will rise to 50 in each group.

Recruitment

Patients will follow the department's normal procedure in terms of in situ bypass. They will then be asked in the outpatient's clinic during a visit to prepare for the operation.

Assignment of Intervention

Allocation

Allocation will be by randomization.

Sequence generation

The study will use an online randomization program. The total distribution between the two groups is 1:1, but a block randomizing will be used in different sizes.

Allocation concealment

Mechanism

Last minute randomization will occur at onset of surgery by study coordinator.

Implementation

Informed consent

Patients with critical leg ischemia that are being assessed for inset bypass will be offered to participate in the trial by ambulatory visit. There will be a sheet with written information handed out and the patients will also receive oral information about the trial. The patient then has the option for consideration until the randomization happens at admission to operation. The oral information will be given by the research nurse and study physician through a phone call from a study room in the outpatient clinic at Department of Vascular Surgery, Lillebaelt Hospital, Denmark. The patient is then given the written information to take home for reading and can have an observer present at the hospital where the patient must submit a statement of participation in the study. The time between ambulatory visit and hospitalization will usually be 7 to 14 days, depending on the severity of the patient's ischemia.

Blinding

Patient and surgeon will be blinded to the allocation during surgery but will need to be unblinded at the time when the intervention is initiated immediately after surgery.

Data Collection, Management, and Analysis

Data Collection Methods

Data Application Sheet

A data application sheet will be created for all the included patients. The information will be fed into the database for analysis.

Data management

Data management will be handled in the Data Analysis and Statistical Software program (STATA version 13). A special data applications model has been constructed for the study in Open (Odense Patient Data Explorative Network).

Statistical methods

Descriptive statistics will be used to report study results. For binary and categorical variables, tests of differences between the intervention and control group will be analyzed by the chi-square test. For continuous variables, initial tests will be performed to check for normality of data by using histograms, Q-Q plots and the Shapiro-Wilk test. Normally and nonnormally distributed variables will be analyzed by *t* test or the Wilcoxon rank sum test, respectively. *P* values <.05 will be considered statistically significant.

Monitoring

Data Monitoring and Auditing

Data monitoring and auditing will be conducted by yearly report. The ethical committee will receive a list on all serious adverse effects in the study (expected and unexpected) and serious incidents together with a report about the security of the patients.

Risks, Side Effects and Disadvantages

The foot pump treatment is noninvasive. Patients should not experience aches or pain relating to the treatment method. The pump is used in other European countries on an empirical basis and Communautés Européennes (CE) mark. Furthermore, the Duplex study is done as routine examinations in the department and is noninvasive. The side effects and risks of pump therapy can be considered insignificant.

Patient Insurance

The subject is covered by the patient compensation scheme in the region of southern Denmark.

Results

Enrollment will begin February 1, 2018, and enrollment will end February 28, 2020. Results are expected by April 30, 2020.

Discussion

In orthopedic surgery of the lower extremities, the use of foot pumps has shown a reduction of edema and thrombosis in risk patients. No reports describe vascular-operated patients, and there does not exist analyses or meta Cochrane reviews in this field. Postoperative edema of the leg increases the risk of other complications (operation wound complications, infections, hematoma and lymph excretion), prolongs the hospitalization, and decreases quality of life. This study can change the postoperative procedures of the patients operated for CLI and reduce the cost of the treatment, increasing the quality of life of patients.

Acknowledgments

The authors acknowledge the financial support of the project initiator, Hans Ravn, Chief MD, Department of Vascular Surgery, Hospital Lillebaelt, Denmark. They also recognize the support of theaccount at Department of Vascular Surgery, Hospital Lillebaelt, Denmark and unrestricted grants. Independent, disposable materials associated with the use of foot pumps will be bought and paid for by the Department of Vascular Surgery. As described above, we are continuing the process of seeking funds for the trial. Covidien does not influence the design of the protocol or analysis, interpretation, and publication of results.

The collection of data was performed by TK. Management of data was performed by TK, MD, and HR. Analysis of data was performed by TK, MD, KH, and HR. Interpretation of data was performed by TK, MD, KH, and HR. The report was written by TK, MD, KH, and HR. The decision to submit the report for publication was made by KH and HR. TK, KH, HR are members of the steering committee.

Conflicts of Interest

None declared.

Multimedia Appendix 1

VascuQol-6.

[PDF File (Adobe PDF File), 37KB - resprot_v7i2e58_app1.pdf]

Multimedia Appendix 2

Eq-5d.

[PDF File (Adobe PDF File), 205KB - resprot_v7i2e58_app2.pdf]

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Abbreviations

CE: Communautés Européennes
CLI: critical leg ischemia
EQ-5D: European Health Related Quality of Life Questionnaire 5 dimension
Open: Odense Patient Data Explorative Network
STATA: Data Analysis and Statistical Software program
VAS: visual analogue scale
VascuQol-6: Vascular Quality of Life Questionnaire-6

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Protocol

Prehospital Advanced Diagnostics and Treatment of Acute Stroke: Protocol for a Controlled Intervention Study

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Abstract

Background: Acute ischemic stroke (AIS) is a medical emergency. The outcome is closely linked to the time elapsing from symptom onset to treatment, and seemingly small delays can mean the difference between full recovery and physical and cognitive dysfunction. Recanalization to allow blood to reenter the affected area is most efficient immediately after symptoms occur, and intravenous thrombolysis must be initiated no later than 4.5 hours after the symptom onset. A liable diagnosis is mandatory to administer the appropriate treatment. Prehospital diagnosis and, in cases where contraindications are ruled out, prehospital initiation of intravenous thrombolysis have been shown to significantly decrease the time from alarm to the treatment.

Objective: The objective of this paper is to investigate the effectiveness of prehospital thrombolysis as measured by (1) time spent from symptom onset to treatment and (2) the number of patients treated within 4.5 hours. In addition, we want to conduct explorative studies. These will include (1) the use of biomarkers for diagnostic and prognostic use where we will collect blood samples from various time points, including the hyperacute phase and (2) the study of magnetic resonance imaging (MRI) images at day 1 to determine the infarct volume and if the time to thrombolysis has an influence on this.

Methods: This is a prospective controlled intervention study. The intervention will involve a computed tomography (CT) and thrombolysis in a physician-manned ambulance called a mobile stroke unit (MSU). The control will be the conventional pathway where the patient is transported to the hospital for CT, and thrombolysis as per current procedure.

Results: Patient inclusion has started and a total of 37 patients are enrolled (control and intervention combined). The estimated time to completed inclusion is 36 months, starting from May 2017. The results of this study will be analyzed and published at the end of the trial.

Conclusions: This trial aims to document the feasibility of saving time for all stroke patients by providing prehospital diagnostics and treatment, as well as transport to appropriate level of care, in a safe environment provided by anesthesiologists trained in prehospital critical care.

Trial Registration: ClinicalTrials.gov NCT03158259; https://clinicaltrials.gov/show/NCT03158259 (Archived by WebCite at http://www.webcitation.org/6wxNEUMUD)

(JMIR Res Protoc 2018;7(2):e53) doi:10.2196/resprot.8110

KEYWORDS

biomarkers; blood analysis; stroke scales; cerebral CT examinations; rtPa; air ambulance model; MSU

Introduction

Background

Stroke is the third leading cause of death in most Western countries. Two-thirds of stroke survivors struggle with moderate to severe disability [1]. Stroke affects approximately 15 million people worldwide each year. Of these, 5 million die and at least another 5 million are left permanently disabled [2]. In Norway, around 15,000 people suffer from stroke each year, and in the next 20 years, the number of stroke victims will increase substantially [3].

Up to 90% of all strokes are ischemic (cerebral infarction), mostly, due to an acute thromboembolic obstruction of a cerebral artery. The remaining 10% are cerebral hemorrhages. In most ischemic strokes (ISs), a small or a large part of the brain (the infarct core volume) will undergo necrosis within few minutes due to hypoxia. However, because of cerebral collateral flow, a significant brain volume (the penumbra volume) may survive for some hours, but this relies on the rapid restoration of the blood flow [4]. Therefore, an AIS is a medical emergency, and successful treatment relies on early recanalization of the obstructed artery. Thrombolytic therapy (recombinant tissue-type plasminogen activator, rtPA) is approved for use within 4.5 hours after symptom onset [5,6], but the efficacy decreases rapidly with time. This is illustrated by the increase in the number needed to treat (NNT) from 4 within 90 min to more than 19 after 4.5 hours [7] . Due to delays and late arrival, only 15% to 40% of all the stroke patients reach the hospital within the designated 4.5 hours, and only about 5% of these patients receive thrombolytic therapy. Even among this 5%, the majority of these patients are treated in the less-efficient end of the approved time window [8].

Differentiation of a cerebral infarction from a cerebral hemorrhage relies on the computed tomography (CT) or the magnetic resonance imaging (MRI) of the brain. This is crucial because thrombolytic treatment of a patient with acute cerebral hemorrhage may be fatal. Therefore, intravenous (IV) thrombolysis is only administered in a hospital at present. The consequence is a multifactorial delay. As a result, very few patients are treated within the most effective period for this drug, which is up to 90 min after the symptom onset. The only way to avoid this detrimental time delay seems evident—establish the diagnosis and the treatment of an AIS outside the hospital and in time as close to symptom onset as possible.

An increasing amount of evidence shows that minimizing prehospital time delay improves the thrombolytic rates in an AIS [9,10], and to take it a step further, in 2012 Fassbender et al demonstrated that prehospital stroke diagnosis is accurate and feasible. Using a mobile stroke unit (MSU), equipped with a stroke neurologist, a CT scanner, and a point-of-care biochemical laboratory, they showed that the time from symptom onset to a diagnostic therapeutic decision for thrombolysis was reduced from 76 min to 35 min. In 95% of the cases, the CT scanner in the MSU provided high-quality brain scans, which enabled them to rapidly and accurately differentiate between cerebral infraction and cerebral hemorrhage on site [8]. Due to the potentially great socioeconomical gain of early treatment of stroke patients [11], other initiatives to investigate and implement a neurologist-staffed MSU have been made [12-14]. They all have in common that they significantly reduce time to diagnosis and treatment. Thus, the question arises if a full hospital staff, including a neurologist, who normally do not operate in the prehospital room, is mandatory for this system to work. To investigate this, we have staffed an MSU with a specially trained anesthesiologist, a specially trained nurse, and a paramedic to mimic the Norwegian helicopter emergency medical service (HEMS) (REK id 2013/2298). On the basis of this, Hov et al published a study on the agreement between anesthesiologists and neuroradiologist in finding radiological contraindications of thrombolytic therapy in cerebral CT scans of an acute stroke [15]. This study showed a 92% interrater agreement between the 2 groups, and it demonstrates that a prehospital diagnosis of stroke patients is feasible on a more general basis and within the Norwegian physician manned emergency service.

The National Institutes of Health Stroke Scale (NIHSS) is a reliable and a much-used tool for clinical recognition and severity estimation of stroke symptoms. The reliability of this scale has been established by several clinical trials performed by trained neurologists. In 1999, Dewey et al proved that the overall agreement in NIHSS scoring between trained nurses and trained neurologists was no different from the agreement among neurologists. The study suggested that trained nurses could administer the NIHSS with reliability similar to stroke-trained neurologists [16]. Thus, the use of NIHSS is accessible in the prehospital system, where specially trained paramedics, nurses, and anesthesiologists can evaluate the patients using NIHSS. This will help with triage and categorization of patients for this study.

The most commonly used brain-imaging method for acute stroke is CT; however, the detection of an ischemic volume is not sensitive in the acute phase. The size of the infarct core can be approximated by the extent of diffusion-weighted imaging (DWI) signal changes [17]. The MRI volumetric in predicting infarct volume in postischemic stroke patients is promising. Recent studies have shown that a large initial DWI lesion volume was an independent predictor of poor outcome in patients managed with intravenous thrombolysis [18], and that lesion volume may decrease more than 30% 2 hours after tissue plasminogen activator (tPA) as an early marker of long-term clinical benefit of thrombolytic therapy [19]. Our aim is to test whether early thrombolysis (< 90 min) may cause lesser infarct volume on DWI MR compared with late thrombolysis (>120 min) and to test DWI MR infarct volume as a predictor of outcome in patients treated with prehospital thrombolysis.

Biomarkers are molecules released by specific organs or types of cells. On the basis of how injuries occur at a cellular level, biochemical markers in the blood after an acute stroke may offer a possibility to gain prognostic, diagnostic, and even therapeutic information. Inflammation in the form of proinflammatory cytokine production, microglia activation, and recruitment of other immune cells after a stroke plays an important role in the pathogenesis [20]. Additionally, as the thrombolytic treatment is extremely sensitive to time and can prevent damage to the

brain tissue, pharmacological interventions must be investigated. The extent of damage after a stroke is closely linked to the time elapsed from symptom onset to treatment, and the influence of this time span might be reflected in the inflammatory response measured by the circulating cytokines in the blood. By studying this, we might gain insight into the outcome and the prognostic values after a stroke.

On the diagnostic side, biomarkers have the potential to distinguish an intracerebral hemorrhage (ICH) from an AIS and a stroke mimic [21]. Concentrations and ratios of such markers may be used as a diagnostic tool, and further investigations are needed to fully utilize these possibilities. It has been shown that as much as a 1-month of additional disability-free life can be obtained by every 15-min decrease in treatment delay [22]. This emphasizes the importance of early diagnosis and treatment onset. The ability to diagnose a stroke already in the prehospital phase makes treatment possible at a much earlier time point than today and renders the search for such methods an important and relevant topic.

The use of biomarkers, as a diagnostic tool, to determine whether a person has suffered from an ICH or an AIS remains a challenge but is in progress. Proteins representative of early pathways involved in the pathophysiology of cerebral ischemia have failed to show sufficient diagnostic accuracy [23,24]. Attempts to identify biomarkers specific to ICH have been made, with a focus on the cell-type-specific proteins that are released upon brain damage. The glial fibrillary acidic protein (GFAP) is a structural protein specifically expressed in astrocytes [25], a type of glial cell that performs a variety of signaling and nonsignaling functions in the brain. Upon cellular disintegration, caused by ICH, the GFAP is rapidly released and can be detected in the plasma. Under the physiological conditions, the GFAP is not secreted from the cells; therefore, it is not detected in the plasma [26]. The plasmatic retinol-binding protein 4 (RBP4) was picked up on a big screen that aimed to identify new biomarkers to differentiate the stroke subtypes. In combination with the GFAP, it shows great potential for distinguishing between an AIS and an ICH [27]. By comparing the results from the neuroimaging and the biomarker measurements, we can elucidate the information that the different concentrations and ratios of the mentioned biomarkers in the blood provide. In turn, we hope this will enable us to establish a biochemical means to define the type and the magnitude of the stroke, which is mandatory before the initiation of a treatment.

Objective

The objective of this study is to investigate the effectiveness of a prehospital diagnosis and, when appropriate, of intravenous thrombolytic treatment of an AIS. At the same time, we will take the opportunity to do an explorative study with the aim to further improve the intervention using biomarkers and volumetric outcome measures measured using MRI images.

The intervention study aims to:

- determine the time from symptom onset to thrombolytic treatment in the MSU compared with the conventional model;
- determine the number of patients receiving thrombolytic treatment within the 4.5-hour window in the MSU compared with the conventional model; and
- determine if thrombolytic treatment in the MSU, when adjusted for time, offers better Modified Rankin Scale (mRS) and Barthel outcome compared with treatment in the conventional model.

The explorative study aims to:

- determine if final AIS infarction volume, estimated by an MRI, is independently correlated with time from symptom onset to thrombolytic treatment;
- define cutoff values for GFAP and RBP4 and explore whether they can distinguish an ICH from an AIS when combined with sufficient specificity and sensitivity; and determine the influence of time to treatment on proinflammatory markers after stroke

Hypothesis

Intervention Study

1. The Treat-NASPP MSU model is feasible and reduces the onset to treatment time (>15 min).
2. The number of patients treated with thrombolysis within 4.5 hours of symptom onset are significantly increased in the Treat-NASPP MSU model.
3. The treatment in the Treat-NASPP MSU model, when adjusted for time, does not result in increased day 90 mRS and Barthel as compared with the conventional model.
4. Prehospital thrombolytic treatment of stroke does not increase the risk of secondary cerebral bleeding as compared with inhospital thrombolytic treatment of stroke (cerebral bleeding worsening within 36 hours <4%, Norsk hjerneslagregister)

Explorative Study

1. The final infarct volume, estimated by an MRI, is significantly reduced when the thrombolytic treatment is initiated in the MSU.
2. Biomarkers are a valid tool in the hyperacute phase of cerebral illness to exclude contraindication to thrombolysis.
3. Reduced onset to treatment time results in lower levels of selected proinflammatory molecules.

Methods

Treat-NASPP is a prospective controlled intervention study. The main aim of this study is to prospectively compare patients with an AIS, who are diagnosed and treated prehospitally in the MSU (intervention), with those who receive conventional pre- and inhospital diagnostics and treatment (control). At the same time, we will perform an explorative study with the aim to further improve the diagnostic (the biomarker study) and the outcome measures (the biomarker study and the MRI infarction volume study).

The MSU will be available on call on weekdays from 8 AM to 8 PM, 2 weeks on and 2 weeks off. The MSU will not be on call during holidays and vacations. When on a call, the MSU will be staffed with an anesthesiologist, a paramedic-nurse, and

a paramedic. During the weeks that the MSU is not operating, data collection will take place from the conventional ambulance on weekdays from 8 AM to 8 PM. Only ambulances that are staffed with a paramedic-nurse and a paramedic who work as staff on the MSU will participate in the study. All emergency calls to the central emergency medical services (EMS) dispatch center (AMK 113) from the catchment region of Østfold County will be screened for stroke symptoms by the EMS dispatcher, as per normal procedures—they will use the Functional Assessment Staging Test scale (one or more of the following neurological deficits: paralysis of arm or leg, facial paralysis, aphasia, or dysarthria) and in accordance to the inclusion criteria (listed below), the MSU will be dispatched when the inclusion criteria are fulfilled on weeks when the MSU is on call. The same inclusion criteria will be applied for the ordinary ambulances on weeks when the MSU is not on call. The intervention (prehospital CT and thrombolytic treatment) can only be administered in the MSU. The control (inhospital CT and thrombolytic treatment) can only be administered in the hospital. The EMS dispatcher will notify the EMS service (MSU anesthesiologist or conventional ambulance staff) with clinical information and history, if available. The procedure is outlined below.

Inhospital NIHSS, Barthel, and mRS in the hyper-acute phase will be conducted by the neurologist on call. Follow-up tests will be conducted by an independent, inhospital neurologist who is not invested in the study.

MSU Procedure

On site, the anesthesiologist will take the actual medical history and conduct a rapid screening using the ABCDEs of trauma care. If the patient is stable and further investigations can proceed, including NIHSS scoring, the patient will get 2 venous lines, and blood samples will be collected. Blood samples for biomarkers (see details below) will be stored and delivered to the laboratory at the hospital for further analyses and storage in a biobank (related to REK 2014/1161). The patient will travel in the stroke ambulance, where the CT scan will be performed and blood tests will be run in the point-of-care laboratory (POC). After completing the CT scan examination, the anesthesiologist will immediately get in contact with the on-call neurologist (stroke team) at the Østfold Hospital. The anesthesiologist will provide the stroke team with the clinical history, the POC blood tests, the NIHSS score, the time of symptom onset, and any known clinical contraindication of thrombolysis. The stroke team and the on-call radiologist will interpret the CT scan by teleradiology, and a treatment decision will be made. If there is an indication of thrombolytic treatment, the stroke ambulance nurse will prepare and initiate intravenous rtPa (Actilyse). The anesthesiologist will fill the prehospital study data in an electronic study form.

Conventional Ambulance Management

Conventional ambulance data collection will only take place when the MSU is not on duty. The conventional ambulance will be staffed with the same personnels (except the anesthesiologist) as the MSU. After the paramedic or nurse-paramedic has taken the patient's actual medical history, performed a physical examination, including NIHSS, established a venous line, and given the emergency treatment needed, the patient will be transported to the Østfold Hospital. The paramedic will contact the EMS dispatcher and inform about the patient's inclusion in the study, and the EMS dispatcher will contact the hospital stroke team. The paramedic will withdraw a blood sample for the biomarker study, and an additional blood sample will be taken at the hospital for standard analysis.

Therapeutic Decision

In both, the conventional and the MSU pathway, a cerebral CT scan will be conducted as soon as possible after the symptom onset. Images from both the pathways will be registered in the hospital PACS system, and they will be interpreted by the on-call stroke team (the neurologist and the radiologist). In the MSU pathway, the anesthesiologist will decide which patients are eligible for CT scan. However, in the conventional pathway, the on-call neurologist in the emergency department will make this decision. Prehospital clinical assessment will include the actual medical history, a stroke scale score, and an ABCDE evaluation. The clinical information and scores will be completed in designated study forms, and in the specialized prehospital patient record system—AMIS. Both the paramedic/nurse in the conventional pathway and the anesthesiologist in the MSU will do a stroke scale score, and the scores will be analyzed for research purposes.

If a thrombolytic-treated patient shows signs of clinical detoriation, expressed as an increase of 4 or more points on the NIHSS scale, an intracranial hemorrhage would be suspected and the thrombolytic infusion would be stopped immediately. A new cerebral CT scan should be conducted in the MSU if the driving distance to the hospital exceeds 20 min, and these CT findings should be transferred and reported to the hospital immediately. On the basis of the CT image, after the identification of the location and the distribution of damage, the treatment will either be initiated on site, in accordance with inhospital procedures, or the patient will be transported directly to the location for neurosurgery.

Prehospital Use of Stroke Scales

Stroke scales will be conducted in the MSU and the regular ambulance. All participants (anesthesiologists, paramedics, and nurses) will attend a 2-day course in stroke clinics, stroke treatment, and the use of stroke scales. An online certification in NIHSS will be mandatory for participation.

Magnetic Resonance Volumetric

An MRI will be completed at day 1 in all patients treated with thrombolysis—prehospital or inhospital. According to the standard MRI protocol at Østfold Hospital, the *final* infarct volume will be estimated using T1-volume, FLAIR, T2, diffusion, and SWI series.

Biomarker

All serum and plasma samples will be stored in a biobank (related to REK 2014/2261). Venous blood for measurements of biomarkers will be drawn from all the enrolled patients at the earliest time points after symptom onset (ie, after arrival of the paramedics/anesthesiologists at the scene) and at different time points (up to weeks after being admitted in the hospital).

The total volume of blood drawn will not exceed 100 mL on any day. All samples will be drawn by personnels certified by the Østfold Hospital. One standard serum tube, 1 EDTA plasma tube, and 1 citrate serum tube will be used for blood collection. Blood samples will be centrifuged within 2 hours of blood collection using a standard centrifuge (10 min at 1500 g-2000 g). Serum/plasma will be transferred immediately in aliquots to Eppendorf tubes (each containing 0.5 mL) and stored at −80 C. The Eppendorf tubes will need to be labeled appropriately mentioning the patient number and the number of tubes collected per patient. Periodically (depending on the number of patients and tubes collected), biomarkers will be analyzed in Professor Sandip Kanses' lab, IMB, UiO, or shipped on dry ice to Professor Christian Förch, Department of Neurology, Schleusenweg 2-16, 60528 Frankfurt am Main, Germany. Acute CT scans will be taken at the same time as blood samples and will be collected prehospitally (this applies for the MSU. Patients brought in by a conventional ambulance will have their CT scans taken after arrival at the hospital). We will compare biomarker levels (index test) with CT findings (reference standard) and optimize cutoff points by using Receiver Operating Characteristics (ROC) analysis. Sensitivity and specificity will be calculated based on cross tabulations. In the wake of a stroke, the broad range of time points will be needed to monitor the rise and fall of biomarker concentrations, inflammatory response, and diagnostic and prognostic windows.

Inclusion

- All patients suspected of having a stroke that are checked by the emergency services within 4 hours of symptom onset.
- Patients experiencing stroke symptoms—sudden weakness of leg or arm, especially on one side; facial asymmetry; sudden trouble walking; and speech disturbance (Norwegian Index of Medical Emergencies 27.03-27.06).

Exclusion

- Under 18 years of age
- Pregnancy
- Female <50 years and uncertain of pregnancy
- Uncertainty regarding symptom onset time

Study Variables

- Age
- Gender
- Prehospital NIHSS
- NIHSS inhospital (day 0, 2 hours after rtPA, day 1, and day 7)
- mRS (at discharge but no later than day 7, day 30, and day 90) and Barthel score (at discharge but no later than day 7, day 30, and day 90)
- Hyperacute CT diagnosis
- CT-angiography (CTA) findings
- MR volumetric at day 1 and day 90
- Time span from symptom onset to MSU/conventional ambulance admission
- Onset to treatment (symptom onset to thrombolysis)
- Onset to thrombectomy/neurosurgery time

Hemorrhagic transformation categorized as:

- Hemorrhagic infarction 1 (HI1) (small petechiae along the margins of the infarct)
- Hemorrhagic infarction 2 (HI2) (confluent petechiae within the infarcted area but no space-occupying effect)
- Parenchymal hemorrhage (PH1) (blood clots in 30% or less of the infarcted area with some slight space-occupying effect)
- Parenchymal hemorrhage (PH2) (blood clots in more than 30% of the infarcted area with substantial space-occupying effect)
- Remote parenchymal hemorrhage (rPH) (bleeding outside the infarcted area)

- Biomarker concentrations at Time 1 (in MSU and conventional ambulance) and 2 (inhospital)
- History of known comorbidity
- History of anticoagulation

Data Monitoring, Harms, and Auditing

An independent safety committee consisting of 2 experienced stroke neurologists will review all safety data after 10, 20, 50, 100, 150, and 200 patients are treated with thrombolysis. The committee will stop the study if they find evidence for an unacceptable increase of symptomatic cerebral bleedings (more than 4%) or deaths. Symptomatic cerebral hemorrhage is assessed as a local or a remote parenchymal hemorrhage combined with a neurological deterioration of 4 points or more on the NIHSS from baseline or from the lowest NIHSS value between baseline and 24 hours, or a significant clinical worsening linked to the bleeding or a bleeding leading to death.

The overall rate of cerebral bleeding complications and the mortality rate at 7 days will be compared with the data from the Norwegian stroke register.

The main safety issues in the acute phase of stroke are linked to respiratory failure, cardiac arrhythmias, and cerebral bleeding secondary to thrombolytic treatment.

The anesthesiologists working in the MSU are highly qualified to take care of acute respiratory and cardiac failure. The MSU is technically equipped as an air ambulance helicopter.

The main aim of our study is to provide early thrombolytic treatment to patients with cerebral infarction. The most serious complication of thrombolytic treatment is cerebral bleeding, which may be fatal. Up to 10% of all patients treated with thrombolysis will have a cerebral bleeding confirmed by CT, whereas only 2% to 4% of all patients will die or have a worsened outcome due to bleeding (called symptomatic bleeding). Cerebral bleeding following thrombolytic therapy will show up during the first few days, sometimes even in the very acute phase. Studies with thrombolytic therapy in MSU models have, however, not shown an increased risk of cerebral bleeding [12].

Inhospital cerebral bleeding will be diagnosed and treated according to the standard routines. Patients will be monitored both in the MSU and in the stroke unit with NIHSS scoring at close intervals for 24 to 36 hours. In the hospital, as a routine, an MRI cerebral scan will be performed at approximately 24 hours after symptom onset.

Statistical Analysis

The Treat-NASPP is designed in accordance with the Standards of Reporting of Diagnostic Accuracy initiative guidelines [28]. For the prospective controlled intervention study, our primary outcome will be (1) onset to treatment time and (2) number of patients treated within 4.5 hours. Our secondary outcome will be mRS and Barthel at day 90 adjusted for onset to treatment time.

For the primary outcomes, we will use the Mann–Whitney *U* test. For power calculation, we want to compare two continuous variables in two groups or compare two means. 2-sample, 2-sided equality. If we estimate the time saved by MSU-treatment (intervention) as compared with the conventional pathway (control) and found the following outcomes:

- Mean group 1: 210 min [29]
- Mean group 2: 180 min (we estimate that 30 min are saved in the MSU)
- SD 70 min
- Sampling ratio: 1

This gives us a number (n) of 86 patients with thrombolytic treatment in each group. As we observed a mean reduction of time from onset of symptoms to diagnostics in the referred to NASPP study (unpublished data, REK 2013/2298) of 100 min, we consider this to be achievable.

As we expect concentrations of biomarkers to have a skewed distribution [21,30], we will use the Mann–Whitney *U* test for comparing concentrations in the patients with an AIS and an ICH. The ROC-curve analysis will be used to calculate the diagnostic accuracy of the biomarkers in distinguishing between an AIS and an ICH.

Sample size calculation for logistic regression is a complex problem, but based on the work of Peduzzi et al [31], the following guideline for a minimum number of cases to include in the study can be suggested:let p be the smallest of the proportions of negative or positive cases in the population and k the number of covariates (the number of independent variables), then the minimum number of cases to include is: N=10 k/p. A statistician (JR) will be consulted for correct data analysis.

Data Storage

Clinical data will be registered and stored at the Østfold Hospital, Kalnes. Study data will be retrospectively collected and registered using the European Cerebrovascular Research Infrastructure (ECRI) database located at the Oslo University Hospital [32]. ECRI is a platform for European stroke research centers, and it provides the essential infrastructure for international cooperation with shared databases, secure network access, and advanced consent handling. The ECRI was established to facilitate high-quality medical research with possibilities of international cooperation.

Consent

The Treat-NASPP Study will be closely linked to the NASPP and Biomarker study (REK 2013/2298 and 2014/1161). This biobank will be a continuation of the specific biobank approved by REK related to project 2014/1161. It is stated that the consent may be collected retrospectively when needed (REK document-id: 436501). Patients (or next of kin) included in the study will be informed about the study and an oral consent in the prehospital acute phase will be obtained when possible. In the stroke unit, before discharge, a specifically assigned neurologist will be in charge of collecting written consent from all patients (or next of kin), who are part of this study. This will be closely monitered by the principle investigator and the responsible PhD candidate.

Results

Patient inclusion has started and a total of 37 patients are enrolled (control and intervention combined). The estimated time to completed inclusion is 36 months, starting from May 2017. The results of this study will be analyzed and published at the end of the trial.

Discussion

Patients suffering from an AIS can have a complete functional and cognitive recovery or suffer from severe disability and death. The outcome prognosis is strongly associated with successful reperfusion treatment [33]. Diversion of suspected traumatic brain injury patients to trauma centers or patients with identified intracranial hemorrhage may improve outcomes by expediting access to specialist neurosurgical care [34]. Prehospital recognition of symptoms and/or diagnostic findings that resemble the need of endovascular thrombectomy or care in neurosurgical department may be transported directly to the regional hospital by the MSU, or by the conventional ambulance, or the HEMS by-passing the local hospital. The Treat-NASPP Study is the first to introduce advanced prehospital diagnostics and treatment of AIS in a well-established prehospital setting run by anesthesiologists.

This study might result in a method that can be used to diagnose a stroke and initiate treatment prehospitally, which might have a significant clinical impact on the patient outcome.

Conflicts of Interest

None declared.

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Abbreviations

AIS: acute ischemic stroke
CT: computed tomography
ECRI: European Cerebrovascular Research Infrastructure
EMS: emergency medical services
GFAP: glial fibrillary acidic protein
HEMS: helicopter emergency medical service
ICH: intracerebral hemorrhage
IS: ischemic stroke
MRI: magnetic resonance imaging
mRS: Modified Rankin Scale
MSU: mobile stroke unit
RBP4: retinol-binding protein 4
ROC: Receiver Operating Characteristics
rtPA: recombinant tissue-type plasminogen activator

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Protocol

Text-Based Program Addressing the Mental Health of Soon-to-be and New Fathers (SMS4dads): Protocol for a Randomized Controlled Trial

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Abstract

Background: Recent estimates indicating that approximately 10% of fathers experience Paternal Perinatal Depression (PPND) and the increasing evidence of the impact of PPND on child development suggest that identifying and assisting distressed fathers is justified on public health grounds. However, addressing new fathers' mental health needs requires overcoming men's infrequent contact with perinatal health services and their reluctance to seek help. Text-based interventions delivering information and support have the potential to reach such groups in order to reduce the impact of paternal perinatal distress and to improve the wellbeing of their children. While programs utilising mobile phone technology have been developed for mothers, fathers have not been targeted. Since text messages can be delivered to individual mobile phones to be accessed at a time that is convenient, it may provide a novel channel for engaging with "hard-to-reach" fathers in a critical period of their parenting.

Objective: The study will test the efficacy of SMS4dads, a text messaging program designed specifically for fathers including embedded links to online information and regular invitations (Mood Tracker) to monitor their mood, in order to reduce self-reported depression, anxiety and stress over the perinatal period.

Methods: A total of 800 fathers-to-be or new fathers from within Australia will be recruited via the SMS4dads website and randomized to the intervention or control arm. The intervention arm will receive 14 texts per month addressing fathers' physical and mental health, their relationship with their child, and coparenting with their partner. The control, SMS4health, delivers generic health promotion messages twice per month. Messages are timed according to the babies' expected or actual date of birth and fathers can enroll from 16 weeks into the pregnancy until their infant is 12 weeks of age. Participants complete questionnaires assessing depression, anxiety, stress, and alcohol at baseline and 24 weeks postenrolment. Measures of coparenting and parenting confidence are also completed at baseline and 24 weeks for postbirth enrolments.

Results: Participant were recruited between October 2016 and September 2017. Follow-up data collection has commenced and will be completed in March 2018 with results expected in June 2018.

Conclusions: This study's findings will assess the efficacy of a novel text-based program specifically targeting fathers in the perinatal period to improve their depression, anxiety and distress symptoms, coparenting quality, and parenting self-confidence.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12616000261415; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370085 (Archived by WebCite at http://www.webcitation.org/6wav55wII).

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KEYWORDS

perinatal; fathers; online intervention; randomized controlled trial; mental health

Introduction

The period surrounding childbirth represents a vulnerable time for families where both women and men may be at increased risk of mental health disorders. However, while maternal perinatal screening and treatment protocols have been introduced within Australia, Paternal Perinatal Depression (PPND) has been largely overlooked [1]. Recent estimates indicating that 9% to 10% of fathers experience PPND [2,3] and the increasing evidence of the impact of PPND on child development [4,5] suggest that identifying and assisting distressed fathers is justified on public health grounds. In similar fashion, high levels of paternal anxiety and stress have also been found to be harmful to children's development [6-8]. However, addressing new fathers' mental health needs requires overcoming men's infrequent contact with perinatal health services and their reluctance to seek help [9,10].

While anxiety, stress and depression are recognized as related negative emotional states, paternal depression has figured most prominently in the published research on fathers' mental health in the perinatal period. PPND can impair the fathers' relationship with his infant and reduce his ability to effectively coparent. Observational studies of depressed fathers have found decreased levels of warmth, sensitivity, synchrony engagement, and positive involvement and increased levels of criticism, hostility, harshness, intrusiveness, withdrawal, and control [11]. For example, fathers of one year olds who had experienced a major depressive episode in the previous year were only half as likely to read to their infants but four times more likely to spank them [12].

The detrimental impact of PPND on fathers' mental wellbeing and on infant development is well documented. Preschoolers whose fathers reported symptoms of depression in the first year had twice the risk of behavioral and emotional problems compared to children of nondepressed fathers [13]. When the children were assessed at 7 years of age, those whose fathers had been depressed following their birth were almost twice as likely to have a psychiatric disorder compared to those of nondepressed fathers [4]. In both studies, findings were consistent after adjusting for maternal depression and paternal educational level. In addition, analysis of an Australian cohort found highly elevated behavior problems in preschool children whose fathers had shown depressive symptoms in their first year [5].

PPND, expressed through hostility and negative comments, is also likely to impact on the relationship between the parents, especially when combined with alcohol dependence [14,15]. Couple conflict and lack of partner support has been linked to maternal postnatal depression [16,17], and marital conflict may help to explain the relationship between postnatal depression in either mothers' or fathers' and child outcomes [18,19].

Given the deleterious effects of PPND on a father's own health, his parenting and coparenting relationship, and the possible ongoing impairment of his child's development, the need to identify and treat or support distressed fathers is clear. Moreover, health service costs of PPND in Australia, using 2012 figures, have been estimated at $17.97 million with an added cost of $223.75 million due to lost productivity [20]. While calls for fathers to be assessed for mood disorders and offered information, support, and counselling during the perinatal period are common, the service response has been absent [21].

Addressing PPND will require overcoming several barriers. Work demands, for example, prevent most fathers participating in perinatal clinic visits with their partner [9]. Those fathers attending antenatal preparation classes or the birth may feel ignored by professionals and feel that they have few opportunities to raise their concerns [22,23]. As well, fathers may have little understanding of perinatal depression in general and may not easily recognize their own symptoms of depression [24,25]. Attempts to engage fathers in early intervention programs have had little success and fathers are badged as "hard to reach" [26,27].

Mobile phone technology may be feasible in identifying distressed fathers and offering support as ownership among Australian adults is high (94%) [28]. Fathers regularly use the Internet to source parenting information [29,30]; however, linking fathers to Web-based parenting resources remains problematic. The low recruitment and engagement of fathers found in face-to-face parenting programs [28] appears to be replicated in online parenting programs [31,32].

Text messaging has been shown to influence health-related knowledge and beliefs among mothers. Text4baby, a United States–based program sending short message service messages to mothers through the perinatal period, has found that 75% of users reported text messaging had given them important medical information. A randomized controlled trial involving 90 Text4baby users found that text messaging was associated with positive alterations in targeted health beliefs [33]. Health behaviors relating to smoking, weight loss, physical activity and the management of diabetes have also shown improvement in response to text messaging [34,35]. Text messaging could therefore provide a novel avenue for delivering support and parenting-related information to fathers during their transition to fatherhood.

While texts, which are delivered at no cost to participants, are able to convey information relevant to a father's role during pregnancy and postbirth, they have limited capacity to engage fathers in help seeking. Self-monitoring to increase participants' awareness of their mood has been incorporated into web and mobile phone programs targeting depression [36,37] with embedded links to websites for further information, education, or support. Providing links within messages to websites that are relevant to fathers' concerns and including interactive text messages inviting mood self-monitoring (Mood Tracking) may encourage fathers to seek out assistance for parenting difficulties and for personal distress.

Text-based interventions delivering information and support have the potential to reduce the impact of perinatal distress in parents and improve the wellbeing of their children. While programs utilising mobile phone technology have been developed for mothers' mental health [38] fathers have not been targeted. The study proposed here will test the efficacy of a program incorporating brief text messages designed specifically for fathers including embedded links to online information and support and regular invitations (Mood Tracker) to monitor their mood (see Multimedia Appendices 1, 2, and 3). Since text messaging is relatively inexpensive and can be accessed across rural and urban areas at a time that is convenient, it may provide a novel channel for reaching "hard-to-reach" fathers in a critical period of their parenting. SMS4dads may offer a low-cost model for improving the wellbeing of families through supporting the male partner in the parenting team.

The aim is to conduct the first randomized controlled trial of a text-based intervention, SMS4dads, which targets fathers' mental health during the perinatal period. The efficacy of the SMS4dads program in reducing depression, anxiety, and stress symptoms among new fathers will be assessed by comparing intervention outcomes with those of a sham program, SMS4health, offering generic health promotion messages. Secondary aims are to assess the effect of SMS4dads on the fathers' coparenting, parenting self-confidence, and use of alcohol.

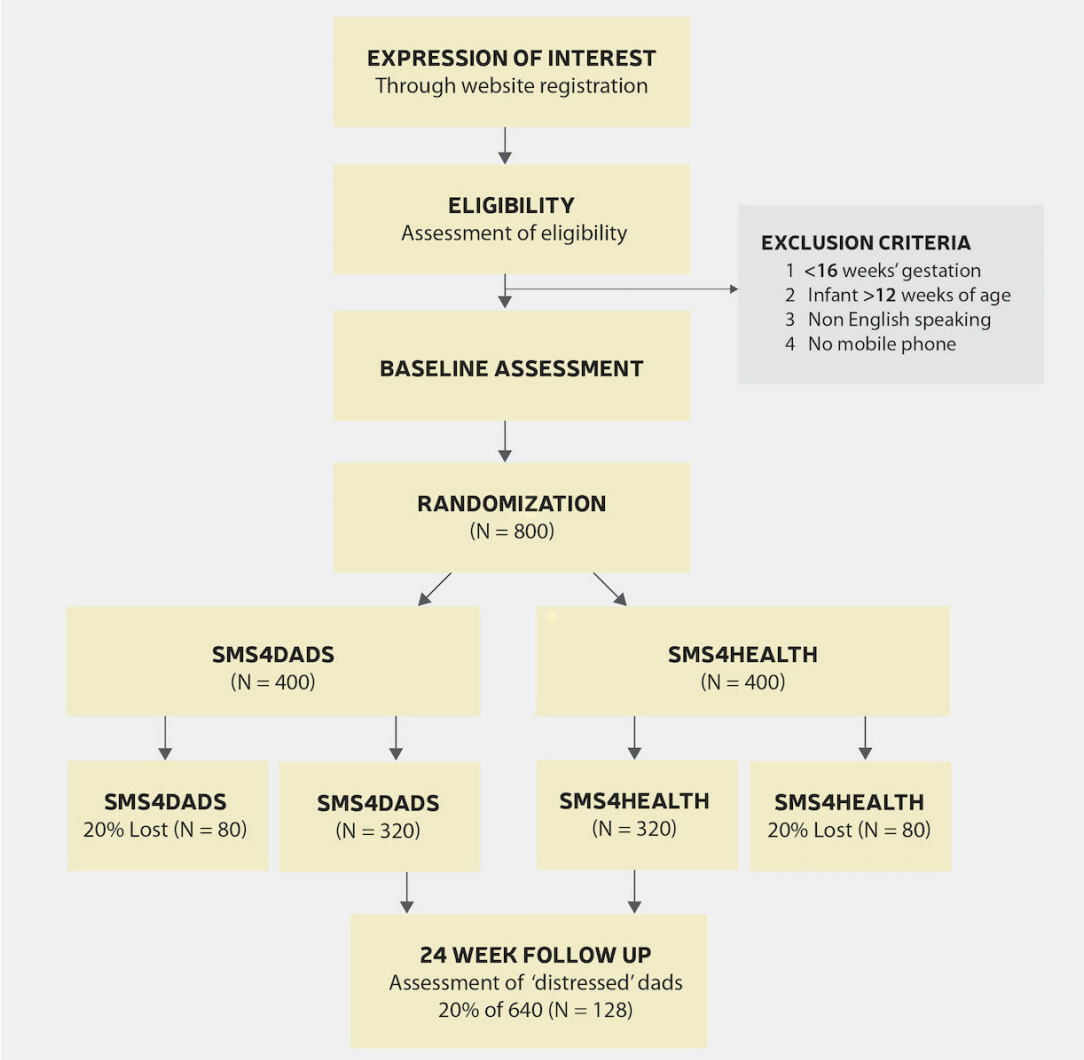
Hypotheses

It is predicted that fathers receiving the SMS4dads program will show lower levels of depression, anxiety, and distress at 24 weeks postbaseline than fathers receiving the SMS4health program. In addition, fathers' coparenting and parenting self-confidence are predicted to be greater and use of alcohol to be less among those receiving SMS4dads than among those receiving SMS4health.

Methods

This randomized controlled trial is designed to assess the efficacy of a text-based intervention targeting mental health in new fathers. Participating fathers will be randomly allocated to receive either the SMS4dads or SMS4health. A summary of participant flow though the trial is provided in Figure 1. This study received ethics approval from The University of Newcastle Human Research Ethics Committee on June 16 2016, approval number H-2016-0055.

Figure 1. Participant flow through the trial.



Study Sample and Procedure

A total of 800 fathers-to-be or new fathers from within Australia will be recruited. Participants will be recruited through the SMS4dads website [36], which houses a brief introductory video explaining the SMS4dads program and information and enrolment pages. Fathers will be made aware of the Web page and the project through social media, through flyers distributed by health staff in contact with parents, and through mainstream media outlets. Interested fathers are provided with email and phone contact to enable further questions about the study to be answered.

Inclusion Criteria

Participants will be included in the trial if they indicate having a partner who is more than 16 weeks pregnant or their infant is less than 12 weeks of age, have a mobile phone capable of receiving text messages, and they can read and understand English. There is no cost involved in receiving the text messages but access to the internet is required to respond to the Mood Tracker texts and to access the links provided to websites in the messages.

Screening and Baseline

Expecting and new fathers will register for participation through the project website where an information statement and other materials about the project are readily available [39]. Fathers wishing to enrol can click on the "Join Up" tab located on the front page of the SMS4dads website, which will take them to the registration pages. The first registration pages assess eligibility and information for messaging purposes including their infant's expected or actual date of birth, full name, email address, and phone number. For demographic purposes, they will be asked for their age, postal address, Indigenous status, and a question about their socioeconomic position [37]. When completing consent questions fathers will be asked to confirm that they have read the information statement and that they have no further questions about the project. They will also be asked if they would like to be informed of study outcomes, if they would be willing to participate in phone interviews about their experience of participation, and whether they would be prepared to pass an information package onto their partner. When fathers have answered these questions they will be asked to respond to four questionnaires (53 items) detailed in the following section on study measures. All questions mandate a response but fathers can report that they have no email address and that they do not wish to supply data about their socioeconomic position.

Follow-Up Assessments

Fathers are also asked to repeat the questionnaires 24 weeks after receiving their first message.

Randomization

Randomization was performed using a custom-built Web-based module attached to the online data collection forms. The actual randomization process was based on a random number generator with a random seed, and using random permuted blocks of 4 or 6. Allocation was 1:1 in the intervention or control arm as new users registered on the site. The Web modules were built using C#.Net (with a Visual studio integrated development environment) and a Microsoft SQL Server backend to store the generated random numbers.

From an architectural perspective, proper separation of code design principles was followed as the complete randomization feature was implemented as a contained application programming interface (API) module. The API module was only accessible from a software Application with the required granted permissions, through calls within the requesting Applications business and data access layer. This also allowed the module to be maintained without effecting the source Web application consuming its resources

Sample Size

Sample size was based on the primary outcome of Depression Anxiety Stress Scales (DASS-21) [40] values in the intervention and control arms at 24 weeks, adjusting for baseline values. We assume an effect size of 0.5 SD Units (Cohen's *d*) among those "distressed" fathers who report Moderate, Severe or Extremely Severe scores on the total DASS-21 (≥ 23). Aiming for power of 80%, significance level of 5%, 1:1 ratio of allocation to control and intervention, we estimate a sample size of 64 "distressed" fathers will be required in each arm of the trial. Assuming 20% of the sample recruited will be distressed (based on feasibility study data) we will require 320 fathers in each arm giving a total sample of 640 fathers. Allowing 20% for attrition and loss to follow-up, 800 fathers in total will be required to be recruited.

Program Content, Tone, and Design

The program content includes an established corpus of relationship-focused messages developed for a related feasibility study using an iterative consultation process with parents, academics, and practitioners (N=46) [41,42]. Messages aim to provide new fathers with information, support them in caring for their own physical and mental health, nurturing strong relationships with their child, and developing strong parenting partnerships with their partner. Messages are timed according the babies expected or actual date of birth and thereby designed to address issues that are likely to be occurring for the father when the information arrives. Messages, including links, are limited to 160 characters and designed to engage with fathers through humor, by use of the baby's voice, and through an encouraging, nonjudgemental tone. Approximately one third of messages (n=98) contain links to online sources of information directly related to the message content [41].

A father participating in the full 77-week program will receive 294 messages. These are usually delivered on a 4-week cycle (5 messages in week 1, 4 in week 2, 3 in week 3, and 3 in week 4) totalling 15 messages. Some messages address particular issues such as alcohol consumption (n=25) and others link to the Mood Tracker application (n=30). Mood Tracker messages ask fathers to respond to questions about their mood on a 5-point scale. Fathers indicating high levels of distress on Mood Tracker will be automatically linked to appropriate websites and offered the opportunity to be contacted by a phone counselling service experienced in paternal perinatal support.

Study Measures

Measures will be constrained to minimise the burden on participants. Questionnaires employed in the study include the DASS-21 (21 items) [38], the Alcohol Use Disorders Identification Test (AUDIT-C) (3 items) [40], the Short Version Coparenting Relationships Scale (CRS) (14 items) [43], and the Karitane Parenting Confidence Scale (KPCS) (15 items) [44].

The DASS-21 is a truncated version of a 42-item measure designed to assess three distinct, but empirically related, states of mental health. The validity of the three scales (depression, anxiety, and stress) that make up the DASS-21 has been demonstrated through strong correlations with established measures of each factor in diverse populations. The reliability of the subscales has been established in a large normative sample (N=717) with correlations between subscales and relevant measures reported for depression (0.81), anxiety (0.73), and stress (0.81) [39].

The AUDIT-C is a 3-item measure of alcohol consumption. The AUDIT-C was found to be more reliable than telephone interview in detecting heavy drinking in a sample (N=243) of known drinkers [45].

The CRS short version is a truncated version of the 35-item multi-domain questionnaire designed to assess parent perceptions of the strength of their parenting relationship with their partner. The validity of the CRS has been determined against established scales of coparenting quality and the total scale reliability (Cronbach's alpha) across three waves of measurements ranging from 0.81 to 0.85 [43].

The KPCS is designed to assess maternal and paternal perceptions of parenting self-efficacy (PSE) in the Australian context. The validity of the KPCS has been demonstrated against established measures of PSE and the authors report a total scale reliability (Cronbach's alpha) of 0.81 in a normative sample (N=27) [44].

Data Analyses

Given that there are multiple measures of the primary outcome, ie, DASS-21 scores at baseline and 24 weeks, we will use a linear mixed–model to analyse the results. This model will handle repeated measures as well as missing data; the model will include terms for group, time, and group x time interaction, which will allow us to see if the effect is more marked in one group versus another at particular time points. Secondary outcomes such as parenting, coparenting, and alcohol scales will be analysed using similar models.

Results

Participant recruitment commenced in October 2016 and will continue until the September 31, 2017. Follow-up data collection has commenced and will be completed March 2018 with results expected in June 2018.

Discussion

Fathers' depression and distress can have serious impacts on the wellbeing of their partner and the healthy development of their infants [4,5,11]. The costs of paternal depression are also significant [18]. Yet, fathers are unlikely to seek support with their new role and may not recognize when they need help with their depressed mood or anxiety [10].

Mobile phones offer a flexible, accessible, and cost-effective channel to provide information that can enhance perinatal well-being in fathers and their families. The SMS4dads project has developed an innovative program with a unique combination of direct communication, linked to online resources and telephone support. The message content, which has been developed with extensive review by new parents and experts from the field of perinatal mental health, addresses fathers' relationship with his infant, his relationship with his partner, and his self-care. The Mood Tracker component provides a safety net for fathers who are not coping and who may benefit from direct telephone contact.

The lack of intrusiveness, high acceptability, and low cost per user indicates the potential to scale up SMS4dads to large numbers of fathers. This study will be the first perinatal trial to assess the efficacy of direct text support for men in their transition to fatherhood. As such, this project may provide guidance for policy development and health care practice across Australia.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Fletcher 2017 SMS4dads slides for presentations.

[PPTX File, 3MB - resprot_v7i2e37_app1.pptx]

Multimedia Appendix 2

SMS4dads brief promotion video.

[MP4 File (MP4 Video), 16MB - resprot_v7i2e37_app2.mp4]

Multimedia Appendix 3

Mood tracker.

[JPG File, 544KB - resprot_v7i2e37_app3.jpg]

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Abbreviations

API: Application programming interface
AUDIT-C: Alcohol Use Disorders Identification Test
CRS: Coparenting Relationships Scale
DASS-21: Depression Anxiety Stress Scales
KPCS: Karitane Parenting Confidence Scale
PPND: Paternal Perinatal Depression
PSE: parenting self-efficacy

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Protocol

Enhancing Lifestyle Change in Cardiac Patients Through the Do CHANGE System ("Do Cardiac Health: Advanced New Generation Ecosystem"): Randomized Controlled Trial Protocol

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Abstract

Background: Promoting a healthy lifestyle (eg, physical activity, healthy diet) is crucial for the primary and secondary prevention of cardiac disease in order to decrease disease burden and mortality.

Objective: The current trial aims to evaluate the effectiveness of the Do Cardiac Health: Advanced New Generation Ecosystem (Do CHANGE) service, which is developed to assist cardiac patients in adopting a healthy lifestyle and improving their quality of life.

Methods: Cardiac patients (ie, people who have been diagnosed with heart failure, coronary artery disease, and/or hypertension) will be recruited at three pilot sites (Badalona Serveis Assistencials, Badalona, Spain [N=75]; Buddhist Tzu Chi Dalin General Hospital, Dalin, Taiwan [N=100] and Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands [N=75]). Patients will be assisted by the Do Something Different (DSD) program to change their unhealthy habits and/or lifestyle. DSD has been developed to increase behavioral flexibility and subsequently adopt new (healthier) habits. In addition, patients' progress will be monitored with a number of (newly developed) devices (eg, Fitbit, Beddit, COOKiT, FLUiT), which will be integrated in one application.

Results: The Do CHANGE trial will provide us with new insights regarding the effectiveness of the proposed intervention in different cultural settings. In addition, it will give insight into what works for whom and why.

Conclusions: The Do CHANGE service integrates new technologies into a behavior change intervention in order to change the unhealthy lifestyles of cardiac patients. The program is expected to facilitate long-term, sustainable behavioral change.

Trial Registration: Clinicaltrials.gov NCT03178305; https://clinicaltrials.gov/ct2/show/NCT03178305 (Archived by WebCite at http://www.webcitation.org/6wfWHvuyU).

(JMIR Res Protoc 2018;7(2):e40) doi:10.2196/resprot.8406

KEYWORDS

cardiac health; lifestyle; behavior change; eHealth; mHealth

Introduction

Cardiovascular diseases are the leading cause of death worldwide and a major driver of health care costs [1]. Evidence shows that a large proportion of the disease burden can be explained by behavioral factors (eg, low physical activity, unhealthy diet) [2], and that approximately 80% of heart disease, stroke, and type 2 diabetes can be prevented by attenuating or eliminating these health risk behaviors [3,4]. Hence, in their recent call for action, the American Heart Association stressed the importance of lifestyle management and called for better lifestyle counseling and the development of interventions to support health behavior change in cardiac patients [5].

Despite evidence showing that changing health behaviors improves (mental) health outcomes and lowers health care costs [5], to date, lifestyle counseling is not routinely implemented in physicians' office [6]. More precisely, physicians provide this type of counseling in only 34% of the clinic visits [7]. One of the important reasons for this is the fact that face-to-face counseling is time-consuming.

Remote technologies offer a new delivery model for promoting healthy behaviors and are increasingly used in health care settings [8]. Although these new developments provide an excellent opportunity to deliver behavior change interventions to large groups of underserved patients, the reported effect sizes have been small [8]. Possible explanations for this are the short duration of the interventions [8], the limited number of health-related behaviors addressed within the intervention program [9], the mismatch between patients' needs or preferences and the intervention, or the lack of sound behavior change methods adopted [10]. Previous trials within the cardiac population have demonstrated that a "one size fits all" approach does not seem to work [11]—revealing the importance of personalizing the care plan and addressing patients' needs and preferences.

Evidence shows that the conventional way of providing education about a healthy lifestyle does not result in adopting desirable health behaviors [12]. In order to produce sustainable change in health behaviors, the Do Cardiac Health: Advanced New Generation Ecosystem (Do CHANGE) study will provide a personalized theory-based behavior intervention program for three months, creating awareness of unhealthy behaviors, addressing multiple health behaviors at the same time, and changing unhealthy habits. [13].

The Do CHANGE service aims to address cardiac patients' unhealthy habits and change these by providing them with monitoring tools (eg, Fitbit) and increasing their behavioral flexibility. The Do Something Different (DSD) behavior change program will be provided, with the objective of disrupting the habit chains that are common in our daily living. Since people generally tend to live in accordance with their habits [14], disrupting these habits may lead to higher behavioral flexibility and eventually to behavior change [13]. The DSD program has been shown to be effective in changing health behaviors in previous studies targeting different populations [15]. The Do CHANGE service will, therefore, not only provide patients with innovative tools to support behavior change, but will also offer behavioral alternatives and carefully assess patients' needs on using these innovative tools.

The objective of the current trial is to evaluate the effectiveness of the personalized Do CHANGE service in changing unhealthy lifestyle and improving the quality of life in cardiac patients. The Do CHANGE service will be developed and evaluated in three different countries (Spain, Taiwan, The Netherlands), in order to represent patients from different cultural backgrounds. This may contribute to a higher generalizability of the study findings.

Methods

Design

Do CHANGE is an international (Spain, Taiwan, The Netherlands), multicenter, randomized (intervention versus care as usual) controlled trial designed to support lifestyle change in patients with cardiac disease. By increasing patients' behavioral flexibility and providing them with innovative devices, the objectives of enhancing lifestyle change and improving patients' quality of life are expected to be reached. The evaluation of the Do CHANGE service delivery consists of two randomized controlled trials—trial 1 (Do CHANGE), which has been registered on www.clinicaltrials.gov (NCT02946281), has provided input for the further development and improvement of the currently described trial 2 (Do CHANGE 2, NCT03178305).

Study Population

Patients primarily diagnosed with coronary artery disease (CAD) (having experienced a myocardial infarction, percutaneous coronary intervention, angina pectoris and/or coronary artery bypass graft surgery), symptomatic heart failure (HF) (New York Heart Association class I-IV), and patients diagnosed with hypertension (HT) will be included in the study. Hypertension is defined by values ≥140 mmHg of systolic blood pressure or ≥90 mmHg of diastolic blood pressure in two different measurements spaced 1-2 minutes apart and after 3-5 minutes in the sitting position. The values associated with the second measure will be used.

Inclusion criteria: Age 18-75 years, diagnosed (primary diagnosis) with CAD, HF or HT, having at least two of the following risk factors: smoking, positive family history, increased cholesterol, diabetes, sedentary lifestyle, and/or psychosocial risk factors. Patients should also have access to the Internet at home, have a smartphone which is compatible with the applications that will be used in the study (and have sufficient knowledge on using a personal computer and smartphone), and speak the countries' native language.

Additional inclusion criteria for only HF patients include a diagnosis of systolic or diastolic heart failure and presence of HF symptoms (eg, shortness of breath, chest pain, and exhaustion).

Exclusion criteria: Significant cognitive impairments (eg, dementia), patients who are on the waiting list for heart transplantation, life expectancy <1 year, life-threatening comorbidities (eg, cancers), with a history of psychiatric illness

excluding anxiety and/or depression, patients who do not have access to the Internet or a compatible smartphone, and patients with insufficient knowledge of the local language (Catalonian, Chinese or Dutch). Patients who have participated in the first phase of the Do CHANGE trial will also be excluded.

Sample Size

A total number of 250 patients will be enrolled in the study at three participating centers (Badalona Serveis Assistencials, Badalona, Spain [N=75]; Buddhist Tzu Chi Dalin General Hospital, Dalin, Taiwan [N=100] and Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands [N=75]). The sample sizes were determined based on the number of patients visiting the outpatient clinic per center.

One hundred and twenty-five patients will be enrolled in the intervention group and 125 in the control group. Considering participation rates in the previously performed Do CHANGE trial and other randomized controlled trials, we expect a significant number (50%) of patients to refuse participation. Hence, we will need to approach 500 patients. As the current trial aims to provide a proof of concept, sample size calculation will not be performed. A total of 250 patients is considered sufficient to meet this purpose.

Randomization

Patients will be randomized (2:2) to either the intervention group or the control group (ie, usual care). Patients will be randomized using computerized block randomization (stacks of 4). The computer will generate randomization sequences that will be sealed by an independent researcher. Due to the nature of the study, the blinding of the researchers and health care providers is not possible.

Study Procedure

Patients who fulfill all the inclusion criteria and none of the exclusion criteria will be approached for participation. Due to differences in health care implementation across the three participating countries, the logistics of patient recruitment per site might slightly differ.

Overall Procedure

The health care professional (cardiologist or cardiac nurse) will inform the patient about the study (orally and in writing). Patients who are willing to participate will be provided with an informed consent and will be given ten days to consider their participation. The research assistant will contact the patients by telephone and schedule a face-to-face appointment if they are willing to participate. During the face-to-face meeting, patients will sign the informed consent (together with the researcher) and will fill in the first set of questionnaires (shown in Table 1).

After completing the questionnaires, they will be randomized to either the intervention or “care as usual” group. Patients randomized to the intervention group will be provided with tools (as described in the “Intervention” section) and instructions on how to use them. Relevant tools and/or applications will be installed on patients’ mobile phone by the research assistant such that the patients will only have to charge the devices. One day after the face-to-face meeting, patients will be contacted by the research assistant by telephone to ensure that all devices are properly charged and that the system is functional. The full intervention (as described below) will be provided for three months. During this period patients will be contacted weekly by the research assistant to evaluate their progress (whether they are compliant or not with the treatment, they will receive feedback about progress).

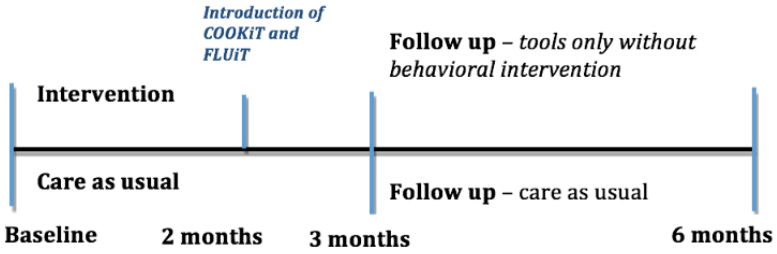
Table 1. Questionnaires.

Questionnaire	No. of items N=177	Construct	Assessment (month)		
			0	3	6
Health Promoting Lifestyle Profile [16]	52	Lifestyle	x	x	x
Do Something Different	45	Behavioral flexibility	x	x	x
World Health Organization quality of life questionnaire [17]	26	Quality of life	x	x	x
Unified Theory of Acceptance and Use of Technology [18]	28	Usability of tools; acceptance of tools; willingness to pay[a]			x
EuroQOL questionnaire [19]	5	Cost-effectiveness	x	x	x
Purpose designed[b]	4	Health care consumption	x	x	x
Patient Health Questionnaire [20]	9	Depression	x	x	x
Generalized Anxiety Disorder scale [21]	7	Anxiety	x	x	x
Distressed Personality scale [22]	14	Type D personality	x	x	x
Client Satisfaction Questionnaire [23]	8	Patient perceived satisfaction[a]			x

[a]These 3 constructs will only be assessed in the intervention group.

[b]Designed by the authors.

Figure 1. Study procedure.



After the three months period, the behavior change component (the DSD program) will be terminated. Hence, between months 3 and 6, patients in the intervention group will only be using the devices that were provided to them at baseline. In addition, to decrease patient burden, some of the tools and/or components will be introduced two months after baseline measurement (see Figure 1 for a schematic overview of the study procedure).

Patients will be instructed to fill in the first set of questionnaires during their face-to-face visit at the hospital. At 3 and 6 months, the patients will receive a link (by email) to access the follow-up questionnaires online with the instruction to complete them within ten working days. If they do not complete the questionnaires within the given time, patients will receive up to three reminder phone calls.

Patients who have been randomized to the intervention group will also be contacted between months 3 and 6 to participate in a qualitative survey (if possible with their partner), which will assess additional properties of the usability and acceptability of the tools.

Study Objectives

Primary, secondary and exploratory objectives will be assessed as described below.

Primary Objectives

Primary objectives of the trial include: 1) lifestyle (eg, sleep, physical activity, nutrition) change and disease management; 2) enhancement of quality of life; and 3) change in behavioral habits and personal flexibility. The assessment of these objectives will be performed using standardized and validated questionnaires (Table 1). In addition, purpose designed questionnaires will be administered to evaluate changes in objective #3. Furthermore, objective measures (ie, data from devices used by the intervention group) will be employed to evaluate changes in lifestyle variables. However, this will be done only within the intervention group since the "care as usual" group will not receive any devices.

Secondary Objectives

Secondary objectives will include: 1) assessment of satisfaction, usability, and acceptance of the intervention (tools); 2) evaluation of the cost-effectiveness of the intervention; and 3) evaluation of changes in health care consumption. Objective #1 will be achieved through validated questionnaires and qualitative interviews with end users and their caregivers (if applicable) and objective #2 will be evaluated using standardized and validated questionnaires only (Table 1). Objective #3 will be assessed using a purpose designed questionnaire.

Exploratory Objectives

The current trial will also cover a number of exploratory objectives where the focus will be on 1) identifying subgroups of patients who might benefit the most from this intervention based on their profile (eg, psychological and/or disease profile); 2) evaluating the effects of the intervention on the electrocardiogram (ECG) data; and 3) gaining more insight in patients sleep patterns and physical activity over a prolonged period of time. These objectives will mainly serve the development of our new hypothesis regarding successful lifestyle change and will be tested using latent class analysis (LatentGold 5.0).

Intervention Versus Care as Usual

Intervention

The Do CHANGE intervention consists of different components, which can be used to provide care that meets patients' needs. All patients included in the intervention group will be provided with the following technology: CarePortal, Moves app, Do Something Different (behavioral program), Beddit, Fitbit, blood pressure monitor, COOKiT, and Vire (the Do CHANGE app). In addition, disease-specific tools will only be provided to those who need them (ie, weight scale and/or FLUiT). Based on patients' primary diagnosis (HF, CAD, or HT) the tools that might be useful will be recommended by the cardiologist. For example, patients with HF will receive a weight scale, since this can assist with monitoring sudden weigh gain, which might be an indication of deteriorating cardiac function. Figure 2 provides a schematic overview of the intervention components. To decrease patient burden, the COOKiT and FLUiT will be introduced to patients two months postbaseline measurement.

Do Something Different

All patients randomized to the intervention group will receive the DSD program, which has previously been developed to change behavioral habits and flexibility [13]. For the current trial, the program has been adapted to cardiac patients' needs and profiles to meet the lifestyle recommendations of this specific population.

The program challenges patients to step out of their comfort zone by sending behavioral prompts (Do's) such as "Explore more today instead of going the same old way, take a different route. Look around, spot ten things you wouldn't see on your usual journey." By breaking the old unhealthy habits, patients are expected to be more flexible and able to change their behavior. The program aims to change behavioral habits, increase flexibility, and subsequently change habits associated

with an unhealthy lifestyle and distress, which are both found to be associated with hypertension and cardiovascular risks. "Typical" behavioral risks have been identified and are addressed within the program. To further adapt the program to patients' needs, all patients, prior to starting the program, will be assessed regarding their daily functioning, distress, and personality such that the Do's will match their personal (unhealthy) habits and challenge them to change.

After assessing patients' personality profile, the intervention will be provided for 11 weeks. Patients will receive a total of 32 Do's messages during this period. Also, 16 ToDo's will be delivered to the patients based on their current functioning (eg, if a patient is not performing sufficient exercise, based on the Fitbit data, he/she will receive a Do based on that). Patients will receive their Do's and ToDo's through the care portal, the Do CHANGE app and via short message service, depending on patients' preferences.

The intervention group will also receive some devices which will help them to monitor their health behaviors and give them some insight into their daily functioning. These devices will include:

CarePortal

The intervention group will also receive a CarePortal (Docobo Ltd), which will be installed at their home. The CarePortal is a clinically certified portable device that will allow the patients to monitor their disease symptoms on a daily basis (ie, by answering a set of predefined questions every day) and send these outputs to a health care professional (cardiologist). The CarePortal will be used to gather ECG data, symptomatic data, blood pressure, and weight on a daily basis. The patient will be able to take the ECG measure at any time. By touching the screen of the CarePortal, the instructions to take the measurement will appear, guiding the patient step by step to take the ECG (which will take 2 minutes). The CarePortal will send the physiological data directly to the cardiologist, who will be able to view them via an online platform and contact the patient if necessary. Also, the patients will see their data (the same data their cardiologist will receive) over a period of 6 months by accessing the online patient portal.

Beddit

To objectively log patients' sleep data and evaluate whether their sleep pattern has changed over time, patients assigned to the intervention group will all receive the Beddit device [16]. Beddit is a certified device to measure sleep, heart rate, and breathing during time spent in bed. The device has been validated [17] and is considered one of the most accurate devices to monitor sleep. For the current trial the Beddit 3 will be used.

Fitbit

Patients' physical activity will be assessed using the Fitbit "Alta HR" [24]. The Fitbit Altra HR is a European Conformity (CE-Marked) activity tracker and can be worn on the wrist. With the Fitbit, patients' step count, the intensity of physical activity, heart rate, calories burned and distance walked will be assessed. Data from the Fitbit will also be used to initiate ToDo's.

Blood Pressure Monitor

All patients in the intervention group will receive the digital blood pressure monitor, UA-767 Plus, which is a CE-Marked medical device. Patients will be asked to measure their blood pressure on a daily basis and log the blood pressure values through the CarePortal.

COOKiT

COOKiT is a smart spatula that can monitor patients' cooking behavior (through a motion sensor which indicates whether the spatula is used) and measure the salinity—for both sodium and potassium—of the food that is prepared. The COOKiT has been developed within Do CHANGE and will be provided to patients two months postbaseline measurement.

Figure 2. Schematic overview of the Do CHANGE intervention components.

Vire (Do CHANGE App)

In order for patients not to feel overwhelmed by the apps and devices that they will have to check every day (if they are interested in their progress), the Vire app (Do CHANGE app) has been developed as the integration point. The Vire app was developed together with end users and health care professionals to provide an overview of the data gathered by all the devices that the patients will be using during the study (eg, Beddit, Fitbit, COOKiT, etc). Through this application, patients will also be able to receive the Do's from the DSD program. In addition, patients will be asked to take pictures (at least 3 per day) of the food which they have consumed each day (via this app). These images will automatically be sent to the health care professional portal (which is also linked to the CarePortal) such that the health care professional will be able to see what the eating habits of the patients are.

Moves App

Moves app is an activity and global positioning system tracking application installed on the mobile phone. The app helps to provide information useful for assessing the behavioral indicators—social opportunity, variety, and activity—used for generating ToDo's. All patients participating in the intervention will have to install the Moves app on their mobile phone.

Additional Devices

Dependent on the primary diagnosis, the patient will decide together with the health care professional which of the following, additional devices they will be using:

FLUiT

Particularly for patients with HF the FLUiT will be recommended. FLUiT is a newly developed device in Do CHANGE which can measure fluid intake. FLUiT is a "smart sleeve" which can be wrapped around a cup, bottle or glass, and will gauge the amount of fluid that it contains. It comprises of an accelerometer and a touch sensor to detect when actual drinking occurs and will log the quantity drank. FLUiT will be provided to patients two months postbaseline measures.

Weight Scale

Patients with HF will be provided with a weight scale to monitor their weight on a daily basis. For the current trial, the Seca Aura 807 model will be used. Patients will be able to communicate their weight on a daily basis by answering the question on the CarePortal.

Patients will all be monitored weekly via telephone to make sure that they are compliant with the program. During these phone calls, patients will also receive feedback on their eating habits.

Care as Usual

Patients who are randomized to the comparator group will receive care as usual. There will be no restrictions on this group. Patients in this condition are allowed to seek additional care and also use other tools, which will enhance their disease and well-being, provided that they report this in the purpose designed questionnaires at follow-up.

Statistical Analyses

Data will be analyzed using SPSS (IBM statistics 22) and LatentGold (Version 5.0) [24,25] statistical package. Continuous and discrete variables will be compared using respectively Students' t-test and Chi-square test. The Linear Mixed Models (LMM) procedure will be performed to evaluate the treatment effectiveness over time. The LMM procedure is similar to linear regression analyses except that in LMM the dependent variable is measured at multiple time points. These analyses will be adjusted for baseline distress levels. If the interaction effects are not significant, only the main effects will be entered in the final model. To examine which patients might benefit from the intervention based on their profiles, Latent Class Analyses will be performed [26,27]. An alpha of .05 will be used to indicate level of significance.

Results

The acquisition of trial data described in this paper is expected to be finished during the summer of 2018. The following data analysis and additional publications are expected in the winter of 2018 and spring 2019.

Discussion

Cardiovascular diseases are the leading cause of death globally, and they pose a significant burden on current health care systems [1,28]. Studies have shown that behavioral factors (eg, physical inactivity, unhealthy diet) account for a large proportion of the disease burden and thus should be addressed (potentially) by health care providers [2]. The Do CHANGE trial aims to address lifestyle behaviors and increase the quality of life of patients with CAD, HF, and HT. By increasing patients' behavioral flexibility and providing them with supportive devices, patients are expected to break with their unhealthy habits and change their unhealthy lifestyle in a sustainable manner.

According to Pine & Fletcher [13] there are multiple reasons why current behavioral programs have not been successful in changing health behaviors. Firstly, our behavior is only partly guided by willpower, hence, most patients fail to use willpower to prevent habitual behaviors (eg, smoking). Secondly, behavior is often guided by everyday environmental cues which trigger certain response (eg, having a beer triggers smoking). Finally, there is a knowledge-doing gap which is demonstrated by the fact that we often know what is good for our health but we fail to do it [12,13]. People tend to live by their habits, which can be stable over time, and seem not to be able to act in accordance with their knowledge. Hence, within Do CHANGE, we aim to increase awareness and knowledge about unhealthy behaviors and at the same time, by using the DSD technique, disrupt habit chains in daily living. This is expected to boost behavioral flexibility and enhance behavior change [15].

A total of 250 patients will be recruited from three pilot sites (Spain, The Netherlands, and Taiwan) and will be randomized to either the intervention group or care as usual. Patients in the intervention group will receive the DSD program (for three months) and will be using devices that will assist them in

behavior change (for 6 months). Patients will be assessed at baseline, and at the third and sixth months.

The current trial might face some challenges due to the international scope and the number of devices that are given to patients. As patient recruitment will take place in Spain, The Netherlands, and Taiwan, cultural differences might affect the outcomes of the trial. Also, due to logistical differences between the pilot sites, patient recruitment will be slightly different per site. Although we do not expect this to have a significant impact on the results, we do consider it as a challenge. Secondly, some patients will receive multiple devices and/or apps that they are expected to use for 6 months. This might be perceived as overwhelming and may potentially lead to lower adherence. However, the current trial implements a behavior change component to the intervention, which aims to increase personal flexibility and enables behavior change. This might lead to more openness for new behaviors (using devices) and thus improve adherence.

Do CHANGE will provide insights into lifestyle changes and the possible mechanism that might drive this change. In addition, it will give valuable information from objective measures about patients' behavioral patterns which, in turn, could serve as input for future studies that will focus on personalized medicine. This information will also provide input for the development of future ecological momentary interventions (real time interventions) that are focused on providing care to patients whenever and wherever they prefer it.

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Conflicts of Interest

MH, EB, JPJ, MW, JD and JW declare no conflict of interest. The Do CHANGE team has received funding for Research and Innovation from the European Union for the current project. Within the consortium, two small and medium-sized enterprises (Docobo, Do Something Different) and one start-up (Onmi – development of COOKiT and FLUiT) are financially supported to develop their products.

Multimedia Appendix 1

Peer-review report.

[PDF File (Adobe PDF File), 302KB - resprot_v7i2e40_app1.pdf]

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Abbreviations

CAD: coronary artery disease
CE-Mark: European Conformity mark
Do CHANGE: Do Cardiac Health: Advanced New Generation Ecosystem
DSD: Do Something Different
ECG: electrocardiogram
HF: heart failure

HT: hypertension
LMM: Linear Mixed Models

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Protocol

Increasing Physical Activity Amongst Overweight and Obese Cancer Survivors Using an Alexa-Based Intelligent Agent for Patient Coaching: Protocol for the Physical Activity by Technology Help (PATH) Trial

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Abstract

Background: Physical activity has established health benefits, but motivation and adherence remain challenging.

Objective: We designed and launched a three-arm randomized trial to test artificial intelligence technology solutions to increase daily physical activity in cancer survivors.

Methods: A single-center, three-arm randomized clinical trial with an allocation ration of 1:1:1: (A) control, in which participants are provided written materials about the benefits of physical activity; (B) text intervention, where participants receive daily motivation from a fully automated, data-driven algorithmic text message via mobile phone (*Coachtext*); and (C) Voice Assist intervention, where participants are provided with an in-home on demand autonomous Intelligent Agent using data driven Interactive Digital Voice Assist on the Amazon Alexa/Echo (*MyCoach*).

Results: The study runs for 5 weeks: a one-week run-in to establish baseline, followed by 4 weeks of intervention. Data for study outcomes is collected automatically through a wearable sensor, and data are transferred in real-time to the study server. The recruitment goal is 42 participants, 14 in each arm. Electronic health records are used to prescreen candidates, with 39 participants recruited to date.

Discussion: This study aims to investigate the effects of different types of intelligent technology solutions on promoting physical activity in cancer survivors. This innovative approach can easily be expanded and customized to other interventions. Early lessons from our initial participants are helping us develop additional advanced solutions to improve health outcomes.

Trial Registration: Retrospectively registered on July 10, 2017 at ClinicalTrials.gov: NCT03212079; https://clinicaltrials.gov/ct2/show/NCT03212079 (Archived by WebCite at http://www.webcitation.org/6wgvqjTji)

(JMIR Res Protoc 2018;7(2):e27) doi:10.2196/resprot.9096

Introduction

There is consistent evidence that identifies poor dietary choice and physical inactivity as major contributors to death in the US and worldwide [1-3]. Physical activity promotion and adverse health behavior prevention strategies can improve health and reduce subsequent disease for individuals and populations [4]. Despite this evidence, only a fraction of the U.S. population adheres to the recommended guidelines [5]. Behavioral interventions for lifestyle modification (walking) have been successful in research settings [6], but translating complex research interventions, particularly in physical activity, into practice remains problematic [7,8].

Recent advances in hardware technologies, statistical methods, big data processing, and cloud-based computing have resulted in artificial intelligence technologies that may offer efficient, low cost and potentially scalable solutions to deliver individualized behavioral interventions to at-risk populations. Further, the development of intelligent technology solutions via ecological momentary assessment provides unique opportunities for behavioral intervention at the individual level, which may increase adherence and promote long-term lifestyle change after the intervention is completed. To test the utility of such technology, our team constructed artificial intelligent agents (IA) to help cancer survivors become more active throughout their daily routines, via a technology-driven clinical trial designed to deliver affordable, scalable, easy to adopt, individualized behavioral interventions. Currently, the IA approach is being tested in a three-arm randomized trial: The Physical Activity by Technology Help (PATH). The trial compares the two technologies—a voice activated intelligent agent and a more traditional intelligent text messaging—compared to a self-driven traditional behavior change (control). The aim of this pilot study is to assess the preliminary effect of a 4-week intervention by different technological approaches to increase daily physical activity, defined as walking (eg, 10,000 steps per day), among overweight and obese cancer survivors, with a special interest in under-represented African American women, in the state of Maryland. In addition, we developed an innovative approach to identify study candidates from review of Epic Electronic Medical Records (EMR). While this IA is specific to cancer survivors, the methods and technology design may be replicated in the general population.

Methods

Design

This is a three-arm single center pilot randomized trial with allocation ratio of 1:1:1. The arms are: (A) control, in which participants are provided with written materials about the benefits of physical activity; (B) text-messaging intervention, where participants receive multiple motivational messages from an automated, data-driven algorithmic text message program via mobile phone (*Coachtext*); and (C) voice-assist intervention, in which participants are provided with an in-home autonomous Intelligent Agent using data driven Interactive Digital Voice Assist on the Amazon Alexa/Echo (*MyCoach*).The trial duration is 5 weeks – a one-week run-in phase to establish baseline physical activity, followed by 4 weeks of intervention (Figure 1). Physical activity outcomes are captured via wearable sensors (Fitbit Charge 2 HR). Table 1 includes a schedule of enrollment, interventions, and assessments.

Figure 1. Physical Activity by Technology Help (PATH) study design.

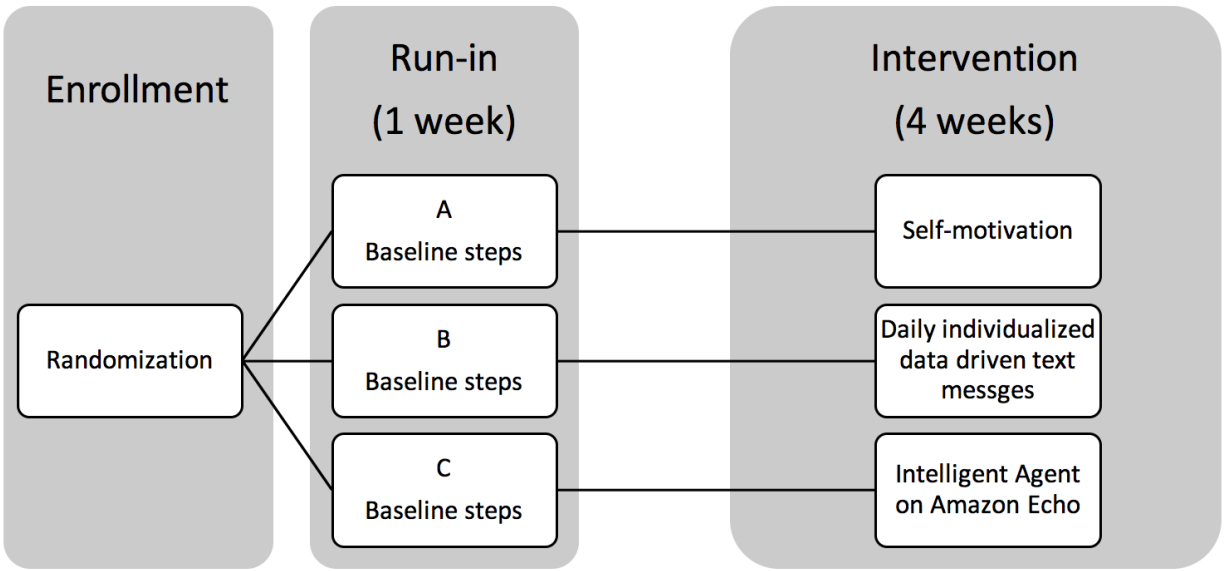


Table 1. Physical Activity by Technology Help (PATH) schedule of enrollment, interventions, and assessments.

Study's activities	Study period							
	Enrollment	Allocation	Postallocation					Close-out
	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	*TBD*
Enrollment								
Eligibility screen	X							
Informed consent	X							
Allocation and wearable installation	X	X						
Alexa Installation			X					
Interventions								
Control				X	X	X	X	
Coachtext				X	X	X	X	
MyCoach				X	X	X	X	
Assessments								
Individual characteristics	X	X						
Baseline physical activity			X					
Outcomes				X	X	X	X	
Analysis and reporting								X

Participant Inclusion and Exclusion Criteria

Participant inclusion criteria are: (i) adult cancer survivors residing in the State of Maryland who have had one or more of the cancers of interest (breast, prostate, colon, lung, cervical, oral, melanoma); (ii) completed active cancer treatment (surgery, chemotherapy and/or radiation) at least three months prior to enrollment, with the exception of anti-hormonal therapy; (iii) overweight or obese (BMI 25 and above) status; (iv) internet access at home via Wi-Fi; (v) access to an Android or Apple smartphone; (vi) ability to perform low-intensity daily steps (walking), with physician approval; (vii) less than 150 minutes per week of physical activity reported during the previous four weeks; (viii) willingness to wear an accelerometer; and (xi) willingness to consent and accept randomization. Due to disparities of cancer survivorship among minority groups [9,10], the study is focusing the recruitment activities to target African American cancer survivors.

Exclusion criteria are: (i) reported engagement in, or more than, 150 minutes per week of physical activity during the previous four weeks (The Godin-Shephard Leisure-Time Physical Activity Questionnaire) [11-13]; (ii) plans to relocate or travel during the course of the intervention; (iii) stage 4 cancer diagnosis; (iv) current use of a physical activity tracker or engagement in a structured physical activity program; (v) participation in another study that may interfere with our outcome of interest; (vi) an unstable mental condition that would prevent performing the study activities and requirements; and (vii) current or planned pregnancy.

Innovative Recruitment

Participants are recruited using both passive and active strategies. In the *passive strategy*, the study team distributes flyers at the Johns Hopkins outpatient oncology clinics, patient education rooms, survivorship clinics, and survivorship meetings to spread study awareness among clinic staff, particularly nurse educators and managers. With the *active strategy* for recruitment, the Epic reporting function is used to generate patient lists of those who match the screening criteria at selected Johns Hopkins clinics in Maryland. Screening for existing cancer patients takes place at the outpatient clinics, by specific providers and on follow-up weekly appointments only; potential participants must have a prior diagnosis of a cancer of interest, a BMI of 25 or above, and reside in the state of Maryland. Once a list is generated, the study team actively reaches out to each patient after the outpatient clinic visit to provide them with study information. All candidates identified by either strategy are included in an electronic Clinical Research Management System (CRMS) linked to the EMR. The study coordinator updates the candidate's status regularly based on candidate eligibility, consent, and enrollment type. Reasons for ineligibility are also recorded in CRMS. Data on the number of eligible patients, along with reasons for not enrolling can be captured and reported to the institution's Institutional Review Board (IRB). Weekly automated reports can be generated from CRMS to track enrollment and pending statuses.

Once eligibility is determined, an IRB-approved consent designee obtains an IRB-approved written informed consent form (ICF) in the outpatient clinic or at the study office. A signed and dated IRB-approved ICF is documented in a secure participant study file prior to initiating study-related procedures. As part of the consent process, the study team 1) informs each participant of study procedures and requirements and allows sufficient time for the individual to decide whether to participate in the study; 2) answers questions about the details of the study; and 3) ensures that the ICF is approved by the IRB when an amendment to the study protocol is made. Participants are free

to withdraw consent for participation in the study at any time, without affecting their current or future treatment.

Sample Size

The investigators designed this study to compare: (i) a dialogue Intelligent Agent, using data driven Interactive Digital Voice Assist on Amazon Alexa/Echo speaker (*MyCoach*) in assisting participants in increasing their physical activity, with (ii) a text messaging intervention and (iii) a written information/self-motivation intervention. To detect at least a 2000 step difference in means at a SD of 1800 steps/day (the standard deviation of the 28-day daily sample mean is 1800 steps), with a 2-sided alpha of 0.05, and power of 0.8, or 80, 13 participants are required per arm (39 participants total (with Bonferroni correction of 2 comparisons)). To account for intention to treat and possibly per-protocol analysis, the study team subsequently added an additional participant to each arm; therefore, 14 participants are being recruited per arm, for a total of 42 participants. Also, to account for dropout, the protocol also allows the addition of patients to replace those who dropout due to a condition/illness that prevents them from participating in the trial during the run-in period.

Randomization

Participants are randomized with an allocation ratio of 1:1:1 to the control self-driven arm (Group A), *Coachtext* (Group B), or *MyCoach* (Group C). Once a participant signs the IRB approved ICF, the randomization procedure is conducted. Since the study is recruiting cancer survivors, the team collects data regarding certain prognostic factors that may affect physical performance and thus ability to perform physical activity, including 1) types of cancer; 2) age; and 3) BMI. To attenuate the impact of such factors the study team is using Stratified Permuted Block Randomization, which generates strata by sex, age group, and BMI, then assigns a unique number for each block. At randomization, the PI or study coordinator assign strata by participant variables, then assign the arm after generating a random number out of all possible blocks using random.org. Subsequent assignment is linked to the strata in which the new participant belongs. If the prior block under the selected strata is completed or not started, a new block is selected/opened using random.org. Only the principal investigator (PI) and the study coordinator are designated to conduct the randomization procedure. The PI or the study coordinator report the randomization procedure to the participant orally and record it on the randomization sheet. The study data analyst is blinded to the random assignments.

Intervention

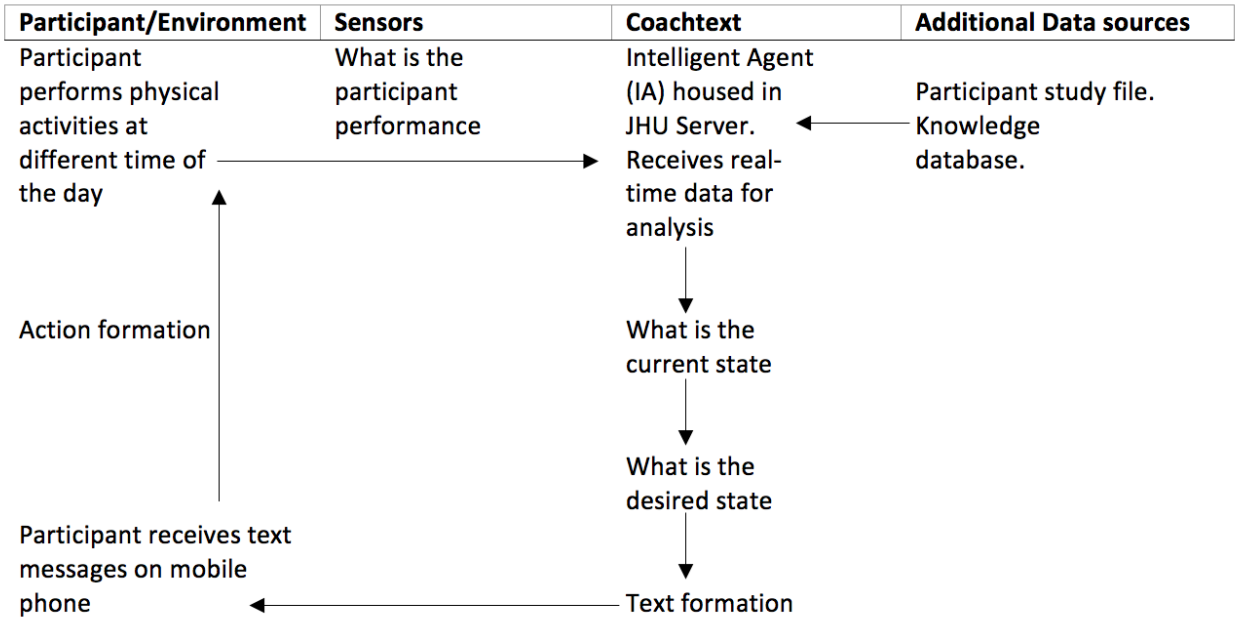
Those assigned to the control arm (A) receive educational materials and are advised to increase physical activities to 10,000 steps per day. Participants in the control arm receive National Cancer Institute (NCI) printed educational materials providing summary evidence about the benefits of exercise for cancer survivors [14]. While the publication by NCI is meant to encourage participants to become active, it does not provide specific goals or a structured program. As in the other arms, participants in the control arm are expected to use walking as a recommended activity type. Participants in this arm receive the same activity tracker (Fitbit Charge 2 HR) and its companion mobile application as those in the other two study arms.

Participants in the *Coachtext* arm (B) receive remote coaching using personalized automated data driven text messages, a system designed and developed by the study team that provides text messages to the participant's cellphone. Those enrolled in this arm provide their cellphone number and complete an online questionnaire about their daily routine, pet ownership, and household information to establish their text messages preferences. The text messages are delivered, based on participant preferences, three times per day for four weeks after the seven-day run-in (baseline data collection). Each message is composed and pushed based on each participant's real time physical activity performance, taking into account the prerecorded preferences and household information. A sophisticated algorithm reads the participant's data in the server, then mixes it with the hourly step performance captured by the wearable sensor transmitted to the server, and generates a personalized coaching message. The *Coachtext* algorithm has a flexible goal-based design using data to support its choice on how and when to push a message. The *Coachtext* incoming and outgoing data as well as the algorithm are housed in a server approved by the Institutional Review Board. Figure 2 illustrates the *Coachtext* design.

Coachtext is completely automated; however, the study investigators can intervene if needed. This is a precautionary measure that was included in case of system failure or errors, and/or to update the knowledge library of *Coachtext* database. However, no such events have been recorded so far, and no knowledge was changed or newly generated. The study team designed and developed the message content after extensive literature reviews and expert opinions. The messages are formulated based on health behavioral theories with a focus on feedback about actual performance vs expected and habit formation to reach expected performance [15]. Health belief theory is also integrated by offering contents to build knowledge about the benefits of exercise for cancer patients [16]. In addition, the study investigators can check a daily dashboard plotting each participant's physical activities. The study PI also receive notification in case the system failed to generate or deliver any message on time. As of November 2017, no such event has been recorded. An example of the generated messages includes:

> *preferred name>, you were too inactive yesterday. You got <#step_count_yesterday steps>. Your goal is 10,000. How about taking a stroll today with <dog_name>. Aim for 10 minutes or more. This will not only be good for you, but is essential to <dog_name's>good health*

Figure 2. *Coachtext* architecture. JHU: Johns Hopkins University.



The third arm is *MyCoach* (C), a conversational Artificial Intelligent Agent delivered via the Amazon Echo home speaker. The investigator chose the Amazon Alexa platform because it has a developer kit that can be utilized to build one's own voice skill. The study team designed and developed *MyCoach* with knowledge representation, planning, learning, perception, and natural language processing (NLP) using the Alexa developer kit. *MyCoach* uses a sophisticated learning algorithm to enable its functions, and its algorithm uses data from different sources, including, but not limited to the: patient study file, physical activity wearable sensor, Echo home spatial microphones, knowledge library, Amazon music library, intents & responses library, user's calendar, geo/location data, National Weather Service UV index, and more. *MyCoach* is delivered to the participant through an Amazon Echo speaker [17]. Amazon Alexa was used as an NLP engine to receive the participant's requests/questions (known as the *Intent*) and the Alexa voice to deliver the answer/advice/coaching (*Response*). In addition, the Alexa companion cellphone application is used to deliver visual responses if needed. The study team designed the *MyCoach* user experience to mimic health coaches. Therefore, the user-initiated request/Intent is the core functionality of *MyCoach*, and no advice/health tip/comments is delivered by *MyCoach* unless the participant requests *MyCoach* advice.

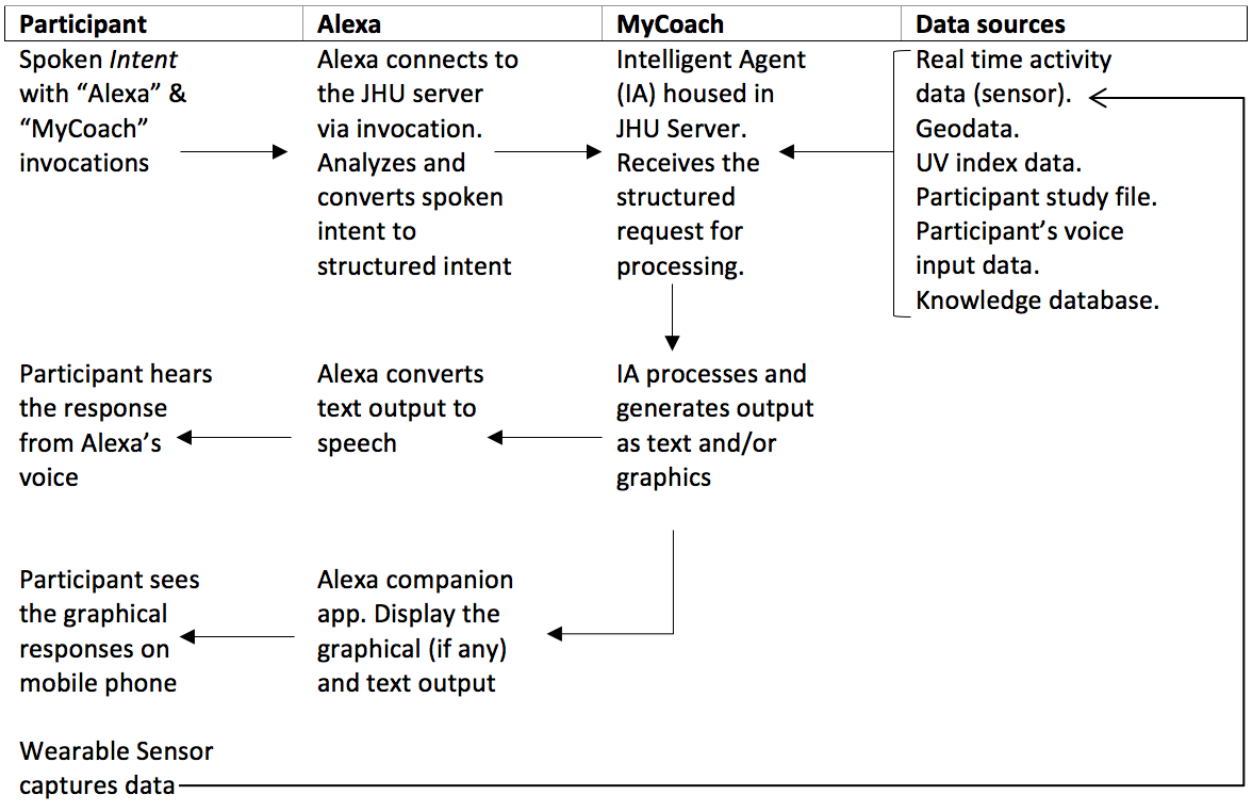
The *Intent* has two triggers words (*Invocations*). The first *Invocation* to ignite/turn on Alexa Echo device is "Alexa," the second, "My coach," is to alert Alexa that this intent needs to be routed to the *MyCoach* server, within the Johns Hopkins University firewall, to process and generate outputs. For example, the user will say "Alexa, ask My Coach...", etc. The Alexa NLP engine is used to process the user's spoken intent into structured representation. The structured request is routed to the *MyCoach* server for processing. During processing, a complex algorithm utilizes multiple data sources and real-time wearable sensor readings to generate a *Response*, which could be a text and/or a graphical response. The servers push the text Response(s) to Alexa, and the graphical responses to the companion app on the user's cellphone. Alexa converts the text to speech and voices it through the Echo speaker at the user's home (see Figure 3).

MyCoach performs a variety of functions. For example, it offers feedback, assists in formulating habits, provides reminders and alarm, informs the user if he/she need UV skin protection before heading outside, provides health tips and knowledge, and more. Like the participants in *Coachtext*, participants in the *MyCoach* arm also experience a question session to personalize coaching, but in voice conversation format with Alexa/ *MyCoach***.** All functions are operated by voice, and since hundreds of ways to state the same intent were programmed by the study team to accommodate each different user's style, no prior training is needed to request each function. An example of intents is as follows:

> *Alexa, I'm planning to go out for a walk. Ask my coach if I need sunscreen.* [User]
>
> *Alexa, ask my coach, "How is my progress so far?"* [User]
>
> *Alexa, I'm not making good progress; ask my coach for health tips to help me become more active.* [User]

The study utilized Amazon's prebuilt user-machine interaction data to track participant utilization of *MyCoach*. Screen shots of the data visualization dashboard used to track interaction by type, time, and intent are provided in Multimedia Appendix 1.

Figure 3. *MyCoach* architecture. JHU: Johns Hopkins University.



Both interventions (B) and (C) have personalized and tailoring components. Each participant completes a questionnaire about personal family status, habits, pet ownership, work status, and preferred schedule to wake up, eat, work, and relax. All of this information, plus the individual physical performance data, are used to personalize and tailor each individual experience with both interventions. All participants are motivated to increase their physical activities to at least 10,000 steps per day regardless of the arm assignment. Participants in all arms are able to keep the Fitbit Charge 2 HR as a gift from the study team at the end of the trial.

The study team designed each intervention for a specific population, cancer survivors, to best fit their needs, thus the current intervention design is only suitable for such a target population. However, the innovative study design, operations, and technology development make this study easily adaptable for the more general population with slight design modification(s).

Blinding

Due to the nature of the study interventions, study participants are not blinded. Data for the principal outcomes, however, are collected using sensors. Therefore, the study data analyst is blinded during data collection and during analysis.

Study Outcomes

The aim of this study is to assess the effectiveness of different technological approaches in increasing physical activity among overweight and/or obese cancer survivors captured by wearable sensors (Fitbit Charge 2 HR). The primary outcome is the percent change in daily steps from the 1-week run-in to the end of the 4-week intervention period. The data for the primary aim is collected in real-time and transferred simultaneously to the computational server of the Johns Hopkins University via an application programming interface (API) that directly transmits the data from the user's wearable device to the server. Participant wear-time is validated using the heart rate sensor readings on a minute-by-minute basis.

In addition to the primary outcome, the study will examine the following secondary outcomes: 1) total number and duration of activity bouts (defined as 3 minutes or more of uninterrupted activity); 2) fragmentation indices (counting transitions between active/inactive periods) and variability indices (counting the magnitude of transitions between different levels of physical activity); 3) daily diurnal patterns of activity that model patterns in minute-by-minute profiles; and 4) weekly and daily trends of total steps. Levels of physical activity intensity will be defined using each participant's personalized heart rate reserve.

Privacy and Safety Aspects

The Johns Hopkins School of Medicine IRB reviewed the protocol, information technology (IT) solutions, safety, and security of the data collection & storage, and approved the study (# IRB00113882). The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (SKCCC)/The Clinical Research Review Committee (CRC) also reviewed the protocol and found that this study poses minimal risk to the participants, and assigned Minimum Risk category to this study. SKCCC/CRC recommended forming Data and Safety Monitoring Board for this study & SKCCC/CRC will conduct random audits. To ensure the safety and security of participant information, the *Coachtext* and *MyCoach* were programmed on the Johns

Hopkins University server, avoiding the use of commercial servers by Amazon Inc. for public developers. Although the commercial-use free Amazon Web Services server is available with Alexa, it is not compliant with the institutional requirements. However, the study team connected Amazon Echo and Alexa's voice to the server behind the Johns Hopkins University firewall to protect the user's privacy. The study also provided a Privacy Policy Statement for the *MyCoach* for the participant who will enable the skills on their Echo devices. This statement explains how data will be shared, stored and processed by Johns Hopkins. The written consent form and the electronic sign-in for each study arm also provide clear descriptions of what data will be collected from each individual and the manner in which it will be used. The study team will assure participants that all automated data collection processes will be stopped after the participant finishes the program or if he/she decides to withdraw from the study. To add another layer of security, *MyCoach* is enabled only for the study participants and not open for public users. Data from the wearable sensors are prescheduled to transfer to our secure server only during the study period. Following the end of the study, the transfer is halted automatically. Regardless of study arm assignment, and in addition to written consent, all users need to complete an online data transfer agreement using their wearable sensor credentials.

Statistical Analyses

As the primary outcome variable is the 4-week change from the baseline in the average number of steps per day, the primary analysis will use a two-sample t-test to compare each active intervention arm with the control arm based on intent-to-treat strategy. A Bonferroni correction will be used to adjust for multiple comparisons.

For the secondary outcomes (activities bouts, fragmentation, and patterns), a linear regression model will be fitted for the 4-week change from the baseline in the number of steps and duration of activity bouts each day. The independent variables include the baseline number of steps, study arm (modeled by two dummy variables for the two active treatment arms, and the control arm is treated as reference group), and any potential baseline confounding factors. Poisson regression will be used to analyze the total number of activity bouts, fragmentation indices, and variability indices. The independent variables include baseline number of steps, study arm, and any potential baseline confounding factors as the independent variables. In all analyses, data will be properly transformed to fit the model assumption before regression analysis. Although missing data is not anticipated to be a challenge, small amount of non-wear time for charging, bathing, etc. will have minimal effects on the primary study aim since it depends on the average steps across the intervention period. Since Stratified Permuted Block Randomization is being employed, we will consider minimization to balance interventions simultaneously over several prognostic factors to ensure equal distribution across arms. To date nearly 80% of the target population has been enrolled, and only one participant stopped wearing the tracker one day a week for religious reasons.

Discussion

Study Rationale

This study designed, developed, and launched a clinical trial to investigate the effect of novel emerging technologies to assist cancer survivors to become more active in their daily lives. The study uses innovative technology and methods to apply autonomous artificial intelligent agents as an intervention. This is an affordable, scalable, and easily deployed personalized and tailored intervention that has the potential to transition from the research setting to general use. It is important to offer a scalable and affordable solution that can assist cancer survivors to become more active. Given the wide general utility of the technology and applicability of the outcome of interest, this approach may also be applicable to the general population with slight modification of the intervention and testing in a larger population study.

The trial operation is minimalist in design and effort. Recruitment activities and enrollment were designed and developed with a focus on low cost and efficiency. The study team developed innovative prescreening in the EMR environment, with remote intervention deployment and data collection processes. The entire trial is operated by the PI and the study coordinator. Data collection processing is autonomous and no interference from the study team or participants is needed. The data flow on a minute-by-minute basis to a structured database for real time analysis allows decision support for the artificial intelligent agent. The same data will be used subsequently to assess the effect of the intervention on the primary outcome. The trial's recruitment is currently active and eligible consented patients have been enrolled.

Intelligent Agents (IA) are not new. Stuart Russell and Peter Norvig researched this topic extensively in their leading textbook in Artificial Intelligence—Artificial Intelligence: A Modern Approach [18]. Russell and Norvig state that the core behavior of an agent is goal-directed and therefore they refer to agents as "Rational Agents". These agents can be classified into five classes: simple reflex agents, model-based reflex agents, goal-based agents, utility-based agents, and learning agents [18]. Amazon Alexa and our agent (*MyCoach*) use a combination of different agent classes. The study team chose to use different classes to adapt to the user's intents.

Artificial intelligence (AI) has promising wide applications in translational research. Enablers to use such technologies, including tools and developer kits, are widely available for interested researchers, while codes libraries are shared among most researchers and powerful platforms are widely used in the form of mobile devices and home speakers. The current study provides insight beyond the target outcomes by its efficient operation. The entire study is operated by 1-2 persons. This is possible because most of the study components, including data collection, have been automated or enhanced by technology solutions. Even the start of the intervention is automated. The study team also automated the instructional communication via scheduled automated emails based on each participant enrollment date. The written consent process is still in paper format, a requirement of the University IRB.

In summary, the current trial demonstrates a very effective and efficient model for intervention that holds the potential to substantially change the way interventions are applied, monitored, and analyzed . The study has been design, developed and launched within the projected cost and timeline. However, challenges still exist. The main challenge for adopting such technologies include understanding the technology's limitations; how behavioral theories can be adapted to human-machine interaction; limited funding sources for such research; privacy concerns; and the limited aggregable performance metrics for such technologies. Developing such interventions requires in-depth knowledge of AI and their operations, specifically programming. Most of the available behavioral change theories have been developed without consideration of human machine interaction and the potential limitations of such interactions. There are also still concerns about the stability and confidentiality surrounding AI in general, particularly in a health care setting; thus, there is no standardization for adopting AI technologies as there is for traditional interventions. As a result, the design concept for adapting the health coach functions to the AI machine was not straightforward. The user experience aspect was not traditional since no interface currently exists, and voice detection was the main interaction method. It was difficult to orchestrate different components, devices, and algorithms and to develop a secure environment/platform for transferring data within the requirements of the IRB. As a result, it was necessary to build our own server and connect all devices and databases via secure APIs. Further, the study team also overcome the security concerns by building creative solutions including transferring the decision of data transmission and devices communication into the hands of the participants in a form of electronic permissions and unique credentials. Lessons from this study are already helping to develop a more advanced Intelligent Agent to tackle common chronic conditions that rely on self-management and coaching and provide evidence that advancement in technology can be an agent of change to improve health outcomes.

Trial Status

The study was approved as IRB #IRB00113882 on March 16, 2017. Recruitment activities were initiated in late April 2017. We started with targeted advertisements throughout Johns Hopkins oncology outpatient clinics. We also started active prescreening on Epic EMR to pre-identify participant prior to clinical encounter. The protocol went through a revision to refine the definition of physically active in the inclusion criteria using the American Heart Association definition of physically active. The recruitment activities are expected to last until March 2018. As of January 2018, we screened 75 patients and 39 are already enrolled in the study.

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Conflicts of Interest

VS received research funding from Pfizer and Novartis. SM has served on scientific advisory boards for Quest Diagnostics, Sanofi/Regeneron, Amgen, and Akcea Therapeutics. He has received research support from the PJ Schafer Cardiovascular Research Fund, David and June Trone Family Foundation, American Heart Association, Aetna Foundation, Maryland Innovation Initiative, CASCADE FH, Nokia, Google, and Apple. The rest of the authors declare no potential conflicts of interest.

Editorial notice: This randomized study was only retrospectively registered. The editor granted an exception of ICMJE rules for prospective registration of randomized trials because the risk of bias appears low and the study was considered formative. However, readers are advised to carefully assess the validity of any potential explicit or implicit claims related to primary outcomes or effectiveness, as retrospective registration does not prevent authors from changing their outcome measures retrospectively.

Multimedia Appendix 1

Dashboard for tracking user machine interaction.

[PDF File (Adobe PDF File), 62KB - resprot_v7i2e27_app1.pdf]

Multimedia Appendix 2

Detailed peer review reports and responses by the scientific review committee at the SKCCC.

[PDF File (Adobe PDF File), 1MB - resprot_v7i2e27_app2.pdf]

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Abbreviations

AI: artificial intelligence
API: application programming interface
CRC: Clinical Research Review Committee
CRMS: clinical research management system
EMR: electronic medical records
IA: intelligent agents
ICF: informed consent form
IRB: Institutional Review Board
IT: information technology
JHU: Johns Hopkins University
NCI: National Cancer Institute
NLP: natural language processing
PATH: Physical Activity by Technology Help
PI: principal investigator
SKCCC: Sidney Kimmel Comprehensive Cancer Center

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Protocol

Evaluating the CARE4Carer Blended Care Intervention for Partners of Patients With Acquired Brain Injury: Protocol for a Randomized Controlled Trial

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Abstract

Background: Support programs for partners of patients with acquired brain injury are necessary since these partners experience several unfavorable consequences of caregiving, such as a high burden, emotional distress, and poor quality of life. Evidence-based support strategies that can be included in these support programs are psychoeducation, skill building, problem solving, and improving feelings of mastery. A promising approach would seem to be to combine web-based support with face-to-face consultations, creating a blended care intervention.

Objective: This paper outlines the protocol of a randomized controlled trial to evaluate the CARE4Carer blended care intervention for partners of patients with acquired brain injury.

Methods: A multicenter two-arm randomized controlled trial will be conducted. A total of 120 partners of patients with acquired brain injury will be recruited from five rehabilitation centers in the Netherlands. The blended care intervention consists of a nine-session web-based support program and two face-to-face consultations with a social worker. Themes that will be addressed are: giving partners insight into their own situation, including possible pitfalls and strengths, learning how to cope with the situation, getting a grip on thoughts and feelings, finding a better balance in the care for the patient with acquired brain injury, thinking about other possible care options, taking care of oneself, and communication. The intervention lasts 20 weeks and the control group will receive usual care. The outcome measures will be assessed at baseline and at 24- and 40-week follow-up. The primary outcome is caregiver mastery. Secondary outcome measures are strain, burden, family functioning, emotional functioning, coping, quality of life, participation, and social network.

Results: The effect of the intervention on the primary and secondary outcome measures will be determined. Additional a process evaluation will be conducted.

Conclusions: The findings of this study will be used to improve the care for partners of patients with acquired brain injury. Barriers and facilitators that emerge from the process evaluation will be used in the nationwide implementation of the intervention.

Trial Registration: Dutch Trial Register NTR6197; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6197 (Archived by WebCite at http://www.webcitation.org/6xHBAxx0y)

(JMIR Res Protoc 2018;7(2):e60) doi:10.2196/resprot.9108

KEYWORDS

caregivers; brain injuries; internet; telemedicine; randomized controlled trial

Introduction

Caregivers of patients with acquired brain injury (ABI), such as stroke and traumatic brain injury, often experience high levels of burden, which profoundly affects their physical and psychosocial well-being [1-5]. About half of the caregivers experience anxiety and emotional distress, and 65% report health problems and a decline in social life with high levels of strain [6]. The majority of caregivers of patients with ABI reporting psychological distress are the partners of the patients [7]. Among partners of patients who were admitted for inpatient rehabilitation, 80% reported poor quality of life one year after stroke [3]. It is especially the return home after inpatient rehabilitation which appears to be a major hurdle for patients and their caregivers [6].

Support programs for partners of patients with ABI are necessary and should be initiated as early as possible after discharge from the rehabilitation facility so partners are better prepared for their new role as caregivers at home [8]. Several reviews show that evidence-based support strategies such as psychoeducation, problem-solving therapy and skill building are effective components of interventions [9-13]. Additionally, support programs should address condition-specific issues, such as the cognitive, emotional, and personality changes of the patient [1]. Furthermore, interventions to increase feelings of mastery also seem important, since mastery can protect against the stressors of caregiving and improve caregivers' well-being [14,15].

Participating in a support program can be challenging for partners of patients with ABI, since being a caregiver already takes up much time and energy [16], in addition to everyday activities such as having a job. Travelling to a rehabilitation center to attend a support program can be experienced as requiring too much time and energy. Web-based interventions may therefore be more suitable, since partners can participate at any time from any location with internet access, and they can keep their own pace [17]. Caregivers in various populations have reported being satisfied and comfortable with web-based interventions [18]. Previous research has shown that web-based interventions can improve family functioning, psychological well-being, coping, and quality of life among caregivers [18,19]. Furthermore, web-based interventions for caregivers are feasible [19] and can save costs [18]. A disadvantage of web-based interventions, however, is that of the higher drop-out rates [20]. Participants of web-based interventions report that adherence can be increased by combining web-based interventions with face-to-face consultations, creating a blended care intervention [21,22]. Another advantage of combining web-based interventions with face-to-face consultations is the opportunity for personalized treatment, elaborating on specific personal problems which cannot be addressed through predefined responses but require input from professional caregivers [22].

This study aims to evaluate the effects and process of a blended care intervention, which includes psychoeducation, skill building and problem solving, on feelings of mastery in partners of patients with ABI. Our hypothesis is that the intervention group will have increased feelings of mastery compared to the control group. This paper describes the study protocol.

Methods

Design

This study is a multicenter two-arm randomized controlled trial investigating the CARE4Carer blended care intervention in addition to usual care, in comparison to usual care alone. The Medical Research Ethics Committee of the UMC Utrecht confirmed that the Dutch Medical Research Involving Human Subjects Act (WMO) does not apply to this study. The Dutch Agreement on Medical Treatment Act (WGBO) and Dutch Personal Data Protection Act (Wbp) do apply. All participating rehabilitation centers have approved the study protocol. Written informed consent is obtained from each participant. The study is registered in the Dutch trial register as NTR6197, registered 2 November 2016.

Participants

The study population consists of partners of patients with ABIs such as stroke, subarachnoid hemorrhage, traumatic brain injury, postanoxic encephalopathy (ie, acute onset, no degenerative neurological diseases). Participants are recruited from five rehabilitation centers in the Netherlands (Adelante, Heliomare, Reade, Sint Maartenskliniek, Tolbrug). Inclusion criteria for both patient and partner are: (1) 18 years or older, and (2) written informed consent. Additional inclusion criteria for the patient are: (1) having an ABI, (2) independent living in the community before the ABI, (3) having been admitted for inpatient rehabilitation, and (4) being scheduled to be discharged home after rehabilitation. Additional inclusion criteria for the partner are: (1) being one of the patient's primary caregivers, and (2) being the patient's partner. Exclusion criteria for the patient are: (1) neurodegenerative or progressive ABI and (2) insufficient command of Dutch, clinically judged by the health care professionals. Exclusion criteria for the partner are: (1) insufficient command of Dutch, clinically judged by the health care professionals, (2) being unable to work on a computer, and (3) having no internet access. Partners can only participate when the patient signs informed consent. If the patient decides to stop study participation, the partner can continue to participate, but data of the patient will not be used in the analyses.

Procedure

The participants are recruited during regular consultations with a social worker during inpatient rehabilitation. The social workers, who are trained in the treatment protocol, check the eligibility criteria and explain the study. Both partner and patient receive an information letter and an informed consent form and

are asked whether the researcher may contact them. After a few days, the researcher calls the partner and asks if there are any questions about the study. When both partner and patient agree to participate, they sign their informed consent forms and return these to the researcher by mail. Reasons for exclusion and reasons to decline research participation are recorded. Randomization takes place after the informed consent forms have been received.

Demographic factors of the partners are recorded at baseline and those of the patients are retrieved from the patient records. The outcome measures for the partners are assessed at baseline, postintervention and at follow-up, except for care consumption, which is not assessed at baseline. The outcome measures for the patients are assessed at baseline and at follow-up. Questions regarding process evaluation are presented after the intervention. All questionnaires are administered through the same platform, which also provides the web-based support program. See Figure 1 for the flow diagram.

Randomization

Participants are randomly assigned to either the group receiving the CARE4Carer intervention or to the usual care control group, using an online randomization tool **.** Participants are stratified by rehabilitation center, and block randomization with two block sizes (2 and 4) is used to achieve a balance across the experimental and control groups. The block size and order of allocation are randomly chosen at the beginning of each block. This minimizes the risk of predicting group assignment and keeps the researcher blinded to the randomization process. Randomization takes place before the baseline measurement to be able to assign a certain route to the partner in the online platform. Partners in the intervention group automatically gain access to the web-based support program directly after completing the baseline measurement, which is only possible when this route is set beforehand.

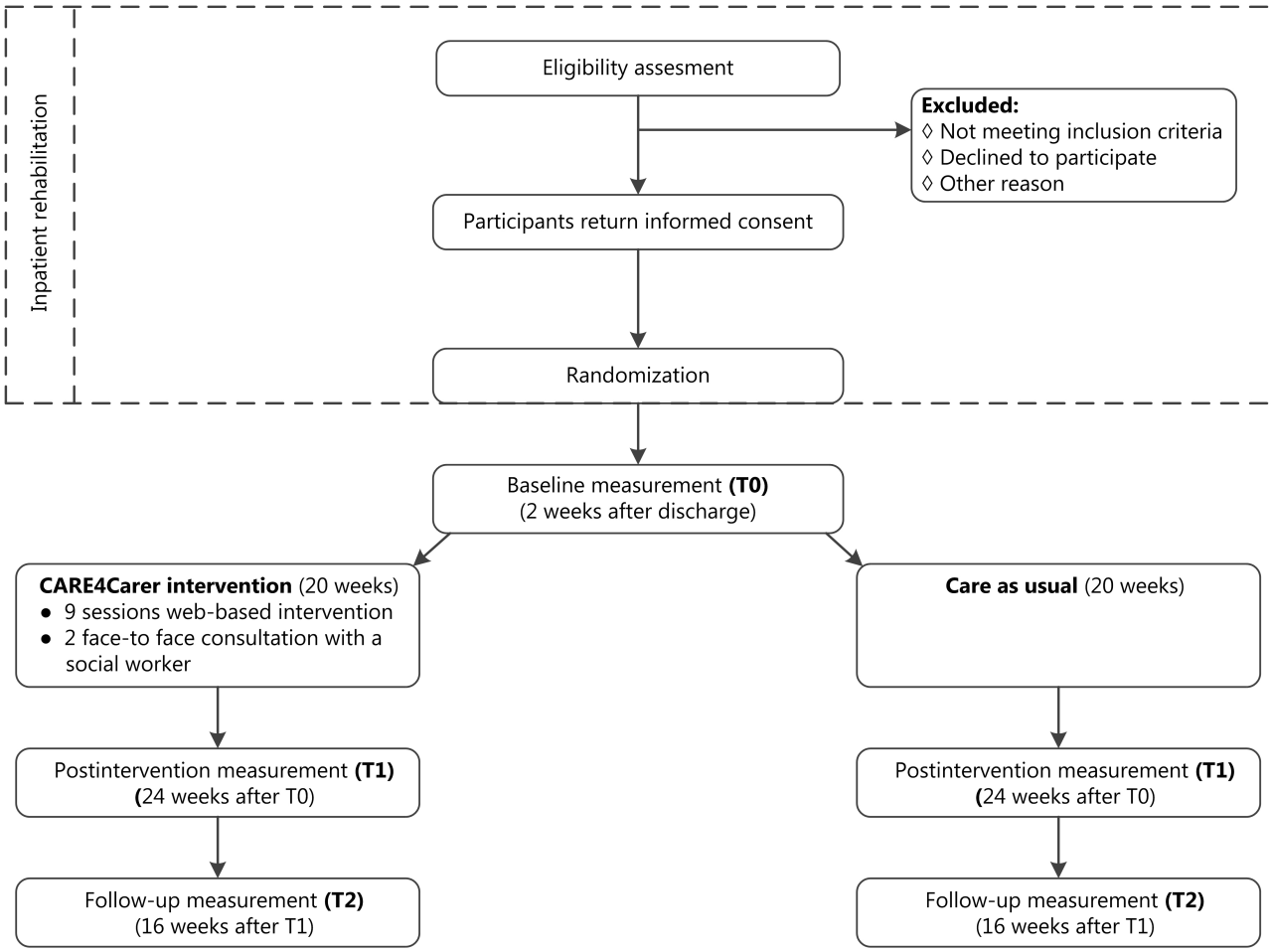
CARE4Carer Intervention

The CARE4Carer intervention starts two weeks after the patient is discharged from inpatient rehabilitation and consists of a web-based support program and face-to-face consultations with a social worker.

Web-Based Support Program

The intervention program, called Brain injury – Moving forward together (in Dutch: “Hersenletsel – hoe samen verder?”), is a web-based support program for partners of patients with ABI. The program comprises 9 sessions, described in Textbox 1. It is based on an existing support program, which was developed by Minddistrict and Heliomare Rehabilitation Centre. They used principles of cognitive behavior theory [23] and solution-focused therapy [24], as well as expert input from social workers, psychologists, and caregivers of patients with ABI.

Figure 1. Flow diagram of the trial.



We have modified this program to tailor it specific to partners of patients with ABI. We have also carried out a pilot study in which three partners of patients with ABI and a member of the patient association tested and evaluated the program. This has led to several further adaptations. Themes within the program are: getting insight into one's own situation, including possible pitfalls and strengths, learning how to cope with the situation, getting a grip on thoughts and feelings, finding a better balance in the care for the patient with ABI, thinking about other possible care options, taking care of oneself, and communication. Each session is informative and easy to use and provides practical tips. The sessions consist of psychoeducation and assignments aimed at problem solving and skill building. Short videos featuring a social worker and videos of partners who are caregivers of patients with ABI are included in each session.

The partners can attend the program over a period of 20 weeks in their own time, at their own pace, and from any location with internet access. Partners are encouraged by automatic email reminders and by the social workers to complete the sessions before the postintervention measurement, although the program is still available for them after this period.

Face-to-Face Consultations

In addition to the web-based support program, partners are offered two consultations with a social worker at the rehabilitation center. The social workers prepare for the meetings by reviewing the completed assignments presented in the web-based sessions. Issues emerging from these answers are addressed and specific personal situations are discussed. The first consultation takes place 10 weeks after discharged, after the first 4 sessions of the web-based program have been completed; the second consultation is after the 9th session, 20 weeks after discharge. The duration of the consultations is about 45 minutes to one hour, depending on the need to elaborate.

Usual Care

Partners randomized to the control group receive usual care. This can consist of consultations with a social worker and/or psychologist and peer support groups. Partners in the intervention group are also allowed to receive usual care in addition to the CARE4Carer intervention.

Measures

The primary outcome is caregiver mastery. Secondary outcome measures for the partners are strain, burden, family functioning, emotional functioning, coping, care-related quality of life, participation, social network and care consumption. Secondary outcome measures for the patients are family functioning, emotional functioning, and participation. Additionally, a process evaluation will be conducted. An overview of all instruments and the time of assessment is presented in Table 1.

Caregiver Mastery

Caregiver mastery is measured by the Caregiver Mastery Scale (CMS) [25]. This instrument is an adaptation of the Pearlin Mastery Scale [26], in order to measure mastery in the caregiving situation instead of global mastery. This questionnaire consists of seven statements about caregiving, such as "You believe you are mastering most of the challenges in caregiving." Partners are asked to indicate their level of agreement (ie, strongly disagree, disagree, neither agree nor disagree, agree, strongly agree) with each statement. Three items with negative statements are reverse-scored. Total scores can range from 7 to 35, with higher scores reflecting greater caregiver mastery. Psychometric quality has been confirmed [25] and the instrument has proved to be able to detect change after intervention [27].

Secondary Outcome Measures

Caregiver Strain Index (CSI)

The amount of strain experienced by the partner is assessed with the CSI. This instrument contains 13 statements which are scored a 1 ("yes") or 0 ("no") [28]. Total scores range from 0 to 13, with higher scores indicating higher strain. Scores of 7 or higher indicate substantial strain. The CSI is a reliable [28] and valid [29] instrument which is commonly used for caregivers of stroke patients [30].

Self-Rated Burden (SRB)

A single question enables the partners to indicate how burdensome caring for the patient with ABI is at that moment. A visual analogue scale is used, ranging from 0 ("not hard at all") to 100 ("much too hard") [29]. The SRB has proved to be a valid instrument to assess the burden of caregiving for informal caregivers of patients with stroke [29].

Textbox 1. Sessions of the CARE4Carer web-based intervention.

1. Welcome
2. Caring for your partner
3. Burden and resilience
4. Which care choices to make?
5. Getting a grip on your thoughts and feelings
6. Taking care of yourself
7. Asking for support
8. Communication
9. And now?

Table 1. Overview of all instruments.

Instruments	T0		T1		T2	
	C [a]	P [b]	C	P	C	P
Caregiver Mastery Scale	x		x		x	
Caregiver Strain Index	x		x		x	
Self-Rated Burden	x		x		x	
McMaster Family Assessment Device Subscale: General Functioning	x	x	x		x	x
Hospital Anxiety and Depression Scale	x	x	x		x	x
Utrecht Coping List	x		x		x	
CarerQol	x		x		x	
Utrecht Scale for Evaluation of Rehabilitation – Participation Subscale: Restrictions	x	x	x		x	x
Social network	x		x		x	
Care consumption			x		x	
Process evaluation			x			

[a]C=caregiving partner.

[b]P=patient.

McMaster Family Assessment Device (FAD)

Family functioning is assessed with the General Functioning subscale of the FAD [31]. Partners indicate their level of agreement (ie, strongly disagree, disagree, agree, strongly agree) with 12 statements. Each statement is scored from 1 to 4, with 1 reflecting healthy functioning and 4 reflecting unhealthy functioning. A mean score of 2.0 or higher indicates problematic family functioning [32]. The FAD has good psychometric properties [31-33].

Hospital Anxiety and Depression Scale (HADS)

Emotional functioning is measured with the HADS. It consists of two 7-item subscales measuring anxiety and depression. Scores above 7 on the subscales indicate an anxiety disorder or depression, respectively [34]. The HADS has good psychometric properties and has proved to be responsive to change [35,36].

Utrecht Coping List (UCL)

Coping is assessed with three subscales of the Utrecht Coping List: (1) active problem solving (7 items), (2) seeking social support (6 items), and (3) passive reacting (7 items) [37]. A 4-point rating scale is used, ranging from “seldom or never” to “very often”. Higher scores on a subscale indicate a greater tendency to use that specific coping style. The UCL has good psychometric properties [37,38].

CarerQol

The CarerQoL instrument measures the care-related quality of life of informal caregivers [39]. It determines the subjective burden in seven dimensions of the caregiving situation (CarerQol-7D) and includes a valuation component (CarerQol-VAS). Low scores on the CarerQol-7D indicate a poor caregiving situation, while high scores on the CarerQol-VAS reflect a higher level of happiness. The CarerQol is a valid tool to measure the impact of caregiving [40].

Utrecht Scale for Evaluation of Rehabilitation – Participation (USER-P)

Participation restrictions are assessed with the USER-P instrument [41]. On 10 items, respondents indicate to what extent they are able to do the activity described. Scores range from 0 (“not possible”) to 3 (“without difficulty”). Higher total scores indicate fewer participation restrictions. The USER-P has good psychometric properties [42,43].

Social network

The social network (ie, number of parents/step-parents, children/grandchildren, other family members, and friends/neighbors) is mapped using a newly developed questionnaire. It also includes items about how easy it is to get practical and emotional help from these persons. Partners answer on a 5-point scale ranging from "very easy" to "very difficult".

Care consumption

Care consumption is assessed during the post-intervention (T1) and follow-up (T2) measurements. Partners are asked whether and how often they have had contact with a psychologist, social worker, general practitioner, practice nurse and/or aftercare nurse, and whether they participated in peer support groups.

Process Evaluation

At postintervention (T1), the partners evaluate the intervention, the individual sessions, and the different elements of the intervention by filling in the online questionnaire. The advantages, disadvantages, satisfaction, and usability of the intervention are investigated.

Using interviews, we assess the experiences of the social workers with carrying out the intervention and working with a blended care program, as well as their views on facilitators and barriers for implementation. Every social worker who supported a caregiver in the intervention group will be interviewed.

Treatment fidelity is determined by reports from the social workers on the number of face-to-face consultations that have taken place and by analyzing how many sessions of the web-based support program have been completed. Partners are obliged to fill in certain assignments to be able to complete a session.

Blinding

The baseline measurements (T0) are self-reported by partner and patient, who do not yet know the allocation outcome at this stage. Blinding to treatment allocation is not possible due to the nature of the intervention. The postintervention (T1) and follow-up (T2) measurements are, therefore, not blinded since these are self-reported by the partner and patient who are aware of treatment allocation by that time.

Power Analysis

The sample size has been calculated on the basis of the primary outcome measure, the Caregiver Mastery Scale. To detect a difference between the groups of 0.5 SD on the Caregiver Mastery Scale, with an alpha of 0.05 and a power of 80%, a total of 50 caregivers is needed in each arm of the trial. Assuming a drop-out rate of 20%, a total of 120 patient-partner couples will be included in the CARE4Carer trial.

Statistical Analyses

Descriptive statistics including frequencies, means, standard deviations, and (for nonparametric data) medians and interquartile ranges will be calculated. Longitudinal data analysis will be performed using a generalized linear mixed model (GLMM), to evaluate differences in efficacy between the experimental and control groups. Data will be analyzed based on an "intention-to-treat" analysis and with an alpha level of 0.05. The analysis software IBM SPSS Statistics version 22 for Windows will be used [44]. Descriptive statistics will be used for the partners' process evaluation and for the treatment fidelity. The interviews with the social workers will be transcribed verbatim and qualitative analyses will be performed.

Results

Participant recruitment for this randomized controlled trial commenced in September 2016 and enrolment is ongoing. The first results are expected to be submitted for publication in 2018.

Discussion

In this paper, we have described the protocol of a randomized controlled trial to evaluate the CARE4Carer blended care intervention to improve feelings of mastery in partners of patients with acquired brain injury. We will also investigate the effect of the intervention on strain, burden, family functioning, emotional functioning, coping, quality of life, participation, social network, and care consumption. A process evaluation will also be part of this study.

Brain injury – Moving forward together is an innovative partner support program. It was developed in cocreation with partners, social workers, and psychologists. Methods that have proved to be effective, such as those based on cognitive behavior theory and solution-focused therapy, have been integrated in the intervention. The program has been pilot-tested among partners of patients with ABI and modified in response to their comments. Another strength of this study is the use of blended care. Integrating the web-based support program with face-to-face therapy combines the best of two worlds, which can enhance the effect of the intervention [22]. To our knowledge, this is the first blended care intervention for partners of patients with ABI.

It is important to note that blended care is probably not suitable for everyone. Not every partner and health care provider may be ready for blended care. Some partners may not be comfortable with receiving support via a web-based program and might prefer to only have face-to-face contacts. Also, health care providers may resist offering support via the internet [45]. In addition, access to internet and possession of a computer, laptop, tablet or smartphone is not standard for everybody; 22% of the Dutch population aged 65 years or older has no internet access at home [46].

The study may have some limitations. First, we only include partners of patients who are admitted for inpatient rehabilitation. Patients who go home after treatment at the hospital and patients who receive geriatric rehabilitation are not included. Second, the control group treatment is not standardized, because care as usual differs between rehabilitation centers.

Support for partners of patients with ABI is clearly needed. Blended care interventions that include psychoeducation, skill building and problem solving have not been investigated in this population yet. Our CARE4Carer intervention could help partners to better deal with their new role as a caregiver, after the patient has returned home. We hypothesize increased caregiver mastery among partners as a result of this intervention. The findings of this study will be used to inform rehabilitation physicians, social workers, and psychologists and to improve the care for partners of patients with ABI. If the intervention proves to be superior to usual care, it will be made available for implementation nationwide, taking into account the barriers and facilitators that emerge from the process evaluation.

Acknowledgments

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Authors' Contributions

JV-M and CvH developed the idea and procured funding for the study. All authors contributed to the design and protocol of the study. VC wrote the study protocol. All authors reviewed the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Screenshot overview of web-based support program.

[JPG File, 246KB - resprot_v7i2e60_app1.jpg]

Multimedia Appendix 2

Screenshot session 3: burden and resilience.

[JPG File, 287KB - resprot_v7i2e60_app2.jpg]

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Abbreviations

ABI: acquired brain injury
CarerQol-7D: care-related quality of life – 7 dimensions of subjective burden
CarerQol-VAS: care-related quality of life – Visual Analogue Scale
CMS: Caregiver Mastery Scale
CSI: Caregiver Strain Index
FAD: Family Assessment Device
GLMM: generalized linear mixed model
HADS: Hospital Anxiety and Depression Scale
SRB: Self-Rated Burden
UCL: Utrecht Coping List
USER-P: Utrecht Scale for Evaluation of Rehabilitation – Participation
Wbp: Wet bescherming persoonsgegevens (Dutch Personal Data Protection Act)
WGBO: Wet op de geneeskundige behandelingsovereenkomst (Dutch Agreement on Medical Treatment Act)
WMO: Wet medisch-wetenschappelijk onderzoek met mensen (Dutch Medical Research Involving Human Subjects Act)

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Protocol

Functional Magnetic Resonance Imaging Evaluation of Auricular Percutaneous Electrical Neural Field Stimulation for Fibromyalgia: Protocol for a Feasibility Study

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Abstract

Background: Fibromyalgia is a chronic pain state that includes widespread musculoskeletal pain, fatigue, psychiatric symptoms, cognitive and sleep disturbances, and multiple somatic symptoms. Current therapies are often insufficient or come with significant risks, and while there is an increasing demand for non-pharmacologic and especially non-opioid pain management such as that offered through complementary and alternative medicine therapies, there is currently insufficient evidence to recommend these therapies. Percutaneous electrical neural stimulation (PENS) is an evidence-based treatment option for pain conditions that involves electrical current stimulation through needles inserted into the skin. Percutaneous electrical neural field stimulation (PENFS) of the auricle is similar to PENS, but instead of targeting a single neurovascular bundle, PENFS stimulates the entire ear, covering all auricular branches of the cranial nerves, including the vagus nerve. The neural mechanisms of PENFS for fibromyalgia symptom relief are unknown.

Objective: We hypothesize that PENFS treatment will decrease functional brain connectivity between the default mode network (DMN) and right posterior insula in fibromyalgia patients. We expect that the decrease in functional connectivity between the DMN and insula will correlate with patient-reported analgesic improvements as indicated by the Defense and Veterans Pain Rating Scale (DVPRS) and will be anti-correlated with patient-reported analgesic medication consumption. Exploratory analyses will be performed for further hypothesis generation.

Methods: A total of 20 adults from the Atlanta Veterans Affairs Medical Center diagnosed with fibromyalgia will be randomized into 2 groups: 10 subjects to a control (standard therapy) group and 10 subjects to a PENFS treatment group. The pragmatic, standard therapy group will include pharmacologic treatments such as anticonvulsants, non-steroidal anti-inflammatory drugs, topical agents and physical therapy individualized to patient comorbidities and preferences, prescribed by a pain management practitioner. The PENFS group will include the above therapies in addition to the PENFS treatments. The PENFS subject group will have the Neuro-Stim System placed on the ear for 5 days then removed and replaced once per week for 4 weeks. The primary outcome will be resting functional magnetic resonance imaging connectivity between DMN and insula, which will also be correlated with pain relief and functional improvements. This connectivity will be analyzed utilizing functional connectivity

magnetic resonance imaging (fcMRI) and will be compared with patient-reported analgesic improvements as indicated by the DVPRS and patient-reported analgesic medication consumption. Pain and function will be further evaluated using Patient-Reported Outcomes Measurement Information System measures and measures describing a person's functional status from Activity and Participation section of the International Classification of Functioning Disability and Health.

Results: This trial has been funded by the Veterans Health Administration Program Office. This study attained approval by the Emory University/Veterans Affairs (VA) institutional review board and VA Research & Development committee. Institutional review board expedited approval was granted on 2/7/17 (IRB00092224). The study start date is 6/1/17 and estimated completion date is 5/31/20. The recruitment started in June 2017.

Conclusions: This is a feasibility study that is meant to demonstrate the practicality of using fcMRI to study the neural correlates of PENFS outcomes and provide information regarding power calculations in order to design and execute a larger randomized controlled clinical trial to determine the efficacy of PENFS for improving pain and function.

Trial Registration: ClinicalTrials.gov NCT03008837; https://clinicaltrials.gov/ct2/show/NCT03008837 (Archived by WebCite at http://www.webcitation.org/6wrY3NmaQ).

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KEYWORDS

fibromyalgia; fMRI; PENFS; PENS; pain; sympathetic; auricular

Introduction

Fibromyalgia is a chronic pain syndrome that affects multiple body systems and is characterized by widespread pain, decreased physical function, fatigue, psycho-emotional and sleep disturbances and various somatic complaints [1,2]. It affects over 5 million Americans with an approximate female to male ratio of 7:1 [3]. A study derived from the US health insurance database found that the healthcare costs over 12 months are about three times higher among fibromyalgia patients when compared to patients without fibromyalgia. It is estimated that fibromyalgia costs the American population over 20 billion dollars per year in lost wages and disability [4]. This syndrome is not only devastating to the patient, but also represents a significant economic burden to the patient and society. Percutaneous electrical auricular stimulation of the vagus nerve has been utilized in the treatment of epilepsy and chronic pelvic pain [18,21]. In addition, we have previously reported a case of a female veteran with fibromyalgia who underwent PENFS with the NSS resulting in 100% relief of her fibromyalgia pain, Visual Analogue Scale (VAS) score from 8 to 0, reduction in opioid consumption and significant improvements in function for 4 months post-treatment, until the death of her father, at which point some pain symptoms began to return [22].

Fibromyalgia remains a poorly understood condition with regards to pathophysiology of the disease process, though maladaptive plasticity in the central (eg, brain) nervous system has been strongly implicated [5]. Current therapies are aimed at reducing the major symptoms of the disorder, such as treating the mood, sleep disturbances, and pain. These therapies include pharmacotherapy such as anticonvulsants and complementary and alternative medicine (CAM) therapies such as acupuncture. The current available therapies are often inadequate and frequently come with significant risks or side effects. These side effects often overlap with the symptoms of the disease, which result in poor patient outcomes. Some of the pharmacotherapy involved in treatment of fibromyalgia is aimed at addressing the pain symptoms. This often involves the utilization of opioids, possibly due to an exhaustion of other options for pain management. For pain conditions such as fibromyalgia, there is little evidence of benefit with chronic opioid therapy, and growing evidence against the use of opioids due to the risks for addiction, overdose, and side effects of long-term opioid use [6]. Given that opioid abuse is a major public health issue and drug overdose deaths are the leading cause of injury death in the United States, opioids should be avoided if possible [7]. With regards to CAM therapies, although these are often low risk and perceived to be beneficial by patients, there is not yet a sufficient level of evidence to support their use in fibromyalgia, limiting the ability of providers to make strong recommendations. More specifically, the combination of the small sample size, scarcity of studies for each comparison, and lack of an ideal placebo control weaken the level of evidence and the clinical implications of therapies such as acupuncture. Therefore, larger studies with higher levels of evidence are warranted [8].

Although the precise pathophysiology of fibromyalgia is not fully understood, there is a large consensus that it is a sympathetically or centrally mediated pain syndrome [9,10,11,12]. Comparisons have been made between fibromyalgia and complex regional pain syndrome (CRPS), a different sympathetically mediated pain syndrome. Fibromyalgia may be a widespread form of CRPS [13]. When treating sympathetically mediated pain syndromes, the goal of treatment is to interrupt the transmission of the sympathetic nervous system [13,14]. The vagus nerve is central to the parasympathetic autonomic nervous system, and modulation of its activity could result in effective treatment of sympathetically mediated pain through increasing parasympathetic outflow and modulating the sympathetic/parasympathetic balance [15]. Percutaneous electrical neural field stimulation (PENFS) via the ear is an intervention that aims to modulate the activity of cranial nerves (eg, vagus nerve at its auricular branches) and thus disrupt centrally mediated pain [16,17].

Percutaneous electrical neural stimulation (PENS) involves the placement of needles near neurovascular bundles within a sclerodermal, myodermal or dermatomal distribution and

delivering current to these structures [15]. The Military Field Stimulator/Neuro-Stim System (MFS/NSS) employs an evolved form of PENS known as PENFS (Figure 1).

Figure 1. Military Field Stimulator/Neuro-Stim System.

PENFS of the auricle is similar to PENS, but instead of stimulating a certain neurovascular bundle it stimulates the entire ear and all the auricular branches of the cranial nerves, including the vagus nerve. The vagus nerve mediates sensation of the auricular tissue that makes up the ear; therefore, auricular stimulation has been used to modulate its activity and treat pain [16]. Napadow et al have demonstrated short-term relief of evoked pain sensation in chronic pain patients using electrical stimulation of the auricular branches of the vagus nerve [18]. PENFS is based on the idea that a central effect may occur through the creation of a field of electrical stimulation over peripheral branches of cranial nerves, and that this effect can be changed by varying the form, intensity and frequency of electrical current delivered to the neurovascular structures [19]. Animal studies have demonstrated that transcutaneous auricular stimulation of the vagus nerve can have antidepressant effects by stimulating the release of melatonin and serotonin in addition to significantly improving dental pain through the endogenous opioid system [20].

Although vagal nerve stimulation for pain relief has been studied, the mechanisms supporting PENFS stimulation to the auricle has not yet been studied with functional magnetic resonance imaging (fMRI) [23]. The basis for analyses of fMRI findings used in the present study is adapted from prior studies by Napadow and Harris et al using functional connectivity magnetic resonance imaging (fcMRI) to examine intrinsic brain connectivity in fibromyalgia patients before and after pharmacological and non-pharmacological therapy with pregabalin and acupuncture, respectively [24,25,26,27]. For example, their prior study demonstrated that fibromyalgia patients had significantly greater connectivity within the default mode network (DMN) and right executive attention network as compared to healthy, age-matched controls [25]. Additionally, greater connectivity was noted between the DMN and the insular cortex [25,26], a region of the brain implicated in evoked pain response and salience detection. Successful therapy was then found to reduce clinical pain and DMN-insula connectivity [27]. Gaining an understanding of the analgesic effects and neural correlates for PENFS therapy in fibromyalgia could result in (1) a better understanding of the pathophysiology of fibromyalgia, (2) cost-savings, (3) improvements in pain therapy, and (4) a decreased need for opioid analgesics.

Methods

Ethics Approval

This study attained approval by the Emory University/Veterans Affairs (VA) institutional review board and VA Research & Development committee. The study protocol will be conducted in accordance with ethical principles from the Declaration of Helsinki.

Aims and Hypothesis

The specific aims of the study are (1) to evaluate the feasibility of using fcMRI as a biomarker for functionally correlated neural substrates of pain in patients undergoing PENFS and (2) to evaluate whether PENFS leads to analgesia and functional improvements as compared to standard treatment in veterans with fibromyalgia. Our primary hypothesis is that PENFS will result in decreased functional connectivity between the insula and default mode network as evaluated by fMRI [24,25,26,27], which will correlate to more significant improvements in pain and function relative to standard therapy for fibromyalgia.

Design

This is a feasibility trial comparing PENFS to standard therapy in veterans with fibromyalgia. Enrollment according to the stated inclusion and exclusion criteria will be conducted and subjects who meet study criteria will undergo baseline assessments. These include a collection of bio-behavioral data

such as cognitive and psychological assessments, eating, sleeping and drinking habits, and Patient-Reported Outcomes Measurement Information System (PROMIS) measures including physical function, anxiety, depression, fatigue, sleep disturbance, social function, pain interference, and global health. In addition, included are measures from the realms "Activity and Participation" from the International Classification of Functioning, Disability, and Health including arm curls, 30 second chair stands, and handgrip strength tests. Information from the Defense and Veterans Pain Rating Scale (DVPRS), and documented baseline analgesic consumption will also be included. Stratification based on age and sex will be performed to account for differential pain perception and neurological responses to pain based on age and gender. fMRI studies will then be conducted within 2 weeks prior to initiation of treatment and will be repeated within 2 weeks after the final treatment. Participants are advised to avoid caffeine and smoking the day of the neuroimaging analysis. The bio-behavioral assessments will be repeated at 4, 8, and 12 weeks after the final treatment.

The PENFS subject group will have the NSS placed on the ear for 5 days then removed and replaced at weekly intervals. The PENFS group will receive treatments once per week for a total of 4 weeks. Participants will be randomized to one of the two treatment groups. See Figure 2 for anticipated timeline for the study. Subjects will be block randomized, stratified by age and sex. This should provide an adequate sample size while minimizing confounding variables between groups. The standard therapy group will receive pharmacologic treatments such as anticonvulsants (ie, gabapentin, pregabalin), nonsteroidal anti-inflammatory medications (ie, ibuprofen, meloxicam), acetaminophen, topical agents and physical therapy individualized to patient comorbidities and preferences, as prescribed by a pain management practitioner, with regular check-ups at corresponding intervals to the NSS group.

Setting

The fMRIs will occur at an Emory Imaging Center. All other visits will be conducted at the VA pain clinic in Atlanta, GA.

Participants

Male and female Veterans age 20-60 with a diagnosis of fibromyalgia as diagnosed by a clinician, by chart review, and by the most recent American College of Rheumatology 2010 criteria for the diagnosis of fibromyalgia. The inclusion and exclusion criteria are listed in Textbox 1 [28,29].

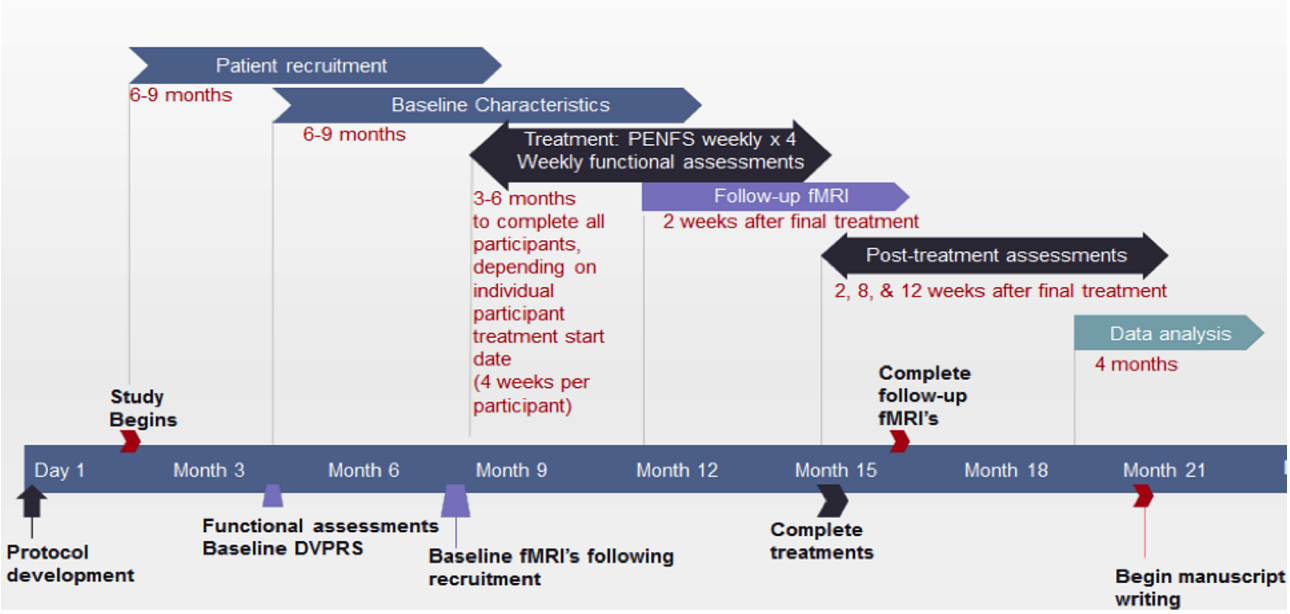
Randomization and Blinding

Subjects will be randomized to one of two groups; the control group will be standard therapy and the treatment group will be the PENFS treatment for this feasibility study. Simple randomization stratified by age and sex with equal allocation to treatment and control groups will be used. An age of 60 years old is set as a limit to minimize brain structural changes due to aging [30]. Subjects age 20-60, male and female with a diagnosis of fibromyalgia by the American College of Rheumatology 2010 criteria for the diagnosis of fibromyalgia will be included in the study [28,29]. Dr Kalangara, a pain physician trained to apply PENFS, will allocate subjects to one of the two treatment groups and will also perform the treatments. The principal investigator, Dr Woodbury, is a pain physician qualified to perform the pain and functional assessments and will perform these, blinded to treatment and control groups.

Outcome Measures

The primary outcome measure is connectivity between the insula and DMN. Areas of the DMN found to be relevant in prior studies regarding fibromyalgia are the inferior parietal lobule (IPL), medial prefrontal cortex (MPFC), and posterior cingulate cortex (PCC) [25]. Based on existing data, fMRI seed-based resting connectivity analyses of the insula and relevant areas of the DMN (IPL, MPFC and PCC) will be performed [24,25,26,27]. Subjects will undergo fMRI studies within 2 weeks prior to initiation of treatment and will be repeated within 2 weeks after the final treatment for comparison.

Figure 2. Anticipated timeline for study. DVRPS: Defense and Veterans Pain Rating Scale; fMRI: Functional magnetic resonance imaging; PENFS: Percutaneous electrical neural field stimulation.



Textbox 1. Inclusion and exclusion criteria.

Inclusion Criteria:

- Subjects must be male and female Veterans age 20-60 with a diagnosis of fibromyalgia as diagnosed by a clinician, by chart review, and by the most recent American College of Rheumatology 2010 criteria for the diagnosis of fibromyalgia [28,29].
- Subjects must self-report consistent, daily pain (greater than 5 on a 0-10 VAS) >90 days.
- Subjects must have intact skin free of infection at the site of implantation.
- Subjects must be willing to participate and understand the consent.
- Subjects must be right-handed in order to provide consistency in brain structure and function.

Exclusion Criteria:

- Subjects must not be currently pregnant, since effects of fMRI and electrical current on the developing fetus are not well-known.
- Subjects must not have an implanted electrical device such as a vagal stimulator, pacemaker, or spinal pain pump, which are not compatible with MRI.
- Subjects must not have a history of seizures or neurologic condition that may alter the structure of the brain.
- Subjects must not have a history of drug abuse or severe, uncontrolled psychiatric illness such as schizophrenia or major depressive disorder with suicidal ideation.
- Subjects must not have psoriasis vulgaris or other skin conditions that may increase the risk of infection at the implantation site.
- Subjects must not have severe anxiety, claustrophobia, or other conditions that may prevent their ability to lie at rest in an MRI scanner. This will be determined after discussion with the patient regarding their own perceived ability to lie at rest in an MRI scanner without the use of additional sedating medications.
- Subjects must not introduce new medications or treatments for fibromyalgia symptoms during the course of the study, expect for those prescribed by the pain practitioners involved in the study, to prevent confounding results.
- Subjects must not have a concurrent autoimmune or inflammatory disease that causes pain such as systemic lupus erythematosus, inflammatory bowel disease or rheumatoid arthritis, since this could decrease the effect of treatment.
- Subjects must not experience trauma, injury or severe disease during the course of the study.

The secondary outcome is whether functional improvements occur with the application of PENFS, as the ultimate goal of reducing pain is to improve function. Secondary dependent variables for the evaluation of functional improvements with PENFS include PROMIS and International Classification of Functioning, Disability, and Health measures, the arm curl, 30 second chair stand and handgrip strength tests. These tests will be performed before treatment initiation and again at 4, 8 and 12 weeks follow-up after the completion of the 4-week treatment period for comparison.

Sample Size

There will be a total of 20 subjects divided into 2 groups, 10 subjects in the control (standard therapy) group and 10 subjects in the PENFS treatment group. Age, gender, and comorbid conditions may confound effects on neurological response to pain, therefore subjects will be block randomized, stratified by age and sex. This will result in an adequate sample size while minimizing confounding variables between groups. Roberts and Brown demonstrated a decrease in VAS for pain using a series of 4 PENFS treatments in a cohort of 20 chronic pain patients [15]. Based on this Roberts and Brown study, we estimate the effect size to be a 4-point decrease in pain score, which is out of 10 points, in the PENFS group and a 2-point decrease in the standard therapy group.

Our study is a feasibility study being conducted with the purpose of providing better estimates of effect size and power calculations for sample size in future studies. The data gathered from this study will be used to inform power analyses for a future pilot study or randomized control trial. Therefore, we will have a power analysis after completing the study.

Recruitment

Recruitment will be performed through direct contact with patients at the pain clinic, and by letter invitation to veterans in the Atlanta VAMC system identified as carrying a diagnosis of fibromyalgia. Patients not already established in the pain clinic will only be contacted by study personnel with permission from the primary care physician.

There are sufficient numbers of patients at the Atlanta VAMC from which to recruit fibromyalgia patients, and due to the principal investigator's role as a pain management physician, she has sufficient exposure to fibromyalgia patients within her own clinical practice. In order to demonstrate the feasibility of recruitment, we performed a data query for the Atlanta VA medical center, excluding satellite clinics, and found that over the course of a 1-year period (from March 26, 2014 to March 26, 2015), a total of 1,451 unique veterans were seen who carried a diagnosis of fibromyalgia. In age groups < 50 years old, there is a preponderance of females who carry the diagnosis, while in age groups > 50 years old, there is a preponderance of males. This is likely due to a gender difference in military enrollment in these age groups. The ratio of female to male veterans with fibromyalgia is more reflective of the general population in the <50-year-old age groups.

On average, 2 patients are seen in the VA pain clinic with fibromyalgia per day, with 10 fibromyalgia patients a week. Of these, 60% would qualify for the present investigation. This is a conservative estimate. The prevalence of patients with fibromyalgia seen at the Atlanta VAMC and the pain clinic supports the feasibility of the study, given the planned recruitment of 20 study subjects from a population of at least 1,451 local veterans who carry the diagnosis of fibromyalgia, many of whom have been referred to and are followed in the pain clinic. We have allotted 6-9 months to recruit all patients. Given that 5 patients have already been recruited within 3 weeks of beginning the study, we don't expect recruitment to be an issue.

Statistical Analysis

In previous studies, the IPL, MPFC, and PCC are DMN regions that have been found to be relevant regarding fibromyalgia [26,27,28,29]. The primary outcome will be analyzed using fcMRI and analysis of functional neuroimages, a program that processes and displays fMRI data. The resting connectivity between the insula and DMN regions will be analyzed within 2 weeks prior to initiation of treatment to obtain a baseline and then again within 2 weeks after the final treatment. Data will be preprocessed and analyzed using the validated fMRI of the brain software library package and cardiorespiratory physiologic artifacts will be mitigated using retrospective image correction [31,32,33]. Further, artifacts related to subject motion will be minimized in fcMRI time series using the validated independent component analysis (ICA) based automatic removal of motion artifacts tool. This algorithm is a data-driven method to identify and reduce motion-related artifacts (ICA components) from fMRI data. Given that drifts in MRI acquisition are typically considered linear, first order polynomial fitting will be utilized to account for MRI signal drift.

The primary outcome measure is connectivity between the insula and DMN as a biomarker for pain. Based on previous research, we hypothesize that the addition of PENFS will decrease connectivity between the insula and DMN structures relative to standard treatment [24,25,26,27]. Z-scores from two correlations described above (ie, between the posterior insula and the IPL and between the posterior insula and the PCC) will be used as the dependent variables for this outcome analysis. Hence, changes in z-scores for the two correlations will be tested for each group using pairwise comparisons. We expect that posttreatment connectivity between the posterior insula and DMN structures will be reduced from pre- to post-PENFS treatment. We do not expect to see significant changes for standard therapy at 2 weeks following the final treatment. Each of the two z-transformed correlations, for both pre- and post-PENFS and pre- and post-standard therapy, will be family-wise error (FWE) corrected (voxel-wise, and cluster-wise) to P<.010, and cluster size of 20 for the two correlations for each group. Patient-reported changes in pain will be evaluated using (1) DVPRS severity scores and (2) analgesic consumption before and after treatment (4 weeks) and at long-term follow-up (8 weeks, 12 weeks) following the 4th week of treatment for each group. We will use 2 groups (PENFS versus control) 4 times (pre- and post- treatment at 4, 8, and 12 weeks follow-up) for repeated measures analysis of variance to compare outcome for the groups over time. We will employ a generalized linear mixed model (GLMM) framework to fit the ANOVA model to the data. GLMM approach is more robust than traditional ANOVA methods as it better handles the possibility for imbalance in the effects due to dropout and other losses to follow-up and provides a stronger estimate of the fixed group effect while controlling for time as a random effect in the model. After the completion of the above analyses, we will use Spearman Rank correlation coefficients to investigate the predictive ability of pre-PENFS (baseline) resting insula connectivity to predict post-PENFS changes in pain levels. Baseline connectivity will be extracted as z-scores from imaging data. Categorical variables such as gender and bio-behavioral

data will be assessed using Fisher's exact test, but continuous variables such as age will be assessed using two-tailed t-tests. All reported *P* values will be 2-tailed and considered significant at the .05 level, FWE corrected.

We will also perform a linear regression with z-scores from fcMRI correlations and baseline pain levels using the DVPRS in order to evaluate links between baseline resting insula connectivity and baseline individual differences in pain sensitivity. In addition, we will also use a linear regression model to assess any association between treatment-modulated clinical pain and changes in the posterior insula resting brain connectivity.

The secondary outcome is whether functional improvements occur with the application of PENFS, as the ultimate goal of reducing pain is to improve function. Secondary dependent variables for the evaluation of functional improvements with PENFS include PROMIS and International Classification of Functioning, Disability, and Health measures, the arm curl, 30 second chair stand and handgrip strength tests at 4, 8, and 12 weeks follow-up after the completion of the 4-week treatment period. Pairwise repeated measures comparisons between pretreatment and posttreatment DVPRS, analgesic consumption and functional assessments will be performed within each group, FWE corrected to $P<.050$. Similar analyses will be conducted at 6 and 12 weeks follow-up. Data from each time point can be considered its own family of comparisons for this purpose. Further, analysis of sample characteristics for the groups, PENFS versus control, will be conducted to assess comparability of the samples. Categorical variables such as gender and bio-behavioral data will be assessed using Fisher's exact test, but continuous variables such as age will be assessed using two-tailed t-tests. All reported *P* values will be 2-tailed and considered significant at the .05 level, FWE corrected. Data collected and analyzed regarding functional changes related to PENFS treatment will be assessed for new hypothesis generation.

Results

This trial has been funded by the Veterans Health Administration Program Office. This study attained approval by the Emory University/VA institutional review board and VA Research & Development committee. Institutional review board expedited approval was granted on 2/7/17 (IRB00092224). The study start date is 6/1/17 and estimated completion date is 5/31/20. The recruitment started in June 2017.

Discussion

Fibromyalgia is a syndrome that, despite affecting millions of Americans, remains a difficult condition to treat. The current therapies continue to fall short and many times leave these patients with intolerable side effects. PENFS is a Food and Drug Administration approved, non-pharmacologic therapy that is currently utilized within the military and VA system, but sufficient evidence regarding its outcomes and neural mechanisms have not been adequately investigated. Auricular PENFS has not been studied with fMRI. Stimulation of the auricle may produce neural changes that differ from traditional therapies. Understanding the underlying neural mechanisms of auricular PENFS could assist in developing targeted treatments for fibromyalgia and chronic pain. An understanding of its neural underpinnings and analgesic effects could lead to improvements in pain management and quality of life, cost-savings, and development of new techniques to address pain.

The present investigation is a feasibility study being conducted with the purpose of providing better estimates of effect size and power calculations for sample size in future studies. The data gathered from this study will be used to inform power analyses for a future pilot study or randomized control trial. This study will not only serve to elucidate neural changes with PENFS, but could provide evidence regarding the relative effectiveness of this already clinically employed non-pharmacologic treatment. This in turn can result in evidence-based implementation that be utilized to treat not only veterans suffering from fibromyalgia but also all fibromyalgia patients. Informed consent will be obtained from all trial participants.

Acknowledgments

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Authors' Contributions

All authors read and approved the manuscript. MG led the writing of this manuscript. AW led the development of this protocol and contributed to writing of this manuscript as well as figures. VN participated in the writing of this manuscript and the initial protocol development. VK, LK, and BC contributed to the neuroimaging protocol development and translating appropriate neuroimaging techniques. RS contributed to the clinical trial design and statistical analysis.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Original NIH peer-review reports.

[PDF File (Adobe PDF File), 175KB - resprot_v7i2e39_app1.pdf]

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Abbreviations

CAM: complementary and alternative medicine
CRPS: complex regional pain syndrome
DMN: default mode network
DVPRS: Defense and Veterans Pain Rating Scale
fcMRI: functional connectivity magnetic resonance imaging
fMRI: functional magnetic resonance imaging
GLMM: generalized linear mixed model
ICA: independent component analysis
IPL: inferior parietal lobule
MPFC: medial prefrontal cortex
MFS/NSS: Military Field Stimulator/Neuro-Stim System
PROMIS: Patient-Reported Outcomes Measurement Information System
PENFS: percutaneous electrical neural field stimulation
PENS: percutaneous electrical neural stimulation
PCC: posterior cingulate cortex
VA: Veterans Affairs
VAMC: Veterans Affair Medical Center
VHA: Veterans Health Administration
VAS: Visual Analogue Scale

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Protocol

Enhancing Survivorship Care Planning for Patients With Localized Prostate Cancer Using a Couple-Focused mHealth Symptom Self-Management Program: Protocol for a Feasibility Study

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Abstract

Background: This project explores a new model of care that enhances survivorship care planning and promotes health for men with localized prostate cancer transitioning to posttreatment self-management. Survivorship care planning is important for patients with prostate cancer because of its high incidence rate in the United States, the frequent occurrence of treatment-related side effects, and reduced quality of life (QOL) for both men and their partners. A key component of comprehensive survivorship care planning is survivorship care plans (SCPs), documents that summarize cancer diagnosis, treatment, and plans for follow-up care. However, research concerning the effectiveness of SCPs on patient outcomes or health service use has thus far been inconclusive. SCPs that are tailored to individual patients' needs for information and care may improve effectiveness.

Objective: This study aims to examine the feasibility of an enhanced survivorship care plan (ESCP) that integrates a symptom self-management mHealth program called Prostate Cancer Education and Resources for Couples (PERC) into the existing standardized SCP. The specific aims are to (1) examine the feasibility of delivering ESCPs and (2) to estimate the magnitude of benefit of ESCPs.

Methods: We will use a two-group randomized controlled pretest-posttest design and collect data at baseline (T1) and 4 months later (T2) among 50 patients completing initial treatment for localized prostate cancer and their partners. First, we will assess the feasibility of ESCP by recruitment, enrollment, and retention rates; program satisfaction with the ESCP; and perceived ease of use of the ESCP. To achieve the secondary aim, we will compare the ESCP users with the standardized SCP users and assess their primary outcomes of QOL (overall, physical, emotional, and social QOL); secondary outcomes (reduction in negative appraisals and improvement in self-efficacy, social support, and health behaviors to manage symptoms); and number of visits to posttreatment care services between T1 and T2. We will assess the primary and secondary outcomes using measurements with sound psychometrical properties. We will use a qualitative and quantitative mixed methods approach to achieve the research aims.

Results: This project is ongoing and will be completed by the end of 2018.

Conclusions: The results from this study will help design a definitive randomized trial to test the efficacy of the ESCPs, a potentially scalable program, to enhance supportive care for prostate cancer patients and their families.

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KEYWORDS

survivorship; prostate cancer; symptom, randomized trial; mHealth; caregiver; Patient Reported Outcome Measures

Introduction

A key component of cancer survivorship care planning is survivorship care plans (SCPs), documents intended in part to improve survivors' understanding of treatment-related symptoms, and ultimately, to improve patient outcomes such as quality of life (QOL) by summarizing cancer diagnosis, treatment, and follow-up care [1-3]. SCP use is recommended by several high-profile organizations such as the Commission on Cancer and Institute of Medicine (IOM) [1-4]. To date, research on SCPs has been largely empirical and inconclusive regarding whether the use of standardized SCPs improves patient outcomes [5-8]. The limited research demonstrating SCP efficacy may relate in part to the failure of standardized SCPs to be tailored to patient-specific information and care needs during care transition [9-11]. To enhance survivorship care planning, SCPs, as part of routine care, may create a channel for distributing interventions to patients to improve their symptom self-management and other outcomes [12,13].

Gaps in Cancer Survivorship Care Planning

Survivorship care planning for patients with prostate cancer is particularly important because of the high incidence rates of prostate cancer among men in the United States [14], the frequent occurrence of side effects due to treatments with curative intent [15-22] (eg, urinary, sexual, bowel, and hormonal symptoms; emotional distress; pain; fatigue; and sleep disturbance), and reduced QOL caused by these symptoms. Most patients are reluctant to talk with professionals or at support groups about their prostate cancer and its impact on their lives due to the sensitive nature of prostate cancer and its symptoms [23]. For patients in an intimate relationship, the effects of prostate cancer symptoms on their partners' QOL are similar to or worse than the effects on their own QOL [24,25]. Management of these negative effects has been an unaddressed supportive care need for survivors and their partners [26-28]. The IOM [3] and American Cancer Society (ACS) [29] cancer care guidelines call for programs that address treatment-related effects, promote healthy behaviors, and maintain QOL for patients and their families.

Using mHealth to Enhance Survivorship Care Planning

To address the unmet care needs of patients and their partners, our interdisciplinary research team developed a couple-focused tailored prostate cancer education mHealth program, Prostate Cancer Education and Resources for Couples (PERC) [30] based on scientific evidence and input from three groups of stakeholders: patients, partners, and cancer care providers. The theory-driven PERC program aims to improve QOL for both patients and partners through tailored content and a set of features that provide information and skills training, as well as increase their self-efficacy, social support, and health behaviors for symptom management [30]. In the two pilot feasibility studies we conducted during PERC development, prostate cancer patients and partners reported high satisfaction with PERC. They reported that PERC was simple and easy to use and that it provided quality information that improved their symptom management and QOL. Our pilot participants also suggested vigorously advertising PERC and "having the program available at physicians' offices" so that "all prostate cancer patients and their families can access it." [30].

To strengthen survivorship care planning for patients with localized prostate cancer and respond to our pilot participants' suggestions, we proposed to use SCPs as a vehicle for consistent and timely delivery of PERC and to enhance the standardized SCPs (hereafter, ESCP: enhanced survivorship care plan). We used the theoretical framework adapted from the Transactional Model of Stress and Coping [31] and family systems theory [32-34] to guide the development of the ESCP for prostate cancer patients in an intimate relationship. In this framework, personal, couple, and cancer-related factors are precursors *(antecedents)* of patients' and partners' QOL (*primary outcomes*) and also have indirect effects on QOL through *secondary outcomes* including appraisals of symptoms and coping resources (self-efficacy in symptom management, social support, and healthy lifestyle behaviors). The framework shows that patients and partners manage prostate cancer symptoms interdependently (when one person functions poorly, the other person is negatively affected [33,35]). This shapes their appraisals, coping resources, and ultimately affects the QOL outcome of each of the individuals.

Research Aims

In this proof-of-concept randomized controlled pilot trial, our primary objective is to examine the feasibility of delivering an ESCP (ie, standard SCP enhanced by the PERC program) to patients and partners. Our secondary objective of this study is to estimate the magnitude of potential benefit of the ESCPs. Compared with patients and partners who received the standardized SCP, we hypothesize that patients and partners using the ESCP will report greater improvement, from baseline (T1) to follow-up (T2), in QOL, self-efficacy in symptom management, social support, health behaviors to manage symptoms, and appraisals of prostate cancer symptoms. In addition, we hypothesize that patients receiving the standardized SCP and ESCP will differ in the number of visits to posttreatment care services between T1 and T2.

Methods

Study Design

This study will test the feasibility of a two-group randomized controlled pilot trial using prepost mixed-method design. Patients and their partners will be randomly assigned to the SCP (control) or the ESCP (intervention) groups. Couples will complete study measures at T1 (before randomization) and T2 (4 months later).

Study Participants and Setting

A total of 50 men who have recently completed initial treatment for localized prostate cancer and their partners will participate in this feasibility and proof-of-concept study. The eligible patients must (1) be within 16 weeks of completing their initial treatment with curative intent for localized prostate cancer (ie, prostatectomy or radiotherapy with or without hormonal treatment) [36] at the genitourinary and radiation oncology clinics of the two comprehensive cancer centers in the southeast of United States; (2) not be receiving treatment currently or within the past year for another cancer; and (3) have a partner who is 18 years of age or older, not receiving cancer treatment currently or within the past year, and willing to participate.

Patients and their partners will be removed from this study if she or he is diagnosed with a new type of cancer, starts a new treatment for another cancer during the study period, or decides to withdraw from the study voluntarily. Patients and their partners will be excluded from the study if either partner does not read and speak English as evidenced by their understanding and responses to screening questions and self-reported ability to read English or has cognitive impairment (assessed by the short portable mental status questionnaire).

Study Procedure

The research staff will use convenience sampling to recruit patients and partners from the genitourinary and radiation oncology clinics of two large comprehensive cancer centers in the southeast United States, where at least 400 men with localized prostate cancer receive treatment annually, and about 25% are African Americans, ensuring successful recruitment for this study. We will recruit couples based on procedures used successfully in the past by other researchers [37] and in our pilot study [30]. After Institutional Review Board approval, the project coordinator will identify potentially eligible patients using patient scheduling systems. The project coordinator then will see patients who meet the inclusion criteria before their SCP follow-up visit. The coordinator will provide study information, screen the patient and his partner for their eligibility and willingness to participate, obtain informed consent, and collect baseline data via telephone survey. For patients whose partners are not present at the clinic, the project coordinator will screen and consent the patients and partners and answer their questions via telephone after eligible patients give permission to contact their partners.

Randomization

After the T1 survey completion, couples will be randomized to the standardized SCP or the ESCP groups using a 1:1 ratio; 25 couples in each group (N=50 couples). The study statistician will generate, using an SAS program (SAS Institute Inc., Cary, NC, USA), a stratified *permuted block randomization plan with varying block sizes.* The randomization will be stratified by type of treatment (surgery, radiation, radiation plus hormonal therapy) because we believe that treatment type correlates with symptoms and QOL [38]. The health educator will administer this allocation sequence and send couples a letter and message via mail, email, and phone explaining their group assignment and study activities. After randomization, all participants will receive the standardized SCPs plus the Web link to our study website that is inserted at the end of the SCP using Smart Phrase in the electronic medical record Epic system. Following SCP delivery by clinicians, the interventionist will assign all participants their usernames and passwords and invite them to log into the study website embedded in the SCP via email, telephone, or mail. Other team members will be blinded to the treatment allocation until the end of the study, whereas the interventionist who knows the treatment allocation will not conduct surveys or interviews.

Control Condition

After logging into the study website that is embedded in the SCPs, control participants will be directed to the National Cancer Institute (NCI) prostate cancer website. A range of sources including NCI and ACS are routinely available in standardized SCPs to all patients. We utilize the auto-direction to the NCI website as an attention control to improve blindness during the randomization process. Furthermore, we include the NCI website to ensure that participants in the control group have structured access to evidence-based and guideline-adherent information and equivalence between control and experimental groups.

The use of SCPs is part of routine care at the genitourinary and radiation oncology clinics. After completing initial treatment for prostate cancer, patients' clinicians will complete and print a standardized SCP adapted from the American Society of Clinical Oncology template, review it with the patient (and their families) in a private room behind a closed door or via telephone, and provide him with a copy. The SCP will also be sent to the patient's primary care provider. The standardized SCP's section about possible late- and long-term treatment effects provides a generic summary of the side effects of the patient's treatment; options for managing the side effects; and recommendations for diet, physical activities, smoking cessation, and stress. All of this information is brief and is nonspecific to individual patients. There is no content about caregiver and caregiving issues during posttreatment survivorship in the standardized SCP.

Intervention

Participants randomized to the intervention group will receive the same SCP but will be directed to the PERC intervention website after logging into our study website instead of the control group's NCI website. PERC includes 12 modules about how couples can work effectively as a team, assess and better manage prostate cancer treatment-related side effects and symptoms (including urinary and bowel problems, sexual dysfunction, hormonal symptoms, pain, fatigue, sleep disturbance, and stress), and improve healthy behaviors. PERC also facilitates social support for the patient and his partner via postmodule assignments, a moderated online forum, meetings with a health educator, and a resource center that connects participants and their partners to tools for symptom tracking and monitoring, as well as local and national support groups and resources. Participants in the intervention group will have 15 weeks to complete the PERC intervention.

Measurement and Data Collection

To achieve our primary objective of testing the feasibility of the ESCP, we will collect both quantitative and qualitative data.

Table 1. Summary of measures at baseline (T1) and 4 months post baseline (T2).

Variables and Measurement[a]	Data source[b]	Group	T1	T2	Cronbach alpha	PERC program[c]
Aim 1: Feasibility of the ESCP						
Screening, enrollment, and retention rates: research activity logs; field notes	AD	Both[d]	Yes	Yes	N/A[e]	N/A
Self-reported program use	PT, SP	Both		Yes	N/A	N/A
Web activity: use NCI versus PERC or not, number of logins	Tracking	Both	Yes	Yes	N/A	Built in tracking system
Program satisfaction and perceived ease of use: Usability Scale [39,40]	PT, SP	Both	Yes	Yes	N/A	N/A
Participants' experiences: exit interview	PT, SP, AD	Both	No	Yes	N/A	N/A
Aim 2: Magnitude of benefits of the ESCPs (compared with couples using SCPs)						
Primary outcomes						
Quality of life (overall, physical, emotional, and social well-being): functional assessment of chronic illness therapy general scale (27-item) [41,42]	PT, SP	Both	Yes	Yes	.90 [25,42]	All[f]
Number of visits to post treatment care services: medical records	EHR, PT	Both	No	Yes	N/A	All
Secondary outcomes						
Appraisal of PCa symptoms: 4-item bother questionnaire [24,25]	SP	Both	Yes	Yes	.74-.9 [24,25]	All
Self-efficacy in symptom management: 9-item cancer self-efficacy scale [43]	PT, SP	Both	Yes	Yes	.91-.96 [24]	All
Social support: PROMIS SF V2.0 informational, instrumental, and emotional support scales [44]	PT, SP	Both	Yes	Yes	.74-.86 [44]	PA; CR
Health behaviors: physical activity and nutrition in health promoting lifestyle profile II. [45-48]	PT, SP	Both	Yes	No	.75-.92 [47,48]	HB; CR
Antecedents (control variables): participant characteristics						
Demographic characteristics: age, race/ethnicity , income, education, and etc	PT, SP	Both	Yes	No	N/A	N/A
Type of PCa treatment: SCP record	PT	Both	Yes	No	N/A	N/A
Comorbidities: 13-item Charlson comorbidity index—brief [49,50]	PT, SP	Both	Yes	Yes	.73-.88 [50]	N/A
General symptoms: 21-item Risk of Distress General Symptom Scale [51]	PT, SP	Both	Yes	Yes	.76-.84 [51]	GS
PCa symptoms: expanded prostate cancer index composite 26 [24,52]	PT	Both	Yes	Yes	.74-.90 [53]	PCa

[a]ESCP: enhanced survivorship care plan; NCI: National Cancer Institute; PERC: prostate cancer education and resources for couples; SCP: survivorship care plan; PCa: prostate cancer related symptoms; PROMIS: Patient Reported Outcome Measures.

[b]AD: administrative data and field notes; PT: patient; SP: spouse/partner; EHR: electronic health record

[c]The elements in PERC that will impact the outcomes. PA: postsession assignment; CR: online chat room; HB: healthy behaviors (healthy eating and physical activity); GS: general symptoms of pain, fatigue, sleep disturbance, emotional distress.

[d]Both: participants in SCP only and ESCP groups.

[e]N/A: not applicable.

[f]All: all elements in PERC (mentioned above).

For quantitative data, we will obtain participants' program satisfaction and perceived ease of use using the usability scale [39,40] and automatically recorded Web activities of the study website (access to the NCI or use of PERC). Table 1 displays the variables, measurements, and data collection information for the study.

To collect qualitative data, we will review research activity logs, field notes, participant screening data, and participant self-reported program use, as well as conduct a qualitative postintervention exit interview after study completion. In preparation for the postintervention exit interview, we will ask all participants at the T2 survey whether they are willing to talk via telephone about their experiences of using SCPs or ESCPs. Research staff will select 20 patient-partner dyads for interviews using purposeful sampling to ensure inclusion of at least one patient from each of the following groups: having/not having Internet access, having an education level of less than high school versus higher than high school, living in rural versus urban residential locations, and being African American versus white. We anticipate that these characteristics influence people's perceptions and use of SCPs or ESCPs. Guided by a set of open-ended questions and probes, patients and partners will be interviewed together (with the telephone speaker on) and then separately (when the interviewee is alone and feels comfortable to speak freely) to learn about their shared and discrepant perceptions about the SCP or ESCP use. All interviews, conducted in a closed room, will be audio-recorded and transcribed for qualitative analysis. Research staff will also collect data about the number of visits to the genitourinary and radiation oncology clinics, patients' primary care provider, and other providers including emergency room visits and hospitalizations.

For our secondary objective, we will evaluate participant outcomes at T1 and T2 to test the potential magnitude of benefits of the ESCP. We will obtain participant responses to structured questionnaires via telephone at T1 and T2. These Likert scales have been developed by research experts and tested for validity and reliability in previous projects [24,25,41-48]. They also demonstrated good psychometric properties in our prior studies (see Table 1 for measurements and their psychometric properties). Research staff (excluding the interventionist who knows the treatment allocation) will complete the telephone surveys where patients and their partners will be interviewed separately. Finally, we will also collect patient participant medical record data on the number of postprostate cancer treatment visits to oncologic services, their primary care providers, and other providers (including emergency room visits and hospitalizations).

Sample Size

There will be 25 couples each in the SCP and ESCP groups. Conservatively, we assume that we will have complete data on 23 couples per group, which is equivalent to assuming an attrition rate of 8%. Our attrition rate is based on a previous pilot study testing the feasibility of PERC in a population of patients with newly diagnosed prostate cancer and their partners recruited from the UNC Medical Center Genitourinary clinic. Unless otherwise specified, all tests will be one-sided at a .05 significance level.

Statistical Analyses

Primary Objectives

For our primary objective, we base our calculations on the percentage of reviewed PERC sessions that are consistent with the symptoms patients reported, where we consider the study feasible if 80% of the reviewed PERC sessions are consistent. On the basis of our assumed sample size, we can estimate the percentage of reviewed PERC sessions that are consistent with reported symptoms with a margin of error of 16% with 95% CI. We will first use a quantitative and qualitative mixed method to analyze the data [54]. We will examine research activity logs and field notes to compute secondary feasibility measures, including enrollment, recruitment, and retention rates that will be reported by the group and by time point, along with 95% CI. Descriptive statistics (including percentages or means, standard deviations) and their corresponding 95% CIs will also be computed for participant characteristics, self-reported use of programs, and the usability scale for couples in both groups.

Interview data will be coded in atlas.ti (ATLAS.ti for Windows. Berlin: Scientific Software Development). Version 7.5.16, 1993-2019) by the investigators and the research assistants using template analysis [55]. Template analysis combines content analysis with grounded theory, applying a priori codes and allowing additional themes to emerge as analysis proceeds [55]. Members of the research team will have discussions to reconcile coding discrepancies. The responses will be analyzed based on participants' experiences using SCP versus ESCP, to help identify the barriers and facilitators that are unique to the ESCP users. These findings will help improve the use of SCPs and ESCPs.

Secondary Objectives

Descriptive statistics will be calculated for secondary outcomes: QOL; appraisal of prostate cancer symptoms; self-efficacy in symptom management, social support, and health behaviors; number of patient visits to posttreatment care services; and Charlson comorbidity index, expanded prostate cancer index composite (EPIC), and General Symptom Subscale scores in the Risk of Distress Scale, for participants and partners, by time point and by group. All analyses will be conducted using an intention-to-treat approach, in which all randomized participants will be analyzed according to their assigned group, regardless of the extent of intervention received. We will use a stratified two-sample *t* test with an effect size measured by Cohen d [56] to estimate power in testing our hypotheses of greater improvement in QOL, appraisal of prostate cancer symptoms, self-efficacy in symptom management, social support, and health behaviors from T1 to T2. We will conduct complete case analysis. After accounting for about 8% attrition, an effective sample size of 23 couples per group yields 80% power to detect a moderate/large effect size of 0.74. In testing our hypothesis that SCP and ESCP patients differ in the number of visits to posttreatment care services at T2, we estimate power using a Poisson regression model. Assuming SCP patients have 6 posttreatment care visits on average at T2, a sample size of 23

patients per group yields 85% power to detect an increase or decrease of 33.3% in the average number of posttreatment care visits for patients in the ESCP group (ie, 4 or 8 posttreatment care visits at T2).

To assess the effect of group on the outcome measures for QOL, self-efficacy in symptom management, social support, and health behaviors, while accounting for the fact that couples have correlated measurements, we will fit a linear mixed model to the change score (ie, change from T1 to T2) for each outcome measure, where we will include the following as fixed effects: group membership (SCP, ESCP), couple member (patient, partner), type of prostate cancer treatment, the outcome's measure at T1, age, income, the Charlson comorbidity index score, and the differences in the Charlson index, EPIC, and general symptom scale scores between T1 and T2. To account for the correlation between each patient and partner in each couple, we will also include couple membership as a random effect. For appraisal of symptoms, which was only measured in partners, we will fit an analysis of covariance model to its change score, including the same fixed effects as those used for QOL, self-efficacy in symptom management, social support, and health behaviors. We will fit a Poisson regression model to the number of patient visits to posttreatment care services at T2, where we will include group membership as a predictor while controlling for the following effects: treatment type, age, income, the Charlson comorbidity index, EPIC, and general symptom scale score at T2.

As this is an exploratory proof-of-concept study, rather than a confirmatory study, we will not adjust for multiplicity when computing the CIs for these feasibility measures or conduct comparisons. Unless otherwise specified, all tests will be one-sided at a .05 significance level. All analyses will be conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

This project will run for 2 years and will be completed by the end of 2018. We have obtained approval from the Institutional Review Board at the two comprehensive cancer centers in the southeast United States. We have hired and trained research staff, including the project coordinator and the interventionist; set up the database using RedCap (Research Electronic Data Caputure, 2009); developed and refined protocols for all research activities; and updated the PERC website content and functionality.

We have also met with the clinical champions at the genitourinary clinics at both institutions and refined the recruitment and SCP implementation process. One of the genitourinary clinics is encountering a major nursing staff turnover, causing omission of SCP implementation to most patients at the clinic. Although the clinic is hiring new nursing staff, an oncology nurse practitioner student who is also a nurse navigator at the cancer hospital will work closely with the nurse practitioners, physician assistant, and physicians to help generate and deliver the SCPs with the embedded study website to eligible patients.

We started recruitment at the end of June 2017. As of the end of September 2017, we have consented 22 patient-partner dyads and completed the baseline survey among 16 couples. These couples have been randomly assigned to either the standardized SCP (with the NCI prostate cancer website) or the ESCP group and received the standardized SCPs. After receiving the SCPs, these couples will start their online programs. We will monitor and facilitate PERC intervention use and recruit participants for the next 6 months or until we successfully enroll 50 eligible patient-partner couples.

Discussion

Principal Findings

To our knowledge, this is the first study to integrate a tailored mHealth symptom self-management program with the SCP via EHR to enhance survivorship care planning and patient and family self-management. This study examines a new model of care that addresses the discord between the mandates and recommendations for survivorship care planning and scientific evidence of SCP effectiveness during care transition from end of treatment to self-management at home. We use SCPs as a vehicle to deliver mHealth programs (such as PERC) that provide a one-stop, comprehensive information and skills training mHealth intervention, as well as a place to receive social support from multiple sources (dyadic, peer, and professional) to help patients and their partners manage prostate cancer, general symptoms, and promote health behaviors. Patients and partners can conveniently access the ESCP and the mHealth program based on their preferences and needs, regardless of time and location. This study is responsive to national priorities aimed to strengthen survivorship care planning, including calls from the IOM, ACS, and Cancer Moonshot for programs that address treatment-related effects and help cancer survivors and their families to maintain QOL.

This study also addresses the great unmet supportive care needs for managing effects of cancer and its treatment for patients and families [26-29]. The substantial travel, time, and expense required to participate in in-person, multi-session, couple-focused supportive care programs limit the accessibility of these programs for patients and partners. Scalable interventions are needed to address the gap in survivorship care planning. The use of SCPs, which is increasingly required components of survivorship care planning, to deliver the tailored mHealth PERC program may facilitate referral and uptake of evidence-based mHealth programs that can reach a larger number of patients and partners at a low cost.

The innovative program has the potential to be used across diverse types of settings to address an important and frequently occurring public health problem in the US health care system as more than 220,000 men each year get diagnosed with prostate cancer. After treatment, many prostate cancer survivors experience significant physical, functional, and emotional disturbances. A scalable low-cost intervention that is widely available through routine care, EHR, and the Web, such as the ESCP, adds a significant improvement over the currently existing options.

Finally, this study innovatively involves family caregivers in posttreatment oncologic care. Family caregivers, especially partners, are often negatively affected by cancer diagnosis and treatment and sometimes have worse QOL than patients with prostate cancer [25]. Partners are a major source of support and part of the care unit [57,58]. Patients and partners often have different perceptions about prostate cancer-related issues and difficulty discussing them [59,60]. Couples lack access to survivorship care programs because of suboptimal services and referrals [61], and the small number of programs available [28] (especially those that are couple-focused [62-68]). In this study, integration of a couple-focused tailored mHealth intervention into standard SCPs is an innovative approach to deliver survivorship care information to both cancer patients and their family caregivers, and to provide family- and patient-centered care.

Limitations

The following limitations of this study warrant discussion. First, this study is conducted in two comprehensive cancer centers, and thus, findings may have limited generalizability to settings that do not have rich resources and support (such as community cancer centers). Recognizing this inherent limitation of pilot/feasibility studies at this stage, this formative work will inform our planned study in a broader range of clinical settings to test the efficacy of the ESCP in the near future. Anecdotally smaller cancer centers and hospitals often devote specific personnel for SCP implementation to be compliant with the mandate of Commission on Cancer, which would facilitate the ESCP delivery. The additional mHealth programs such as PERC may also have more significant effects for patients receiving care at local community hospitals and cancer centers that lack personnel and resources for posttreatment care and educational resources for patients and their families.

Second, some patients and their partners may not have access to the Internet and/or a computer. We will provide cellular-ready touchscreen tablets with a 1-year 3G data plan to these couples to ensure equal access to the mHealth program.

Next, some patients and their partners may have low computer/Internet literacy, which may reduce their enthusiasm in participating in this study. To address this concern, our research staff will bring an iPad when recruiting potential participants at the clinics and show them that we designed our study website so that it requires minimum skills to navigate. Participants in our pilot studies rated our program as very simple and intuitive to use. We have developed step-by-step instructions on how to use the Internet and the study website and will provide participants these instructions by mail, email, or phone. We have also posted an instructional video on the homepage. We will provide technical support to help troubleshoot operational problems, although, in the previous testing, no pilot participants used the support.

Because PERC is a couple's intervention that is tailored to the needs of intimate couples, we will exclude nonpartnered patients because they face different challenges than patients with partners [69]. Finally, at this time, our intervention is only available to English-speaking patients and their partners.

Comparison With Prior Work

Compared with the standardized SCPs, ESCPs will take patients' and partners' specific needs into consideration and provide more detailed content that is tailored to their preferences. Implementing ESCPs will change the status quo of patients receiving relatively generic SCPs. Compared with the standardized SCPs with generic information, the ESCP will provide an empowering mHealth program (PERC) that allows patients and partners to assess their own symptoms and care needs, as well as provide resources to address their needs as they transition to posttreatment self-care at home. Compared with traditional face-to-face or telephone consultations that provide posttreatment care and education, the ESCP in this study will empower patients and their families to self-manage their symptoms and promote healthy behaviors, and thus, enable health care providers to focus their limited resources on patients who experience the most severe issues and symptoms. Survivorship care plans enhanced by a mHealth or Web-based program can also help consistently deliver posttreatment supportive care services to a larger number of patients and their families, at a low cost.

Conclusions

The study will explore a new model of care that enhances survivorship care planning. Innovative integration of PERC with SCPs (ESCPs) will provide a tool that helps patients and partners to tailor their posttreatment symptom self-management programs based on their needs and preferences. Findings from this study will help design a definitive randomized clinical trial to test the efficacy of ESCP, a potentially scalable program.

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Conflicts of Interest

None declared.

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Abbreviations

ACS: American Cancer Society
AD: administrative data and field notes
CR: online chat room
EHR: electronic health record
EPIC: expanded prostate cancer index composite
ESCP: enhanced survivorship care plan
GS: general symptoms of pain
HB: healthy behaviors
IOM: Institute of Medicine
NCI: National Cancer Institute
PA: postsession assignment
PCa: prostate cancer related symptoms
PERC: prostate cancer education and resources for couples program
PT: patient
QOL: quality of life
SCP: survivorship care plan
SP: spouse/partner

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Protocol

Substance Use Prevention Programs for Indigenous Adolescents in the United States of America, Canada, Australia and New Zealand: Protocol for a Systematic Review

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Abstract

Background: Indigenous adolescents are at a higher risk of experiencing harms related to substance use compared with their non-Indigenous counterparts as a consequence of earlier onset and higher rates of substance use. Early onset of substance use has been identified as a risk factor for future substance use problems and other health, social, and family outcomes. Therefore, prevention of substance use among adolescents has been identified as a key area to improve health of Indigenous Peoples. Evidence exists for the effectiveness of prevention approaches for adolescents in mainstream populations and, most recently, for the use of computer- and Internet-delivered interventions to overcome barriers to implementation. However, there is currently no conclusive evidence about the effectiveness of these approaches for Indigenous adolescents.

Objective: The purpose of this review is to synthesize the international evidence regarding the effectiveness of substance use prevention programs for Indigenous adolescents in the United States, Canada, Australia, and New Zealand.

Methods: A total of 8 peer-reviewed databases and 20 gray literature databases will be searched, using search terms in line with the aims of this review and based on previous relevant reviews of substance use prevention. Studies will be included if they evaluate a substance use prevention program with Indigenous adolescents (aged 10 to 19 years) as the primary participant group and are published between January 1, 1990 and August 31, 2017.

Results: A narrative synthesis will be provided about the effectiveness of the programs, the type of program (whether culture-based, adapted, or unadapted), delivery of the program (computer- and Internet-delivered or traditional), and the setting in which the programs are delivered (community, school, family, clinical, or a combination).

Conclusions: The study will identify core elements of effective substance use prevention programs among Indigenous adolescents and appraise the methodological quality of the studies. This review will provide researchers, policy makers, and program developers with evidence about the potential use of prevention approaches for Indigenous adolescents.

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KEYWORDS

prevention; Indigenous population; minority groups; Indians; North American; Alaska Natives; Aborigines; Australian; adolescent alcohol use; substance abuse; tobacco; marijuana smoking

Introduction

Substance Use Among Indigenous Adolescents

Indigenous people have the oldest continuing cultures in the world [1,2]. A common experience among Indigenous people is the lasting impact of colonization, which continues to impact the health and well-being of many Indigenous people today [3,4]. Combined with lower outcomes in many social determinants of health such as education, poorer access to health services, ongoing racism, and housing and employment opportunities, one of the most visible consequences is the increased susceptibility to substance use and related harms experienced by Indigenous adolescents aged 10 to 19 years. This is evident in the lower age of initiation and higher rates of use; For instance, in Australia, substance use initiation among Aboriginal and Torres Strait Islander adolescents is reported to be 2 to 6 years earlier than the national average [5], with some adolescents trying tobacco and petrol sniffing as young as 8 to 10 years old [6,7]. Additionally, Aboriginal and Torres Strait Islander adolescents are 3 times more likely to report injecting drugs [8]. American Indian and Alaskan Native adolescents, aged 14 to 15 years, are 5 times more likely to report cannabis use and more than twice as likely to report excess alcohol use, compared with their non-Indigenous counterparts [9]. A total 21% of American Indian adolescents living on reserves have tried cannabis in their lifetime, compared with 5% of non-Indigenous adolescents [10]. In Canada, Indigenous adolescents aged 12 to 18 years have been estimated to be twice as likely to report being a current smoker, compared with the non-Indigenous population [11]. Early onset of substance use among Indigenous adolescents has been identified as a risk factor for problematic substance use later in life, as well as other adverse health, social, and family outcomes [12-18]. Prevention of adolescent substance use has therefore been identified as a key strategy to improve Indigenous health [3,19].

Potential of Web-Based Substance Use Prevention Programs

A number of prevention strategies have been developed and evaluated with the aim of delaying and reducing adolescent substance use and preventing associated harms. For mainstream populations, school-based prevention programs have been found to be highly effective in reducing the onset and escalation of substance use [20-22]. Community-based and family-based approaches show considerable promise of effectiveness [23,24], whereas mass media campaigns are deemed not effective in improving drug-related knowledge or reducing substance use [24]. Despite the availability of effective prevention strategies, these programs are not widely implemented, with time and lack of resources commonly cited as barriers to implementation [24,25]. To address these barriers, a number of programs facilitated by computers (including other electronic devices such as tablets or mobile phones) or the Internet have been developed, with promising results in mainstream populations [26-30]. Champion et al [31] systematically reviewed 9 randomized controlled trials (RCTs) of computer- and Internet-delivered prevention programs, of which 6 achieved significant benefits for drug and alcohol outcomes. Advantages of computer- and Internet-delivered prevention programs include reduced implementation costs, higher degrees of implementation fidelity, and less need for personnel to deliver the program [30,31]. Computer- and Internet-delivered prevention programs may be particularly beneficial for disenfranchised populations, such as Indigenous adolescents, because these programs can overcome issues with access, provide engagement opportunities, and have been found to be culturally compatible for Indigenous adolescents [32-35]. Moreover, recent research has shown that Internet and technology use is higher or just as high among Indigenous people, compared with non-Indigenous people, and that Indigenous adolescents feel comfortable using technology and expressing themselves on the Internet [35,36].

Need for Evidence-Based Prevention for Indigenous Adolescents

Although there is evidence to support computer- and Internet-delivered substance use prevention approaches in mainstream populations, the effectiveness of these programs cannot be assumed for Indigenous populations. Indigenous populations may require a cross-cultural translation of these approaches, mapped against situational contexts including different communication styles, languages, and different understandings of health and identity [37-39]. This may involve adaptation of an existing mainstream program to align with cultural identity and practices (culturally adapted programs), or development of programs specifically for the local Indigenous cultural context (culture-based programs) [40]. Although it is generally accepted that prevention programs should have a good cultural fit with the local cultural context, no studies have systematically assessed whether culture-based, culturally adapted, or culturally unadapted programs are most effective. Furthermore, no conclusive evidence currently exists for the effectiveness of substance use prevention approaches for Indigenous adolescents, including evidence about the most effective type, setting, or delivery method. A recent Australian systematic review of substance use prevention for Aboriginal and Torres Strait Islander youth found limited evidence for the effectiveness of the 8 reviewed programs, primarily due to poor evaluation designs [41]. Other previous reviews have not been able to provide a comprehensive synthesis of international evidence regarding effective prevention approaches for Indigenous populations, because they have focused on one substance [42,43], one program setting [44,45], or were primarily focused on one country [43-46]. This systematic review will address this gap by reviewing the evidence regarding the effectiveness of prevention programs in reducing substance use and related outcomes for Indigenous adolescents in the United States, Canada, Australia, and New Zealand. These four countries were chosen because Indigenous people have a comparable history of colonization and dispossession by English settlers, resulting in predominantly English-speaking culture in which Indigenous people are a minority. In all the four countries, there is an unequal distribution between Indigenous and non-Indigenous people in terms of the distribution of economic, social, and health care resources. Indigenous people are more likely to live under the poverty line and are over-represented in measures of low socioeconomic position [3]. Consequently, Indigenous people in these four countries experience poorer

health and social outcomes compared with their non-Indigenous counterparts [3,4,47]. Although there are differences between Indigenous Peoples' culture between these countries and within these countries, similarities exist including an ongoing occupation of the ancestral lands; common ancestry of the occupied land; and cultural norms and values such as ancestors, connection to ancestors, country, family and community, the concept of health as being holistic, and spirituality [1].

Aims of Literature Review

For Indigenous adolescents, this review will investigate the following: (1) the effectiveness of culturally adapted substance use prevention programs compared with culture-based or culturally unadapted programs in reducing substance use and related outcomes; (2) the effectiveness of prevention programs delivered in a school setting, compared with community, family, clinical, or multisetting (ie, school, community and/or family) in reducing substance use and related outcomes; (3) the effectiveness of computer- and Internet-delivered programs, compared with traditional delivery; (4) the elements of effective substance use prevention programs; and (5) the methodological quality of evaluations of substance use prevention programs.

Methods

Protocol Registration

The protocol for this systematic review has been registered in the PROSPERO registry of the University of York (registration number: CRD42017081885) and has followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) guidelines; see Multimedia Appendix 1 [48].

Search Strategy

Peer-reviewed and gray literature databases will be searched. Searches in the following 8 electronic databases of peer-reviewed journals will be conducted: DRUG, Cochrane, Embase, PsycINFO, Medline, ProQuest, Informit, and CINAHL. Searches of the gray literature will be conducted in the 20 databases listed in Textbox 1. These databases were based on searches conducted in previous literature reviews on topics related to the health of Indigenous Peoples [49,50] and recommendations from experts and University libraries in Australia and the United States. The reference lists of selected studies will be assessed for further relevant publications. The researchers will also solicit publications from researchers in the field.

Search terms are based on previous systematic literature reviews about Indigenous substance use programs [40,46], and computer- and Internet-delivered substance use prevention [21,31]. For the peer-reviewed databases, the search strategy will consist of combinations of keywords related to the participants ("Aboriginal," "Torres Strait Islander," "Indigenous," "Australia," "New Zealand," "Canada," "United States of America," "Maori," "First Nation," "Inuit," "American Indians," "Alaskan Indians" OR "Alaska Native" and "youth," "young," "adolescen*" OR "teen"), type of intervention ("evaluat*," "effect*," "efficacy," "review," OR "trial" and "prevention," "intervention" "program" "educat*"), and substance-related outcomes ("substance," "drug," "alcohol," "tobacco," "petrol," "cannabis," "kava," "methamphetamine," "MDMA," "inhalant," "marijuana," "amphetamine," "psycho stimulant," "smok*," "illicit drug" OR "volatile drug"). Textbox 2 outlines the detailed proposed search strategy to be used in Medline. For the gray literature databases, the search strategy will consist of combinations of keywords and/or topic headings related to the participants and the substance-related outcomes.

Eligibility Criteria

Studies will be included if they are published in English language and evaluate a substance use prevention program with Indigenous adolescents from the United States, Canada, Australia, and New Zealand as the primary participant group. Studies will be included if they are published between January 1, 1990 and August 31, 2017. This will capture studies conducted in the early days of substance prevention as well as the most recent studies. Studies will be included in the review provided the participants are Indigenous adolescents, or a mixed sample of adolescents and adults, but with adolescents as the primary target group of the program. The World Health Organization defines adolescents as people aged 10 to 19 years [12,51]. To be eligible, at least 50% of the sample must identify as Indigenous or the study must report a separate analysis for Indigenous participants.

Studies will be included if they evaluated a prevention program. The search will not be limited to randomized controlled trials (RCTs), as previous reviews in Indigenous substance use evaluations have recorded a lack of RCTs being conducted within this population [52]. Evaluation is therefore defined as either comparing an experimental group with a control group (eg, no intervention, education as usual, or an alternate intervention) and/or comparing change in outcomes across two or more time points. Following a previous review in substance use prevention among Indigenous adolescents [46], studies will be included if the evaluated prevention program has one or more of the following aims: (1) reduce substance use; (2) increase knowledge of substances and their effects; (3) change attitudes toward substances; (4) increase substance use resistance skills; (5) delay substance use initiation; and/or (6) reduce intention to use substances. This review will include both computer- and Internet-delivered and traditional (face-to-face) prevention programs. It will include universal (everyone in the population), selective (members who are at risk of alcohol and other drug use), and indicated (individuals experiencing early signs of alcohol and other drug use) prevention programs.

Study Record Management

All publications identified in the search of peer-reviewed databases and relevant publications from the gray literature will be exported into a bibliographic software Endnote (Clarivate Analytics, Philadelphia, PA, USA), including the citation and abstract. Duplicate publications will be removed.

Textbox 1. Gray literature databases included in search strategy (n=20).

United States

- American Indian Health
- Arctic Health
- One Sky Center
- Turtle Island Native Network
- SAMHSA's National Registry of Evidence-based Programs and Practices

Canada

- National Collaborating Centre for Aboriginal Health
- National Aboriginal Health Organization
- Indigenous Studies Portal

Australia

- The Australian Indigenous Health InfoNet
- Closing the Gap Clearinghouse
- Analysis and Policy Observatory

New Zealand

- Maori Health

International

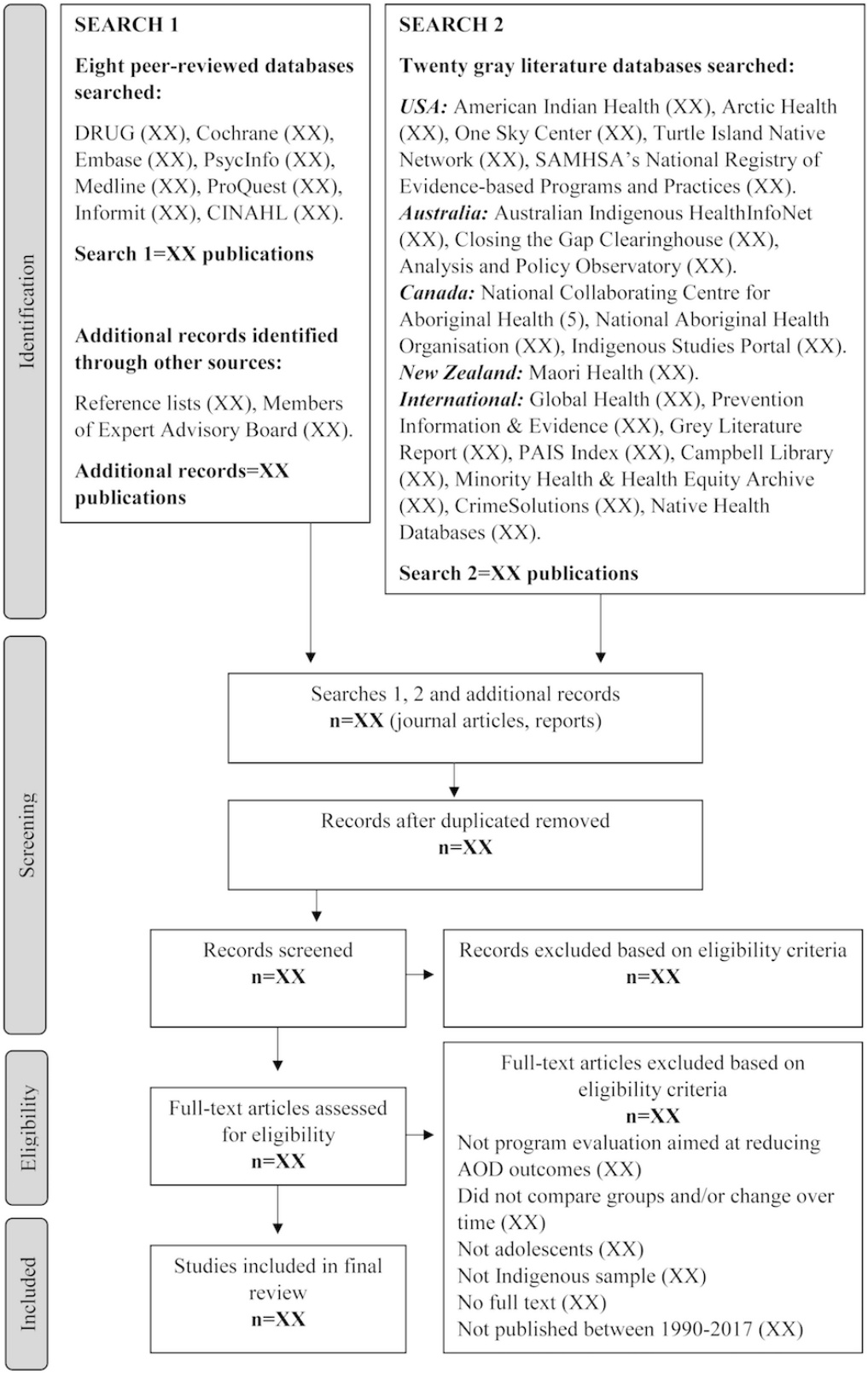
- Global Health
- Prevention Information & Evidence
- Gray Literature Report
- PAIS Index
- Campbell Library
- Minority Health and Health Equity Archive
- CrimeSolutions
- Native Health Databases

Textbox 2. Search strategy for systematic review of substance use prevention programs for Indigenous adolescents (example: Medline search).

1. ((substance OR drug OR alcohol OR tobacco OR petrol OR cannabis OR kava OR methamphetamine OR MDMA OR inhalant OR marijuana OR amphetamine OR "psycho stimulant" OR smok* OR "illicit drug" OR "volatile drug") AND (evaluat* OR effect* OR efficacy OR review OR trial) AND ((Indigenous OR Aborigin* OR "Torres Strait*" OR Maor* OR "First Nation" OR Inuit OR "American Indian*" OR "Alaskan Indian*") AND (Austral* OR "New Zealand*" OR Canad* OR Americ*)) AND (youth OR young OR adolescen* OR teen*)).mp. AND (educat* OR prevent* OR interven* OR program).m_titl.
2. limit 1 to yr="1990 - 2017"

[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA) flow diagram of search and selection strategy.



Selection Processes

Figure 1 illustrates the steps to be taken in the study selection process. One reviewer (BL) will screen all titles and abstracts of papers identified in the searches and assess their eligibility against the inclusion criteria. A second reviewer (MS) will screen a random selection of 25% of the publications to ensure accuracy in the study selection. Agreement between the two reviewers will be assessed, and where there is disagreement, this will be reconciled in consultation between the two authors.

After initial screening, full text copies of the publications identified as potentially relevant will be downloaded and further assessed for their eligibility by the two reviewers (BL and MS).

Cohen kappa will be calculated to evaluate the inter-rater agreement between the two reviewers at the full text screening stage. Where there is disagreement, this will be reconciled in discussion between the two authors. If there is no consensus, expert consultation will be sought from the other, more senior authors. The first reviewer (BL) will screen the reference lists of the eligible studies for further publications to be added into the systematic review.

Data Extraction

One reviewer (BL) will extract the following data from the publications into Microsoft Excel: authors, year of publication, country, name of the evaluated program, study design, sample size, targeted age, Indigenous status of participants, target substance, geographical area, setting, type of program, intervention strategy, duration and frequency of program, whether booster sessions were provided, follow-up time points, mode of delivery, community and stakeholder involvement in development, program facilitation, language consideration, control group, outcome measures used, overall quantitative and overall qualitative outcomes related to substance use, and harms. Detailed qualitative and quantitative outcomes (substance-use related or other outcomes measured) for each study will be extracted.

Setting of the programs will be classified into school-based, community-based, family-based, clinical, or multi-setting. School-based programs are defined as those implemented either in a classroom setting during school hours, or as an out-of-school activity delivered by the school. Community-based programs are those implemented with groups within the community (ie, adolescents, parents, or whole community). Family-based are the programs targeting the family unit. Clinical settings are based within a health service, such as a community health service or a general practice. Multi-setting programs have a combination of any of the aforementioned settings.

Type of programs will be classified following recommendations by Leske et al [40] into culture-based, culturally adapted, or culturally unadapted programs. Culture-based programs are developed to reflect and incorporate the unique cultural values and beliefs of the Indigenous participants. Culturally adapted programs are modified from existing non-Indigenous programs to be more culturally appropriate to the Indigenous participants. Culturally unadapted programs are developed for other cultural groups (eg, European, African American, or Mexican) and delivered to Indigenous participants without modification.

Program delivery will be identified as computer- and Internet-delivered or traditional. Computer- and Internet-delivered programs are those that are delivered completely or partially using computers or other Web-based technology. Traditional programs are those in which no part of the program is delivered using technology.

According to the most commonly measured substance-related outcomes following Lee et al [46], this study will group outcomes as follows: substance-related knowledge, substance use, and attitudes toward substance use. These 3 outcomes capture most substance-related outcomes studied in substance use prevention programs. To identify the elements of beneficial substance use prevention programs for Indigenous adolescents, two reviewers (BL and MS) will extract the program elements from all studies to identify the key elements of prevention programs that lead to beneficial substance-related outcomes for Indigenous adolescents.

Data Synthesis

A narrative summary will be provided of the outcomes of the included studies. On the basis of previous reviews of evaluation studies in Indigenous populations, we expect the number of studies to be too low and the quality of studies too varied to warrant a quantitative synthesis of the data [52-54]. The narrative summary will include a discussion of whether programs are beneficial to prevention of substances among Indigenous adolescents. Programs will be identified as beneficial if there are beneficial effects on more than 50% of substance-related outcomes, studies reporting positive findings on 50% or less of the evaluated outcomes will be classified as mixed, studies reporting negative outcomes will be classified as iatrogenic, and studies without significant outcomes will be classified as null. The narrative summary will discuss the number of beneficial programs for each program type (culture-based, culturally adapted, and culturally unadapted), type of delivery (computer- and Internet-delivered and traditional), and program setting (school, community, family, clinical, and multi-setting). It will also detail the elements used in the beneficial programs and summarize the most commonly implemented elements.

Critical Appraisal of Risk of Bias in Individual Studies

The methodological quality of both quantitative and qualitative elements of the studies will be assessed. The quality assessment will be conducted by one reviewer (BL), with a second reviewer (MS) appraising a random selection of 25% of the publications to ensure reliable coding. Following previous systematic reviews of prevention programs for Indigenous people [49,55,56], this review will assess the quality of quantitative studies using the Dictionary for Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies [57]. Sections A (selection bias), B (study design), C (confounders), E (data collection), and F (withdrawals and dropouts) of this tool are rated as strong, moderate, or weak to assess possible bias. Section D (blinding) will be excluded from this study because double-blinding is not feasible in school-based or community-based studies [23]. As prescribed, sections G (intervention integrity) and H (analysis appropriateness) will receive a narrative description rather than categorical ratings. Following standard procedures of this tool, each study will receive a summary rating defined as weak (two or more weak scores), moderate (one weak score is given), or strong (no weak scores are given).

The methodological quality of qualitative study components will be assessed using a modified version of the qualitative tool by Long and Godfrey [58], which has also previously been used in a systematic review of programs for Aboriginal and Torres Strait Islander people in Australia [56]. The adapted version assesses quality in 3 domains related to evaluation: (1) data collection, the need for clear descriptions of the data collection process; (2) analysis and potential research bias, the transparency

of the description of data analyses processes, description of researchers' positioning in the study and the interpretation of findings in line with the literature ; and (3) policy and practical implications, assessment of the populations to which the findings are generalizable and implications for policy and practice.

Results

Data analysis is underway and the results of this systematic review are expected to be submitted for publication in 2018.

Discussion

This paper summarizes the protocol for a systematic review of substance use prevention programs for Indigenous adolescents in the United States, Canada, Australia, and New Zealand. The purpose of this review is to synthesize international evidence regarding the effectiveness of substance use prevention programs for Indigenous populations. It will identify the setting in which prevention programs are most effective, the most beneficial delivery and types of programs, and the elements of effective substance use prevention for Indigenous adolescents.

This review will provide researchers, policy makers, and program developers with up-to-date information about the strength of the international evidence to support the use of substance use prevention approaches among Indigenous adolescents. It will evaluate whether mainstream programs are effective when implemented in culturally unadapted form among Indigenous adolescents, and will assess evidence supporting the effectiveness of culturally adapted mainstream programs and specific culture-based programs. Finally, this review will provide evidence about the potential to use computer- and Internet-delivered prevention approaches among Indigenous populations.

Given the high rates of technology and Internet use amongst Indigenous adolescents [34,36] and effectiveness of computer- and Internet-delivered substance use prevention in mainstream populations [30], there is considerable potential for the use of computers and Web-based technology in the delivery of substance use prevention with Indigenous adolescents [32]. This review will inform the development of future computer- and Internet-delivered prevention programs for Indigenous adolescents, which have the potential to be highly advantageous for Indigenous adolescents, due to the sustainable, low cost, and engaging format that is well-aligned to the preferences of adolescents [34,59].

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Conflicts of Interest

None declared.

Authors' Contributions

LS, MT, and NN conceptualized the study. MS, BL, and LS developed the study design and protocol. MS wrote the first draft of the manuscript. All authors read, revised, and approved the final manuscript.

Multimedia Appendix 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) checklist.

[PDF File (Adobe PDF File), 156KB - resprot_v7i2e38_app1.pdf]

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Abbreviations

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol

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Protocol

Influence of Radiofrequency Electromagnetic Fields on the Fertility System: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Due to the increased number of users of mobile phones, tablets, and other devices over the past few years, concerns about the potential impact of mobile phones on health are growing. The influence of mobile phone exposure on male fertility has been studied in recent years. Other research has shown that electromagnetic fields (EMFs) increase macrophages in the corpus luteum and growing follicles. Due to conflicting results among studies and since no systematic review has been performed to analyze the effects of radiofrequency EMF exposure from electronic devices on the fertility system in recent years, this evidence-based study is necessary.

Objective: The main objectives of this study are to determine the best evidence associated with the influence of radiofrequency EMFs on the fertility system and to provide insight into a potential mechanism using our observations.

Methods: In this systematic review, the databases and gray literature will be searched with no language and date limitation. The following databases will be searched: Cochrane Library, MEDLINE, PubMed, EMBASE, CINAHL, ProQuest, Scopus, Science Direct, Google Scholar, and other Persian databases. The combination of the Medical Subject Heading terms “radiofrequency electromagnetic” and “male reproductive system” or “female reproductive system” will be searched. Observational study designs will be included but case reports, case series, reviews, and letters to the editor will be excluded. Papers selected for retrieval will be evaluated by two independent referees for methodological validation before entering a review using the Newcastle-Ottawa Scale for nonrandomized studies and cohort studies.

Results: The results of this study will be submitted to a peer-reviewed journal for publication and also presented at PROSPERO.

Conclusions: This systematic review will provide evidence-based data on the effect of radiofrequency EMFs on the fertility system. This article will also classify the harmful effect of radiofrequency waves on primary and secondary infertility. This study could be useful for decreasing infertility. This is important because the rate of infertility is growing, leading to negative outcomes for couples and the health care system.

Trial Registration: PROSPERO CRD42017072462; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=72462 (Archived by WebCite at http://www.webcitation.org/6wjiE9R2q)

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KEYWORDS

electromagnetic field; fertility; reproduction

Introduction

Concerns about the potential impact of mobile phones on health are growing due to the increased use of the mobile phones, tablets, and other devices over the past few years. Mobile phones, wireless telephones, mobile base stations, and power lines are some of the main sources of our daily exposure to radiofrequency electromagnetic fields (RF-EMFs). There are more than 2 billion mobile phones in use worldwide [1-3].

Exposure to RF energy depends on the frequency of the mobile phone used. The most common frequency of phones used in the United States is 900 to 1900 MHz, while in many parts of the world, phones work at frequencies from 850 to 1800 MHz. The higher the frequency, the higher the energy. Radiant energy is absorbed by 3 main mechanisms in the human body: (1) Aural effect; the body receives and absorbs the RF signal depending on the size of the body part and the signal wavelength; (2) RF signal binds with tissue; and (3) absorption intensification [4,5].

The effects of electromagnetic radiation (EMR) can be divided into two main categories: thermal properties and nonthermal properties. Thermal properties are caused by the increase in temperature due to the energy absorption of oscillating electric fields. This can lead to heat in the exposed parts of the body. Thermal effects are calculated in terms of specific absorption rate. The specific absorption rate depends largely on the antenna, location, and frequency settings [6]. Some studies show that human exposure to RF waves can cause cognitive and behavioral impairments and decreased learning and memory. Significant thermal effects may be associated with adverse health effects such as problems with sleep, hearing, reproduction, impairment of the nervous system and increased cancer risk [7].

Infertility is defined as the inability to get pregnant after one year of intercourse without the use of contraceptive methods, and it affects 15% of couples worldwide. Male infertility is the cause of 30-50% of infertility, of which 30-40% of the causes are referred to as sperm disorders [8]. The influence of mobile phone exposure on male fertility has been studied in recent years [9]. In normal physiological conditions, spermatogenesis is a balanced process of maturation, cell division, and storage, which is particularly susceptible to environmental stimuli and chemicals. The mechanism is unclear, but its hypothesized that the component involved is the cytoskeleton which consists of charged proteins. The cytoskeleton is a structural and functional part of the cell that plays a main role in motility of the sperm and actively participates in the morphological alterations that happen during mammalian spermatogenesis [9,10].

A study of the effect of EMFs on female rats using transmission electron microscopy showed the increased existence of numerous drops of lipid in patches and luteal cells, as well as an increase in the number of autophilic antibodies and macrophages in some granulosa cells [11]. Other researchers showed that EMFs increase macrophages in the corpus luteum and growing follicles, and they believe that EMFs increase apoptosis in mice ovaries. In addition, most researchers showed that EMFs damage stromal cells in the uterus and uterine tubes through apoptosis of the glandular epithelium, ovarian cortex, and luminal epithelium [12,13].

It is necessary for future research to explore the safety criteria of RF-EMR. As electronic devices that emit RF-EMR are used very close to the body, RF shielding could be used in electronic devices to block RF-EMF waves and increase distance from them. Systematic review papers are a type of review that analyze the findings of other studies and provide the best evidence for a decision about a health approach [14]. Some studies demonstrated the potential harmful effects of RF on various sperm parameters, such as sperm motility, due to mobile phone usage [15]. Due to conflicting results among published research and since no systematic review has been performed to analyze the effects of RF-EMF exposure from other electronic devices on the fertility system in recent years, this evidence-based study is necessary.

The aims of this study are to clarify the best evidence associated with the influence of RF-EMFs on the fertility system and to make observations that could provide insight on a potential mechanism. The other objective of this study is to determine the effect of an RF-EMF on primary or secondary infertility.

Methods

Inclusion Criteria

This systematic review will include studies with infertile couples, defined by the inability to get pregnant after one year of intercourse without the use of contraceptive methods, of which the male and female are 18-65 years of age and use a device omitting RF-EMF for various exposures. We will include studies that used various methods of analysis to assess the reproductive system, including hormonal assessments, diagnostic imaging techniques, biopsies, and spermatograms.

This systematic review will only include human studies and the intervention can be the use of any device that exposed a user to RF-EMFs for any frequency and duration. There will be no restrictions on exposure condition, type of signal device, distance, exposure time, and location of participant.

All studies with or without the control group will be included in this study.

Any observational study designs will be included. Case reports, case series, reviews, and letters to the editor will be excluded. Articles with incomplete data will be excluded from the study. We will try to contact the authors of studies that are related but not accessible by email.

Outcomes

This systematic review will consider papers that include a rate of change in reproductive system parameters (sperm, endocrine

parameters [luteinizing hormone, follicle-stimulating hormone, and testosterone], testis, and ovary function) after the use of devices with an RF-EMF as primary outcomes. The potential mechanism of RF-EMF on the fertility system and primary or secondary infertility will be the secondary outcome of this systematic review.

Search strategy

In this systematic review, databases and gray literature will be searched without language or date restrictions. The following databases will be searched: Cochrane Library (Wiley), MEDLINE (Ovid), PubMed, EMBASE, CINAHL (EBSCO), ProQuest, Scopus, Science Direct, Google Scholar, and other Persian databases. All databases will be scanned for articles from the year 2000 until the present. The reference lists of articles and reports will be checked. The gray literatures includes the International Clinical Trials Registry Platform and ProQuest Dissertations & Theses Global. The combination of the Medical Subject Headings terms “radiofrequency electromagnetic” and “male reproductive system” or “female reproductive system” will be used for our search. To ensure the inclusion of all the related articles, the search will be sensitive and accurate. The title and abstract of the articles will be evaluated and any disagreement over the inclusion of an article in the review will be resolved through discussion between the authors. The full-text of articles will be assessed to meet the objectives of this systematic review.

Quality assessment

Papers selected for retrieval will be evaluated by two independent referees for methodological validation before entering the review using the Newcastle-Ottawa Scale to evaluate the quality of cohort studies and nonrandomized controlled trials [16]. Any disagreements that arise between reviewers will be resolved through discussion or with a third reviewer.

Data extraction

The data from the articles used in this study will be extracted by two independent reviewers using the standard data extraction tool, Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information. The data extracted will comprise of specific details about the populations, interventions, study methods, and results which are important to the objectives of the review. Any disagreements that arise will be resolved through discussion between the reviewers or with a third reviewer. Authors of papers will be contacted to request missing or additional data where required. We will try to contact the corresponding authors of studies by email if it is necessary to obtain data missing from published articles.

Data synthesis

Analyses will be conducted using the STATA V.12 software. Heterogeneity will be evaluated with the I^2 statistic and chi-square (χ^2) test (recommended by the Cochrane Handbook for Systematic Reviews of Interventions). We will explain the I^2 statistic using the following example. When substantial heterogeneity (I^2>50%) is evident among the articles, the results of this study will be presented in the text qualitatively. The author’s decision to use the random-effects model will be based on an understanding of whether all included trials share a common effect size, not only for results of tests but also for statistical heterogeneity. For classified data, the effect sizes are calculated as odds ratios, and for continuous data, the weighted average difference and their 95% CI are analyzed. By using the standard chi-squared, non-correlation will be evaluated. The results of this article will be presented in the appropriate tables and figures. Publication bias will be explored using a funnel plot and Begg's and Egger's tests. If it is possible, this systematic review will be performed using subgroup meta-analysis based on the type of device and exposure time disagreement.

Results

This is a protocol for a systematic review, so the results are not presented. The results of this study will be submitted to a peer-reviewed journal for publication and also presented at PROSPERO (international prospective register of systematic reviews). The PROSPERO registration number is CRD42017072462.

Discussion

The purpose of systematic reviews is to present a comprehensive summary of articles related to a study question and to provide solutions to disagreeing results between studies. While the greatest source of evidence for informed decisions is provided by systematic reviews and meta-analyses, to the best of our knowledge, this will be the first systematic review evaluating the radiofrequency electromagnetic field on fertility. This systematic review will provide evidence-based data on the effect of radiofrequency electromagnetic waves on fertility system. This article will also classify the harmful effect of RF waves on primary and secondary infertility and will validate the use of radiofrequency electromagnetic devices during reproductive period. This study could be useful for decreasing infertility. This is important due to the growing rate of infertility, which has negative outcomes for couples and health care system. The absence of studies evaluating the effects of radiofrequency electromagnetic waves on the fertility system will be a limitation of this study.

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Authors' Contributions

LD and NR developed the protocol study. FA prepared the primary manuscript draft and selected the related papers. All of authors were responsible for assessment of articles, data collection, and approval of the main manuscript.

Conflicts of Interest

None declared.

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Abbreviations

EMF: electromagnetic field
EMR: electromagnetic radiation
RF: radio frequency

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Protocol

Attention Bias in Individuals with Addictive Disorders: Systematic Review Protocol

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Abstract

Background: Globally, substance disorders, particularly that of opiate use, cannabis use, and stimulant use disorders, are highly prevalent. Psychological treatments are an integral aspect of intervention, but a proportion of individuals still relapse despite having received such an intervention. Recently, the dual-process theory proposed that the unconscious processes of attention biases are responsible for these relapses. Prior meta-analyses have reported the presence of attention bias in alcohol and tobacco use disorders. More recent research has examined attention bias and its effectiveness in opiate use, cannabis use, and stimulant use disorder. The evidence syntheses to date have not examined whether attention bias is present in these disorders and could be subjected to manipulation. This is important information and would support the introduction of psychological interventions for attention bias for such patients. Such psychological interventions would help individuals maintain their abstinence and minimize the risk of relapse.

Objective: This paper aims to undertake a systematic review to synthesize the existing evidence for the presence of attention bias in all the disorders mentioned above, and to determine the clinical efficacy of attention bias modification.

Methods: A systematic review will be conducted. A search will be conducted on the respective databases up till 2017. Selection of the studies will be determined by the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. Quality assessment of the included studies will be assessed using the Cochrane Risk of Bias tool. A narrative synthesis will be conducted, with a meta-analysis considered only if there are sufficient studies for statistical analysis.

Results: The results of the systematic review will be available 12 months after the publication of this protocol.

Conclusions: This review is important as it will support the introduction of psychological interventions for attention bias for such patients. Such psychological interventions would help individuals maintain their abstinence and minimize the risk of relapse.

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KEYWORDS

attention bias; substance addiction; systematic review

Introduction

Background

The recent statistics from the United Nations Office on Drugs and Crime reported that a quarter of a billion individuals experimented with drugs in 2015, and 29.5 million individuals are currently diagnosed with a substance disorder [1]. The most commonly abused drugs include cannabis, opioids and amphetamines [1] with a prevalence of 3.8%, 0.7% and 0.77%, respectively [1]. Drug usage and dependence is also associated with comorbidities, such as that of retroviral diseases and hepatitis C. Among the 12 million individuals who have used drugs intravenously, 1.6 million individuals have acquired a retroviral disease and another 6.1 million individuals have acquired hepatitis C [1]. In response to this huge problem, the World Health Organization and the United Nations Office on Drugs and Crime have been working jointly in the formulation of various policies, and to improve the existing levels of care in low- and middle-income countries [2].

The treatment options for drug abuse are both pharmacological and nonpharmacological. Psychosocial treatments complement and augment the effectiveness of pharmacological treatments, and prior reviews have reported the effectiveness of a combination treatment for opioid use disorders [3]. A variety of psychological approaches are used, such as contingency management and cognitive behavioural therapy (CBT). While therapies such as CBT have been demonstrated to be efficacious in the treatment of cannabis use disorder [4], other studies have reported that despite its effectiveness, at least 40%-50% of individuals relapse within a year of successful treatment, and 70% of individuals relapse within three years [5]. Pharmacological options for the treatment of addictive disorders are varied; for cannabis and amphetamine disorders, these are limited, whereas for opioid use disorders, opiate substitution therapies (eg, methadone and buprenorphine) can be used [6]. Current evidence supports the use of symptomatic medications in the management of individuals who are acutely intoxicated, such as benzodiazepines for its sedative properties, and antipsychotics for individuals experiencing psychotic symptoms [7]. Recent research has addressed the use of gabapentin in the treatment of cannabis withdrawal, but further trials are necessary to determine its efficacy [7].

The observed high relapse rates into substance usage suggest that current psychosocial interventions do not completely address the issues leading to either lapse or relapse. The dual process model of addiction [8,9] has been posited to explain the lapse and relapses; this model proposes the involvement of two disparate processes, the reflective and the automatic process [8]. The reflective process involves conscious decision-making, and this has been the target of CBT treatment. Automatic processes refer to that of attentional bias [10], which are unconscious processes that lead individuals to focus on substance-related cues in their naturalistic environment and, having done so, experience a corresponding difficulty in disengaging from cues [10]. Such an automatic process increases the salience of substance-related cues and could potentially draw abusers towards substances. Attention bias could be assessed using indirect measures, like that of Stroop test or a Visual Probe task, or the use of direct measures through eye movement tracking [10]. Indirect measures have the potential to be incorporated into an attention bias modification task, to help individuals cope with automatic processes that increase their intrinsic risk for relapse [11].

To date, there have been several studies that have evaluated the efficacy of attention bias modification paradigms for addictive disorders. Cristea et al [12] undertook a meta-analysis of attention bias modification for alcohol and tobacco disorders and found no significant effect of cognitive bias modification on craving and addiction outcomes, even though there was a moderate effect on cognitive bias. Their findings are important as they demonstrate the presence of cognitive bias. In addition, attention bias modification was effective against such biases. Unfortunately, Cristea et al's [12] meta-analysis was unable to demonstrate significant changes in secondary outcomes, but this could be because more follow-up time is required before a change in symptomatology is detectable. This review was further limited by the high risk of bias amongst the studies included and its focus being limited to alcohol or tobacco. Christiansen et al's [13] review had a wider target, including individuals who were using alcohol, tobacco, cocaine and cannabis. They attempted to appraise the existing evidence to determine whether attention bias assessed in treatment settings are predictive of relapse and whether modifying attention bias can help improve outcomes. Their review found mixed evidence. This study, however, had a number of limitations: the intrinsic methodological weaknesses of the included studies, the lack of clarity about inclusion and exclusion criteria, the time frame during which the search was conducted, and using search results from only PubMed and Scopus.

To date, there has been research that has examined attention bias and determined the effectiveness of attention bias modification in other addictive disorders, like opiate use disorder [14], cannabis use disorder [15] as well as amphetamine or stimulant use disorder [16]. However, there has been no evidence synthesis of these studies. There is a need to synthesize the information about attention bias and bias modification among opiate use, cannabis use and stimulant use disorder. This gap needs addressing urgently as these substances are being increasingly utilized globally. It will also be pertinent to determine the efficacy of attention bias modification interventions among these disorders.

Review Aims

The primary aim of this systematic review is to synthesize the current evidence with regards to attention bias among opioid use, cannabis use and stimulant use disorders. As a secondary aim, it will determine the efficacy of attentional bias modification interventions, including attentional bias reduction, cravings score and addiction outcomes. These will be correlated with the methodology that is being utilized in attention bias assessment and modification.

We will undertake a systematic review to synthesize the existing evidence for the presence of attention bias in the disorders mentioned above, and to determine the clinical efficacy of attention bias modification. The studies will be selected by

independent assessors and screened against our inclusion and exclusion criteria. A risk of bias assessment will be conducted to assess the quality of the included studies.

If there are sufficient studies, a meta-analytical review will be conducted to determine the effect size of attention bias modification intervention for opioid use, cannabis use and stimulant use disorders.

Methods

Search Strategy

To identify the relevant articles, search terminologies as outlined in Textbox 1 will be used. The search terms will be combined using the Boolean operator "OR" and the search terms between two disparate concepts will be combined using the Boolean operator "AND".

A comprehensive search will be conducted on the following databases: PubMed, MEDLINE, Embase, PsycINFO, Science Direct, Cochrane CENTRAL and Scopus. If full-text access is not available, the original authors will be contacted for their articles. Proceedings from scientific meetings and conference abstracts will also be included.

Inclusion and Exclusion Criteria

Only articles written in English will be included. The inclusion criteria are as follows: (a) attention bias assessed using a validated measure (such as that of Stroop test or Visual Probe/Dot-Probe Task); (b) participants in the studies must have a primary diagnosis of opiate use, cannabis use or stimulant use disorder; and (c) the study design must be a randomized trial. Studies will be excluded if (a) they have not included a validated measure for the assessment of attention bias (such as Stroop Test or Visual Probe/Dot-Probe Task); (b) participants in the studies have been diagnosed with another mental health disorders as their primary disorder (eg, depression as the primary disorder and substance use disorder as the secondary diagnosis); (c) studies involved a pharmacological intervention in which medications were utilized to determine their effects on attention bias; and (d) the randomized trial involved a cross-over design (given the high risk of bias associated with a cross-over design).

Condition or Domain Being Studied

This systematic review focuses on substance use disorders, and in particular, opioid use, cannabis use and stimulant use disorder.

Participants

Participants must be diagnosed with a substance use disorder, that of opioid use, cannabis use or stimulant use disorder, as the main or primary disorder. Participants may include individuals from the general population or a treatment-seeking cohort, and can be adolescent or adult.

Intervention / Exposure

The intervention administered to participants is either that of a Stroop or Visual Probe/Dot-Probe attention modification task.

Comparison with Placebo Group

Individuals may be compared with individuals who have received a placebo training or sham training interventions or individuals who have received only normal routine care.

Outcome

For the primary aim, the outcome will be the presence of attention bias as measured using a validated assessment tool. Attention bias is deemed to be present if participants are noted to have a longer reaction time spent on drug-related stimuli as compared to neutral stimuli.

For the secondary aim, the outcomes will be: a) reduction in the mean reaction time following the attention bias modification intervention; b) score reductions on validated craving measures (either a single-dimensional score, or a visual analogue scale or a multidimensional score such as that of the obsessive-compulsive craving score); and c) addiction outcomes, such as the mean time to relapse or the time maintained in abstinence.

Data Extraction, Sorting and Selection

The search strategy will identify articles that may have potential relevance. Selection of relevant publications will be conducted independently by two authors (MWBZ and JY). Articles will be first screened based on their title and abstract. Those shortlisted will be evaluated against the inclusion and exclusion criteria. Any disagreement between the two reviewers will be resolved through a discussion with the third author. An electronic form will be utilized to record the reasons for the inclusion and exclusion of each article. The current systematic review protocol will adhere to the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols [17].

The following data and information will be extracted from each article, recorded on a standardized electronic data collation form and cross-checked by the second author:

1. Publication details: author(s) and study year.
2. Study design and methodology: study design, sample size (intervention and control group), types of sample (treatment seeking or individuals in general population), country in which study was conducted, demographics of sample (mean age, age range, proportion of males and females), diagnosis of participants (opioid use, cannabis use or stimulant use disorder), methodology in which diagnosis is made.
3. Attention bias assessment and modification methodology: types of attention bias tools utilized (Stroop test or Visual Probe task).
4. Outcomes of interest: craving scores (as assessed using a validated questionnaire or toolkit), addiction outcomes (time to next relapse, amount of substances used), effect size (Cohen's *d* or Hedges' *g*) for attention bias modification procedure.

Textbox 1. Search terminologies.

("attention bias" OR "approach bias" OR "avoidance bias" OR "cognitive bias") AND ("addiction" OR "substance" OR "drug" OR "abuse" OR "Dependence" OR "Alcohol" OR "Drinking" OR "Opiates" OR "Heroin" OR "Cannabis" OR "Marijuana" OR "Stimulants" OR "Amphetamines" OR "Cocaine")

Quality Assessment

For the risk of bias assessment, the Cochrane Risk of Bias tool [18] will be used.

Strategy for Data Integration and Synthesis

For the systematic review, we will synthesize and report whether attention bias was present and how its presence was determined. We will also synthesize the findings of the studies narratively and report whether attention bias modification was effective.

If there are sufficient studies for each of the conditions, a meta-analysis will be conducted to synthesize statistically the pooled effect size for attention bias modification for opiate use disorder, cannabis use and stimulant use disorders. For the meta-analytic study, the statistical analysis will be performed using Comprehensive Meta-Analysis Version 2.0 based on the random-effects model. The random effects model assumes that there are varying effect sizes between the studies, due to the underlying differences in study designs and intrinsic heterogeneity of the sampled populations. The statistical analysis will compute the pooled effect size to determine the clinical efficacy of attention bias modification and to identify potential moderators (both categorical and continuous variables) that could account for the heterogeneity in the effect size computed. Between-study heterogeneity will be assessed with the I^2 statistic, which describes the percentage of variability among effect estimates beyond that expected by chance. As a reference, I^2 values of 25% are considered low, 50% moderate and 75% high in heterogeneity. Meta-regression analysis will be conducted to identify demographic variables that could contribute to the heterogeneity and the effect size computed. The regression coefficients and the associated *Z* and *P* values will be reported. Subgroup analysis will be undertaken to investigate the effects of categorical variables on the effect size obtained. For the meta-analysis, Egger's regression test will be conducted to determine if publication bias is present. If there is significant publication bias, the classic fail-safe test will be performed to determine the number of missing studies that will be required for the *P* value of the publication bias to be higher than .05.

Results

We expect that the review will be completed 12 months from the publication of this protocol. We will report the results based on the identified outcomes as specified above.

Discussion

We are aware of the prior reviews investigating the efficacy of attention bias modification among substance use disorders, but these have been limited by the inclusion of select studies involving cohorts who have either alcohol use or tobacco use disorders. As there is a proliferation of research examining attention bias and bias modification among other highly prevalent substance use disorders, particularly that of opiate use, cannabis use and stimulant use disorders, there is a need to synthesize the evidence for attention bias and attention bias modification for these disorders. It is important to establish that attention bias is present in these disorders, and that it could be amenable to modification using conventional paradigms such as the Stroop testing or Visual Probe task.

The findings of this proposed review will have important clinical implications. Should attention biases be found among individuals with opioid, cannabis and stimulant use disorder, clinicians will need to review their treatment strategies. Rather relying on a single modality of therapy to modify conscious control, they will need to augment the conventional psychological interventions with one that targets attention bias. The current review will also determine which indirect method of bias modification is more efficacious for bias modification in substance using cohorts.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioural therapy

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Protocol

Clinical Feasibility of Continuously Monitored Data for Heart Rate, Physical Activity, and Sleeping by Wearable Activity Trackers in Patients with Thyrotoxicosis: Protocol for a Prospective Longitudinal Observational Study

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Abstract

Background: Thyrotoxicosis is a common disease caused by an excess of thyroid hormones. The prevalence of thyrotoxicosis about 2% and 70-90% of thyrotoxicosis cases are caused by Graves' disease, an autoimmune disease, which has a high recurrence rate when treated with antithyroid drugs such as methimazole or propylthiouracil. The clinical symptoms and signs of thyrotoxicosis include palpitation, weight loss, restlessness, and difficulty sleeping. Although these clinical changes in thyrotoxicosis can be detected by currently available wearable activity trackers, there have been few trials of the clinical application of wearable devices in patients with thyrotoxicosis.

Objective: The aim of this study is to investigate the clinical applicability of wearable device-generated data to the management of thyrotoxicosis. We are analyzing continuously monitored data for heart rate, physical activity, and sleep in patients with thyrotoxicosis during their clinical course after treatment.

Methods: Thirty thyrotoxic patients and 10 control subjects were enrolled in this study at Seoul National University Bundang Hospital. Heart rate, physical activity, and sleep are being monitored using a Fitbit Charge HR or Fitbit Charge 2. Clinical data including anthropometric measures, thyroid function test, and hyperthyroidism symptom scale are recorded.

Results: Study enrollment began in December 2016, and the intervention and follow-up phases are ongoing. The results of the data analysis are expected to be available by September 2017.

Conclusions: This study will provide a foundational feasibility trial of the clinical applications of biosignal measurements to the differential diagnosis, prediction of clinical course, early detection of recurrence, and treatment in patients with thyrotoxicosis.

Trial Registration: ClinicalTrials.gov NCT03009357; https://clinicaltrials.gov/ct2/show/NCT03009357 (Archived by WebCite at http://www.webcitation.org/6wh4MWPm2)

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KEYWORDS

activity tracker; pulse rate; thyrotoxicosis; hyperthyroidism; Graves' disease

Introduction

Thyrotoxicosis is clinical term that refers collectively to all symptoms that occur when an excess of thyroid hormones (free thyroxine [T4] and/or free triiodothyronine [T3]) is supplied to the peripheral tissues. The term "hyperthyroidism" is used in a similar way and refers to thyrotoxicosis caused by excessive production and secretion of thyroid hormone from the thyroid gland. Thyrotoxicosis is caused by hyperthyroidism, but it can occur without hyperthyroidism. Graves' disease is an organ-specific autoimmune disease in which autoantibodies to thyroid-stimulating hormone receptors stimulate the thyroid gland, which causes hyperthyroidism. The prevalence of thyrotoxicosis is about 2%, and 70-90% of cases are caused by Graves' disease, although the rates and causes vary between different geographic areas [1,2]. The incidence and prevalence rates of thyrotoxicosis have not been reported in Korea. However, among thyrotoxic patients treated in the thyroid clinic of Seoul National University Hospital, the rates of Graves's disease and thyroiditis were reported to be 82.7% and 16.8%, respectively [3]. Graves' disease is an autoimmune disease. There are 3 options for treating patients with this disease: antithyroid drugs (ATDs), radioactive iodine ablation, and surgery. The choice of treatment for Graves's disease differs between geographical regions. Radioactive iodine therapy is frequently used as the first-line therapy in North America [4]. In Europe and Asia, ATDs such as methimazole, propylthiouracil are preferred as the primary treatment [5,6]. A drawback of ATD therapy is the high rate of relapse of hyperthyroidism after the drug has been discontinued. Relapse is more frequent in the first year than in subsequent years, particularly in the first 6 months after stopping the medication [7]. The risk of recurrence varies greatly between patients but is estimated to be 50-55% according to a Cochrane review of 26 randomized clinical trials [8]. Patients with recurrent Graves' disease often wait a considerable time after recurrence to visit the clinic and often present with aggravated symptoms. Therefore, having a simple effective monitoring tool for evaluating disease status would be helpful for monitoring patients with Graves' disease after they stop taking an ATD.

Excess thyroid hormone affects many different organ systems. The clinical symptoms signs are fatigue, anxiety, palpitations, sweating, heat intolerance, anxiety, disturbed sleep, and weight loss [9]. These clinical manifestations are relatively nonspecific and can vary depending on several factors, such as the patient's age, sex, comorbidities, and duration and cause of the disease [10,11]. The variety of nonspecific symptoms and signs makes it difficult to diagnose or assess the disease status based on conventionally obtained information about symptoms and signs. Therefore, thyrotoxicosis is diagnosed by blood tests showing increased thyroid hormone levels. The diagnosis is often delayed because patients do not recognize their symptoms as those of thyroid dysfunction and visit a clinic only when the symptoms become severe.

Wearable activity trackers have grown in popularity over the past few years. The American College of Sports Medicine survey of fitness trends reported that wearable technology was the top-rated trend for 2016 [12]. It was projected that about 32 million wearable activity trackers will have been sold by the end of 2016, and forecasts indicate that sales of these devices will exceed 82 million by 2019 [13]. These devices are typically worn on the wrist or hip and provide information about physical activity measures such as steps taken, horizontal and vertical distances moved, sleep pattern, and even heart rate. Many newer wearable devices use photoplethysmography to monitor heart rate by measuring the differential reflection of light from the skin based on the pulsatility of superficial blood vessels [14]. Several studies have been published on the accuracy of these wrist-worn heart rate monitors and have shown that they are accurate for measuring heart rate in the resting state [15-17]. Therefore, it is now possible to analyze more detailed, precise, and continuously collected "high-definition data" of the changes in heart rate, physical activity, and sleep patterns. This may allow the identification of key symptoms and signs of thyrotoxicosis, which can be nonspecific and difficult to detect by only conventional on-site history taking or physical examination [18]. However, few trials have examined the clinical applicability of wearable devices in monitoring patients with thyrotoxicosis.

The aim of this trial is to investigate whether changes in symptoms and signs of thyrotoxicosis, such as heart rate, physical activity, and sleep pattern, can be monitored by wearable devices during the course of thyrotoxicosis and whether these have clinical applications.

Methods

Study Setting

This is a single-centered, prospective observational study to analyze the changes in heart rate, physical activity, and sleep patterns monitored by commercially available wearable devices during the clinical course of thyrotoxicosis. Subjects have been recruited from the outpatient clinic of the endocrinology department at Seoul National University Bundang Hospital (SNUBH). Among those with newly diagnosed or recurrent thyrotoxicosis, we have included 30 patients who met the inclusion criteria. Ten healthy age- and sex-matched volunteers were also included as a control group.

Table 1. Inclusion and exclusion criteria for patient and control groups.

Group	Inclusion criteria	Exclusion criteria
Patients	1. Aged 15-60 years 2. Diagnosed with newly developed or recurrent thyrotoxicosis 3. Who can use a wearable device and smartphone apps 4. Planned to be treated with ATDs if affected by Graves' disease	1. A history of thyrotoxic periodic paralysis 2. Thyrotoxicosis caused by toxic nodular goiter 3. Taking medications that can affect heart rate (except short-acting beta-blockers prescribed to relieve thyrotoxic symptoms)
Controls	1. Aged 15-60 years 2. Confirmed euthyroid state by TFT 3. Who can use a wearable device and smartphone apps	1. A history of thyroid disease or taking thyroid hormone or an ATD 2. Taking medications that can affect heart rate

[a]ATD: antithyroid drug

[b]TFT: thyroid function test

Inclusion and Exclusion Criteria

The inclusion criteria for enrolment are listed in Table 1. We have included patients and controls aged 15-60 years because this age range is generally expected to be able to use wearable devices, smartphones, and apps. Patients were excluded from the study if they have a history of thyrotoxic periodic paralysis because paralysis itself can interfere with daily activities. Patients with thyrotoxicosis caused by toxic nodular goiter were also excluded because this condition needs treatment options, such as surgery or radioactive iodine therapy, and gradual improvement is not observed after these treatments. Prescription of beta-blockers to the patients is the usual treatment for the symptoms of thyrotoxicosis. Therefore, we prescribed short-acting beta-blockers to symptomatic patients and recorded their dosing times to minimize the impact on the study.

The healthy control group included euthyroid people who have no history of thyroid disease. We recruited the control group from SNUBH staff and confirmed that they had no history of thyroid disease and no abnormal findings or medications that can affect heart rate through their medical history, which included employee health examinations and an interview.

When patients or controls visited the clinic and agreed to participate in this study, we explained how to use and manage the wearable device (eg, synchronization, charging, basic settings), download and install smartphone apps, and create an account. We then check that they can use and manage their devices by letting them repeat all processes mentioned above.

Protocol

This protocol has been approved by the SNUBH Institutional Review Board (IRB #: B-1609-363-004) and is registered at ClinicalTrials.gov (trial registration number NCT03009357). The study design is displayed in Figure 1. All patients participating in the study were informed of the study and signed a written consent form.

Blood tests include a thyroid function test, serum levels of antithyroid-stimulating hormone receptor antibody, and other biochemical tests. Tc-99m is used in the thyroid scan. P/Ex, physical examination; HSS, hyperthyroidism symptom scale; ATD, antithyroid drug.

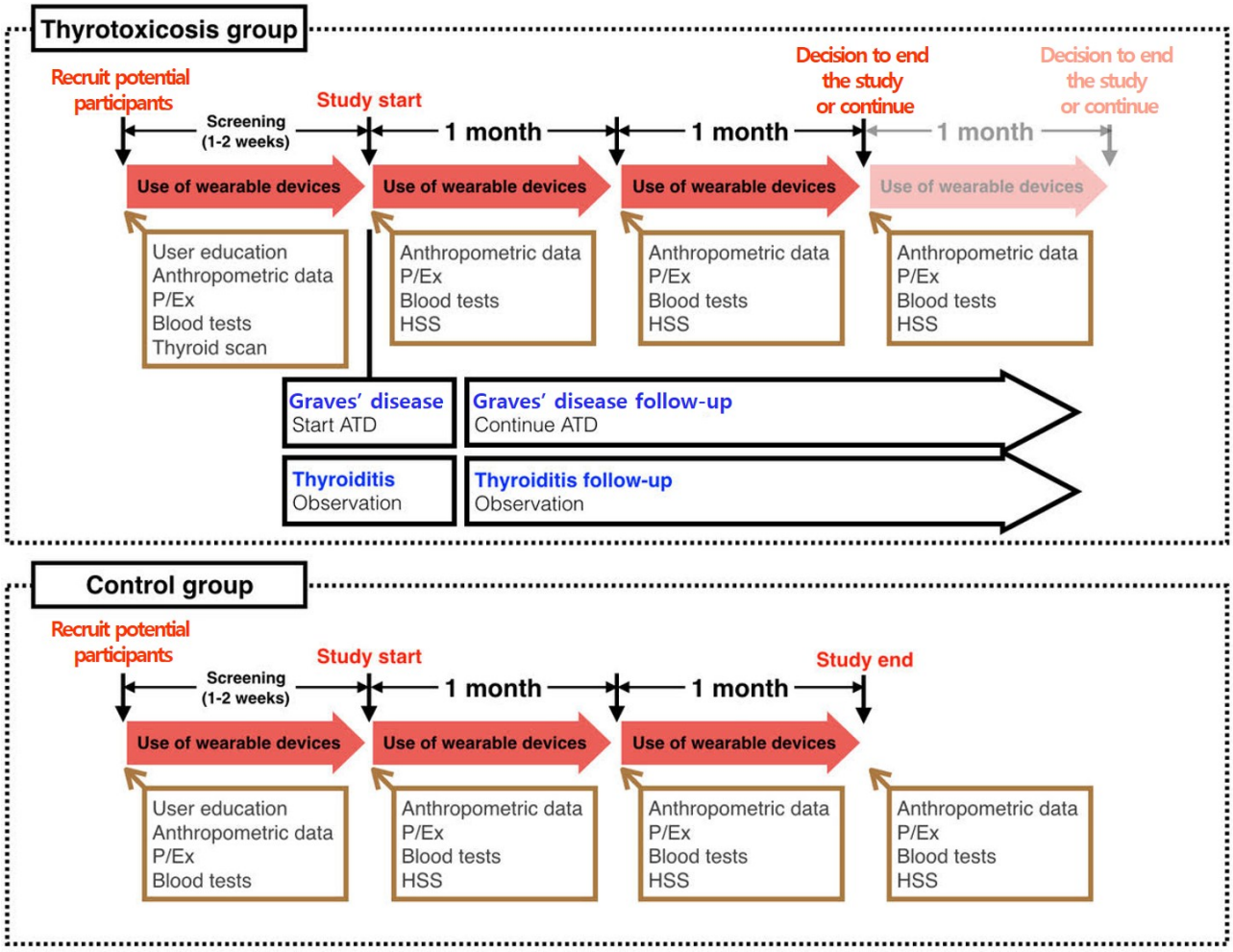
The potential candidates of this study are patients with newly detected or recurrent thyrotoxicosis who meet the eligibility criteria. They are provided with a device and given brief on-site instructions for using the device and app, which is installed on their own smartphone. They are instructed to wear the device as much as possible throughout the day including when asleep. We also explain that if they do not wear the device or sync to the app for more than 5 days in a row, they will be excluded from the study because of poor compliance. After 1 to 2 weeks of screening period, the patients visit the clinic to confirm the results of the thyroid function test (TFT) and other tests to distinguish the cause (eg, autoantibodies, thyroid scan) and to start treatment according to the cause of thyrotoxicosis. At this point, patients are finally enrolled, and the study period starts.

Patients with Graves' disease are prescribed a specific dose of an ATD as decided by the physician. Patients with transient thyrotoxicosis caused by thyroiditis are provided reassurance that the symptoms and signs are benign and self-limited. Patients taking a beta-blocker for control of symptoms, such as palpitations and tremor, are advised to take the drug when the symptoms are severe and to inform the investigator the dose and timing of the drug, which are recorded in the care report form (CRF). Regardless of the cause of thyrotoxicosis, all patients are being followed up once a month, when they undergo blood tests and a physical examination, complete the hyperthyroidism symptom scale (HSS), and have their anthropometric parameters measured. The ATD dose is adjusted as necessary. The study will end after the third visit for each patient. At the discretion of the attending physician and if the patient agrees, the duration of this observational study may be extended if thyroid function is not fully restored. Additional consent for extension of the study period is not necessary because it is already specified in the initial consent form.

Healthy adults have been recruited as a control group through an official announcement in SNUBH. The controls visit the hospital on the same schedule as the patients with thyrotoxicosis. They are provided the same instructions as the patients about using the device and apps installed on their own smartphone, and the importance of compliance. They also undergo the same blood tests as the patients and are instructed to inform the investigator if there is any change in their medication; this information is recorded in the CRF.

After the research process is completed, the subjects who were not excluded from the study during the study observation period will be allowed to keep the device.

Figure 1. Study design and flow.Blood tests include a thyroid function test, serum levels of antithyroid-stimulating hormone receptor antibody, and other biochemical tests. Tc-99m is used in the thyroid scan. P/Ex, physical examination; HSS, hyperthyroidism symptom scale; ATD, antithyroid drug.



Hyperthyroidism Symptom Scale

To assess the clinical status of hyperthyroidism, the endocrinologist in charge of this study evaluated the patients using the HSS [19]. This scoring system has been reported to reflect the status of thyroid function well [20,21]. This allows us to compare the relationships between the data from the wearable devices and TFTs with those between the HSS and thyroid function. The HSS is a 10-item scale that rates symptoms and signs of thyrotoxicosis; the information needed to rate each item is obtained through history taking and physical examination. Among the 10 items of the HSS, those corresponding to nervousness, sweating, heat intolerance, hyperactivity, weakness, diarrhea, appetite, and assessment of daily function were evaluated through history taking, and tremor and hyperdynamic precordium were evaluated by physical examination. The item scores are totaled to obtain the overall score, which can range from 0 to 40 points.

Wearable Devices and Apps

We are using the Fitbit charge HR or Fitbit charge 2 (Fitbit, San Francisco, CA, USA) and Fitbit apps for iOS or Android. The firmware version of this app is currently 18.122 and this latest version has been maintained continuously over the observation period.

During the study period and with the patient's consent, each participant's account information from the Fitbit app, including identification number and password, are shared with researchers, which allows researchers to access the account of Fitbit website [22] and monitoring of sync status between the Fitbit app and the individual patient's Fitbit tracking device. At the end of the study, we will separate the account from the device and allow each participant to have their own account.

Anthropometric and Biochemical Measurements

Height and weight are measured with the subject in light clothing and without shoes to the nearest 0.1 cm and 0.1 kg, respectively. Body mass index is calculated as the ratio of weight and to the square of height (expressed in kilograms per square meter). Blood pressure and heart rate were measured on the right arm with the subject in a seated position. Serum levels of blood urea nitrogen, creatinine and glucose were measured by automated standard laboratory methods (Hitachi 747; Hitachi, Tokyo, Japan). Serum total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase were measured with an autoanalyzer (TBA-200FR; Toshiba, Tokyo, Japan). For TFT, concentrations of serum T4 (DiaSorin, Saluggia, Italy) and thyroid-stimulating hormone (TSH; CIS Bio International, Gif-sur-Yvette, France) were measured using immunoradiometric assays. The free T4 assay had an analytical sensitivity of 0.05 ng/dl, while that for

TSH had an analytical sensitivity of 0.04 mIU/l and a functional sensitivity of 0.07 mIU/l. The reference ranges for free T4 and TSH were 0.89-1.79 ng/dl and 0.3-4.0 mIU/l, respectively. Thyrotoxicosis was defined based on the results of the TFT: that is, overt thyrotoxicosis was defined as high free T4 and low TSH, and subclinical thyrotoxicosis as normal free T4 and low TSH. All subjects were examined for the presence of anti-TSH receptor antibody by radioimmunoassay (Cis Bio International) and the cutoff for positivity was >1.0 U/ml.

Outcome Measures

The primary goal of this study is to verify the changes in heart rate, physical activity, and sleep-related values generated from wearable devices during the clinical course of thyrotoxicosis. We will compare these device-generated data with conventionally evaluated symptoms and signs and analyze the relationships between each parameter and disease status.

Heart Rate

Using the heart rate data recorded by the device and provided by the Fitbit database mentioned below, we will analyze all summary and detailed heart rate data including resting heart rate for the study duration.

Physical Activity

We will analyze all summary and detailed data for physical activity, including total steps per day and total moving distance per day in both the horizontal and vertical directions.

Sleep

We will analyze the sleep data including total time asleep, total number and time of awakening, and sleep efficiency, which is calculated as the total time asleep divided by the total time in bed. We will also assess the data for “minutes to fall asleep” using the app mentioned above.

Data Collection

We can download interday summary and intraday detailed data for heart rate, physical activity, and sleep from the Fitbit database in JSON format using an app programming interface which is provided by Fitbit [23]. An example of the downloaded data is shown in Figures 2 and 3.

Data Analysis

To compare variables between the patient and control groups, we will use the Mann–Whitney test or Student’s *t* test for continuous variables and the chi-square test for categorical variables. Repeated-measures ANOVA or the Friedman test will be used to analyze the changes in TFT, blood pressure, heart rate, and physical indices measured by wearable devices. The relationships between disease status and heart rate, physical activity, and sleep will be derived from the linear model of generalized estimating equation (GEE) analyses. Models to prediction thyrotoxicosis will incorporate variables related to heart rate, physical activity, and sleep derived from the binary logistic model of the GEE analyses. Odds ratios with 95% confidence intervals will be computed per standard deviation increase in these variables in relation to the risk of thyrotoxicosis. All statistical analyses will be performed using IBM SPSS Statistics (version 20.0; IBM Corp, Armonk, NY, USA) and R (version 3.3.3; The R Foundation for Statistical Computing, Vienna, Austria).

Figure 2. Examples of downloaded heart rate data. Summary.

Date	Rest. Heart Rate	Normal				Fat Burn				Cardio				Peak			
		Min HR	Max HR	Calories	Minutes	Min HR	Max HR	Calories	Minutes	Min HR	Max HR	Calories	Minutes	Min HR	Max HR	Calories	Minutes
2017-04-21	66	30	88	1249.18612	992	88	123	799.0346	307	123	150	0	0	150	220	0	0
2017-04-22	65	30	88	1277.5945	1168	88	123	467.44698	224	123	150	0	0	150	220	0	0
2017-04-23	68	30	88	929.18098	889	88	123	1081.5532	368	123	150	0	0	150	220	0	0
2017-04-24	65	30	88	1139.30908	1061	88	123	692.05318	282	123	150	20.3476	4	150	220	14.55636	2
2017-04-25	64	30	88	1265.15116	1201	88	123	265.22314	100	123	150	0	0	150	220	0	0
2017-04-26	63	30	88	1306.942	1092	88	123	760.60894	307	123	150	0	0	150	220	0	0
2017-04-27	65	30	88	1050.48398	987	88	123	742.37436	363	123	150	9.23468	2	150	220	0	0
2017-04-28	66	30	88	1267.73374	1075	88	123	690.95754	300	123	150	0	0	150	220	0	0
2017-04-29	66	30	88	1005.56274	1001	88	123	777.35658	310	123	150	5.32168	1	150	220	0	0
2017-04-30	67	30	88	1043.51884	994	88	123	678.35768	321	123	150	11.26944	2	150	220	0	0

Figure 3. Examples of downloaded heart rate data. Intraday.

HEART RATE DATE/TIME	VALUE
2017-04-21 00:00:00	64
2017-04-21 00:00:10	65
2017-04-21 00:00:25	65
2017-04-21 00:00:40	65
2017-04-21 00:00:50	64
2017-04-21 00:01:00	65
2017-04-21 00:01:15	65
2017-04-21 00:01:20	64
2017-04-21 00:01:35	64
2017-04-21 00:01:40	64
2017-04-21 00:01:50	65

2017-04-21 00:02:00	64
2017-04-21 00:02:10	65
2017-04-21 00:02:20	64
2017-04-21 00:02:30	65
2017-04-21 00:02:40	66
2017-04-21 00:02:55	66
2017-04-21 00:03:00	65
2017-04-21 00:03:10	65
2017-04-21 00:03:25	65
2017-04-21 00:03:30	64
2017-04-21 00:03:45	64
2017-04-21 00:03:50	64

2017-04-21 00:04:00	63
2017-04-21 00:04:10	65
2017-04-21 00:04:25	65
2017-04-21 00:04:30	66
2017-04-21 00:04:45	66
2017-04-21 00:04:50	67
2017-04-21 00:05:05	67
2017-04-21 00:05:10	66
2017-04-21 00:05:20	65
2017-04-21 00:05:30	64
2017-04-21 00:05:40	65
2017-04-21 00:05:55	65

Results

Study enrollment began in December 2016. The recruitment of the patient group was completed, and two of the total 30 patients were excluded. One discontinued the study because of a skin reaction to the device (Fitbit Charge HR) on the wrist, and one patient was dropped from the study because of poor compliance in using the device. The remaining 28 patients and all controls completed the study. The data collection process was completed by August 2017. We expect to report the data analysis results in early 2018.

Discussion

In this prospective, observational study, we will investigate the clinical applicability of wearable device-generated data to the management of thyrotoxicosis by analyzing continuously monitored data for heart rate, physical activity, and sleep for patients with thyrotoxicosis during their clinical course after treatment.

Monitoring heart rate in patients with thyrotoxicosis is required because palpitations or tachycardia are among the most common symptoms of thyrotoxicosis [24]. However, heart rate measurement only in the clinic is not enough to obtain valuable information about the disease status because heart rate can be affected by various physical, mental, and circumstantial factors. Therefore, continuous monitoring of heart rate and physical activity using wearable devices can generate much more precise data about heart rate. For example, conventionally, resting heart rate is measured after at least 10 minutes of lying position and it can vary with patients' emotion, body position, or air temperature. Wearable devices continuously measure patients' heart rate and activity and calculate resting heart rate according to the algorithm they have. Generally, resting heart rate of a specific day can be calculated from all heart rate data which are recorded in the time windows with no physical activity during at least 10 minutes (the algorithm can weight to the heart rate data recorded in sleep time). Although user's heart rate still can be affected by other factors mentioned above, this method based on "high-definition data" can generate more consistent and precise data.

Abnormalities in sleep regulation often occur in patients with thyrotoxicosis [25]. However, there are few reports that specifically address sleep problem related to thyrotoxicosis. Sridhar et al performed a retrospective review of medical records to assess the quality of sleep in patients with thyrotoxicosis and found that thyrotoxicosis was associated principally with difficulty falling asleep and maintaining sleep, and that these were related to hyperkinetic features (tremor, appetite change, bowel disturbances) [26]. In our study, we will analyze various indexes related to sleep prospectively according to later changes in thyroid function, which will provide valuable information on the relationship between the quality of sleep and thyroid function.

Patients with hyperthyroidism exhibit a characteristic resting tremor and self-reported increase in voluntary physical activity, heat intolerance, and weight loss [27]. Studies on physical activity and hyperthyroidism in humans have been rarely reported. A study of rats focused on whether physical activity increases because of hyperthyroidism and found that the thyroid hormone excess was associated with increased voluntary physical activity [28]. There are many ways to measure physical activity in humans, such as accelerometers, pedometers, heart rate monitors, and armbands, but this is quite complex [29]. It is also important to choose the most appropriate method for obtaining the data we intend to collect because none of these methods alone can assess all facets of physical activity. Moreover, because thyrotoxicosis can increase heart rate,

assessing physical activity using only heart rate monitoring is not suitable for this study. Therefore, wearable devices with an accelerometer, global positioning system, and heart rate sensor in one device will provide more accurate physical activity data.

The major strength of this study is that it is the first study to monitor heart rate, physical activity, and sleep throughout the day using commercially available wearable devices in patients with thyrotoxicosis. This study also has some important clinical implications. We expect that the data derived from the continuous monitoring of these clinical parameters will be useful for the differential diagnosis of thyrotoxicosis. The two most common causes of thyrotoxicosis are Graves' disease and thyroiditis. Although the clinical symptoms and signs tend to be more abrupt in patients with thyroiditis, clinically it is difficult to distinguish these through conventional interviews and physical examination. Therefore, continuously collected "high-definition data" should help to differentiate the clinical presentation according to the cause of thyrotoxicosis. If so, this will save time and cost in not having to perform the biochemical and radiological tests currently needed to make the differential diagnosis.

We also expect that these high-definition data may be useful for predicting the therapeutic response and clinical course. After starting the medication, patients must repeat blood testing for thyroid hormone levels every 1 or 2 months. If the dose of medication is insufficient or the disease is unresponsive to the medical treatment, the patient must endure the clinical symptoms until the next visit. Ideally, more frequent tests will provide more detailed information about the clinical course, but more frequent tests also inconvenience the patient and add to the cost. Being able to monitor the clinical course using biosignals from wearable devices may provide patients with faster and more accurate interventions during the treatment and follow-up process. In addition, if these detailed clinical parameters accurately reflect the changes in thyroid function, we expect that the recurrence of thyrotoxicosis may be detected earlier. We hope that the results of this study will allow us to develop apps to calculate the real-time risk of thyrotoxicosis for patients who discontinue their medication and therefore encourage the patient to attend the clinic promptly to receive the diagnosis of and treatment for recurrent thyrotoxicosis.

There are some limitations, which should be considered when interpreting the results. First, to control their symptoms, about 50% of the patients with thyrotoxicosis have been prescribed the nonselective beta-blocker propranolol with a relatively short duration of action. However, patients in the current study who have been prescribed medications have so far reported that they have not taken it continuously for more than 1 day; the drug's maximum effects appear 60-90 minutes after oral administration [30]. The heart rate will be monitored constantly even when it is not expected to be affected by the propranolol taken. Therefore, the effect of beta-blockade on the primary outcome of this study should be minimized by recording the date and time of taking each propranolol dose. In addition, the small sample size and single study site will provide useful results, but the study will need to be replicated with more participants and study sites.

The technologies to measure and analyze biosignals have not been developed fully, but have been extended from specific medical uses, such as in intensive care units or surgical monitoring, to everyday life. This evolution of technologies will eventually allow for easy, effective, and continuous monitoring of chronic diseases. Thyrotoxicosis changes various biosignals including heart rate and physical activity through the effect of excessive thyroid hormone. Currently available commercial wearable devices are expected to detect these changes in biosignals in thyrotoxic patients. We expect our study to provide clinical evidence of the usefulness of wearable devices for managing thyrotoxicosis.

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Conflicts of Interest

None declared

Authors' Contributions

JEL and JHM designed the study. JEL, JHM, DHL, TJO, KMK, SHC, SL, YJP, DJP, and HCK contributed data interpretation. JEL and JHM collected and analyzed the data. JEL and JHM drafted the manuscript. All authors agreed on the final content of the manuscript.

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Abbreviations

ATD: antithyroid drug
CRF: case report form
GEE: generalized estimating equation
HSS: hyperthyroidism symptom scale
SNUBH: Seoul National University Bundang Hospital
T3: triiodothyronine
T4: thyroxine
TFT: thyroid function test
TSH: thyroid hormone stimulating hormone

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Protocol

Implementation of the Enhanced Moderated Online Social Therapy (MOST+) Model Within a National Youth E-Mental Health Service (eheadspace): Protocol for a Single Group Pilot Study for Help-Seeking Young People

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Abstract

Background: There is a substantial need for youth electronic mental health (e-mental health) services. In addressing this need, our team has developed a novel moderated online social therapy intervention called enhanced moderated online social therapy (MOST+). MOST+ integrates real-time, clinician-delivered Web chat counseling, interactive user-directed online therapy, expert and peer moderation, and private and secure peer-to-peer social networking. MOST+ has been designed to give young people immediate, 24-hour access to anonymous, evidence-based, and short-term mental health care.

Objective: The primary aims of this pilot study were to determine the feasibility, acceptability, and safety of the intervention. Secondary aims were to assess prepost changes in key psychosocial outcomes and collect qualitative data for future intervention refinement.

Methods: MOST+ will be embedded within eheadspace, an Australian youth e-mental health service, and will be evaluated via an uncontrolled single-group study. Approximately 250 help-seeking young people (16-25 years) will be progressively recruited to the intervention from the eheadspace home page over the first 4 weeks of an 8-week intervention period. All participants will have access to evidence-based therapeutic content and integrated Web chat counseling. Additional access to moderated peer-to-peer social networking will be granted to individuals for whom it is deemed safe and appropriate, through a three-tiered screening process. Participants will be enrolled in the MOST+ intervention for 1 week, with the option to renew their enrollment across the duration of the pilot. Participants will complete a survey at enrollment to assess psychological well-being and other mental health outcomes. Additional assessment will occur following account deactivation (ie, after participant has opted not to renew their

enrollment, or at trial conclusion) and will include an online survey and telephone interview assessing psychological well-being and experience of using MOST+.

Results: Recruitment for the study commenced in October 2017. We expect to have initial results in March 2018, with more detailed qualitative and quantitative analyses to follow.

Conclusions: This is the first Australia-wide research trial to pilot an online social media platform merging real-time clinical support, expert and peer moderation, interactive online therapy, and peer-to-peer social networking. The importance of the project stems from the need to develop innovative new models for the efficient delivery of responsive evidence-based online support to help-seeking young people. If successful, this research stands to complement and enhance e-mental health services in Australia.

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KEYWORDS

internet; social networking; young adult; adolescent; mental heath

Introduction

Relative to the burden of disease, engagement rates with mental health services fall disappointingly below those for physical ill health [1]. This is especially true for young people aged 16 to 25 years—a period known for the peak onset of high prevalence and severe mental disorders such as depression and anxiety [2]. Given young people's enthusiasm for Web-based communication, the development of innovative, online psychosocial interventions may assist to improve treatment acceptability and access for young people experiencing mental ill health [3]. Furthermore, social networking sites are rapidly becoming an essential avenue for social communication and support [4] and are likely to be pivotal to youth engagement with mental health services [5].

Mobile and digital technologies are developing at a phenomenal rate and hold great promise for influencing and transforming treatment delivery for emerging mental health conditions [6]. These technologies can be particularly useful for young people, as individuals under 25 years are by far the greatest users of internet resources [7]. For instance, over 95% of young Australians use the internet daily, and 97% have access to mobile phones, most of which are internet-enabled [8].

Although young people tend to nominate face-to-face support as their preferred mode of help-seeking for depression [9], a significant number indicate preference for online intervention because of the added anonymity and immediacy associated with the online environment [10]. Given their ability to transcend geographical boundaries and provide 24-hour accessibility, online interventions have the added potential to reach young people who may not be able or inclined to seek help from traditional sources [11,12].

In recent years, a range of online interventions have been successfully trialed for the management of a number of mental disorders, with research supporting the efficacy of these interventions in alleviating anxiety and depressive symptoms [13-15]. Online interventions have been reported as being as effective as face-to-face therapy [11], and a number of countries now recommend the use of online interventions within clinical guidelines for the treatment of high prevalence mental disorders such as depression [16].

At present, electronic mental health (e-mental health) services provide either nonclinical peer-to-peer support or clinical support or online therapy with no integrated online social networking and peer support or moderation [17-19]. In 2011, Australia's headspace—National Youth Mental Health Foundation (headspace) began providing an e-mental health service (eheadspace) to extend the enhanced primary care services that had been provided through headspace centers across Australia since 2006 [12]. The headspace centers provide youth-friendly and low-stigma access to mental health care and have been effective in improving the mental health outcomes of those who access their services [20]. The eheadspace service delivers online chat, email, and telephone counseling provided by qualified clinicians at no cost to the young person in an effort to support young Australians who are unable or disinclined to seek professional support in person [12]. The eheadspace service is very popular among young Australians with over 25,000 clinical contacts per year across the country. Given the high demand and acceptability of this service, the next generation of eheadspace could harness the potential of Web 2.0 by fully integrating online professional support with high-quality, engaging, user-directed therapy and peer-to-peer social networking capability. These innovations have the potential to cater for the needs and preferences of more young people and provide a 24/7 therapeutic environment that extends beyond 1:1 clinical support to enable its scalability.

We have pioneered a new model of online behavioral interventions entitled *Moderated Online Social Therapy* (MOST) [21-27]. The MOST model integrates (1) Peer-to-peer online social networking, (2) Individually tailored interactive psychosocial interventions focused on using and developing self-identified strengths, and (3) Involvement of expert mental health and peer moderators to ensure the safety of the intervention. This model has been successfully piloted with young people experiencing first episode psychosis (the *Horyzons* study [21]) and major depression (the *Rebound* study [25,27]), as well as with carers of young people recovering from a first episode of psychosis (the *Altitudes* study [23]) and diagnosed with anxiety or depression (the *Meridian* study [24]).

To meet the specific needs of young people accessing eheadspace services, the MOST model has been upgraded to integrate Web chat services provided by eheadspace within a secure online social media environment. Referred to as MOST+, this enhanced moderated online social therapy model offers

short-term interventions that capitalize on anonymity, social networking, and the broad availability and comparative low cost of social media–based interventions. By supplementing Web chat and telephone services with a wider array of online support, MOST+ stands to offer young people access to multiple modes of therapy, catering to the needs of different individuals.

Primary aims of the MOST+ pilot (Trial Registration: ACTRN12617000370303) were to determine the feasibility, acceptability, and safety of the intervention for young people aged 16 to 25 years who have accessed eheadspace services for mental health support. A secondary aim of the project was to assess changes in key psychosocial outcomes (ie, psychological distress, functional impairment, satisfaction with life, mental well-being, social support and isolation, and strengths use and knowledge) from the point of engagement to post intervention.

Methods

Study Design and Setting

In this single-group prepost pilot, the MOST+ intervention is embedded within existing eheadspace services. eheadspace is a national, federally funded e-mental health service for young Australians. eheadspace provides a youth-friendly, confidential, and free internet-based mental health support and information service. The eheadspace service is professionally staffed by qualified and supervised clinicians offering synchronous Web chat, email support, and telephone-based mental health intervention to young people aged 12 to 25 years Australia-wide. Clinicians working within the MOST+ platform will be based at the eheadspace operation center. They will be allied health professionals (eg, clinical and generalist psychologists, social workers, occupational therapists, and mental health nurses) who have specialist training and experience in the delivery of e-mental health support to young people in distress. Approximately 20 eheadspace clinicians will be trained for the MOST+ study, with two or three clinicians rostered on to provide support via MOST+ per day.

Ethics, Consent, and Permissions

Research ethics approval for the MOST+ pilot was provided by the University of Melbourne Human Research Ethics Committee; Ethics ID: 1545798. All participants will be required to provide informed online consent.

Participants

Inclusion criteria for participants will reflect the real world clinical characteristics of young people accessing e-mental health support, that is, (1) Help-seeking young people with concerns about their own mental health, (2) Age of 16 to 25 years inclusive, and (3) Ability to give informed consent and comply with study procedures. By the age of 16 years, young people in Australia are considered able to make independent decisions regarding their health care [28]. An age range of 16 to 25 years reflects the agency of young people to make their own health service choices, while ensuring the age appropriateness of the therapeutic material and social networking features of the MOST+ platform. Existing eheadspace clients meeting these criteria will be eligible to use the MOST+ intervention.

Consistent with current eheadspace practice, participants will not be excluded from the study on the basis of clinical characteristics. However, the following exclusions will apply for access to the social networking component of the intervention: (1) acute risk of self-harm requiring urgent intervention (ie, suicidal ideation with a current plan and intent to enact this plan) indicated by a young person in Web chat or by endorsing screening questions 7 and 8 in the registration survey; (2) an eheadspace clinician, in consultation with a supervisor, deems participation in the MOST+ social network likely to interfere with appropriate clinical management of mental health symptoms (eg, psychosis) or increase risk of harm to self or others (see Figure 1); and (3) inability to confirm age and conduct induction via research assistant (RA) telephone contact.

Recruitment

Participants will be progressively recruited into the study, via an opt-in process, at point of entry to eheadspace through a link on the home page [29]. This link will be active during times when eheadspace clinicians are available on the MOST+ platform (ie, 4 PM to midnight Australia Eastern Daylight Time). Given high monthly eheadspace Web chat traffic (ie, >1000 new users aged 16-25 years), a recruitment period of approximately 4 weeks is considered adequate to ensure that the target of 250 participants is achieved. The availability of MOST+ will be highlighted on the eheadspace home page throughout the recruitment period. Study information will indicate beneficial features associated with the intervention (ie, instant access to specifically designed therapy content, potential access to social or emotional support from other help-seeking young people, clinicians, and peer moderators via the social network).

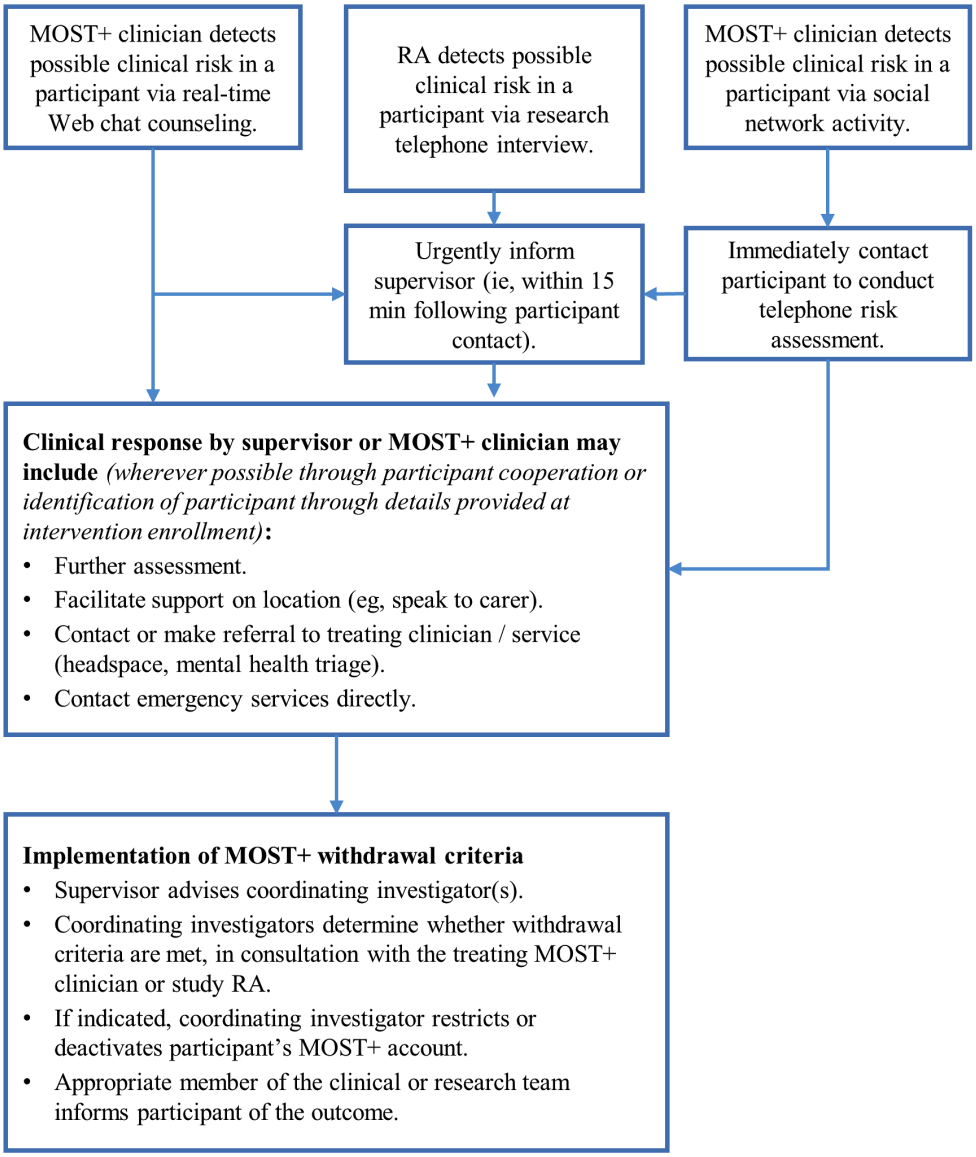
Intervention

Participants will use MOST+, an interactive, purpose built online platform designed to deliver responsive evidence-based support to help-seeking young people. The intervention is designed to better meet the increasing demand for youth e-mental health support and is not intended as a replacement for recommended treatments for ongoing mental illness.

Accessing Enhanced Moderated Online Social Therapy

Only young people who indicate online that they understand and consent to study procedures will continue to the online MOST+ registration survey. This survey will assess outcomes at baseline and will consist of items administered within the registration process for standard eheadspace services, with additional questions included to assess all outcomes (see Table 1). This will take approximately 10 min to complete. Following this survey, all users will be granted access to real-time, clinician-delivered Web chat and user-directed psychosocial interventions (ie, partial access). Additional access to moderated peer-to-peer social networking (ie, full access) will be granted based on a three-tiered screening process designed to determine the safety and appropriateness of this component of the intervention for each user. Further details of the procedures for intervention implementation are provided in Figure 2.

Figure 1. Enhanced moderated online social therapy (MOST+) intervention safety algorithm. RA: research assistant.



Partial Access and Strengths

Partial access will comprise access to clinician-delivered Web chat counseling between 4 PM and midnight Australia Eastern Standard Time and 24/7 access to interactive psychosocial interventions. MOST+ adopts a strengths-based approach [45] through which users are guided and prompted to identify, discuss, and exercise key personal strengths within the online social environment and in real life to foster positive mood, enhance social connectedness and self-efficacy, and build resilience. This approach is based on the novel positive psychology model which proposes that psychosocial interventions should aim to build strengths, meaning, and purpose, as well as relieve symptoms. Participants will be prompted to choose their top five strengths from a list of 24 on the MOST+ platform. Each strength is presented with an image and a short description to help participants choose those which apply to them best.

Therapy Steps

Psychosocial interventions in MOST+ take the form of brief therapy comics, called "Steps," designed to guide the user through various situations and address salient concerns for the broad population of young people seeking eheadspace services (eg, managing immediate distress, identifying depression and anxiety, accessing offline social and professional support, substance abuse, and vocational choices). Participants will also have access to short descriptions of specific actions, called "Do its," which can be completed to practice using their personal strengths. Therapeutic content in MOST+ is informed by evidence-based psychosocial interventions developed by our group using participatory design principles [46,47]. In MOST+, content has been adapted to address salient concerns for the broad population of young people seeking eheadspace services.

Table 1. Schedule of assessments.

Measures	Assessment time point	
	Baseline	Follow-up
Self-report assessments		
Demographics questionnaire[a]	✓	
Internet usage	✓	
Presenting problems[b]	✓	
Kessler Psychological Distress Scale (K10)[a] [30,31]	✓	✓
Functional impairment[a]	✓	✓
3 items from the Warwick-Edinburgh Mental Wellbeing Scale[a] [32]	✓	✓
Satisfaction with Life Scale[a] [33,34]	✓	✓
UCLA Loneliness Scale [35,36]	✓	✓
Friendship Scale [37]	✓	✓
Strengths Use and Knowledge Scale [38,39]	✓	✓
Patient Health Questionnaire-9 [40] (depression)	✓	
Freiburg Mindfulness Inventory [41]	✓	✓
Perceived Stress Scale [42]	✓	✓
Basic Psychological Need Satisfaction Scale [43,44]	✓	✓
User experience assessments		
MOST+[c] usability questionnaire		✓
Semistructured phone interview		✓
Online usage monitoring	Throughout trial	Throughout trial

[a]Assessment items included in the eheadspace Minimum Data Set (MDS).

[b]Assessed using six eheadspace MDS items and one additional item used to identify users who require urgent clinician-delivered Web chat on the basis of possible clinical risk.

[c]MOST+: enhanced moderated online social therapy.

Social Networking

In addition to this content, participants with full access will be able to communicate with other users and peer moderators in "The Café" and "Talk It Out" sections of the MOST+ platform. The "cafe" includes a Web feed (or news feed) where users and moderators can create posts to share thoughts, information, pictures, and videos and respond to other users' posts by commenting or "liking" content. The system includes a "network" (similar to a "friends" function on Facebook) that displays personalized profiles for all active members. Users can also communicate in a collaborative problem-solving forum called "Talk It Out." Participants can suggest topics and discuss solutions with moderators and other young people. Moderators will encourage users to define the problem, brainstorm possible solutions, identify pros and cons, and summarize possible choices. This function uses an evidence-based, problem-solving framework and has been piloted successfully within the MOST model [21].

Duration of Access

Regardless of level of access, all participants will be enrolled in the MOST+ intervention for 1 week, with the option to extend their enrollment on a weekly basis across the study intervention period. Thus, participants' period of enrollment in the intervention will range from a minimum of 1 week to a maximum of 8 weeks. Participants will be able to reactivate an expired account at any time during the study intervention period, and this will be treated as a second episode of care. Following the conclusion of the pilot study, participants will be redirected to eheadspace if they attempt to log into the MOST+ platform. See Figure 3 for examples of participants' possible enrollment time lines, with each colored line representing a different potential time line over the duration of the pilot.

Acute Risk

Any signs of possible acute risk or inappropriate use of the MOST+ system will be discussed with the principal investigators (PIs). eheadspace clinical staff, in consultation with the MOST+ coordinating investigators, will decide whether to withdraw participants from the pilot, and this will be communicated to the participant by the most appropriate member of the clinical or research team. A return to partial access, with close monitoring by the MOST+ clinicians, will be implemented in preference to full withdrawal wherever possible.

Figure 2. Study procedure. MOST+: enhanced moderated online social therapy; RA: research assistant; TAU: treatment as usual.

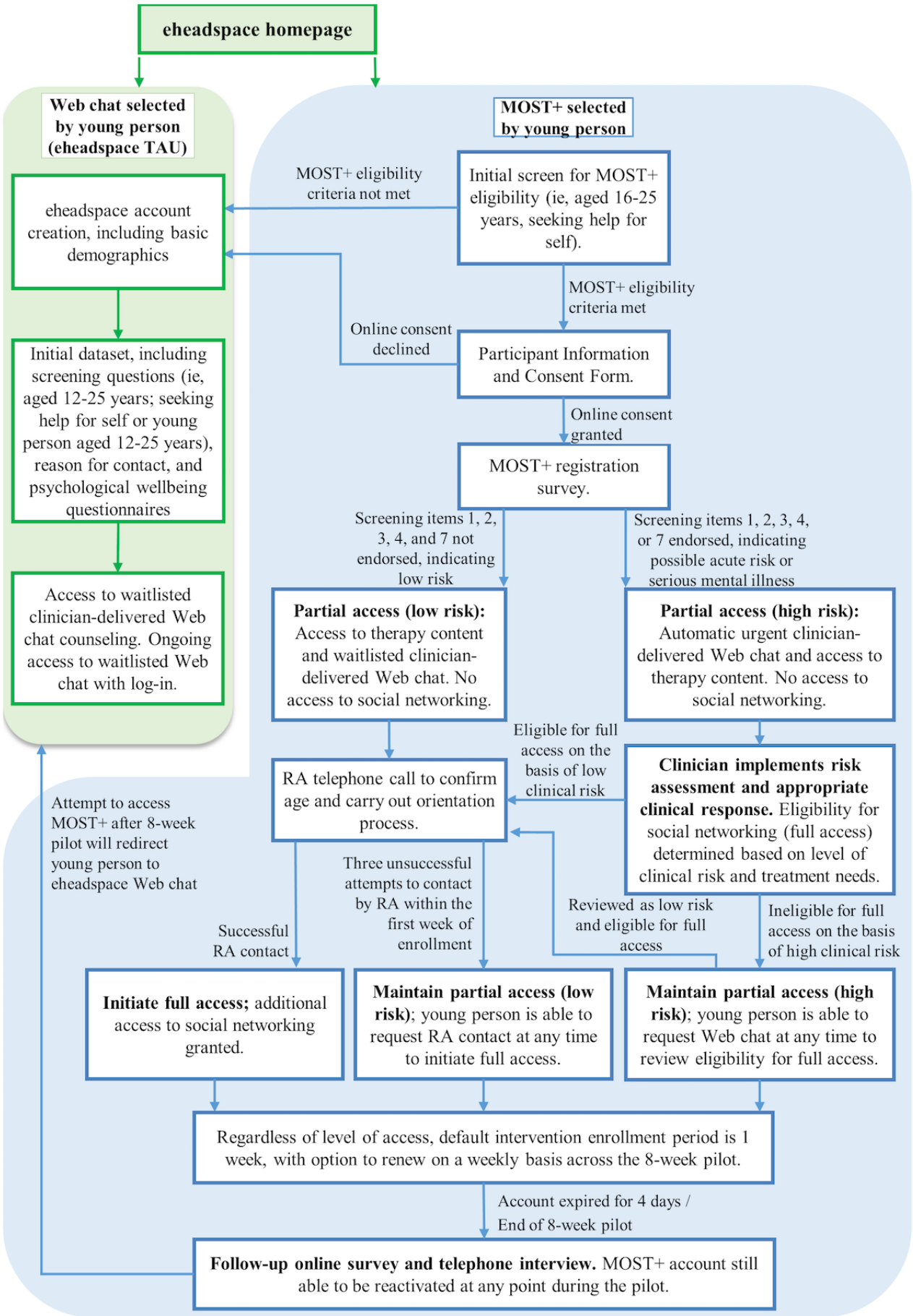
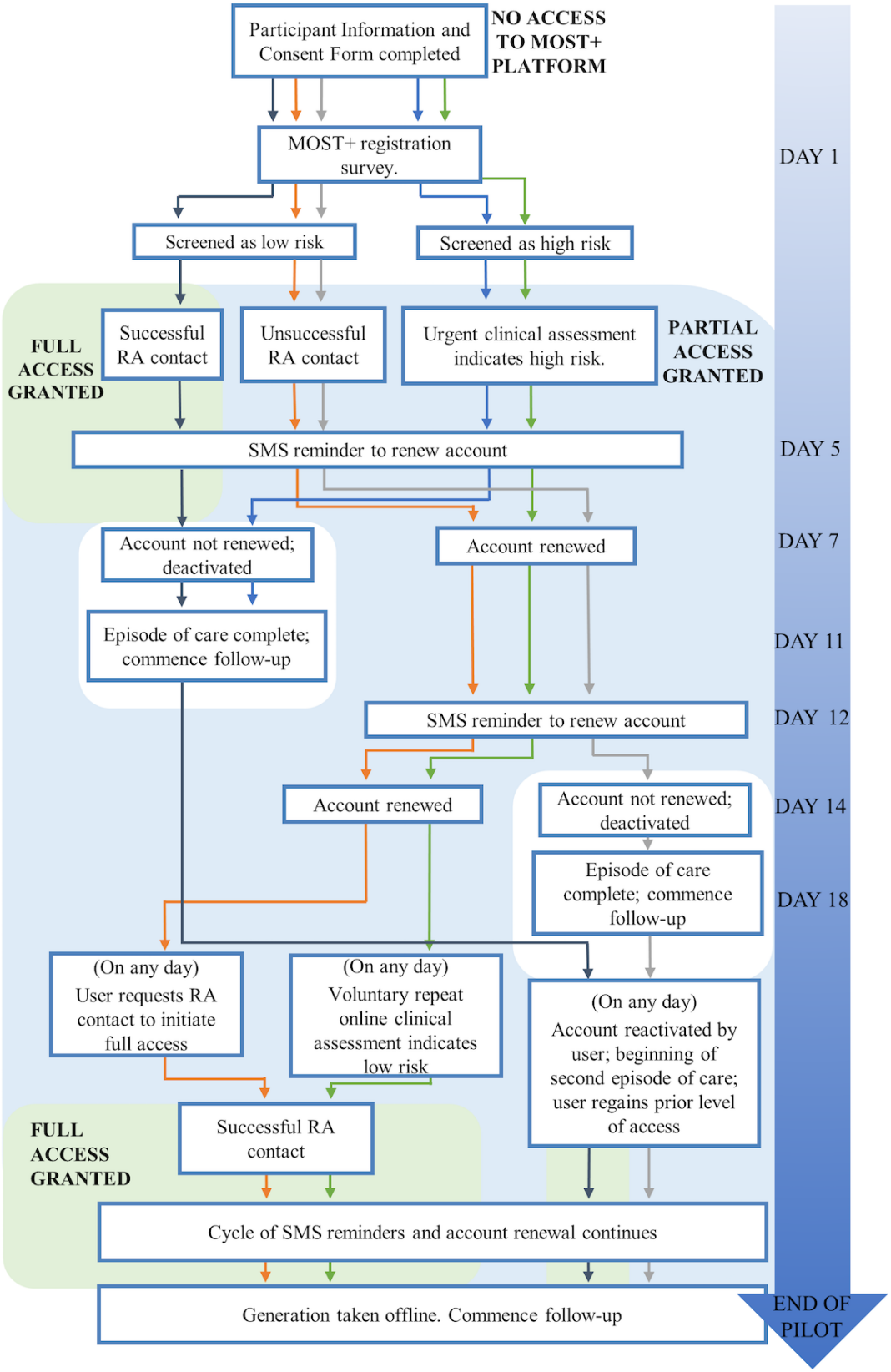


Figure 3. Example participant timelines through the enhanced moderated online social therapy (MOST+) intervention. RA: research assistant; SMS: short message service.



Integration With eheadspace

eheadspace Web chat will be fully integrated with evidence-based therapeutic content and social networking features within MOST+. Clinicians will facilitate real-time Web chat sessions via a function within the MOST+ platform. eheadspace Web chat involves clinician-delivered online counseling in real time and is focused on reducing immediate

distress, supporting positive self-care, and facilitating referral to additional supports where appropriate. Web chat may also include therapeutic interventions targeting high prevalence mental health conditions and coordinated care responses for complex and high risk clients. Wherever appropriate at the conclusion of a Web chat session, MOST+ clinicians will suggest that users complete specific, relevant content from within the online platform based on the context of their chat session. This will be bolstered outside of the live Web chat sessions by the clinicians, who will engage active users with therapeutic content by posting links within the social network, or via messaging for those participants without access to peer-to-peer social networking.

Moderation

The MOST+ social network incorporates two types of moderation: expert moderation by eheadspace clinicians and peer moderators. Moderation will follow a manualized, theory-driven model (ie, the supported accountability model), which has been successfully utilized in previous MOST studies [21,25] to encourage use of the platform through participants' sense of accountability to a trustworthy and experienced online "coach" [48]. MOST+ peer moderation has been informed by social cognitive theory and recent evidence from the computing and information systems field, which posit that peer moderators can model appropriate online behaviors through demonstrating desired actions and behaviors [49].

MOST+ clinicians will monitor new contributions to the network for indicators of clinical risk. The social network will be moderated by an on-duty MOST+ clinician daily. Safety checks will be undertaken during weekdays and also on weekends. MOST+ clinicians will receive initial training from experienced clinicians from the research team, and will be in close contact throughout the trial. Clinicians will receive regular supervision throughout the trial from their usual eheadspace shift supervisors.

Peer moderation will be conducted by "super users," who will be active members of the MOST+ social network, providing guidance and peer-to-peer support and fostering hope and empowerment [50]. Their role will include welcoming new members of the social network and modeling positive engagement with the system. Super users will post content and interact with other users in The Café and guide problem-solving discussions in Talk It Out. Individuals eligible to become super users will be aged 16 to 25 years and known to be in the later stages of recovery following a recent lived experience of mental ill health, as indicated by the youth participation coordinator within Orygen, The National Centre of Excellence in Youth Mental Health. A precondition of super users' involvement is the development of a plan indicating early warning signs. For example, a super user may identify patterns of irritability, withdrawal, and sleep disturbance as early warning signs for more significant distress.

Super users are trained in how to use the MOST+ platform and employed to moderate discussions and help participants use the site. Eligible young people will be selected to become super users if they can demonstrate via an interview process that they have (1) Comprehensive self-care strategies, (2) Nominated support services or people, and (3) Self-awareness of early warning signs indicating possible wellness fluctuation. The interview process will be facilitated by an experienced youth participation coordinator at Orygen and will provide an opportunity to ensure that all selected super users have a clear understanding of their role and are eager and able to meet the time commitments involved. Consistent with the Orygen Youth Health policy for peer support workers, MOST+ super users will be treated as "reimbursed volunteers" and compensated AUS $30 per hour for training, supervision meetings, and moderation shifts.

Moderation integrity will be ensured through a detailed moderation manual. The research team will regularly review recorded Web chat sessions and contributions to the MOST+ social network to assess clinician adherence to the moderation manual and identify areas for discussion within supervision meetings.

Supervision with MOST+ peer moderators and clinicians during the course of the pilot will provide ongoing opportunities to receive feedback and collaboratively identify opportunities for further improvements to the intervention. At the conclusion of the pilot, all MOST+ clinicians and peer moderators will be invited to attend an audio-recorded focus group or individual interview that will be aimed at gaining detailed feedback on their experience of providing support within the MOST+ platform. Information gained through this process will indicate the acceptability of MOST+ from moderators' perspectives and be used to further refine the intervention and moderator training resources before any future implementation of MOST+.

User Anonymity and Privacy

The MOST+ platform has been designed to maximize user privacy and choice within the social network. Participants are able control their level of identification within the network (ie, first name and/or photo, or complete anonymity). Should a participant become concerned about their privacy during their course of participation, they are able to "switch off" their profile to hide all of their past activity within "The Café" and anonymize their contributions to "Talk It Outs." With the exception of the research and clinical team, user contributions to the network are viewable by current members of the network only. In addition, user activity (eg, posts and profile information) is not permanent within the network. That is, users' accounts are renewed on a weekly basis through a user driven "opt-in" system, and all user activity is automatically hidden from the social network for those who choose not to renew their account. Although users are able to reactivate their account and regain their profile information at any point, all other user activity is permanently removed following a 4-day grace period during which users can reactivate their account. Users will be made aware that any user activity information that disappears from the social network is retained by the researchers for the purpose of analysis.

Outcomes

The primary outcome variables will be intervention feasibility, acceptability, and safety. Assessment of intervention feasibility will involve reviewing a log of participants' access to, and usage

of, the MOST+ platform. Access data will include the number of participants recruited and retained through the study, participants' level of access, reasons for maintained partial access following initial intervention enrollment, and details of any full or partial withdrawals from the intervention. Usage data will include the number of log-ins, steps completed, and contributions to Talk It Out and The Café. This is the first study piloting an intervention of this nature and scale for help-seeking young people and, as such, registration and usage rates are difficult to predict. For this reason, an *a priori* criterion for the number of active users that would indicate study feasibility has not been defined.

Acceptability will be assessed at follow-up using specially designed questions administered within a semistructured feedback interview. Acceptability will be considered achieved if (1) Participants provide ratings of the MOST+ platform averaging above three out of five across feedback questions regarding ease of use, relevancy, helpfulness, and overall experience; (2) At least 60% of participants report that the MOST+ intervention provided timely, relevant, and helpful support at semistructured follow-up interview; and (3) At least 80% of respondents would recommend MOST+ to other young people experiencing difficulties.

The pilot will be considered to indicate safety of the MOST+ intervention if (1) At least 90% of participants report the online intervention to be safe via semistructured feedback interview at follow-up; (2) None of the participants experience a serious adverse event as a result of their engagement with the system during their intervention period (ie, none of the participants experience a significant deterioration in mental health or self-harm in response to intervention content, as reported by the participant or determined by treating health care professionals); and (3) There are no unlawful entries into the MOST+ system detected by study programmer during the 8-week pilot.

As shown in Table 1, all secondary outcomes will be assessed at both baseline and follow-up, with additional MOST+ user experience items assessed at follow-up. Secondary outcome variables will include self-report measures of perceived stress, psychological distress, functional impairment, mental well-being, satisfaction with life, social support and isolation, strengths use, depression, mindfulness, and components of self-determination theory. These outcomes have been chosen as they are relevant to young people's perceptions of well-being and quality of life and may be amenable to change via the intervention. Strengths use represents a key target of MOST+ therapeutic content and will be investigated as a potential mediator of pre- to postintervention changes to other assessed indicators of psychosocial well-being. The registration survey will also include questions assessing frequency of internet use.

A number of additional quantitative and qualitative intervention feedback items will be administered within a semistructured telephone interview format at follow-up to gain a detailed understanding of areas for improvement within the system. The interview questions are based on the user experience approach as described by Bargas-Avila and Hornbaek [51]. Interviews will allow the study RA to explore six themes: overall impressions of MOST+, patterns of system use, feedback on specific aspects (eg, psychosocial interventions), Web chat and moderation, interactions with other MOST+ users (if relevant), and suggestions for system improvements.

Sample Size

The majority of young people who access eheadspace make use of the service on one or two occasions only, and a primary objective of MOST+ is to facilitate responsive and effective intervention within this short window. To mirror likely real-world implementation of the MOST+ model, we will also be recruiting young people to the online intervention regardless of whether they can be contacted via telephone within the first week of study enrollment (see Figure 2). Although follow-up periods will be tailored to participants' initial period of intervention engagement, it is likely to be challenging to retain participants who have engaged only briefly and/or were unable to be contacted via telephone at enrollment. A sample size of approximately 250 participants will therefore be necessary both to provide an adequate buffer against attrition during the study and to ensure that there is a sufficient number of active users of MOST+ for the social networking aspect of the intervention to function effectively throughout the 8-week pilot.

Data Collection and Management

All participants will receive one AUS $30 voucher as reimbursement for their time in completing registration and another for completing follow-up. Follow-up assessment will occur approximately 4 days after initial account deactivation (ie, 4 days after a user has opted not to renew their account for an additional week). For those participants who maintain active enrollment across the intervention period, follow-up will occur as soon as possible following conclusion of the pilot. The exact duration of follow-up cannot be estimated as the number of participants enrolled in MOST+ will not be capped. To minimize attrition, participants will receive a short service message notification that their online follow-up survey is due and will be able to complete survey items either online or via telephone. Participants who do not complete the follow-up survey will be reminded via phone call by an RA. Both baseline and follow-up assessments will be designed to minimize participant burden, while ensuring that requirements for the eheadspace Minimum Data Set (MDS; ie, routine data about each occasion of service) are met.

The MOST+ system and data generated through participants' use of the online platform will be hosted on a secure University of Melbourne Web server. Data collected via online surveys and telephone interviews will be entered electronically and also centrally stored on a University of Melbourne Web server. At the conclusion of the study, this data will be exported and stored securely in a password protected file on the server at Orygen. In addition, data collected as part of eheadspace MDS requirements will be provided to headspace at the conclusion of the study. For each MOST+ account, clinical content collected via Web chat and surveys will be copied into an eheadspace account to ensure continuity of care should the participant continue using eheadspace services post trial.

All of the PIs will have access to the final pilot dataset for the purpose of characterizing the participant sample, characterizing the activity within the MOST+ system, and testing the study hypotheses. The study RAs will also have access to the dataset for the purpose of data entry and management. Expert moderators and eheadspace clinicians working within MOST+ will have access to individual and aggregated usage data available within the moderator interface.

Given the relatively small scale, brief duration and primary aims of assessing the feasibility, acceptability, and safety of the intervention, an independent data safety monitoring committee will not be established for this study.

Data Analysis

Frequency, duration, and patterns of use of MOST+ will be tracked in real time. Up-to-date charts will be visible on demand to MOST+ staff via the moderator interface of the online platform. This data will be aggregated into simple descriptive statistics to characterize participants' use of the intervention. In addition, overall rates of MOST+ participation and aggregated data from the user feedback questionnaire will be compared with the *a priori* acceptability and safety criteria to determine success of the pilot. Supplementary paired samples *t* tests will be conducted to assess pre- to postintervention changes to outcomes. System usage will be examined as a covariate.

Harms

System and privacy protection will be monitored by the study programmers. All attempts, both successful and unsuccessful, to log into the site are recorded in a database table that can be monitored. This table also informs a security mechanism whereby if five incorrect log-in attempts are made from the same internet protocol (IP) address within a 1-hour period, then an email alerting the development team is sent, and log-in access to the site is blocked for that IP address for the next hour. Online safety will be monitored proactively by the MOST+ clinicians, with supervision from the senior researchers. MOST+ clinicians will have the authority to respond to users' reports of inappropriate material within the online platform and to automated email reports of posts that include potentially offending material. eheadspace staff will respond to indications of clinical risk according to the MOST+ safety algorithm (see Figure 1).

An important function of eheadspace and MOST+ is to facilitate support, containment, and appropriate referral wherever possible in instances of acute clinical risk. Successful implementation of the MOST+ clinical safety protocol will therefore be treated as appropriate use of the intervention and will not be automatically recorded as an adverse event. All activations of the safety protocol will nevertheless be recorded and reviewed by the coordinating investigators as part of ongoing monitoring of the feasibility and safety of the intervention. In addition, serious adverse events will be monitored, recorded, and reported to the study sponsor and ethics committee in accordance with Good Clinical Practice guidelines. Serious adverse events will be tracked throughout the duration of the study. Serious adverse events are defined as events that (1) Result in death, (2) Are life-threatening, (3) Require inpatient hospitalization or prolongation of existing hospitalization, (4) Result in persistent or significant disability or incapacity, or (5) Are other medically important events or reactions.

For each moderate to high-risk case, eheadspace documentation includes: (1) The facts of the case; (2) A clear opinion as to the level of risk; (3) A rationale for this opinion; (4) A statement of any consultations with carers and other involved agencies; and (5) Completion of a care plan. This reporting process will be followed by all eheadspace clinicians working within the MOST+ interface, and case notes involving activation of the MOST+ clinical safety protocol will be reviewed by the coordinating investigators.

In the event that clinical deterioration in a research participant is evident and attributable to usage of the MOST+ system, the relevant MOST+ clinician will communicate with the PIs. The investigators will subsequently inform the ethics committee. In addition, the coordinating investigators will inform the ethics committee in the unlikely event of a security breach of the online platform which compromises the privacy of participant information. The occurrence of either of these two events will be taken to indicate an unacceptable safety risk of the MOST+ system, as per the *a priori* intervention safety criteria.

Results

Recruitment for the study commenced in October 2017. We expect to have initial results in March 2018, with more detailed qualitative and quantitative analyses to follow.

Discussion

The aim of this project was to pilot test the next generation of eheadspace services. As such, MOST+ has been designed to harness the popularity and high demand of eheadspace by integrating a state-of-the-art online social media–based platform that weaves together attractive evidence-based, therapeutic content; peer moderation; peer-to-peer online social networking; and one-to-one online clinical support. This novel platform has the potential to deliver an enriched 24/7 youth-led therapeutic environment that caters for the needs of more young people and increases the overall scalability of clinical e-mental health services.

To date, we have developed and implemented the MOST model for individuals, in particular clinical groups, who are already in contact with mental health services [21,25]. The current research will provide valuable insights into the implementation of MOST on a platform accessible to young people whose characteristics, including location, access to face-to-face health services, and mental health concerns, may vary considerably. The flexibility required for MOST+ to be suitable and useful for individuals with a range of concerns is built into the platform. Specifically, the use of user-driven social networking and problem solving and therapy content that focuses on users' positive traits and well-being are intended to ensure the intervention is widely applicable. Furthermore, with this flexible, online model of care, MOST+ could be implemented across cultural and geographic boundaries.

By investigating feasibility, acceptability, and safety, the data from this pilot will indicate the suitability of progressing to a large randomized controlled trial to assess the clinical effectiveness and cost-effectiveness of this model. In addition, feedback from users, super users, and clinicians will inform the development of future MOST+ interventions, allowing for improvements to both content and implementation. As a first step in providing nation-wide access to integrated user-directed psychosocial interventions, peer-moderated social networking, and clinician chat, this pilot study stands to advance clinical e-mental health services in Australia.

The final trial dataset will be retained by Orygen, The National Centre of Excellence in Youth Mental Health.

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Authors' Contributions

MAJ and JG conceived the study, secured funding, and along with SR, led the development of the MOST+ system. SL, SB, EK, AP, and OSE provided expertise in the evaluation of the therapeutic content of the MOST+ intervention and integration within the eheadspace service. SB and EK will additionally provide supervision to the intervention clinicians. RL has overseen information system design and will oversee its implementation and evaluation. GW is responsible for the engineering of the MOST+ application. SD is responsible for the engineering and maintenance of the MOST+ application. SL oversees clinical management of the eheadspace service. He has provided advice on the integration of the MOST+ platform within eheadspace and will oversee the clinical aspects of the study. TG and IP have contributed to drafting the manuscript and SR and DM revised it critically for intellectual content. IP and DM are RAs on MOST+ and will be responsible for contacting young people in the study, administering baseline and follow-up surveys, and coordinating the procedural aspects of recruitment to the study. AR acts as study doctor and will assess adverse events over the course of the study. All authors have read and approved the final version of this protocol.

Conflicts of Interest

None declared.

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Abbreviations

e-mental health: electronic mental health
IP: Internet protocol
MDS: Minimum Data Set
MOST: moderated online social therapy
MOST+: enhanced moderated online social therapy
PI: principal investigator
RA: research assistant
SMS: short message service
TAU: treatment ass usual

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Original Paper

Confocal Laser Endomicroscopy for the Diagnosis of Urothelial Carcinoma in the Bladder and the Upper Urinary Tract: Protocols for Two Prospective Explorative Studies

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Abstract

Background: Visual confirmation of a suspicious lesion in the urinary tract is a major corner stone in diagnosing urothelial carcinoma. However, during cystoscopy (for bladder tumors) and ureterorenoscopy (for tumors of the upper urinary tract) no real-time histopathologic information can be obtained. Confocal laser endomicroscopy (CLE) is an optical imaging technique that allows for in vivo high-resolution imaging and may allow real-time tumor grading of urothelial lesions.

Objective: The primary objective of both studies is to develop descriptive criteria for in vivo CLE images of urothelial carcinoma (low-grade, high-grade, carcinoma in situ) and normal urothelium by comparing CLE images with corresponding histopathology.

Methods: In these two prospective clinical trials, CLE imaging will be performed of suspicious lesions and normal tissue in the urinary tract during surgery, prior to resection or biopsy. In the bladder study, CLE will be performed in 60 patients using the Cystoflex UHD-R probe. In the upper urinary tract study, CLE will be performed in 25 patients during ureterorenoscopy, who will undergo radical treatment (nephroureterectomy or segmental ureter resection) thereafter. All CLE images will be analyzed frame by frame by three independent, blinded observers. Histopathology and CLE-based diagnosis of the lesions will be evaluated. Both studies comply with the IDEAL stage 2b recommendations.

Results: Presently, recruitment of patients is ongoing in both studies. Results and outcomes are expected in 2018.

Conclusions: For development of CLE-based diagnosis of urothelial carcinoma in the bladder and the upper urinary tract, a structured conduct of research is required. This study will provide more insight in tissue-specific CLE criteria for real-time tumor grading of urothelial carcinoma.

Trial Registration: Confocal Laser Endomicroscopy: ClinicalTrials.gov NCT03013894; https://clinicaltrials.gov/ct2/show/NCT03013894?term=NCT03013894&rank=1 (Archived by WebCite at http://www.webcitation.org/6wiPZ378I); and Dutch Central Committee on Research Involving Human Subjects NL55537.018.15; https://www.toetsingonline.nl/to/ccmo_search.nsf/fABRpop?readform&unids=6B72AE6EB0FC3C2FC125821F001B45C6 (Archived by WebCite at http://www.webcitation.org/6wwJQvqWh). Confocal Laser Endomicroscopy in the upper urinary tract: ClinicalTrials.gov

NCT03013920; https://clinicaltrials.gov/ct2/show/NCT03013920? term=NCT03013920&rank=1 (Archived by WebCite at http://www.webcitation.org/6wiPkjyt0); and Dutch Central Committee on Research Involving Human Subjects NL52989.018.16; https://www.toetsingonline.nl/to/ccmo_search.nsf/fABRpop?readform&unids=D27C9C3E5755CFECC12581690016779F (Archived by WebCite at http://www.webcitation.org/6wvy8R44C).

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KEYWORDS

confocal laser endomicroscopy; optical imaging; urothelial carcinoma; nonmuscle invasive bladder carcinoma; upper urinary tract carcinoma; urothelial cancer grading; transurethral resection bladder tumor; ureterorenoscopy; nephroureterectomy; segmental ureter resection; biopsy

Introduction

Urothelial carcinoma is the most common malignancy of the urinary tract. The majority of these tumors are located in the bladder and only 5% are located in the upper urinary tract [1]. For bladder cancer, direct visualization of the urothelium with white light cystoscopy (WLC) is the cornerstone for diagnosis and follow-up. Despite its effectiveness and established role, WLC has limitations, such as, its diagnostic accuracy, especially for carcinoma in situ (CIS) [2]. Histopathologic grading and staging of urothelial carcinoma are essential for diagnosis, prognosis and choice of therapy. However, real-time histopathologic assessment is lacking during cystoscopy in an outpatient setting as well as in the operating theatre. For upper tract urothelial carcinoma (UTUC), ureterorenoscopy (URS) with endoscopic biopsies of suspicious areas is considered the diagnostic standard. Also for UTUC, histopathologic evaluation is essential for prognosis and treatment selection as endoscopic treatment is reserved for low grade tumors only [3]. Similar to the diagnostics of bladder cancer, real-time histopathologic assessment is lacking during URS. The use of optical imaging techniques, such as Confocal Laser Endomicroscopy (CLE), may enable real-time optical biopsies to overcome these limitations for bladder cancer and UTUC evaluation.

CLE is a fiber optic probe–based imaging technique that enables real-time in vivo optical sectioning of tissue. The Cellvizio CLE system uses a low-energy 488 nm laser source. The presence of a pinhole limits the detection to in-focus backscattered fluorescent light, enabling high resolution imaging in a single horizontal plane. CLE imaging requires the administration of a fluorescent contrast agent. The most commonly used fluorescent dye is fluorescein. Topical or intravenous application of fluorescein stains the extracellular matrix and enables visualization of the cellular microarchitecture and morphology. Tissue types can be differentiated based on these specific cellular features. For in vivo endoscopic CLE imaging, various sized probes with different image properties are commercially available. CLE was initially applied for in vivo imaging in the gastrointestinal tract and applications in pulmonology are explored [4-6]. In urology, CLE was first examined in the bladder. It seemed feasible to differentiate between normal mucosa and urothelial carcinoma using CLE imaging in a pilot study. Based on histopathology from resected bladder tumors, CLE criteria to differentiate between normal bladder tissue, low-grade, and high-grade bladder tumors were proposed.[7,8] These criteria have also been suggested for the upper urinary tract as the histologic morphology and microarchitecture are alike. However, a CLE probe with different imaging properties is used in the upper urinary tract and only small patient cohorts have been evaluated [9,10].

The development of CLE towards real-time optical biopsies of urothelial carcinoma may lead to advances in diagnosis and prognosis and may affect the cost-benefit of the disease management. Currently, bladder cancer is the most expensive solid malignancy per patient. The high recurrence rate of early stage tumors with long-term survival and adjuvant treatments with close follow-up results in high costs [11,12]. Even though laser fulguration of low-risk tumors has been performed in outpatient settings, it is not widely used due to the lack of histologic confirmation and, therewith, the risk of inadequate treatment [13,14]. Immediate evaluation of tumor grade with CLE could potentially increase the application of laser fulguration and enable treatment of real-time confirmed low-grade tumors in an outpatient setting. Application of laser fulguration in an outpatient setting would lead to an increase in availability of treatment of low-grade bladder cancer and reduction of medical costs. Potentially, CLE may also allow for real-time evaluation of surgical radicality and, therewith, reduce recurrence rates in urothelial cancer. In the upper urinary tract, CLE has the potential to improve the diagnostic approach for UTUC.

Accurate staging and grading of UTUC remains challenging. Visual white light assessment of UTUC grade during URS is inaccurate in approximately 30% of the cases [15]. Moreover, the restricted anatomic space of the upper urinary tract and the subsequent miniaturization of tissue-harvesting instruments limit the yield of ureteroscopic biopsies. The diagnostic yield and the diagnostic accuracy for tumor stage of endoscopic biopsies are limited [16,17]. However, tumor grade from endoscopic biopsies may indicate tumor stage [18,19]. As such, tumor grade from endoscopic biopsies is a major decisive factor for endoscopic treatment eligibility. Though, in 69-90% of endoscopic biopsies, tumor grade is in concordance with the histopathologic grade from radical resection [17,18,20,21]. Moreover, endoscopic biopsies hold a risk of complications.

CLE may overcome such diagnostic limitations for tumor grade assessment. Optical real-time assessment of tissue type and tumor grade could aid perioperative clinical decision-making. Histologic assessment without tissue biopsies could prevent possible impaired endoscopic vision after biopsies during URS. Additionally, the digital data from CLE imaging allows for real-time computer aided diagnosis with software, augmenting

the practical and diagnostic value of optical imaging techniques. Further exploration of different optical imaging modalities for tumor diagnosis may lead to multimodal optical biopsies for real-time tumor grading and staging, possibly replacing tissue biopsies in future. However, a structured conduct of research is required to guide us towards optical biopsies. The aim of these two study protocols is to contribute to the development of essential knowledge for CLE-based diagnosis of urothelial carcinoma in the bladder and the upper urinary tract. In this paper, we describe two study protocols for CLE in the urinary tract together as both protocols share many methodological and disease-specific similarities.

Methods

Study Objectives

The primary objective of both studies is to develop descriptive criteria for in vivo CLE images of urothelial carcinoma (low-grade, high-grade, CIS) and normal urothelium by comparing CLE images with corresponding histopathology.

Secondary objectives are to develop a CLE image atlas of the urinary tract, to assess the technical feasibility and procedure-related adverse events, to assess CLE image quality, to qualitatively evaluate CLE images, to preliminarily assess the diagnostic yield, and to establish an estimation of the diagnostic accuracy of CLE-based diagnosis in comparison with histopathology and to assess inter-observer agreement.

Study Design

Approval of the local medical ethical committee was obtained for both study protocols (registry number: NL55537.018.15 and NL52989.018.16). Both studies are prospective, single-centre, in vivo, observational human studies to assess CLE features of normal urothelium and urothelial carcinoma (low-grade, high-grade or CIS) in the bladder and in the upper urinary tract. Both explorative studies are in agreement with the IDEAL stage 2b recommendations [22]. The two study protocols differ mainly in the location of urothelial carcinoma, and subsequently, the surgical approach, the type of CLE probe, the administration of fluorescein, and the reference standard. Differences in protocols are explained separately and listed in Table 1.

For both studies, CLE images are recorded with a fiber optic probe–based system (Cellvizio 100 series, Mauna Kea Technologies, Paris, France). The Cystoflex UHD-R probe of 8.4 Fr (Mauna Kea Technologies, Paris, France) is used for CLE imaging in the bladder. The Uroflex-B probe of 2.7 Fr (Mauna Kea Technologies, Paris, France) is used in the upper urinary tract. The smaller Uroflex-B probe contains less optical fibers and, therewith, a lower image resolution compared to the Cystoflex UHD-R probe. Both forward-looking probes are illustrated in Table 1 and Figure 1.

CLE imaging requires the application of a fluorescent contrast agent. Fluorescein (fluoresceinedisodium, Fresenius Kabi, Zeist, The Netherlands) is a non-toxic and commonly used fluorescent dye for CLE imaging [23]. It stains the extracellular matrix and is administered topically prior to CLE imaging during the surgical procedure.

In both studies, patients will undergo in-vivo CLE imaging during surgery, prior to resection or biopsy of suspicious areas for standard histopathologic assessment. The probes are introduced through the working channel of the standard endoscopes. In the bladder, a Karl Storz cystoscope of 22 Fr with 0° optics is used for CLE imaging. Transurethral resection is subsequently performed with a Karl Storz or Olympus resectoscope of 26 Fr. For CLE imaging of the upper urinary tract, a flexible digital ureterorenoscope of 8.5 Fr is used (Karl Storz Flex Xc or Olympus V2). After placing the probe in direct contact with the region of interest, image sequences of 8–12 frames per second of the real-time visualization of the cellular microarchitecture are recorded (Multimedia Appendices 1 and 2). In general, recording is conducted in both protocols twice for 1 minute of the region of interest. In case of multiple regions of interest, multiple CLE recordings are performed. At a later stage, recorded CLE images will be analyzed independently by three blinded observers and compared to the corresponding histopathology. For CLE imaging in the bladder, the reference standard for comparison of histopathology will be the specimen of the en-bloc resected lesion. For the upper urinary tract, the reference standard will be the specimen of the radical resection (radical nephroureterectomy [RNU] or segmental ureter resection [SU]). Histopathology analysis is performed according to the standard clinical protocol and is performed by a specialized uropathologist (CDSH), who is blinded for the CLE images. A follow-up of 30 days is considered to register any adverse events following the study procedure.

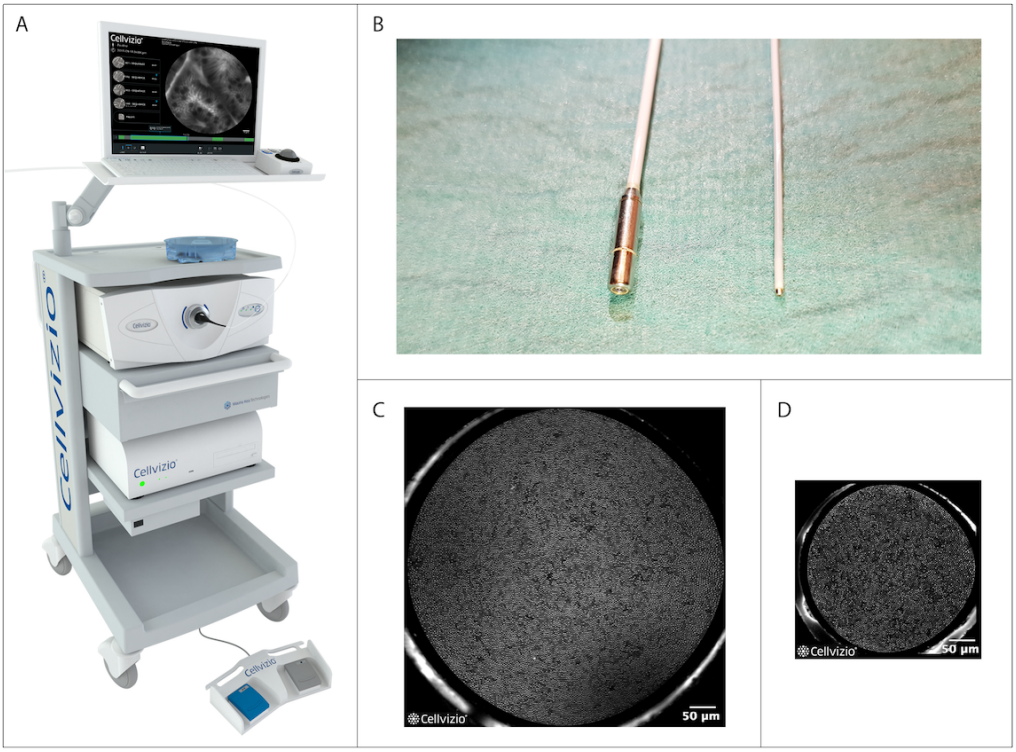
Population and Sample Size

Patients eligible for either study are >18 years with a suspicious lesion in the urinary tract, scheduled for either transurethral resection (TURB) (lower urinary tract) or diagnostic URS (upper urinary tract). The main exclusion criteria are fluorescein allergy and pregnancy (Table 1). All patients will be recruited in the AMC Hospital (Amsterdam, The Netherlands), and all study procedures will be performed in this institution. Patients will be informed about the study in oral and written form. Patient inclusion is confirmed by signing written informed consent. Patients will only be included in one study at the time. A total of 60 consecutive evaluable patients with bladder tumors or suspicion of CIS will be included in the bladder cancer study. Based on prevalence, we expect to include 32 low-grade, 22 high-grade, and 6 CIS lesions. For the upper urinary tract study, 25 patients with UTUC that will undergo a radical treatment after the diagnostic URS will be included. However, the indication for radical treatment is determined after diagnostic URS. In general, about one-third of the UTUC patients are treated with radical surgery in our centre. Therefore, we expect to include 70 consecutive UTUC patients to reach the total number of 25 patients who will undergo radical treatment. Considering the possible selection bias for radical treatment, we expect to include 10 low-grade, 12 high-grade, and 3 CIS lesions. These sample sizes are based on prior publications and comply with the IDEAL recommendations for explorative studies [7,9,22].

Table 1. Differences between the two study protocols. CIS: carcinoma in situ; CLE: Confocal Laser Endomicroscopy; RNU: radical nephroureterectomy; SU: segmental ureter resection, TURB: transurethral resection bladder tumor; URS: ureterorenoscope; UTUC: upper tract urothelial carcinoma.

Variables	CLE bladder study	CLE upper urinary tract study
Population	60 consecutive patients with primary or recurrent bladder tumor	25 patients with UTUC that will undergo a RNU or SU after diagnostic URS with CLE imaging
Inclusion criteria	• bladder tumor or possible CIS • scheduled for TURB • signed informed consent	• suspicion of UTUC • scheduled for diagnostic URS • signed informed consent
Exclusion criteria	• allergy for fluorescein • possible pregnancy or lactating women	• allergy for fluorescein • possible pregnancy or lactating women • Patients not eligible for RNU
Urologic instruments at use	Karl Storz 22 Fr cystoscope with 0° optics for CLE imaging, and Karl Storz or Olympus 26 Fr resectoscope for transurethral resection	Karl Storz Flex Xc or Olympus V2 8.5 Fr flexible digital ureterorenoscope
Contrast agent	Topical application of 300-400 mL of 0.1% fluorescein via Foley catheter and left indwelling for 5 minutes	Topical application of 0.5 mL 2.5% fluorescein via working channel for immediate imaging
CLE probe	Cystoflex UHD-R • diameter 2.6 mm • lateral resolution 1 µm • field of view 240 µm • imaging depth 50-65 µm	Uroflex-B • diameter 0.85 mm • lateral resolution 3.5 µm • field of view 320 µm • imaging depth 40-70 µm
Histopathologic reference standard	En-bloc resected bladder tumor	RNU or SU

Figure 1. Cellvizio CLE (Confocal laser endomicroscopy) system and the probes used for the urinary tract. (A) Cellvizio CLE system; (B) The two different probes used in the urinary tract. On the left the Cystoflex UHD-R probe with a diameter of 2.6 mm, which is used in the bladder. On the right the Uroflex-B probe with a diameter of 0.85 mm, which is used in the upper urinary tract; (C) RAW image of the Cystoflex UHD-R probe displaying the single fibers; (D) RAW image of the Uroflex-B probe displaying the single fibers.



Study procedures

Protocol for Confocal Laser Endomicroscopy in the Bladder

In the operating theatre prior to the TURB under general or regional anaesthesia, visual inspection with WLC and image enhancement modalities (narrow band imaging or Image1S) will be performed. At least one suspicious lesion (papillary or flat) and one region of normal appearing bladder tissue will be selected for CLE imaging. The regions of interest will be marked laterally with the cautery electrode for topographic matching. After marking the regions of interest, 300-400 mL of fluorescein (0.1% fluorescein diluted in saline) will be administered intravesically using an indwelling catheter. After instillation of the fluorescein for 5 minutes, the bladder will then be emptied and excessive fluorescein will be rinsed out. The Cystoflex UHD-R probe will be introduced through the working channel of a 22 Fr Karl Storz cystoscope with 0° optics. After placing the probe into direct contact and perpendicular to the tissue, CLE images will be recorded twice for approximately 1 minute of each marked region. After CLE imaging, the tumor will be resected en-bloc and a small chip of the marked normal urothelium will be resected for histopathologic matching. Transurethral resection is performed with a Karl Storz or Olympus resectoscope of 26 Fr.

Protocol for Confocal Laser Endomicroscopy in the Upper Urinary Tract

The complete ureter and renal pelvis are inspected with WLC and image enhancement modalities (narrow band imaging or Image1S) during standard flexible digital ureterorenoscopy under general anaesthesia to identify regions of interest. Only in case of visually confirmed upper tract tumors during URS, study-related activities will be performed. If regions of interest are identified, the region that is most easily accessible for endoscopic biopsies is selected for CLE imaging. Fluorescein (0.5 mL of 2.5% fluorescein diluted in saline) is administered through the working channel. The Uroflex-B probe is introduced via the working channel of the 8.5 Fr flexible digital ureteroscope (Karl Storz Flex Xc or Olympus V2) and placed into direct contact with the region of interest for immediate CLE imaging. Each region of interest is imaged twice for approximately 1 minute with CLE. After imaging, endoscopic biopsies for the standard diagnostic process are taken from the same location. Depending on the histopathologic diagnosis, the indication for a radical treatment will be determined.

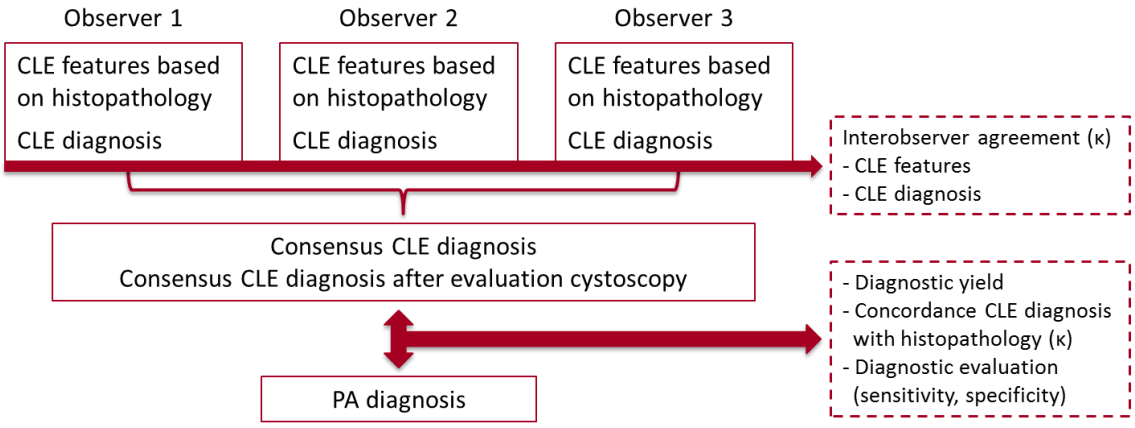
Data Analysis

The method of analysis is identical for both study protocols. Demographic- and disease- specific characteristics of the study populations (eg, age, sex, medical history of urothelial carcinoma, tumor focalitiy, tumor location, and tumor size) will be collected. Three blinded observers, consisting of two researchers (EL & JF) and one uropathologist (CDSH), will independently analyze CLE images frame by frame in an offline setting with the Cellvizio Viewer software (Mauna Kea Technologies, Paris, France). Modified criteria for CLE image evaluation will be used for analysis (Table 2) [8]. The CLE image quality per region of interest will be scored on a Likert scale as poor, fair, or good. Image quality will be used for qualitative evaluation of the technique and for subgroup analysis. Based on histologic features, for each region of interest, a CLE-based diagnosis will be made by each observer as benign urothelium or urothelial carcinoma. The diagnosis of urothelial carcinoma is subdivided in low-grade or high-grade urothelial carcinoma (WHO 2004 classification), CIS, or as inconclusive. An inconclusive CLE diagnosis is defined as poor image quality where CLE features cannot be assessed. After individual analysis, a consensus will be reached for the CLE-based diagnosis by all three observers for each region of interest. The appropriateness of consensus of the CLE-based diagnosis is evaluated by viewing the endoscopic images. After determining CLE-based diagnosis and consensus, CLE images will be compared to the corresponding histopathology specimen (either en-bloc resected bladder tumor or RNU/SU specimen) for evaluation of the concordance of CLE-based diagnosis with histopathologic diagnosis. Differences between diagnosed groups will be analyzed with a chi-square test. For an initial evaluation of the diagnostic value, sensitivity and specificity will be calculated based on a 3x3 table where CIS is classified as high-grade tumor. Proportions of specific agreement and Fleiss Kappa analysis will be used for interobserver agreement of CLE-based diagnosis. A schematic overview of the data analysis is displayed in Figure 2.

Table 2. Modified confocal laser endomicroscopy (CLE) image characteristics and their variables for analysis.

CLE feature	Variables
Papillary aspect	Present or not present
Polarity of cells	Present or not present
Organisation of cells	Organized or disorganized
Cohesiveness of cells	Cohesive or discohesive
Cellular morphology	Monomorph or pleiomorph
Definition of cell borders	Distinct or indistinct
Vasculature	Capillary network, fibrovascular stalk, or large vessels

Figure 2. A schematic overview of the data analysis plan. CLE: confocal laser endomicroscopy; PA: histopathology.



Safety

The investigators will monitor patient safety. They can withdraw a patient from the study for medical reasons. In accordance to section 10, subsection 4, of the "Wet Medisch-Wetenschappelijk Onderzoek met Mensen" (medical research involving human subjects act in The Netherlands), the investigators will suspend the study if there is sufficient ground that continuation of the study will jeopardise patient health or safety. The investigators will notify the accredited Institutional Review Board if this is the case. In case of an adverse event or serious adverse event, the responsible authorities will be informed.

Risks and Benefits

There are no direct benefits for patients participating in these two studies. In the future, however, the results of these studies may be important for patients diagnosed with a tumor in the urinary tract. All patients participating in both studies are scheduled for standard treatment of tumor(s) of the urinary tract; either TURB or URS with endoscopic biopsies. CLE is a minimally invasive imaging technique that can be performed in conjunction with conventional endoscopic treatment. Previous studies of CLE combined with topical administration of fluorescein have proven to be safe [7,24]. Fluorescein is a commonly used fluorescent dye, and its safety is well established for its use in ophthalmological angiography [25]. In patients not at risk for a previously demonstrated allergic reaction, this dye is safe. Patients with a known allergic reaction to fluorescein cannot participate in this study.

Results

Presently, recruitment of patients is ongoing in both studies. Results and outcomes are expected in 2018.

Summarized raw data will be made available through publication in an international peer-reviewed medical journal.

Discussion

CLE is an optical imaging technique that may enable real-time optical biopsies. The exploration of tissue specific CLE criteria is essential for the development towards real-time tumor grading of urothelial lesions. Both trials will provide more insight into CLE features of urothelial carcinoma in the bladder and the upper urinary tract and into its diagnostic value.

The design of the bladder protocol aims for topographic matching of CLE images with the resected specimen. The cauterisation marks placed laterally to the region of interest prior to CLE imaging ensures that imaging and resection is done of the exact topographic tissue. Nonetheless, it will be challenging to create an identical histopathological slide of the resected specimen in exactly the same plane as the imaged tissue. We assume that this approach is the closest approximation for topographic matching without interference in the standard clinical histopathologic process.

The study design of the upper urinary tract protocol will lead to a surplus of study measurements, considering that only about one-third of the UTUC patients will receive radical surgery as treatment. Since mainly patients with high-grade or high-volume low-grade tumor will qualify for radical treatment, selection bias could be a risk. The data acquired of patients who are not suitable for radical treatment enables secondary analysis for the comparison of CLE images with the histology of endoscopic biopsies of the imaged regions of interest. In the current study design, identical topographic matching of CLE images in the upper urinary tract with the specimen of the RNU is limited by the fact that in general the diagnostic URS with CLE imaging is not performed during the same procedure as the radical resection. However, topographic matching is approximated by tumor mapping during URS (mapping and annotation of location, size, and appearance) for identification of lesions during the histopathologic assessment.

As with all new techniques, a learning curve for the handling and image interpretation may be expected for CLE. Besides potential intraobserver variability, the learning process might also influence the CLE image quality of the first cases. We aim to limit the number of users to a minimum number of experienced endourologists to minimize the potential effect of a learning curve.

Despite these limitations, we expect that the results of these trials will contribute to determining the role of CLE imaging for the diagnosis of bladder cancer and UTUC in clinical practice. In the light of the limitations of cystoscopy and URS, CLE holds the potential to enable real-time tumor grading of urothelial carcinoma.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

A demonstration of CLE imaging of a bladder tumour. The CLE probe is in direct contact with the bladder tumour for CLE imaging.

[MP4 File (MP4 Video), 21MB - resprot_v7i2e34_app1.mp4]

Multimedia Appendix 2

A demonstration of CLE imaging of an upper urinary tract tumour. The CLE probe is in direct contact with the tumour for CLE imaging.

[MP4 File (MP4 Video), 21MB - resprot_v7i2e34_app2.mp4]

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Abbreviations

CIS: carcinoma in situ
CLE: confocal laser endomicroscopy
PA: histopathology
RNU: radical nephroureterectomy
SU: segmental ureter resection
TURB: transurethral resection of bladder tumor(s)
URS: ureterorenoscopy
UTUC: upper tract urothelial carcinoma
WLC: white light cystoscopy

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Protocol

Therapist-Assisted Rehabilitation of Visual Function and Hemianopia after Brain Injury: Intervention Study on the Effect of the Neuro Vision Technology Rehabilitation Program

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Abstract

Background: Serious and often lasting vision impairments affect 30% to 35% of people following stroke. Vision may be considered the most important sense in humans, and even smaller permanent injuries can drastically reduce quality of life. Restoration of visual field impairments occur only to a small extent during the first month after brain damage, and therefore the time window for spontaneous improvements is limited. One month after brain injury causing visual impairment, patients usually will experience chronically impaired vision and the need for compensatory vision rehabilitation is substantial.

Objective: The purpose of this study is to investigate whether rehabilitation with Neuro Vision Technology will result in a significant and lasting improvement in functional capacity in persons with chronic visual impairments after brain injury. Improving eyesight is expected to increase both physical and mental functioning, thus improving the quality of life.

Methods: This is a prospective open label trial in which participants with chronic visual field impairments are examined before and after the intervention. Participants typically suffer from stroke or traumatic brain injury and will be recruited from hospitals and The Institute for the Blind and Partially Sighted. Treatment is based on Neuro Vision Technology, which is a supervised training course, where participants are trained in compensatory techniques using specially designed equipment. Through the Neuro Vision Technology procedure, the vision problems of each individual are carefully investigated, and personal data is used to organize individual training sessions. Cognitive face-to-face assessments and self-assessed questionnaires about both life and vision quality are also applied before and after the training.

Results: Funding was provided in June 2017. Results are expected to be available in 2020. Sample size is calculated to 23 participants. Due to age, difficulty in transport, and the time-consuming intervention, up to 25% dropouts are expected; thus, we aim to include at least 29 participants.

Conclusions: This investigation will evaluate the effects of Neuro Vision Technology therapy on compensatory vision rehabilitation. Additionally, quality of life and cognitive improvements associated to increased quality of life will be explored.

Trial Registration: ClinicalTrials.gov NCT03160131; https://clinicaltrials.gov/ct2/show/NCT03160131 (Archived by WebCite at http://www.webcitation.org/6x3f5HnCv)

(JMIR Res Protoc 2018;7(2):e65) doi:10.2196/resprot.8334

KEYWORDS

stroke; vision; rehabilitation; brain injury

Introduction

Worldwide, stroke is the second most common cause of death and the third most common cause of disability [1]. Serious and often lasting vision impairments affect 30% to 35% of people with stroke [2]. In general, vision may be considered the most important sense in humans, and even small permanent deficits can dramatically affect the quality of life.

Lack of vision (anopia) after brain damage limits rehabilitation and enhances other invalidating effects. Impaired vision results in impaired balance, increased risk of serious falls, increased support needs, reduced quality of life and an impaired ability to perform activities of daily living [3]. Recovery of visual field deficits occurs primarily and only to a modest extent the first month after brain injury [4], and thus the time window for spontaneous improvements is very limited. Hence, brain-impaired persons with visual impairment will most likely experience chronically impaired vision already 4 weeks after brain injury, and the need for visual compensatory rehabilitation is substantial [4].

Neuro Vision Technology is a supervised training course where people with visual field deficits are trained in compensatory and restorative techniques. The course includes a special computer program, a light panel and a special training program, and the course is conducted by occupational therapists with Certified Orientation & Mobility Instruction (O&M instructors) with visual expertise [2]. Through the Neuro Vision Technology course, the individual's specific vision deficits are carefully identified through a five-step program. Personal data is used to organize individual training and thereby teaching the individual to cope with situations that cause problems in everyday life. In spite of reported positive results of Neuro Vision Technology training among several individuals [5], there are currently no scientific studies [2] on whether rehabilitation with Neuro Vision Technology results in lasting and clinically significant improvements in people with severe and chronic visual field impairments.

The aim and hypothesis of this study is to test whether rehabilitation with Neuro Vision Technology can lead to significant and lasting improvements in persons with chronic visual impairments after brain injury. Improving eyesight is expected to increase both physical and mental functioning, thus improving the quality of life. Study participants will be investigated in terms of both visual and mental functions, including quality of life, cognition and depression.

Methods

This study is designed as a prospective study in which the same subject is examined before and after the intervention.

Participants

Participants are suffering from chronic visual field impairments; thus, participants will not experience significant spontaneous remission or deterioration. Participants have typically experienced a stroke (ischemic or hemorrhagic) or traumatic brain injury. There is a high risk of injury worsening in participants with malignant or progressive tumors, making it difficult or impossible to document a beneficial effect of the intervention; Participants with such progressive diseases as well as participants worsening (eg, from secondary strokes and with further visual impairment) will be excluded from participation in the trial.

Recruitment

Suitable subjects are consecutively included from the Institute for Blind and Partially Sighted, Herlev University Hospital (especially Neurological Department N108), and other neurological departments (see Textbox 1). A screening will be performed to assess the suitability of a person to participate in the trial. Attendance is voluntary and all sessions are free for the participant. Written consent is required.

Neuro Vision Technology Intervention and Mobility

The term "orientation & mobility" is understood as the ability to move safely in physical space and in the surrounding community. By controlling orientation and mobility techniques, a person with a restricted field of vision can be able to move not only safely, but also freely and independently. The Neuro Vision Technology method uses a special device in the form of light panels and neurological vision tests providing an overview of visual and cognitive difficulties. The light panel is connected to a computer, and an example showing the setup together with a male participant and a female investigator can be seen in Figure 1. Study participants are then placed at the light panel, where the scan pattern is automated and gradually transferred to indoor mobility routes. When the procedures are automated, the exercise is done outdoors using progressively increasing complexity.

A Neuro Vision Technology course includes 3 hours of cognitive (baseline) testing, then a total of 22 hours of teaching and training given 1.5 hours twice a week for 2.5 to 3 months. Participants are provided with about four weeks of dynamic scanning training using the Neuro Vision Technology scanning device and about four weeks of mobility training using Neuro Vision Technology.

Dynamic scanning is investigated using the special light panel with 24 light bulbs divided into two rows, the panel length is corresponding to the 180 degrees that normal and well-functioning human eyes can see. When considered relevant, a participant is referred to an ophthalmologist, specialist optician, or a reading/visual clinic to ensure the optimal starting point for using the participant's vision. Records are obtained and used to store test results.

Initially the Neuro Vision Technology assessment process uses presentations of a single light to determine a participant's ability to perform spontaneous scanning of the affected field, and the participant's degree of visual field loss. Then the participant will perform exercises with different complexities using sequences of multiple lights. A participant's response to an exercise indicates his or her ability to attend to multiple stimuli, to systematically search the visual fields and how fast each participant is able to detect changes in the visual field. The Neuro Vision Technology is used to teach each participant visual search strategies from the perimeter of the affected visual field towards the intact visual field.

Textbox 1. Eligibility

Inclusion criteria

- 14 years or older with brain injury
- persons with significant vision impairment
- eye sight must be 6/18 or better
- the time from symptoms onset to study inclusion is between 12 weeks and 3 years

Exclusion criteria

- severe cognitive dysfunction
- persons with anosognosia or severe neglect

  inability to move independently at least 35 meters with or without assistance, including wheelchairs
- inability to understand Danish or with communication disorders that prevent participation in tests
- terminal disorder, other progressive disorder
- significant abuse of alcohol or euphoric or narcotic drugs
- serious disorders such as mental illness, especially severe depression

  new brain injury or other significant disorders emerging after study inclusion
- impaired vision not due to brain damage, where the disorder is not considered to be permanent or where the field of vision does not cause significant disability

Figure 1. An example of NVT training, where a brain damaged participant in need of vision rehabilitation is given compensatory rehabilitation using a special computer system controlling a light panel.

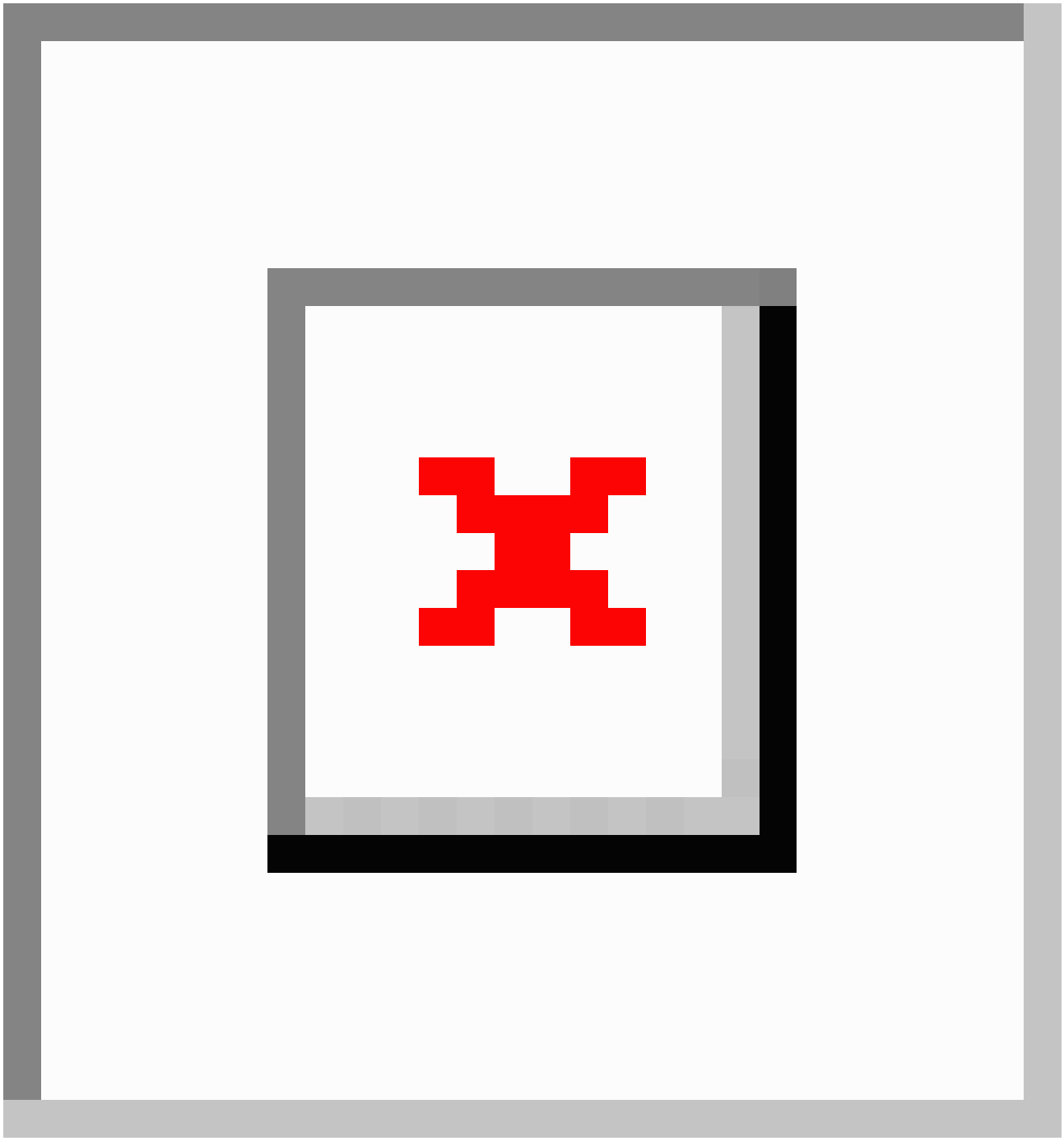
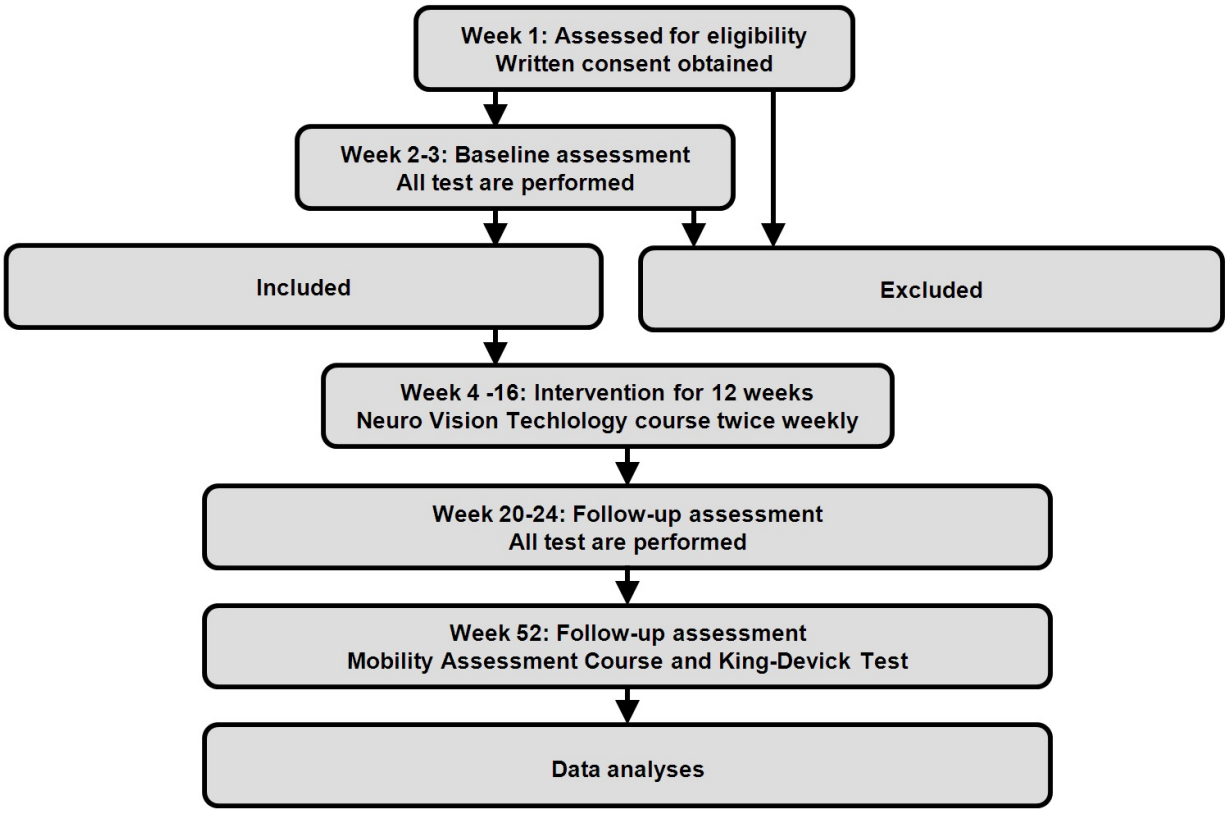


Figure 2. Flow Chart.



The Neuro Vision Technology training program is then used to transfer visual scanning strategies into the real world while doing therapist-assisted walking, with the aim of making participant perform these strategies automatically. Thus, scanning strategies are gradually implemented, learned and improved by participant first being exposed to quiet and then more busy locations, like moving participants from small and quiet rooms at our training facility into for example shopping centers or to a busy road, where participants have to safely cross at traffic light junctions safeguarded by a therapist. Depending on individual needs training may also involve the use of public transport, safely riding a bicycle and exercises in order to safely move in the traffic. A re-test of 3 hours duration is performed 6 weeks after the Neuro Vision Technology course has been finished and 52 weeks after a participant's inclusion in the study (Figure 2).

All participants receive Neuro Vision Technology course training and are tested at baseline and at the end of the study for primary and secondary endpoints; the time frame is expected to be 5 to 6 months for study participation for each participant, although the Neuro Vision Technology course is ended after 4 months (Figure 2).

Primary Hypothesis and Endpoint

It is our main hypothesis that participants will increase awareness of their surroundings, will improve navigating their surroundings, and will be able to experience a greater quality of life – including reduced symptoms of both fatigue and depression.

At the start of the intervention, standardized route training (mobility route training) is performed that participants must be able to perform independently, this intervention is also known as Mobility Assessment Course [2,6]. Mobility Assessment Course performance is the primary endpoint inspired by a similar trial, where the protocol was published, but currently the trial seems to have been cancelled [2]. On the route there are a number of targets (stars) that participants should locate. Investigators measure the number of targets ignored by any participant. Ability to perform correct target identifications by comparing how many targets participants identify before and after the intervention is the primary outcome measurement.

Secondary endpoints

Time consumption in seconds and thus speed to complete the mobility route will be measured as a secondary endpoint. Investigators measure the time spent by participants to complete the route, and faster speeds indicate improved outcome as long as correct target identification has not been reduced.

Several other secondary endpoints will be used in the study. Visual functions will be estimated using the following five tests:

1. The National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25), which is a questionnaire for measuring vision problems and concerns associated with a person's visual function [7,8]. It has been shown that the VFQ-25 is a reliable and valid 25-item version of the 51-item National Eye Institute Visual Function Questionnaire (NEI-VFQ). The VFQ is useful in clinical trials where interview length is a consideration [9]. The

VFQ-25 consists of 25 questions related to a person's activities in daily life.

2. Test of Attentional Performance (TAP) Test 2.3 Visual Field will be used to test for visual field defects. During the test a participant must respond quickly to stimuli in a circumscribed area of the visual field (eg, whenever a flicker stimulus is presented at varying intervals). This happens while participants are engaged in a simultaneous central task to ensure that participants fixate on the middle of the screen throughout the entire test run. When the peripheral stimulus appears, the patient should press the reaction key as quickly as possible [10].
3. Behavioral Inattention Test will be used to assess attention and vision among participants [11]. Also known as Rivermead Behavioral Inattention Test, it is a battery of short tests to assess the presence and the extent of visual neglect on everyday problems faced by persons with visual inattention.
4. Rey-Osterrieth's complex figure test will be used but limited to copying an advanced visual figure (without recall) [12]. Rey-Osterrieth's complex figure test is a well-known neuropsychological assessment in which participants are asked to reproduce a complicated drawing by copying it freehand. Many different cognitive abilities are needed for a correct performance, and the test therefore permits the evaluation of different functions, for example visuo-spatial abilities, attention, planning, and executive functions [12].
5. The King-Devick Saccade Test will be used as to estimate eye movement disorders, especially a participant's ability to perform saccades and horizontal eye movements [13].

Cognitive abilities will be measured by the Montreal Cognitive Assessment (MoCA), which is a cognitive screening test providing an estimate of the intellectual functional level [14]. Originally the MoCA was designed as a short screening instrument for mild cognitive dysfunction and dementia. MoCA assesses cognitive domains, for example: attention, executive functions, working and long-term memory, language and visuo-constructional skills [14]. A score of 26 to 30 is considered normal, while lower scores may indicate cognitive dysfunction.

Participants will be screened for potential psychiatric and psychological disturbances as depression and debilitating fatigue using the following 3 questionnaires:

1. The Major Depression Inventory will be used to measure and estimate symptoms of depression, which have been present for the last 2 weeks. It is a 12-item self-report mood questionnaire, which was developed by the World Health Organization's Collaborating Center in Mental Health [15].
2. The Fatigue Severity Scale is a 9-item self-administered questionnaire originally developed for measurements of fatigue in multiple sclerosis and systemic lupus erythomatosus. Each item is scored from 1 to 7 with higher scores reflecting increased levels of fatigue. In a recent study, investigators found more valid results if items 1 and 2 were excluded [16]. We refer to the reduced form as FSS-7 and will use the FSS-7 instead of the FSS to estimate fatigue in participants.
3. The Multidimensional Fatigue Inventory 20 (MFI-20), which is a 20-item self-administered questionnaire designed to measure 5 fatigue domains: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue, will be performed. The MFI-20 general fatigue domain can be used as an overall measure of fatigue, and a score of 12 or more may indicate presence of debilitating fatigue [17-19].

Quality of life will be estimated using the European Quality of Life–5 Dimensions questionnaire (EuroQol-5D) with the health status from each subscale of the EuroQol-5D transformed into a single value by the use of population-based preference weights for Denmark [20]. The EuroQol-5D is applicable to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for health status in participants. EuroQol-5D is designed for self-completion by participants and is ideally suited for use in clinics, and in face-to-face interviews [20].

For assessment of invalidity and ability to perform activities of daily living, the modified Barthel-100 Activities of Daily Living Index score will be used with scores ranging from 0 to 100. A score of 100 indicates no problems in general daily living activities, such as mobility, eating, personal hygiene, dressing and toilet use [21].

Furthermore, as part of the study, it will be assessed whether persons with lesion of right hemisphere (ie, left-field hemianopia) may be more likely to be disorientated and due to neglect will overlook more details - this is done by comparing trial participants with right vs. left hemispheric lesions.

Blinding

Participants are not randomized as there is only an intervention group and no controls. As far as possible, it is ensured that the investigator who measures the subjects' functional level at the end of intervention has not previously had contact with, or knowledge of, the particular participant. Thus, the level of function of participants is evaluated by different persons before and after intervention to ensure impartial assessments.

Sample Size Estimation

The primary endpoint is the ability to identify the highest number of correct targets on the mobility route test. Based on unpublished pilot data, we expect participants to correctly identify 40% of the mobility targets at baseline, and to be able to identify 65% of correct target 6 weeks after ending the Neuro Vision Technology course. As a basis for power calculation, alpha = .05 and beta = .2 are used. Sample size is calculated to 23 participants. Due to age, difficulty in transport, and the time-consuming intervention, up to 25% dropouts are expected. Thus, we aim to include 29 participants with permanent visual impairment after brain damage corresponding to hemianopia, quadrant hemianopia or scotoma resulting in functional impairment at activity or participation level.

Data Collection

Data collection and databases are prepared for registration and data processing. Data at baseline include: age, living single vs cohabitant at home, in-home care services, mobility aids, social network, height, weight, smoking, and alcohol consumption.

Statistical Analysis

Data comparisons of ranks before and after performances are calculated using Wilcoxon non-parametric test and optionally categorical variables with chi-2 test. Nonlinear correlations will be evaluated using the Spearman Rank correlation coefficient. Unused or incomplete data is not included in the statistical evaluation and is treated as missing data (ie, no calculations are made using such data). Lack of data is acceptable as long as an assessment of the primary endpoint is still possible. Data from participants that make it possible to assess the primary endpoint will be used as a minimum; however, we hope that data from all subjects can be used to evaluate secondary effect targets. *P* values of less than .05 will be considered significant.

Ethics

The project is in accordance with the Helsinki Declaration, has been assessed by the Scientific Ethics Committee (protocol number H-17001534) and can be initiated. The ClinicalTrials.gov identifier is NCT03160131. The law of protecting personal data will be upheld.

There are no invasive treatments, and no adverse events or risks are expected in the trial. Regardless of the reason, any subject may at any time cease to participate in the trial.

Results

Funding was provided in June 2017. Results are expected to be available in 2020. Sample size is calculated to 23 participants. Due to age, difficulty in transport, and the time-consuming intervention, up to 25% dropouts are expected; thus, we aim to include at least 29 participants.

Discussion

Overview

To the best of the authors' knowledge, this is the first time an investigation will evaluate the effects of Neuro Vision Technology complementary vision rehabilitation and we have received all necessary funding. Previously a similar trial was announced, but there have been no updates on progress for years and we assume that trial may never be finished [2]. According to the Australia and New Zealand Clinical Trials Register no updates have been received regarding the before mentioned trial since June 16 2010. Furthermore, our broad spectrum of secondary endpoints ensures a thorough examination of possible changes in quality of life, beyond previous investigations and case studies [3,5].

Limitations

Before planning the current trial, for years we evaluated the number of eligible participants, and finding eligible patients have been difficult. Therefore, we have omitted using a control group, since this may double the number of needed participants.

Conclusion

This trial will evaluate the effects of Neuro Vision Technology rehabilitation therapy and provide answers to the efficacy of such treatment methods. Vision is the most important sense in humans; thus, even small permanent deficits can dramatically affect the quality of life and we hope to be able to improve compensatory treatments by our current investigation.

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Authors' Contributions

AMHS, RSR and KO are responsible for the design of the study. All authors helped by providing methodological considerations and English editing of the manuscript. RSR and KO provided the statistics. RSR wrote the first draft and the final version of the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

EuroQol-5D: European Quality of Life–5 Dimensions questionnaire
MCA: Montreal Cognitive Assessment
MFI-20: Multidimensional Fatigue Inventory 20
VFQ: Visual Functioning Questionnaire

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Original Paper

Healthy Body Image Intervention Delivered to Young Women via Facebook Groups: Formative Study of Engagement and Acceptability

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Abstract

Background: There is increasing interest in using social media sites such as Facebook to deliver health interventions so as to expose people to content while they are engaging in their usual social media habit. This formative intervention development study is novel in describing a preliminary test of using the secret group feature of Facebook to deliver a behavioral intervention targeting users of indoor tanning beds to reduce their risk of skin cancer. Intervention content was designed to challenge body image-related constructs associated with indoor tanning through the use of dissonance-inducing content.

Objective: To evaluate engagement with and acceptability of using a secret Facebook group to deliver a healthy body image intervention to young women engaged in indoor tanning.

Methods: Seventeen young women completed a baseline survey and joined a secret Facebook group with intervention content delivered via daily posts for 4 weeks. Engagement data was extracted and acceptability was measured via a follow-up survey.

Results: The study had a high retention rate (94%, [16/17]). On average, posts were viewed by 91% of participants, liked by 35%, and commented on by 26%. The average comment rate was highest (65%) for posts that elicited comments by directly posing questions or discussion topics to the group. Average intervention acceptability ratings were highly positive and participants reported feeling connected to the group and its topic. Average rates of past 1-month indoor tanning reported following the intervention were lower than the baseline rate (P=.08, Cohen d=0.47).

Conclusions: This study is novel in demonstrating participant engagement with and acceptability of using Facebook secret groups to deliver a dissonance-inducing intervention approach that utilizes group-based discussions related to body image. The study is also unique within the field of skin cancer prevention by demonstrating the potential value of delivering an indoor tanning intervention within an interactive social media format. The findings suggest that Facebook metrics of intervention post engagement (ie, likes and comments) may vary based on post types and that designing specifically labeled discussion posts may be helpful for soliciting engagement as well as challenging beliefs.

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KEYWORDS

body image; dissonance-based intervention; indoor tanning bed; social media; Facebook; behavioral intervention; prevention

Introduction

Social media allows for the unlimited exchange of information, images, and interactive peer communication. Researchers have begun to utilize Facebook, the most popular social media site [1-3], to deliver health interventions so as to expose people to content while they are engaging in their usual social media habit [4]. This proof-of-concept study examined the use of Facebook to deliver intervention content designed to reduce indoor tanning bed use among young women. The intervention utilized persuasive techniques to shift unhealthy attitudes and perceptions linked to indoor tanning toward healthier perspectives. Indoor tanning is linked to an increased risk of melanoma [5] and is implicated as a central contributor to rising melanoma rates among young US women [6].

The intervention approach is guided by body image theories that demonstrate cultural experiences can negatively impact how young women view their bodies and may lead to a preoccupation with obtaining an unrealistic, culturally-derived ideal appearance [7,8]. The negative body image and body dissatisfaction associated with endorsing these appearance ideals represent core motives for a variety of unhealthy appearance-oriented behaviors, including use of tanning beds [9]. Efficacious behavioral health interventions (eg, [10,11]) have targeted risky body image beliefs through the use of persuasive techniques based in cognitive dissonance theory. These techniques encourage participants to engage in cognitive exercises and discussions during which they endorse, and ultimately adopt as their own, attitudinal perspectives that are counter to and conflict with their unhealthy ideals and negative body image beliefs [12]. The conflict between these counter perspectives and held beliefs leads to psychological discomfort (ie, cognitive dissonance) [12]. The person is then motivated to seek psychological relief by altering their original unhealthy beliefs to be more consistent with the healthier perspective being advocated. Adapting such healthier perspectives can lead to reductions in body dissatisfaction and resulting risk behavior such as tanning. Dissonance-based interventions are often delivered within small in-person groups since engaging with counter-attitudinal information in a group format increases the amount of dissonance experienced and leads to a greater likelihood of attitude and behavior change [12,13]. Social media features such as “secret” (ie, private) Facebook groups are designed to share information and generate conversations among groups of users with common interests [14]. Social media represents an intriguing but unexplored approach to delivering these interventions given features that easily connect groups of people.

The purpose of this proof-of-concept study was to test engagement with and acceptability of delivering a dissonance-based, body image focused intervention to reduce indoor tanning using Facebook secret groups. For this intervention, content was posted daily on the group page for four weeks and group members were encouraged to share and discuss their opinions about the posts. We also examined the preliminary efficacy of the intervention by comparing rates of participants’ tanning bed use before and after the intervention.

Methods

Participants

Participants were 18 to 25-year-old women who used Facebook at least once a day and a tanning bed at least once in the past year. Recruitment utilized multiple methods including: emailing study invitations to participants from our prior focus group study on tanners’ intervention preferences; distributing recruitment flyers to students on a large northeastern US college campus; posting study flyers on social media accounts (including investigators’ personal Facebook and Twitter pages); and ads on local Craigslist pages. Research staff conducted study screening phone calls with interested participants to evaluate study eligibility. A total of 17 participants were enrolled (6 recruited from prior focus groups, 3 campus flyers, 6 social media and Craigslist, and 2 referrals from enrolled participants).

Procedures

Study procedures included a baseline survey, participation in a four-week Facebook group, and a post-intervention survey 5 weeks after baseline. The study was conducted from July to August 2016. Enrolled participants were emailed a link and a unique PIN to complete the online baseline survey. Participants received a US $30 gift card for each survey and those who completed both were entered in a US $100 gift card raffle. The university’s Institutional Review Board approved all study procedures and participants provided online consent.

Intervention

The intervention consisted of a secret invitation-only Facebook group named “RU Facebook Project”. The group feature of Facebook is designed to connect and share information with a subset of Facebook users based on shared interests. With Facebook secret groups, Facebook users receive a private invitation to join a group, which in this study was used to post the intervention messages. Further, secret group membership and content is limited to invited group members and their group membership and in-group activities are not publicly viewable to outside Facebook users. A study Facebook account was created and used to deliver all intervention content via daily group posts. Two authors, JS and AD, joined the group with study-specific Facebook user accounts to provide a “face” for the researchers and increase study credibility. Our involvement was purposefully limited to include: encouraging initial comments and responses to discussion questions by JS and AD—commenting once each on the first “icebreaker” post and AD commenting once on each of the next two discussion posts—and liking comments from participants throughout the study to reinforce participation.

The goals of the dissonance-based Facebook intervention approach mirrored those of existing interventions for disordered eating and indoor tanning [11,15-17] including: raising awareness and promoting reflection of sociocultural and media influences on body image and risk behaviors; 2) promoting dissonance by encouraging participants to speak out against idealistic thinking and endorse counter perspectives by commenting on the group Facebook page; and 3) encouraging body acceptance. The process of creating Facebook messages

involved developing a posting strategy to cover the type and range of content typically provided within group-based disordered eating interventions [15-17] and our website tanning intervention [11]. This process resulted in four posting categories, or posting types, designed to specifically address each goal (Table 1). JS wrote or adapted posts designed to address each goal and refined them based on feedback from other study authors. Several of the *Your Thoughts* posts, the primary approach for encouraging dissonance processing, were adapted from group-based discussion questions from prior disordered eating interventions. Content for inspirational posts were primarily procured from popular media sources including Facebook. Most posts (93%) were written to generally focus on body image and women's experiences rather than specifically addressing indoor tanning in order to reduce possible reactance to content from tanners while still addressing an important predictor of tanning behavior. There was no predetermined order of presentation of post types and we varied their order across the 4-week intervention period to avoid making repetitive post types across multiple days. Your Thoughts discussion posts were made every 2-3 days and the homework posts were made in weeks 3 and 4 as they were designed to have group members apply knowledge learned earlier in the intervention period.

Intervention Receipt and Engagement Metrics

Intervention receipt was defined as the percent of posts viewed by participants. Engagement was assessed as interactions with group posts (ie, likes and comments). Engagement results are presented both as "post engagement", defined as the mean number of likes and comments received by post types, and "participant engagement", defined as the number of likes and comments averaged across participants. Facebook data was manually extracted from the group newsfeed after the posting period ended.

Intervention Acceptability Measures

Intervention acceptability was measured on the follow-up survey in two ways. First, four general intervention evaluation items assessed the extent participation in the Facebook intervention was interesting, understandable, useful, or positive (measured on an 11-point scale anchored with 0= *not at all* and 10= *extremely*) [11,20].

Table 1. Description of intervention content delivered in Facebook group posts.

Description of content within each post type	Number (total %)	Source(s)	Example post
Information-based content intended to provide context for the intervention content and counter-perspectives to idealistic thinking. Designed to raise participants' awareness of their thoughts, feelings, and actions with regard to their appearance, including the sociocultural experiences that lead to an overemphasis on appearance and cause body dissatisfaction.	9 (32%)	Adapted from disordered eating [10,15-17] and indoor tanning intervention research [11] as well as popular sources.	"We've talked about the excessive use of Photoshop to create images of 'ideal' women by making body parts thinner or changing the appearance of skin by smoothing wrinkles, removing blemishes, and often altering skin tone to appear tanner. One reason that the use of Photoshop is so common is that images of 'ideal' women are used to sell products. For example, fashion magazine covers, articles, and images are designed to make a woman feel bad about her looks. These magazines try to convince women that something is wrong with how they look and that they can fix the problem by buying the products in the magazine ads. The worse the images make women feel, the more money the magazine makes in advertising sales." This post included a link to a web article showing celebrity photographs before and after they were altered with Photoshop.
Inspirational or humorous quotes related to resisting idealistic thinking, empowerment, or body activism.	9 (32%)	Images curated from internet searches or sharing postings from other Facebook pages, for example [18,19].	A meme with a quote from Tina Fey describing her view on the female body image.
Questions or discussion topics that elicited comments and responses from group members. Posts were clearly identified with the label: "Your Thoughts **Please read and comment**". Designed to encourage comments that were critiques of or counterarguments against unrealistic beauty ideals.	8 (29%)	Adapted from disordered eating [10,15-17] and indoor tanning intervention research [11]	"Several members have mentioned the "ideal" for women in their comments and now we would like to define the ideal to understand exactly what we are talking about. What are we told that the ideal or perfect woman looks like?"
Skill-building, homework-type activities were programmed with online survey software. Appeared as a webpage accessed with an outside link from Facebook posts. Given the personal nature of some questions, participants' responses to homework were not directly viewed by the group. Designed to promote media literacy and self-acceptance.	2 (7%)	Adapted from disordered eating [10,15-17] and indoor tanning intervention research [11]	A positive body image task that asks participants to create a top ten list of their own best attributes.

Second, participants answered several Facebook-specific evaluation items related to their perceptions of their experience as members of the Facebook group [21-23] that included perceived connectedness with group, identification with posts and other group members, enjoyment, ease of participation, and willingness to continue to engage with the group. (measured on 5-point Likert-type scales anchored with 1= *strongly disagree* and 5= *strongly agree*)

Preliminary Outcome Measure

Number of past 1-month tanning sessions was measured on the baseline and follow-up assessment using an expert-recommended survey item ("How many times in the past month have you used a tanning bed or booth?") [24].

Data Analysis

Descriptive statistics are presented for the Facebook engagement metrics and the intervention acceptability measures. A paired-sample 2-tailed t-test was used to compare mean differences in baseline and follow-up responses to the preliminary indoor tanning outcome measure.

Results

Participant

Participants reported a mean age of 20.8 years (SD 1.7) and 9 out of 17 (53%) were White, 5 out of 17 (29%) were other/multiracial, 2 out of 17 (12%) were Asian, and 1 out of 17 (6%) refused to answer. Five out of seventeen participants identified as Hispanic (29%). Most participants were currently enrolled in college (82% [12/17]) with the remaining having a bachelor's degree or higher (18% [3/17]). Eleven out of seventeen (65%) participants used Facebook multiple times a day and 5 out of 17 (29%) reported daily use at baseline.

Retention

All enrolled participants completed the baseline assessment and accepted our invitation to join the Facebook group. Sixteen out of seventeen participants completed the post-intervention survey, producing a 94% study retention rate.

Intervention Receipt

Twelve out of seventeen participants (70.6%) viewed every post and an additional four (23.5%) viewed at least 75% of posts. An average of 91.4% participants viewed each post (See Table 2) and the mean post view rate was similar across each post type.

Engagement

Table 2 also presents post engagement averaged across the posting period. Posts were liked on average by 34.6% (SD 21.1) of participants with the highest like rates for inspirational (50.3% [SD 12.5]) and psycho-educational (42.5% [SD 11.3]) posts. An average of 26.2% (SD 28.7) of participants commented on a typical post with the highest rates for Your Thoughts posts (64.7% [SD 14.4]). Nearly half of participants (41.2%) commented within the webpages that were linked to in the homework posts. For participant-level engagement, participants, on average, liked 9.1 posts (SD 6.1) and commented on 7.6 (SD 4.1).

Table 2. Descriptive statistics for post views and engagement metrics by post type.

Engagement Metric and Post Type	Mean percentage (SD)
Views	
All[a]	91.4 (7.1)
Psycho-educational	90.2 (7.2)
Inspirational	89.5 (7.1)
Your Thoughts	94.9 (6.6)
Likes	
All	34.6 (21.1)
Psycho-educational	42.5 (11.3)
Inspirational	50.3 (12.5)
Your Thoughts	8.1 (7.7)
Comments	
All	26.2 (28.7)
Psycho-educational	13.0 (14.3)
Inspirational	5.2 (4.6)
Your Thoughts	64.7 (14.4)

[a]Homework posts are not included in descriptive statistics given the low number of posts relative to other post types and the nature of the posts that contained links to an external webpage for participants to leave comments.

Table 3. Perceptions of the Facebook group intervention experience. Survey items were measured with a 5-point, Likert-type response scale: 1= *strongly disagree*, 2= *disagree*, 3= *neither*, 4= *agree*, 5= *strongly agree*.

Survey Type and Items	Mean (SD)
Connection with intervention and group	
I could identify with a lot of the posts.	4.3 (0.6)
The posts were relevant to me.	4.4 (0.5)
I could identify with other people in the group.	4.3 (0.6)
I felt connected to the other people in the group.	3.9 (0.7)
I paid attention to other people's comments in the group.	4.4 (0.6)
I felt like I was actively involved in the Facebook group.	4.2 (0.8)
Perceptions of the Facebook group experience	
I enjoyed expressing my opinions in the group.	4.2 (1.0)
I enjoyed reading other people's comments in the group.	4.2 (0.7)
I enjoyed reading the posts made in the Facebook group.	4.4 (0.5)
I felt comfortable participating in the study.	4.6 (0.8)
It was easy to participate in the Facebook study.	4.8 (0.5)
The study was too time consuming.	2.2 (1.3)
I would be willing to continue as part of the Facebook group if the study were to continue.	4.8 (0.5)

Intervention acceptability

Participants provided favorable ratings on general intervention evaluation items including: interesting (mean 7.5 [SD 1.7]); understandable (mean 9.1 [SD 1.3]); useful (mean 8.2 [SD 1.7]); and positive (mean 9.1, [SD 1.5]). Means for Facebook-specific evaluation items indicated a general level of agreement with regard to perceived connectedness to the group (Table 3) including items that assessed: identification with posts (mean 4.3 [SD 0.6]), identification with other group members (mean 4.3 [SD 0.6]), connectedness to the group (mean 3.9 [SD 0.7]), and perception of active involvement with the group (mean 4.2 [SD 0.8]). Participants also indicated high ratings on items of enjoyment with various aspects of the group and comfort in participation (mean 4.6 [SD 0.8]). Participants indicated they would be willing to continue as a part of the Facebook group if the study were to continue (mean 4.8 [SD 0.5]).

Preliminary Outcomes

The mean number of reported past 1 month indoor tanning sessions was lower at the post-intervention assessment (mean 0.7 [SD 2.3]) compared to baseline (mean 2.3 [SD 4.4]) although this difference was not significant at the α=.05 level (t_{15}=1.90, *P*=.08: Cohen d=0.47).

Discussion

Intervention receipt was high as a typical post was viewed by 91.4% of participants. In addition, the majority of participants (70.6% [12/17]) viewed every post, and an additional 23.5% [4/17] viewed at least 75% of posts. Post engagement, measured by likes and comments, differed according to post type. Posts specifically designed to elicit comments by posting questions and discussion topics to the group (ie, those titled, *Your Thoughts*) received higher rates of comments than other post types. The labeling of posts as discussion posts may be helpful for soliciting engagement as well as challenging beliefs. For participant-level engagement, mean number of likes was slightly higher than comments. Overall, the observed rates of intervention engagement compare favorably to Facebook interventions on other topics (eg, physical activity, weight loss, tobacco cessation) [25-28].

Ratings on general measures of intervention acceptability (eg, interesting) were favorable and comparable to other tanning interventions delivered via booklet or website [11,20]. Facebook-specific acceptability measures were highly favorable including the perception the group allowed for social connection and self-expression, both key reasons people use social media [22]. These intervention features, along with the focus on positive body image, may increase participants' interest and lead to a more impactful intervention. Favorable scores were also reported for enjoyment, comfort, ease of participation, and willingness to continue in the group. The study also demonstrates that participants may engage in an intervention with minimal input or guidance from moderators, an important feature likely to lead to a more sustainable intervention with greater potential for dissemination. Overall, the study expands the literature of social media interventions to include tanning and body image among young women. No significant change in past month indoor tanning was observed, however this formative study was not adequately powered to detect changes. Our next step is to conduct a fully powered efficacy trial to assess the ability of Facebook group approach to positively influence body image and reduce indoor tanning.

This formative study has some notable limitations. First, the study had a single arm design, small sample size, and was not fully powered to detect behavior change or examine

psychosocial intervention mediators. Second, the sample was primarily recruited from a single geographic area using specific inclusion criteria that reduce generalizability of the findings. Our discussion posts were adapted from in-person, group-based disordered eating interventions that utilize discussion questions designed specifically to generate counter-attitudinal responses to challenge image ideals [12] (eg, "Describe your biggest pet peeve/complaint with the media, the fashion industry, or social media"). Although it is promising that a large percent of participants engaged with the discussion posts by commenting, we did not code the comments for counter-attitudinal content and the design of this formative study did not allow for a formal test of cognitive dissonance as an intervention mediator. The general lack of research in this area results in a dearth of empirical support that using dissonance-based discussions in social media groups can lead to counter-attitudinal responses although research suggests such discussions on Internet-based forums can be efficacious [10]. Thus, the question of whether the intervention is working as designed by encouraging the generation of counter-attitudinal information through Facebook group discussions and promoting cognitive dissonance among group members needs to be examined in future research. Finally, some participants (35% [6/17]) were recruited from our prior focus group research study, which may have biased responses in a positive manner.

In conclusion, social media represents an unexplored platform for delivering dissonance-based interventions for disordered eating and indoor tanning. The current formative study demonstrates the feasibility and acceptability of using Facebook as a delivery mechanism for these types of interventions. The use of Facebook groups to deliver dissonance-based interventions capitalizes on features key to the success of these interventions including group-based discussions and peer support. Embedding the intervention into the target population's social media routine facilitates both engagement and reaches with less expense than in-person groups and developing websites incurs. The utilization of Facebook groups for delivering group-based interventions is appealing given the potential for creating highly sustainable intervention approaches with strong potential for dissemination across multiple geographic locations.

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Conflicts of Interest

None Declared.

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Protocol

Psychosocial Distress of Patients with Psoriasis: Protocol for an Assessment of Care Needs and the Development of a Supportive Intervention

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Abstract

Background: Psoriasis is a chronic inflammatory disease that is often associated with a number of somatic and mental comorbidity. Patients with psoriasis show an increased risk of depression and (social) anxiety.

Objective: The aims of this study are 1) to explore the psychosocial distress of patients with psoriasis and to assess their care needs; and 2) to develop a supportive intervention based on the prior results.

Methods: A multi-stage design with four phases combining quantitative and qualitative methodology will be used and conducted in two centers. 1) A scoping review and focus groups will be used to design a questionnaire to assess the psychosocial distress and care needs of the patients. 2) The questionnaire developed in phase 1 will be used in a cross-sectional survey to assess the extent of psychosocial distress and supportive care needs in 400 patients with psoriasis. 3) A systematic review and meta-analysis will be conducted to identify psychosocial and psychoeducational interventions for patients with psoriasis and to describe their effectiveness. 4) Based on the results of the phases 2 and 3 a manualized supportive intervention will be developed and the feasibility and acceptance of the intervention will be assessed.

Results: Currently, phase 1 of the project has been completed and the recruitment for phase 2 has been started. The systematic review and meta-analysis of phase 3 are conducted simultaneously to phase 2 and results are expected soon. Phase 4 has not been started yet.

Conclusions: The expected results of this study will show the extent of psychosocial distress of patients with psoriasis in Germany and supplement previous research with findings about the supportive care needs of this patient group. Moreover, the developed intervention will help to address the psychosocial support needs of patients with psoriasis. Research shows that psychosocial support is strongly needed.

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KEYWORDS

psoriasis; psychosocial distress; care needs; supportive intervention

Introduction

Psoriasis is one of the most common chronic inflammatory skin diseases with a prevalence of 1 to 3 % in western industrial countries. In Germany about 2 million patients are affected [1,2]. The most common type of psoriasis is “psoriasis vulgaris” also called “plaque psoriasis.” It is assumed that about 25% of patients have moderate to severe disease, and a relevant proportion needs a lifelong treatment [3]. Studies indicate that psoriasis often is associated with other medical conditions, especially in severe cases with a long history of the disease [4]. Known comorbidity includes psoriatic arthritis (PsA) [5]; inflammatory bowel disease [6]; cardiovascular disease [7]; and diabetes [8], influencing morbidity and mortality [9,10]. Increased rates of comorbidity are already found in young children and adolescents [11]. In addition to somatic comorbidity psoriasis can be associated with psychosocial stress and mental illness. Patients with psoriasis show an increased risk of depression, anxiety, and suicidal ideation [12-15]. Especially an early onset of psoriasis increases the risk for depression and social anxiety [14,16]. Moreover, alcohol consumption and nicotine abuse seems to be greater in patients with psoriasis than in the general population [17,18].

Reasons for the psychosocial burden of patients with psoriasis are experienced stigmatization in social situations, the workplace, difficulties with body image, self-esteem, and self-concept [14,19-22]. These factors can be substantial components leading to impaired health-related quality of life (HrQoL) [23]. Other predictors of HrQoL impairments are pruritus [24,25], the time needed for daily treatment and treatment dissatisfaction [26]. Accordingly, patients show a large variety of needs related to disease management which go far beyond symptomatic treatment and include a plurality of psychosocial aspects [27].

Research suggests that psychosocial stress is not just a consequence of psoriasis but can also be involved in the exacerbation of the symptoms [28]. Reich et al [29] found that the itch intensity experienced during psoriasis exacerbation correlated positively with stressful events one month earlier. The concept of the “brain-skin-axis” describes the interaction between mental aspects, immune system, and cutaneous inflammation. In patients with psoriasis, psychosocial stress can worsen the condition, which increases disease-associated and experienced stress, impairs quality of life, and increases psychosocial strain and comorbidity [28]. The individual stress reactivity can affect both adherence as well as treatment response [28]. Besides the individual stress reactivity, age, sex, psychosocial, disease-specific, and treatment-specific factors predict the adherence or compliance [30]. Also in a study by Eskin et al, psoriasis patients showed lower scores in social problem-solving skills as well as higher degrees in negative problem orientation and impulsive-careless problem-solving style compared to healthy controls [31], which indicates that those patients might profit from interventions like problem-solving trainings.

For these reasons, current concepts of psoriasis management include screening for mental comorbidity and recommend interdisciplinary teamwork and psychosocial support if applicable [4].

Until now, different reviews subsumed studies on the effects of psychosocial interventions on psoriasis patients. Larsen et al [32] reviewed nine randomized controlled trials (RCTs), quasi-randomized trials, and controlled clinical trials of patient education and self-management interventions on disease severity and HrQoL and found that little evidence is available. They point out that compared with other chronic conditions, only few effective disease-specific tailored educational programs for psoriasis are available [32]. A narrative review found an overall positive effectiveness of existing psychological and/or educational interventions in psoriasis especially in psychological and HrQoL outcomes [33]. However, they stated that the strength of evidence to support the effectiveness of the published interventions was limited due to methodological weakness in the included studies and suggest further research and RCTs to increase validity of intervention studies. Despite a clear need and some existing evidence-based psychosocial treatments, access to psychological and psychosocial interventions within dermatological services remains limited [34]. Moreover, since evidence on psychosocial interventions is still equivocal, it can be concluded that it is important to find out more about the individual information and support needs of these patients to design interventions that are especially tailored to patient preferences. Therefore, the aims of the described study are:

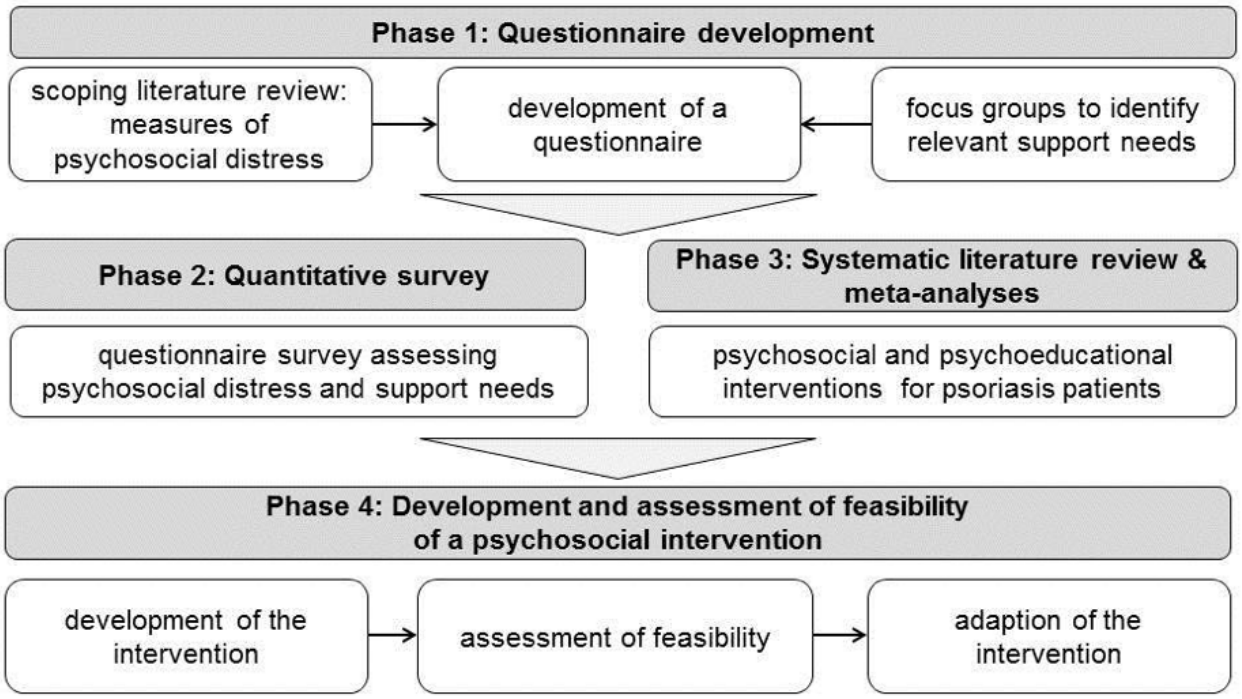
1. To assess the psychosocial distress of patients with psoriasis
2. To investigate their needs for information and psychosocial support
3. To develop a psychosocial intervention to educate and support psoriasis patients
4. To test the feasibility, acceptance and effectiveness of this intervention

Methods

A multi-stage design with four phases combining quantitative and qualitative methodology will be conducted. It is displayed in Figure 1.

The project will be carried out at Department of Medical Psychology in cooperation with the Institute for Health Services Research in Dermatology and Nursing at the University Medical Center Hamburg-Eppendorf and the Psoriasis Center at the Department of Dermatology of the University Medical Center Schleswig-Holstein Campus Kiel in Germany.

Figure 1. Flow-chart of study phases.



Phase 1: Questionnaire Development

A scoping review [35] will be conducted to identify measures to assess psychosocial distress in chronic conditions and skin diseases. Measures that focus on mental illnesses, like the Patient Health Questionnaire (PHQ-9) [36,37] to assess depression symptoms, the Generalized Anxiety Disorder 7 (GAD-7) [38] to measure anxiety symptoms or the Somatic Symptom Disorder (SSD-12) [39] to evaluate somatic symptoms will be used. Risk factors as alcohol consumption will be assessed, for example with the Alcohol Use Disorders Identification Test (AUDIT-C) [40]. Moreover, measures to evaluate the information needs and supportive care needs, as well as the utilization of supportive interventions, empowerment, and resources of psoriasis patients will be searched for and included. The study aims to complement the questionnaire with items, to detect patients that are in need for counseling and supportive interventions. Moreover, questions on sociodemographic data will be included.

Based on the results of the scoping review a complete questionnaire will be developed to assess the psychosocial burden of psoriasis patients. Following, two focus groups with n=10 patients with psoriasis in each focus group will be conducted to validate and complement the results of the scoping review.

Recruitment of the Patients

The patients will be consecutively recruited during consultations at the Psoriasis Centers of University Medical Center Schleswig-Holstein Campus Kiel and Institute for Health Services Research in Dermatology and Nursing of the University Medical Center Hamburg.

Inclusion Criteria

Adult patients (age ≥ 18) will be included. Patients need to be diagnosed with a mild, moderate, or severe psoriasis and need to agree by signing informed consent. Inclusion criteria will be checked from the treating physician, who will also fulfill a short questionnaire on the patients' clinical data (severity of the psoriasis, presence of psoriasis arthritis or other comorbidity).

Focus Groups

One focus group will be conducted at the Psoriasis Center in Kiel and the second at the Department of Medical Psychology in Hamburg. Each focus group is planned to take 120 minutes and patients will receive 50€ for their participation. The main issue of the discussion will be to critically review the developed questionnaire in terms of feasibility and understanding with the patients and to add missing topics regarding information and supportive care needs.

Analysis

The focus groups will be recorded and transcribed. The results will show if any adaption of the questionnaire will be necessary or if further items should be developed and included based on the feedback of the patients. The final questionnaire will then be used in a quantitative survey in phase 2.

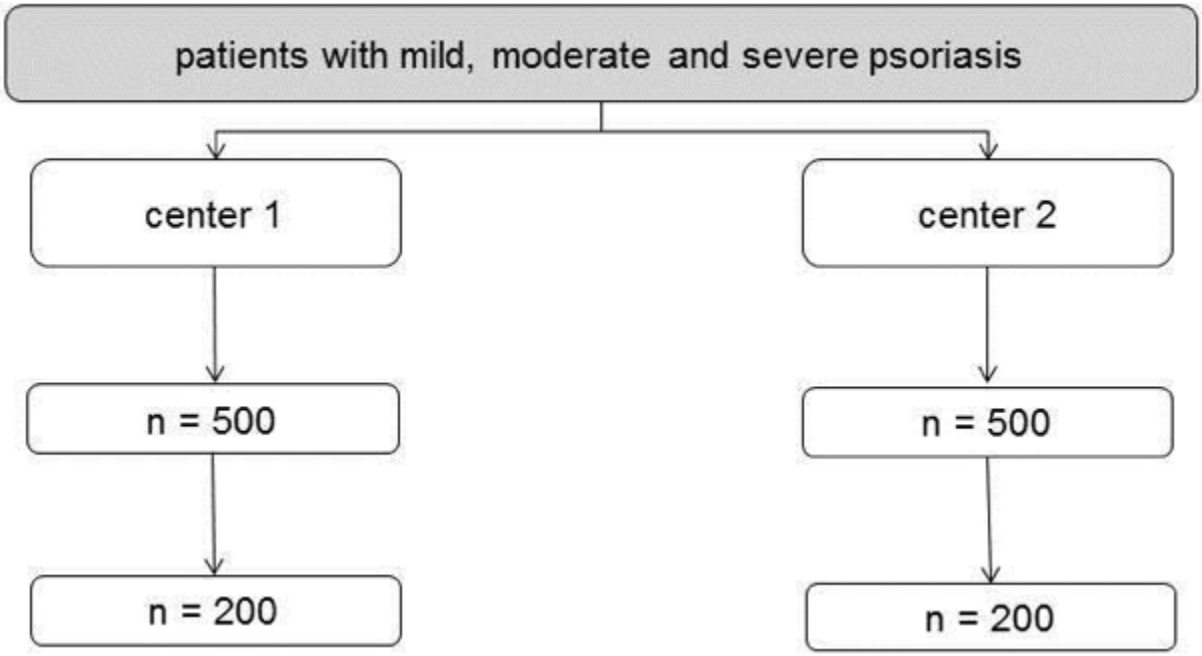
Phase 2: Quantitative Survey

The questionnaire developed in phase 1 will be used in a cross-sectional survey to assess the extent of psychosocial distress and supportive care needs in patients with psoriasis.

Recruitment of Patients

Participants for phase 2 will be recruited again through consecutive consultations in the two cooperating dermatology centers.

Figure 2. Survey flow-chart for the questionnaire. Calculated with an expected return rate of 40%.



Inclusion Criteria

The inclusion criteria are the same as for phase 1.

Sample Size

A sample size of N=400 is projected (Figure 2). Based on an expected return rate of 40% we will approach 1.000 patients, 500 per center.

Measures

Based on the results of the scoping review in phase 1 we expect to include measures on mental disorders, quality of life, psychosocial distress, health and risk behaviors, information needs and utilization of supportive interventions, needs for supportive care, empowerment, and resources of psoriasis patients. Moreover, sociodemographic data will be assessed. The health status in terms of psoriasis severity and comorbidity will be rated by the treating physician.

Analyses

The primary analyses for phase 2 will be descriptive (percentages, means, and standard deviations). The results of this phase will inform the focus of the treatment elements contained within the intervention.

Phase 3: Systematic Literature Review and Meta-Analyses

To identify which psychosocial and psychoeducational interventions for patients with psoriasis already exist and which are effective, a systematic review will be conducted. The methods and results will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [41]. First a search strategy will be defined followed by an electronic database search in the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and PsycINFO. Two independent reviewers will stepwise screen titles, abstracts, and full-texts according to predefined inclusion criteria. Within the title and abstract screening all references that were rated as possibly relevant by one reviewer will be included. In the full-text screening disagreements will be resolved by discussion. In addition to the electronic search reference and citation tracking will be performed with all included references and systematic reviews that dealt with similar questions to check for further relevant references.

Data will be systematically extracted from the included references on the study population, details of the intervention and the outcomes. Furthermore, the risk of bias will be rated for all controlled trials by two independent reviewers according to the Cochrane Handbook for Systematic Reviews of Interventions [42]. Disagreement will be resolved by discussion as well.

For the most relevant patient-reported outcomes a meta-analysis will be performed on all controlled trials that assessed these outcomes. Primary outcome will be HrQoL. Additional outcomes will be chosen depending on whether there will be enough data for a meta-analysis. Furthermore, if the data allows it, subgroup analysis on HrQoL will be performed to compare different aspects of the interventions in their effectiveness.

Phase 4: Intervention Development and Assessment of Feasibility

Based on the results of the phases 2 and 3 a supportive intervention will be developed.

Intervention Development

Based on the needs assessment and the meta-analyses an intervention will be developed addressing the needs of the patients with the most promising intervention type, which can be face-to-face in a group or single setting or an internet-based approach. Internet-based interventions may reach larger parts of the patient population and allow a high degree of flexibility.

Existing Internet-based programs (eg, for depression, alcohol consumption, or stress reduction) could be adapted for these patients or certain modules could be tailored [43,44]. Furthermore, barriers such as privacy concerns and fear of being stigmatized could be overcome by the anonymity of Internet-based interventions. Systematic reviews show favorable effects of Internet-based (cognitive behavioral) interventions for chronic somatic conditions [45,46], but research in dermatological conditions is rare [47]. However, a final decision about the type of intervention will be based on the patients care needs explored in phase 2 and the results of the meta-analysis in phase 3.

We plan to use qualitative methods to explore how professionals and people with psoriasis view the draft of the intervention. In the first step, a focus group with 6 health care professionals (four dermatologists and two psychologists) and 2 patient representatives (eg, of the "Deutscher Psoriasis Bund e.V." [48] or self-help groups organized in Internet forums) are planned to discuss the developed intervention. The participants will be presented the intervention materials and asked to comment on content, acceptability, and usability. The experts will also be asked to discuss where in treatment procedure the intervention is most useful and realizable. The focus groups will be recorded and transcribed.

In the second step, n=8 patients with psoriasis will be sought using convenience sampling recruited from the participating clinics. Think aloud methodology [49] will be used, whereby participants will be asked to detail their 'live' reactions on the content and layout of the intervention. Patients will be encouraged to voice their views on all aspects of the intervention including likely usefulness of the content, appearance of the content, feasibility of following the advice etc. The intervention will be modified on the basis of these qualitative results.

Assessment of Feasibility

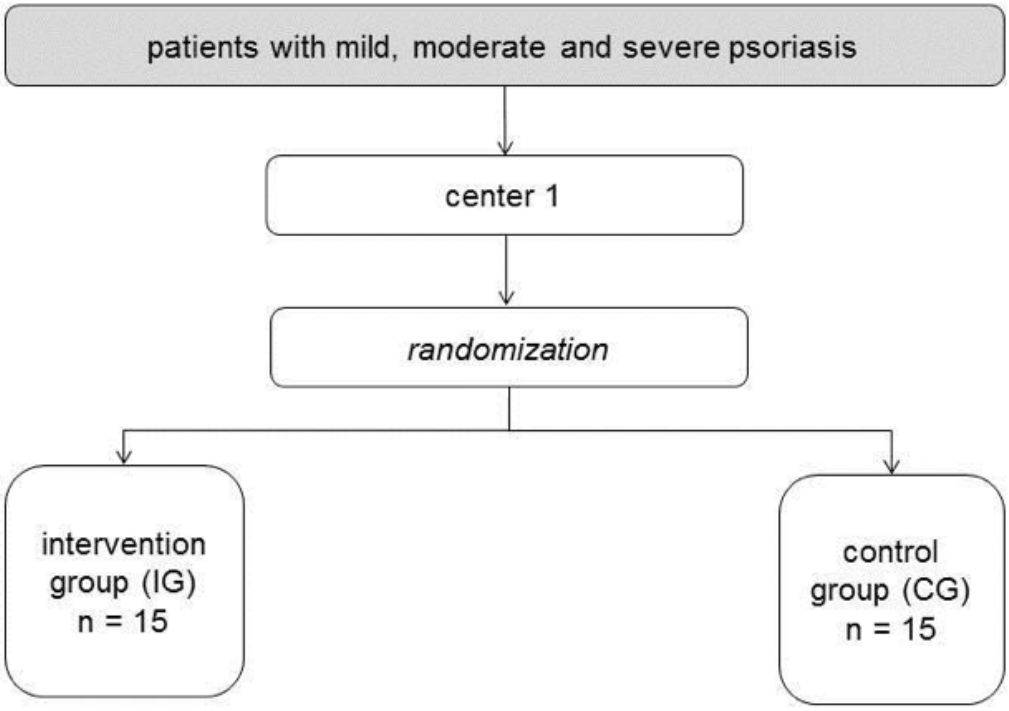
When the manual for the intervention is finally developed, the feasibility of the intervention will be assessed. The primary aim of this feasibility assessment will be to examine the potential of the intervention to cause clinical relevant changes on the patient's side and to identify the methodological requirements for a future trial.

Therefore, if it suits the intervention type, the study aims to recruit a sample of approximately 30 participants. These participants will be randomized into an intervention group and a control group (Figure 3). The measures for this assessment of effectiveness will be partly the same as used in phase two. Primary outcome will be patient reported distress and/or HrQoL. Additionally, information about the utility of the intervention and satisfaction with the intervention will be assessed. Open ended question will be included which ask about participants' experience of using the intervention.

Analyses

The group means and standard deviations for the intervention group and control group before and after the intervention will be presented. In addition, inferential comparisons between both groups will be calculated. Yet due to the small population of the pilot study we do not expect to have enough power to reliably detect meaningful differences.

Figure 3. Survey flow-chart for the intervention.



Results

At the current state of the project the questionnaire development of phase 1 has been completed. The recruitment for the quantitative survey of phase 2 has been started and to date (19 of September 2017) n=185 patients have been included. The systematic review and meta-analysis of phase 3 are conducted simultaneously to phase 2 and results are expected to be completed soon. Phase 4 has not been started yet.

Discussion

Previous research showed that patients with psoriasis are likely to suffer from psychosocial distress and various somatic and mental comorbidities [4]. Moreover, recent research found that intensity of pruritus experienced during psoriasis exacerbation can be related to stressful life events [29]. Therefore, screening for mental illnesses and needs for psychosocial information and care needs are clearly recommended within the treatment of psoriasis [4]. First studies were conducted to test psychosocial interventions for psoriasis; however, results on effectiveness were little to moderate and methodical flaws were criticized [32,33].

The described study will respond to the necessity of focusing on the psychosocial burden of this patient group in a multi-center project combining qualitative and quantitative methodologies. In four phases, relevant research questions will be addressed to close current research gaps. In the first phase an extensive questionnaire development will be conducted. This includes a scoping review on measures on psychosocial distress and information and supportive care needs as well as discussions on the questionnaire with patients in focus groups that will result in a comprehensive and validated questionnaire. In the second phase with the quantitative survey using the questionnaire developed in the prior phase data on the psychosocial distress and information and supportive care needs of patients from two psoriasis centers in Germany will be gained. Moreover, the pre-test of a screening measure will help to develop an instrument to screen for patients with support needs in future consultations.

In the third phase, a meta-analysis will be conducted that adds on prior systematic reviews by summarizing the effectiveness of previous studies on psychosocial/psychoeducative interventions for psoriasis patients. Up-to date, to our knowledge no systematic review including all psychosocial/psychoeducative interventions on psoriasis exists. Effects of these interventions have not been shown in a meta-analysis yet.

In the final phase, the results of the prior phases will be used for the development of psychosocial interventions that is tailored to the specific needs of this patient group. It is hoped that due to the comprehensive knowledge gained from the survey and the expert and patient focus groups the intervention will be found as effective.

The expected benefits from this study are to find out about the psychosocial support needs of patients with psoriasis and to add on previous research on patients' goals in psoriasis treatment. Blome et al found that besides skin treatment related goals of psoriasis patients, like "to be healed of all skin defects," goals like "to be comfortable showing yourself more in public," "to be able to have more contact with other people" or "to be more productive in everyday life," are from high relevance for the patients [50]. The latter treatment goals are difficult to realize with somatic treatment only and again show the necessity of interdisciplinary treatment of this disease and the need for patient-centered care that values the individual patients needs [51] and, for example, in psychosocial offers for patients with psoriasis.

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The study is being conducted in compliance with the Declaration of Helsinki [52]. Approval was obtained from the Ethics Committee of the State Chamber of Physicians in Hamburg, Germany (reference number: PV5299).

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Conflicts of Interest

UM, MA and MH declare financial interests with the project funder Lilly Deutschland GmbH. Lilly Deutschland GmbH provided support in the form of salaries for authors JZ, JD, and EC. The other authors do not declare any competing interests.

Authors' Contributions

JD, SD, UM, MH and MA are responsible for the overall design of the study. JZ has drafted the manuscript. MH and JD are the principal investigators of the study. UM and MA are the responsible investigators at the cooperating institutes: the Institute for Health Services Research in Dermatology and Nursing at the University Medical Center Hamburg-Eppendorf and the Psoriasis Center at the Department of Dermatology of the University Medical Center Schleswig-Holstein Campus Kiel in Germany. EC supported with the methods and design of the study. All authors have read and approved the final manuscript.

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Abbreviations

AUDIT-C: Alcohol Use Disorders Identification Test
CENTRAL: Cochrane Central Register of Controlled Trials
GAD-7: Generalized Anxiety Disorder 7
HrQoL: health-related quality of life
PHQ-9: Patient Health Questionnaire
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PsA: psoriatic arthritis
RCTs: randomized controlled trials
SSD-12: Somatic Symptom Disorder

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Protocol

National Food, Nutrition, and Physical Activity Survey of the Portuguese General Population (2015-2016): Protocol for Design and Development

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Abstract

Background: The assessment of food consumption data using harmonized methodologies at the European level is fundamental to support the development of public policies. Portugal is one of the countries with the most outdated information on individual food consumption.

Objective: The objective of this study was to describe the design and methodology of the National Food, Nutrition and Physical Activity Survey, 2015-2016, developed to collect national and regional data on dietary habits, physical activity (PA), and nutritional status, in a representative sample of the Portuguese general population (3 months-84 years).

Methods: Participants were selected by multistage sampling, using the National Heath Registry as the sampling frame. Data collection, during 12 months, was harmonized according to European guidelines (EU-MENU, European Food Safety Authority [EFSA]). Computer-assisted personal interviewing (CAPI) was performed on a specific electronic platform synchronized with nutritional composition data and considering the FoodEx2 classification system. Dietary assessment was performed using 24-hour recalls (two nonconsecutive, 8-15 days apart) or food diaries in the case of children aged <10 years, complemented with a food propensity questionnaire; PA data (International Physical Activity Questionnaire [IPAQ], the Activity Choice Index [ACI], and 4-days PA diaries); sociodemographic data, and other health-related data were also collected.

Results: A sample of 6553 individuals completed the first interview, and 5811 participants completed two dietary assessments. The participation rate among eligible individuals was 33.38% (6553/19,635), considering the first interview, and 29.60% (5811/19,635) for the participants with two completed interviews (about 40% in children and adolescents and 20% in elderly individuals). Results of the survey will be disseminated in national and international scientific journals during 2018-2019.

Conclusions: The survey will assist policy planning and management of national and European health programs on the improvement of nutritional status and risk assessment related to food hazards, and the enhancement of PA. The infrastructures and data driven from this Survey are a solid basis to the development of a future national surveillance system on diet, PA, and other health behaviors reproducible over time.

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KEYWORDS

surveys; nutritional surveys; exercise; public health; children; adults; elderly

Introduction

Monitoring food consumption at the national level is imperative to assist health policy making, to provide a solid basis for the development of nutritional and food security policies, and to plan future research. According to the European Report on Food Consumption Survey Methods (EFCOSUM) [1], Portugal is one of the European countries with the most outdated information on individual food habits. The first national dietary survey was conducted in 1980 [2], and since then no nationwide individual information has been collected using harmonized instruments capable of answering official European indicators.

The European Food Safety Authority (EFSA) has conducted the Pan-European Survey "What's in European menu?" (EU-Menu), promoting the development and testing of harmonized instruments and protocols for evaluating food consumption across Europe [3], in which Portugal has been involved by conducting the National Food, Nutrition and Physical Activity Survey in 2015-2016 (acronym: IAN-AF 2015-2016).

This paper aims to describe the design and data collection methodologies used in the IAN-AF 2015-2016. The survey aimed to collect nationwide data (from 3 months to 84 years of age) on dietary habits (foods, nutrients, dietary supplements, food safety, and insecurity), physical activity (PA) (sedentary behaviors, sports, and active choices in daily living) and their relation with health determinants, namely, socioeconomic factors.

Methods

Sampling

A probabilistic sample of the Portuguese general population aged between 3 months and 84 years was selected by multistage sampling, using the National Health Registry (RNU coding) as the sampling frame. Participation was independent of the regular attendance to the National Health System.

The first step of sampling was based on the random selection of primary health care units, stratified by the 7 Statistical Geographic Units of Portugal (NUTS II), weighted by the number of individuals registered in each health unit. The second step of sampling was based on the random selection of registered individuals in each health unit, according to sex and age groups.

The sample selection was performed in consecutive recruitment waves to use the most updated versions of the National Health Registry lists (4 recruitment waves for infants and toddlers and 2 recruitment waves for the remaining age groups). Individuals with the following criteria were excluded: (1) living in collective residences or institutions (eg, elderly in retirement homes or individuals in hospitals, at prisons, or military barracks); (2) living in Portugal for less than 1 year (nonapplicable to infants); (3) non-Portuguese speakers; (4) with diminished physical and/or cognitive abilities that hamper participation (eg, blind, deaf, with diagnosed dementias); and (5) deceased.

Individuals with no established contact after all planned attempts were considered with unknown eligibility. Eligible participants without availability for the 2 interviews during the evaluation period or who missed appointments were classified as eligible nonparticipants. In addition, for eligible participants aged 65 years or more, a screening of cognitive impairment was performed by using the Mini-Mental State Examination test [4]. The classification of cognitive impairment was performed using the scale's score according to the education level [5,6]: illiterate and 15 points or less; 1 to 11 years of education and 22 points or less; and at least 11 years of education and 27 points or less. For these individuals only few socio-demographic and anthropometrics information were collected.

Estimated Sample Size

The sample size was estimated by assuming a mean population energy intake of 2000 kcal/day (standard deviation, SD=500) and an effect size of 8%, with a confidence level of 95%. The sample size for each geographical region was estimated in 603 individuals (a total of 4221 individuals in the 7 regions).

To estimate the study design effect, the following information was taken into consideration: (1) a coefficient of variation of cluster sizes defined as 0.4; (2) data from cluster-based studies with primary health care setting in Portugal, measuring the dependency effect of exposures such as body mass index or energy intake (mean intracluster correlation coefficient of 58%); and (3) a mean number of participants reachable in each primary health care unit, depending on the field work management (30 individuals were estimated to be evaluated during 4 weeks). Considering these data, a design effect of 1.20 (an increase of 20% of the sample size) was estimated.

As a result of the settled design effect, the number of individuals to be assessed in each region was estimated as 724, resulting in a total sample of 5068 individuals in the 7 regions. Thus, taking into consideration the distribution of the Portuguese population according to the Census 2011 [7], the sample size required to have representativeness at the national level was of 5068 individuals: 935 children and adolescents (0-17 years), 3262 adults (18-64 years), and 871 elderly (65-84 years). To accomplish the EFSA requirements of including 260 individuals in each age group (130 by sex), an oversampling of children

less than 1 year (3-11 months) (6 times the initial proportion) and 1 to 2 years (3 times the initial proportion) was considered, followed by a redistribution of the sample size for the other age groups. In each health unit, the number of individuals to be assessed by sex and age group was fixed.

An additional sample of pregnant women was also estimated (n=200) using the same sampling frame, resulting in 2 to 3 pregnant women by each health unit. A potential participation rate of 70% in the first interview and in the second interview was defined, resulting in 50% (70%×70%=49%) of nonresponse, unreachable individuals, incomplete questionnaires, and drop-offs expected. Thereby, the number of participants to be selected and contacted was estimated to be 10,204 (5102 x 2). After a pilot study, a more conservative participation rate of 20% (5102 x 5=25,510) was assumed.

Assuming a one-month period for data collection in each health unit, and an estimation of approximately 30 participants by unit, the number of health units needed to be selected was 21 by region. This number was applied to the North, Centre, and Lisbon regions, but due to logistic constraints related to field work efficiency and the low number of health units in the other regions, 12 health units were selected in Alentejo and Algarve, and 6 health units were selected in Madeira and Azores. Figure 1 shows the spatial distribution of the health units, randomly selected in each of the 7 regions (NUTS II), weighted by the number of registered individuals.

Field Work Management and Recruitment

The field work management team included a national coordinator, a subnational coordinator, and 5 regional coordinators. The field work team included 40 interviewers with nutrition or dietetics background and one statistician.

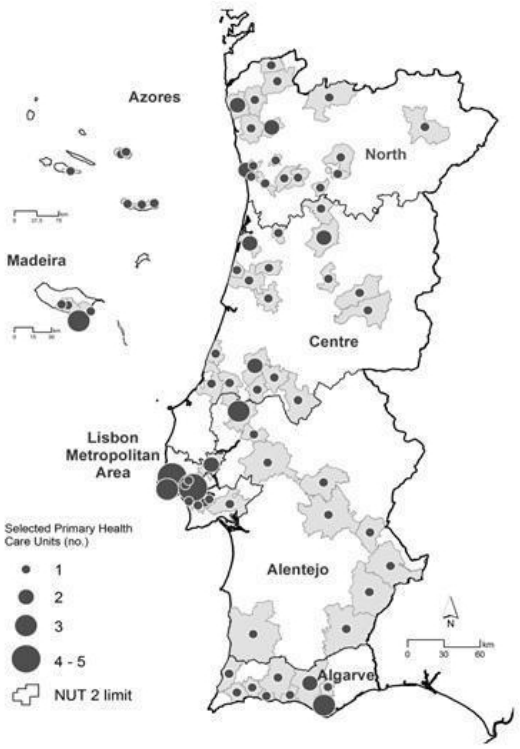
All the procedures related to the management of the field work and participants' recruitment were performed through an electronic platform ("You eAT&Move") based on a client-server software architecture, which was specially developed for the survey purposes.

Participants were contacted by telephone to check their willingness to participate. At maximum, 6 contact attempts in different daytimes and day hours were performed. If participants did not answer after 4 attempts, a short message was sent, followed by more 2 contacts attempts, before they were classified as unknown eligibility. If an oral acceptance was provided by individuals, an invitation letter with participation details was sent by post. If individuals refused to participate, some questions included in a short refusal questionnaire were collected. The examination location was selected according to participant's preference. One of the following two options was provided: the participant's home or the health units they belong to.

Data Collection

Overall, the survey includes the evaluation of the following dimensions: (1) dietary and nutritional intake, (2) eating habits and behaviors, (3) dietary and nutritional supplements use, (4) food insecurity, (5) PA and sedentary behaviors, (6) sociodemographics, (7) general health data, (8) anthropometrics, and (9) biochemical indicators of nutritional intake (subsample).

Figure 1. Spatial distribution of the primary health care units, weighted by the number of registered individuals: the IAN-AF 2015-2016 survey (NUT: Statistical Geographic Units of Portugal).



Most of the procedures of data collection were adapted from the EFSA Guidance in view of the EU Menu methodology [3]. Data were collected by trained fieldworkers using computer-assisted personal interviewing (CAPI), during 12 months (October 2015-September 2016), distributed over the 4 seasons and including all days of the week to incorporate seasonal effects and day-to-day variation in food intake. For interviews, the "You eAT&Move" software includes the following 3 main modules:

You module, that includes sociodemographic questions, anthropometric measures, general health data, food consumption by a food propensity questionnaire (FPQ), and food insecurity

eAT24 module, which allows the collection and description of food consumption data by 24-hour recalls (or food diaries) with food pictures for portion size estimation, synchronized with nutritional composition data of foods and recipes

Move module, which allows the collection of PA data and includes the IPAQ questionnaire, the Activity Choice Index (ACI), and PA diaries, synchronized with metabolic equivalents data associated with each type of PA.

Table 1 shows the overview of data dimensions collected in the IAN-AF 2015-2016 survey, by first and second interviews and age groups (plus pregnant women).

Dietary Assessment Methods

Dietary intake was obtained by 2 nonconsecutive one-day food diaries for children aged less than 10 years and 2 nonconsecutive 24-hour recalls for the remaining age groups. The time between interviews was set at 8 to 15 days. The days of reporting were randomly selected, but participants were able to change them according to their own availability for the interview. For Saturdays, a 24-hour recall was performed on Mondays. For adolescents from 10 to 14 years, the 24-hour recall was administered with the presence of one of the parents or other main caregiver; for adolescents from 15 to 17 years, the 24-hour recall was administered without the need of parents' help. For children aged less than 10 years, the 2 nonconsecutive one-day food diaries were followed by a face-to-face interview, allowing the parent or other main caregiver to add details related to food description and quantification.

To validate nutritional intake in participants aged 18 years or more, data from the 24-hour recall were compared against urinary biomarkers. In a subsample of adults (n=94), 24-hour urinary samples were collected during the day before the second interview. The urinary concentration of sodium, potassium, iodine, and total nitrogen were assessed.

The eAT24 Module

Dietary intake data were collected using the "eAT24" module (electronic assessment tool for 24-hour recall), which allows the assessment of dietary data by an automated multiple-pass method for 24-hour (5 steps) [8]. All foods, including beverages and dietary supplements consumed during a 24-hour period, were recorded per eating occasion and quantified and described as eaten.

The eAT24 methodology requires the description of consumed foods during the dietary interview through several facets and respective descriptors, using the FoodEx2 classification system [9]. The place and time of meal consumption are also recorded for each eating occasion.

The software allows subsequent conversion of foods into nutrients, using by default the Portuguese food composition table [10]. Several activities were performed for updating or developing the food-related lists and the classification and description of foods. The initial food list was based on the 962 food items from the Portuguese food composition table updated with several other food items, such as infant formula, baby foods, and ready-to-eat items (such as desserts and drinks), resulting in a list of 2479 food items and 117 dietary supplement items. A recipe module was also created including 1696 recipes. In this module, recipes were disaggregated into raw ingredients allowing the description and quantification of each item. Recipes were described as 5 facets (production method, brand, preservation method, packaging material, and reheating method) and subsequently disaggregated into their ingredients. Recipe ingredients were also described according to the FoodEx2 classification system [9]. Nutritional composition of recipes is calculated according to the methodology proposed by the European Food Information Resource (EUROFIR) network of excellence "Proposal for the harmonization of recipe calculation procedures" [11]. The software allows the inclusion of a new food item or a new recipe during the data collection process.

Different methods are available for use for food and recipe quantification: (1) weight or volume method, (2) standard unit method, (3) photo method (food picture book including 186 food photo series [with 6 portions each food/recipe], and 11 household measures photo series), (4) household measure method, and (5) default portion method.

The Food Propensity Questionnaire

A FPQ was also used for usual intake modeling purposes [3], adapted from a previous version proposed by the "Pilot study in the view of a Pan European dietary survey" (PANEU project) [12]. The main objective is to identify never-consumers, to minimize problems with the day-to-day variation of intake that might affect the estimation of usual intake, typical of single or few short-term measurements (such as 24-hour recalls) [13]. The FPQ includes a general list of food and beverage groups and a list of specific foods and beverages important for risk assessment. The number of items in the list and the reference period of consumption differ by age group: children <9 years—45 food items, reference period: the last month; adolescents and adults—49 food items, reference period: the last 12 months; and pregnant women—49 food items, reference period: the last 3 months.

Table 1. Overview of data dimensions collected in the National Food, Nutrition and Physical Activity Survey, 2015-2016, (IAN-AF) by age groups (plus pregnant women).

Modules and dimensions	Age groups (years)							Pregnant women
	3 months-2	3-5	6-9	10-14	15-17	18-64	65-84	
You								
Sociodemographics (SD)[a]	SD1	SD1	SD1	SD2	SD2	SD3	SD3	SD3
General health (G)[b]	G1	G2	G2	G3	G3	G4	G4	G5
Eating behaviors (EB)[c]	EB1	EB2	EB2	EB2	EB2	EB3	EB3	EB3
Anthropometrics (A)[d]	A1	A2	A2	A2	A2	A2	A2	A3
Household food security (HFS)	-	-	-	-	-	HFS	HFS	HFS
Food Propensity Questionnaire (FPQ)[e]	-	FPQ1	FPQ1	FPQ2	FPQ2	FPQ2	FPQ2	FPQ3
eAT24								
Food diaries 1 (FD1)[f] and 2 (FD2)	FD1	FD2	FD2	-	-	-	-	-
24-h recall 1 (24R)	-	-	-	24R	24R	24R	24R	24R
24-h recall 2 (24R)	-	-	-	24R	24R	24R	24R	24R
Move								
Physical activity diaries (PAD)	-	-	PAD	PAD	-	-	-	-
International Physical Activity Questionnaire (IPAQ)	-	-	-	-	IPAQ	IPAQ	IPAQ	IPAQ
Activity Choice Index (ACI)					ACI	ACI	ACI	ACI
Sedentary behaviors (SB)[g]	-	SB1	SB2	SB3	SB4	SB5	SB5	SB6

[a]SD1 and SD2 differ from SD3 by including also questions on country of origin, nationality, professional activity, education of parents, and the current school year (in SD2 only). These versions do not have questions on marital status and household income (only included in SD3).

[b]G1 assesses previous diseases with need of regular medical care (predefined list of diseases) and identifies the health professional assistant. G2 only assesses previous diseases with need of regular medical care. G3 assesses previous diseases with need of regular medical care, and also the general health condition and current and past smoking habits. G4 evaluates previous diseases with need of regular medical care, and also diseases previously diagnosed by a physician, the general health condition, current and past smoking habits, and gynecological history in women. G5 assesses the general health condition before and during pregnancy, smoking habits before and during pregnancy, gynecological history, and data on current pregnancy (gestational weeks, health problems, etc).

[c]EA1 include questions relating to breastfeeding, consumption of different milk options, food diversification, and a brief food frequency questionnaire (FFQ) of interest items. EA2 only includes a fruit and vegetables FFQ. EA3 include besides a fruit and vegetables FFQ, questions about organic foods consumption, food safety, and a salt consumption scale.

[d]A1 includes weight and length driven from the child health booklet and measured weight and height. A2 includes self-reported weight and height and measured weight, height, and waist and hip circumferences. A3 does not include waist and hip circumference measurements, and evaluates self-reported height and weight before pregnancy.

[e]FPQ1 assesses the consumption of 45 food items in the last month. FPQ2 assesses the consumption of 49 food items (including alcoholic beverages) in the last 12 months, and an option for seasonal consumption is available. FPQ3 is similar to FPQ2, but the reference period is the last 3 months.

[f]FD1 differs from FD2 because it has a specific structure for registering breastfeeding and formula feeding.

[g]All SB include information about sleep habits on weekdays and weekend days and questions about regular and programmed PA. SB1 differs from SB2 and SB3 on the type of sedentary behaviors asked. SB4 and SB5 include also a question about physical or sedentary choices.

Dietary Supplements

The use of dietary supplements was retrieved by 2 methods. The first method used the 24-hour recall, in which dietary supplements and foods consumed during a 24-hour period were recorded per consumption occasion and quantified and described as consumed. Supplements were described according to 6 facets (supplement source, target group, place of acquisition, packaging material, brand, and physical state). This interview-based dietary assessment instrument allows a very detailed description of supplements consumed in the course of the preceding day.

The second method asked the frequency of use, in the last 12 months, of a predefined list of 16 different dietary supplement types (eg, supplements of vitamins, such as C, D, and folate; supplements of minerals, such as calcium and iron; supplements of multivitamins; supplements of fatty acids, herbs, plants, and probiotics).

Food Insecurity

Food insecurity [14] assessment was obtained by applying a slightly modified questionnaire developed by Radimer et al [15], widely applied in the evaluation and monitoring of public food assistance programs in the United States and in other countries, and by Bickel [16], which was adapted for Portugal by INSA and ERS/USDA. The 3-stage design questionnaire keeps respondent burden to the minimum needed to get reliable data. It provides estimates of food insecurity for households with or without children under the age of 18 years by collecting information on 4 underlying dimensions and experience of food insecurity: availability, access, utilization, and stability or resilience. In this way, food insecurity is associated not only with structural poverty but also with transitional—but not less serious—conditions of scarce, in particular, financial resources. The food insecurity status of each household lies somewhere along a continuum, extending into the following 3 categories: food security (households had no problems or anxiety about consistently accessing adequate food), moderate food insecurity (households reduced the quality, variety, and desirability of their diets, but the quantity of food intake and normal eating patterns were not substantially disrupted), and severe food insecurity (at times, eating patterns of one or more household members were disrupted and food intake was reduced because the household lacked money and other resources for food during the year).

Physical Activity Assessment Methods

For children (6-9 years) and adolescents (10-14 years), PA was assessed by diaries (2 consecutive days during the week and 2 of the weekend), and for the other age groups (≥15 years), the assessment methods included the International Physical Activity Questionnaire (IPAQ) short version [17] and the ACI [18].

The PA diaries were an adaptation of a model proposed by Bouchard et al [19] in which children registered their activities in a logbook for each 15 min interval during 4 days, according to previous written instructions.

Additional questions on sedentary behaviors were also asked in all age groups (including children aged 3-6 years). From the age of 15, self-reported activities representative of "opportunistic" active choices in daily routine during the last month (eg, taking the stairs, parking further away from an entrance, or choosing to stand instead of sitting) were assessed with 6 item response options on a 5-point Likert scale (ie, 1=never, 5=always), by using the ACI scale [18]. Composite scales can be calculated by averaging the items. A question on structured leisure time PA activity, detailing the type and time of activity, was also asked in all age groups from 6 years of age.

The collection of PA data was performed using the e-module "Move," including the IPAQ questionnaire and PA diaries, synchronized with metabolic equivalents data associated with each type of PA. For all types of activity, daily energy expenditure was computed using the energy cost of each activity as estimated from reference values for participants aged 15 years or more [20,21] and using an adaption for children based on values proposed by Ridley et al [22].

In children, energy expenditure was estimated by multiplying the related MET by the self-reported time spent in each activity (min/day) recorded in the diary. Individual daily energy expenditure was computed as the mean expenditure of the 4-day diaries. To validate the information from PA diaries, PA was objectively measured by accelerometry in a subsample of 35 participants from 6 to 14 years. Participants were asked in the first interview to wear an accelerometer (ActiGraph GT3X models; Pensacola, FL) during 4 days, including 2 consecutive weekdays and 2 consecutive weekend days, the same registered in the PA diary.

Anthropometrics

Adolescents and adults were asked to self-report their actual height and weight before the performance of objective measurements. In children, this information was retrieved from their health booklets, the last registry was considered. In pregnant women, weight and height was reported before pregnancy.

Anthropometric measurements, including length/height, weight, and body circumferences, were performed in both children and adults according to standard procedures [23] by trained observers. Height was measured to the nearest centimeter, with participants in a standing position with light clothing and barefoot, using a portable wall stadiometer (SECA 213, Hamburg, Germany). For participants whose height was not possible to measure, the hand length was measured using a pocket ruler as an alternative [24]. For children under 2 years, recumbent length was measured to the nearest 0.1 cm with a measuring rod with large calipers (SECA 207; Hamburg, Germany).

Body weight was measured in the same conditions to the nearest tenth of a kilogram using a digital scale (SECA 813, Hamburg, Germany). For children under 2 years, a specific pediatric digital weight scale was used (SECA 354, Hamburg, Germany), and measurements were conducted with participants naked and without diaper, to the nearest 0.01 cm.

Arm, waist, and hip circumferences were measured, using an anthropometric tape, in all age groups except in children under 3 years and in pregnant women. Arm circumference was measured at the marked level of the mid-acromiale-radiale. Waist circumference was measured at the level of the narrowest point between the lower costal border and the iliac crest. Hip circumference was measured at the level of greatest posterior protuberance of the buttocks. All these circumferences were performed to the nearest 0.1 cm.

As part of quality control procedures, a bubble level was used to check the best position for the equipment in the room; a small platform was used to allow the direct observation of values from the stadiometer and the calibration of scales using standard weights of 5000 g and 500 g and their combinations was performed.

Quality Control

Several quality control actions were undertaken before, during, and after the fieldwork process, including the following: (1) testing the e-platform in several pilot studies performed across

the different geographical regions, (2) recruitment of interviewers with thorough knowledge of the available foods on the market and traditional recipes, (3) on-going training of those interviewers (distance electronic devices were used to assist interviews, when needed), and (4) control of individual energy and macronutrient intake at the end of interview, and definition of a maximum food weight to easily identify information biases. This control is directly integrated in the software. For example, for the total energy intake, a minimum of 122 Kcal or 500 Kcal and a maximum of 2816 Kcal or 4000 Kcal were considered according to the age groups 3 months to 9 years or 10 years to 84 years, respectively. An outlier is signalized with an alert message allowing the interviewer to perform the corrections during the interview. Few other quality control actions that were undertaken are as follows: (1) preliminary statistical analysis during fieldwork to check possible information bias, the distribution of interviews by days of the week and seasons, (2) registry of doubts in an editor book to be solved by the research team, (3) calibration of anthropometric devices each 3 months, (4) application of a refusal questionnaire to nonresponders to check the representativeness of the final sample, (5) identification of under- and over-reporters of energy intake [3,25], outliers, and removal of intra-individual variability of dietary intake.

Ethics

Ethical approval was obtained from the National Commission for Data Protection, the Ethical Committee of the Institute of Public Health of the University of Porto, and the Ethical Commissions of each one of the Regional Administrations of Health.

All participants were asked to provide their written informed consent according to the Ethical Principles for Medical Research involving human subjects expressed in the Declaration of Helsinki and the national legislation. Written agreements from the parents were required for children and adolescents below 18 years. Adolescents (10-17 years) were also asked to sign the consent form together with their legal representative.

All documents with identification data were treated separately and stored in a different dataset.

Results

Sample Size

A total of 5819 participants completed 2 interviews (5811 with two complete dietary assessments) and 6553 completed only the first interview (Table 2). Approximately 23% are children under the age of 10 years, 11% are adolescents (10-17 years), 53% are adults (18-64 years), and 13% are elderly (65-84 years). An additional sample of 184 pregnant women was evaluated.

Table 2. Final sample size by sex and age groups—the National Food, Nutrition and Physical Activity Survey, 2015-2016, (IAN-AF).

Age groups	Children (<10 years)		Adolescents (10-17 years)		Adults (18-64 years)		Elderly (≥65 years)		Total
	Male	Female	Male	Female	Male	Female	Male	Female	
Selected participants, n	1923	1965	952	988	8336	9384	3094	2541	29,183
Unknown eligibility, n	388	404	197	163	1677	1960	458	369	5616
Known eligibility, n	1535	1561	755	825	6659	7424	2636	2172	23,567
Eligible, n	1410	1422	658	719	5725	5971	2037	1693	19,635
Noneligible, n	125	139	97	106	934	1453	599	479	3932
Contact rate, n (%)[a]	1410 (78.42)	1422 (77.88)	658 (76.9)	719 (81.5)	5725 (77.34)	5971 (75.29)	2037 (81.64)	1693 (82.10)	19,635 (77.76)
Participants' 1st interview									
Cooperation rate, n (%)[b]	769 (54.54)	745 (52.39)	351 (53.3)	349 (48.5)	1881 (32.86)	1563 (26.18)	429 (21.06)	466 (27.53)	6553 (33.37)
Participation rate, n (%)[c]	769 (42.77)	745 (40.80)	351 (41.1)	349 (39.6)	1881 (25.41)	1563 (19.71)	429 (17.19)	466 (22.60)	6553 (25.95)
Participants with 2 dietary assessments									
Cooperation rate, n (%)[b]	667 (47.30)	660 (46.41)	319 (48.5)	313 (43.5)	1674 (29.24)	1428 (23.92)	358 (17.57)	392 (23.15)	5811 (29.60)
Participation rate, n (%)[c]	667 (37.10)	660 (36.14)	319 (37.3)	313 (35.5)	1674 (22.62)	1428 (18.01)	358 (14.35)	392 (19.01)	5811 (23.01)

[a]Contact rate: eligible/(eligible + unknown eligible individuals).

[b]Cooperation rate: participants/eligible individuals.

[c]Participation rate: participants/(eligible + unknown eligible individuals).

The contact rate was 77.76%. The cooperation rate among eligible individuals was 33.37%, considering the first interview, and 29.60% for the participants with 2 completed dietary assessments. Similarly, the participation rate was 25.95% and 23.01%, respectively. The participation rates were higher in children and adolescents (approximately 40%) and much lower in the elderly (approximately 20%) (Table 2).

The characteristics of participants were compared with characteristics of individuals who refused to participate and who accepted to fill out a small refusal questionnaire by phone.

Information on some important indicators, such as sex, age, and region of residence; frequency of consumption of fruit and vegetables; regular practice of leisure-time PA; and self-reported weight and height; were available. Individuals who refused to participate were older (over 65 years: 22% vs 13%) and less educated (over 12 years: 19% vs 27%), although for variables representing the main areas of the survey—fruit and vegetables consumption (≥5 portions/day: 18.6% vs 18.1%), practice of regular leisure-time PA (33% vs 39%), and obesity (12.4% vs 12.7%)—the differences are of a small magnitude.

Data Analysis

All statistics that will be used to calculate future estimates driven from this survey, both at national or regional levels, will include the weighting of the sample data. The weighted sample represents the number of individuals from the national general population that are represented by each individual in the study sample. The sample weighting includes the following: (1) initial weights to overcome the different probability of sampling units selection; (2) a second weight to overcome the different probability of individuals selection in each unit, by sex and age (considering the total population, by sex and age groups in the closest recruitment wave); and (3) correction of these initial weights for nonresponse bias.

The distribution of the interviews by week days and seasons was also analyzed. The distribution of interviews by day of the week was 18.3%, 20.5%, 18.5%, 16.9%, 8.2%, 5.1%, and 12.6% from Monday to Sunday, respectively. The distribution of the interviews by season showed that spring was the season where most interviews were performed (35.9%), followed by winter (28.3%), summer (24.7%), and finally by autumn (11.1%).

Final databases were already checked and ready for analysis. Specific statistical analysis for identification of outliers and removal of intra-individual variability preceded the final analysis. Results of the survey will be disseminated in national and international scientific journals during 2018-2019.

Discussion

Strengths and Limitations

The response rates were lower than expected, particularly among adults and elderly individuals, despite several dissemination activities (eg, through regional media) that were undertaken to promote the survey close to the population. However, results were similar to other national European dietary surveys using the same sampling approach [26,27]. Participants in the survey were older and less educated than those who refused to participate but did not differ on the prevalence of fruit and vegetables consumption, practice of regular leisure-time PA, and obesity.

The used sampling frame covers the entire population resident with a national identification card, which means that illegal residents such as refuges or irregular immigrants are not included. However, most of these individuals, even if included in the survey by the sampling strategy, would be noneligible, since they are non-Portuguese speakers (considered as an exclusion criteria). Moreover, the proportion of legal foreign residents is only 3.7% [7]. Some other vulnerable and marginalized population groups, such as homeless people, despite not having participated, represent a small part of the Portuguese population (696 according to Census 2011) [7]. The absence of these individuals in the sample is not expected to influence the final results and the representativeness of the sample.

The distribution of interview week days and seasonality was checked and, although not exactly as planned, it follows the minimum requisites of having a considerable number of registries in all the week days and seasons. Fewer registries on Saturdays result from the fact that no interviews were scheduled on Sundays, as the report of both Saturdays and Sundays was conducted on Mondays. Friday also had fewer registries than other weekdays because not all health care units were opened on Saturdays, despite the continuous efforts of the fieldwork team to have alternative spaces for the interviews on Saturdays. Additionally, autumn was the season with the lowest proportion of interviews, because it coincided with the beginning and the end of the field work, when there are less concentrated interviews.

Following the European standards of dietary assessment is a major strength of this project as it will allow the comparison of important indicators in Europe in several different domains of food and nutrient intake, eating behaviors, nutritional status, food safety, and food insecurity. Information of the major contributors for sugar, sodium, or fat intake will orient new community interventions. The information could also give support to the assessment of the impact of current legislative measures, such as those related to the reduction of sugar in soft drinks or reduction of salt in bread. Furthermore, accurate and detailed food consumption data are important for the assessment of risk exposure to potentially hazardous substances. The use of the Foodex2 food classification system, proposed by EFSA [9], improves the possibility of getting information of risk assessment related to food biological and chemical hazards, namely, main exposures to chemicals added intentionally to food such as additives (eg, artificial sweeteners, preservatives, and artificial colors) and to chemical compounds from food processing (eg, nitrosamines, heterocyclic amines, and aromatic hydrocarbons) and packaging materials (eg, bisphenol A and phthalates) that enter the food supply inadvertently.

For PA, the harmonization of procedures in Europe is still under discussion, but having information on different domains such as overall activity level, structured leisure-time physical exercise, and sedentary behaviors could be useful for supporting

the estimation of indicators and to better develop new population interventions.

Future Perspectives

Findings from this survey will allow having national updated knowledge on the distribution of diet, PA, and other health-related risks according to sex, age, education, and geographical region. It also serves as an important descriptive starting point for future follow-up surveys in specific target groups. It expects to contribute to the development of national and European evidence-based policies that translate research into effective nutrition and health strategies, sustainable over time. A comprehensive analysis according to socioeconomic dimensions will also contribute to the development of policies with impact in equity and human well-being.

It is expected that the structure and information driven from this survey could also contribute to develop and consolidate solid infrastructures for epidemiological and public health research by building a future national functioning surveillance system on diet, PA, and other health behaviors, reproducible over time.

Authors' Contributions

The IAN-AF 2015-2016 Survey was conducted by a Consortium, coordinated by CL. All authors are members of the Consortium and were involved in the design of the study and contributed for the writing of the manuscript. All authors critically revised and approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACI: Activity Choice Index
CAPI: computer-assisted personal interviewing
eAT24: electronic assessment tool for 24-hour recall
EB: eating behaviors
EFSA: European Food Safety Authority
FD: food diary
FPQ: Food Propensity Questionnaire
G: general health
HFS: household food security
IAN-AF: The National Food, Nutrition and Physical Activity Survey, 2015-2016 (Portuguese acronym)
IPAQ: International Physical Activity Questionnaire
PA: physical activity
PAD: physical activity diaries
SB: sedentary behaviors
SD: sociodemographics
24R: 24-h recall

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Protocol

Input of Psychosocial Information During Multidisciplinary Team Meetings at Medical Oncology Departments: Protocol for an Observational Study

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Abstract

Background: Multidisciplinary team meetings (MDTMs) have become standard practice in oncology and gained the status of the key decision-making forum for cancer patient management. The current literature provides evidence that MDTMs are achieving their intended objectives but there are also indications to question the positive impact of MDTMs in oncology settings. For cancer management to be patient-centered, it is crucial that medical information as well as psychosocial aspects—such as the patients' living situation, possible family problems, patients' mental state, and patients' perceptions and values or preferences towards treatment or care—are considered and discussed during MDTMs. Previous studies demonstrate that failure to account for patients' psychosocial information has a negative impact on the implementation of the treatment recommendations formulated during MDTMs. Few empirical studies have demonstrated the predominant role of physicians during MDTMs, leading to the phenomenon that medical information is shared almost exclusively at the expense of psychosocial information. However, more in-depth insight on the underlying reasons why MDTMs fail to take into account psychosocial information of cancer patients is needed.

Objective: This paper presents a research protocol for a cross-sectional observational study that will focus on exploring the barriers to considering psychosocial information during MDTMs at medical oncology departments.

Methods: This protocol encompasses a cross-sectional comparative case study of MDTMs at medical oncology departments in Flanders, Belgium. MDTMs from various oncology subspecialties at inpatient medical oncology departments in multiple hospitals (academic as well as general hospitals) are compared. The observations focus on the "multidisciplinary oncology consultation" (MOC), a formally regulated and financed type of MDTM in Belgian oncology since 2003. Data are collected through nonparticipant observations of MOC–meetings. Observational data are supplemented with semi-structured individual interviews with members of the MOC–meetings.

Results: The protocol is part of a larger research project on communication and multidisciplinary collaboration in oncology departments. Results of this study will particularly focus on the input of psychosocial information during MDTMs.

Conclusions: The concept of an MDTM should not merely be a group of care professionals who mostly work independently and occasionally liaise with one another. Interventions aiming to enhance the input of psychosocial information are crucial to ensure that MDTMs can benefit from their diverse membership to achieve their full potential. The findings from this study can be used to design nonclinical and organizational interventions that enhance multidisciplinary decision-making in oncology.

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KEYWORDS

multidisciplinary collaboration; oncology; multidisciplinary communication; health services; qualitative research; multidisciplinary oncology consultations

Introduction

Multidisciplinary team meetings (MDTMs) have become standard practice in oncology and gained the status of the key decision-making forum for cancer patient management [1]. MDTMs aim for collaborative decision-making on treatment plans, ensuring that they are consistent with the best available evidence. MDTMs are considered to facilitate communication between healthcare professionals by gathering the relevant specialties around the table to share their knowledge and expertise and make collective evidence-based recommendations for patient management [2]. The current literature provides evidence that MDTMs are achieving intended objectives [3,4]. MDTMs lead to significant changes in the way cancer patients are assessed and managed [1,5] and lead to improved outcomes [6-8]. But there are also indications to question the positive impact of MDTMs in oncology settings [9].

The original Calman-Hine report (1995) recommends that "…cancer services should be patient centred and should take account of patients', families' and carers' views and preferences as well as those of professionals involved in cancer care. Individuals' perceptions of their needs may differ from those of the professional…" (page 6) [10]. According to this argumentation, it is crucial that medical, as well as nonmedical, information about the patient is discussed during MDTMs. Among the nonmedical information are psychosocial factors such as the patients' living situation, possible family problems, patients' mental state, and patients' perceptions and values or preferences towards treatment or care. These aspects help to put the results of the medical investigations and staging modalities in a broader perspective with a potential impact on the treatment plan and patient management [11]. Failure to account for patients' psychosocial information has a negative impact on implementing treatment recommendations formulated within an MDTM [11,12].

Concerns arise over the lack of consideration for psychosocial information during multidisciplinary meetings [13-16]. Some individual studies demonstrated how the predominant role of physicians during MDTMs lead to medical information being shared, almost exclusively, at the expense of psychosocial information [13-16]. However, more in-depth insight on the underlying reasons why MDTMs fail to take into account psychosocial information of cancer patients is needed to enhance the effectiveness of the meetings given that MDTMs consume considerable time, effort, and financial resources [17-20].

This paper presents a research protocol for a cross-sectional comparative case study that will focus on the research question, "What are the personal, professional, organizational, and system-related barriers to consider psychosocial information during MDTMs at medical oncology departments?" This overall research question will be disentangled through subquestions addressing whether personal traits (gender, age, or experience) of MDTM participants facilitate or hamper the consideration of psychosocial information; whether professional background (medical, paramedical, psychological, nursing, etc.) of the participants affects positively or negatively the consideration of psychosocial information; whether department and organizational aspects (structural as well as cultural) affect the content and processes of a multidisciplinary dialogue; and to what extent health system characteristics (formal regulations, financing, and reimbursement rules) hamper or facilitate the uptake of psychosocial information during MDTMs. Moreover, as we want to develop a true understanding of the group dynamics during the MDTMs, we will address subquestions relating to how meeting habits, power plays and authority relationships, time constraints, and organizational values and norms potentially impact the consideration of certain information and the ultimate decision-making process. All these questions will be addressed on a case-by-case basis and with the additional research question: "What are the differences and commonalities between different MDTMs?"

Methods

Study Design

As part of a larger research project on communication and multidisciplinary collaboration in oncology departments [21], this protocol encompasses a cross-sectional comparative case study of MDTMs. A case study examines in rich detail the context and features of a social phenomenon within its context. The comparative part of the study aims at understanding and identifying general patterns and causal mechanisms over different contexts [22-25].

We use an interpretative research methodology grounded in the theoretical assumption that social realities (such as in MDTMs) are socially constructed through interaction and are very much context dependent. Emerging social patterns will be deduced from empirical fieldwork. The researchers aim for a better understanding of the determinants of the interaction processes and the factors influencing the participants' experiences. This is done in an iterative process of reflection, data collection, data-ordering and triangulation, use of theories, and thus, interpretation. This also implies that no detailed or standardized rules are put forward to guide data acquisition; observations are guided by research questions and inductively emerging issues. Interviews are done in a semi-structured way offering variation in the framework for respondents. This qualitative research method aims at a holistic approach to capture the social reality of decision-making by combining induction and deduction to disentangle pathways of interdependent determinants for considering psychosocial information during MDTMs in oncological settings [26,27].

Units of Analysis

MDTMs from various oncology subspecialties at inpatient medical oncology departments in multiple hospitals (academic as well as general hospitals) in Flanders (Belgium) are

compared. MDTMs are defined as formally organized team meetings where medical (physicians) and nonmedical (nonphysicians) disciplines meet (whether physically in one place or by video- or teleconferencing) to discuss patient cases and to decide on treatment recommendations [21]. For this study, we focus on the "multidisciplinary oncology consultation" (MOC), a formally regulated and financed type of MDTM in Belgian oncology since 2003. It aims to foster multidisciplinary consultations within oncological settings and to ensure a systematic transparent multidisciplinary approach across all Belgian hospitals providing oncological programs [4,15,28]. Within the MOC, the multidisciplinary team should agree on the diagnosis of the patient and recommend a treatment plan based on clinical treatment guidelines.

An MOC is requested by the treating physician (general practitioner or specialist) and is legally mandatory in the following cases: a newly diagnosed cancer patient; when cancer treatment does not follow the accepted and written guidelines of the oncology department; when radiation therapy is repeated within one year; and when the administration of a new line chemotherapy is indicated. The MOC is a prerequisite for the reimbursement of certain chemotherapeutic treatments. The Belgian law states that the MOC must be chaired by a medical coordinator (preferably with oncological specialization). At least four different medical specialists (eg, radiotherapy, surgery, organ specialism, or pathology) from the hospital staff and one participant from outside the hospital (eg, the general practitioner or the treating physician of the patient if he/she is not part of the hospital team) participate [4,28].

In the daily hospital practice, MOCs (a legally required meeting per individual patient) are clustered in a collective meeting moment for all patients at stake, generally per tumour group, so called "MOC–meetings" [21]. The MOC–meetings are the units of analysis for this protocol.

Data Collection

Nonparticipant Observations

Data are collected through nonparticipant observations of MOC–meetings. Nonparticipant observation is particularly useful as it allows the researchers to give an insider view about behavior, communication patterns, and other interactions between participants [29]. Data sources include audio recordings of the meetings and researchers' field notes. Observations are guided by a supportive template of dimensions and issues to be considered. The template aims to organize descriptive data such as 1) frequency of the meeting, 2) duration, 3) composition and participation of disciplines, as well as more substantive data, such as 4) participants' role during the meetings, 5) topics discussed during the meeting, and 6) the process of decision-making. The template can change when new dimensions emerge inductively from observations. Iteration in qualitative data collection and analysis is a reflexive process that involves continuous meaning-making, facilitating an in-depth understanding of the observed social reality.

Individual Interviews

Observational data are supplemented with semistructured individual interviews with members of the MOC–meetings. The interviews aim to increase understanding of the perspectives of the participants in the MOC–meetings.

We use interview guides with open-ended questions. All interviews start with an open-ended question to explore the respondents' experiences of sharing psychosocial information during MOC-meetings. Subsequently, the interviews will focus on issues and dimensions emerging from the observations. The interviews aim at filling observation gaps, understanding how participants give meaning to emerging issues, and aim at respondent validation of the researchers' interpretations. The interviews will collect data on what the respondents perceive as barriers and facilitators to considering psychosocial information during the MOC–meetings. The individual interviews are recorded using a digital voice recorder.

All data will be anonymized and stripped of all sensitive personal and patient identifiers. Additional consent will be obtained for this data collection. Digital audio files are stored on a secured laptop and access to the data is only granted to the research team.

Data Analysis

The individual interviews are transcribed. Transcripts as well as the researchers' field notes and written comments from the observations are used in the analysis process. Two researchers independently code the data thematically and then discuss and compare emerging categories, subcategories, and interpretations of the findings. A third researcher will be consulted in case of disagreement. A preliminary thematic analysis is performed after each observation. Initial content issues or identified patterns are used to support subsequent observations for targeted topics to expand upon or validate hypotheses (the iterative cycle of qualitative research) [30].

Results

The protocol is part of a larger research project on communication and multidisciplinary collaboration in oncology departments which is funded by The Research Foundation – Flanders (G035813N). Preliminary results on MDTMS in oncology settings have been published previously [15]. Results of this study will particularly focus on the input of psychosocial information during MDTMs.

Ethics Approval

Ethics approval for this study was given by the central Medical Ethics Commission of the Brussels University Hospital (BUN 143201318799). Additional approval will be obtained from the participating organizations.

Discussion

Qualitative research focusing on multidisciplinary collaboration and organizational issues within the health system that determine the content and work processes of MDTMs is rather scarce. Within oncology, most studies on MDTMs are quantitative and focus on the impact of MDTMs on patient assessment, management, and outcomes [1]. This qualitative cross comparative case study approach aims to contextualize variables which cannot be captured with quantitative research methods

due to the complexity and circumstantial factors affecting interactions. This research strategy aims to get a true insider-view on the MOCs and to capture the experiences and meanings of the professionals involved. It aims to reveal patterns of the professional interaction in multidisciplinary team meetings and how different professionals contribute, use, and assess psychosocial information in the process of collective decision making. Moreover, the study aims to better understand barriers and facilitators in the practice of oncology to considering psychosocial information during MDTMs.

This type of research has the potential for practical value as MDTMs are costly in terms of both time and money [17-20]. Major concerns arise surrounding the practicality of integrating "overhead tasks," such as MDTMs, into the heavily loaded work schedules of many professionals. There is a need to explore how MDTM practices can be integrated efficiently considering health care professionals' limited time. Determinants of organizational and health system decisions could potentially explain why MDTMs do not incorporate psychosocial factors [21].

The concept of a MDTM should not merely be a group of care professionals who work essentially independently and occasionally liaise with one another. One of the main goals is to develop recommendations for integrating psychosocial information that are empirically grounded in an understanding of the patterns of multidisciplinary dialogue and decision making in oncology in various types of hospitals. This research protocol will be the first step to enabling future international comparative studies that take into account health system characteristics. The findings from this study can also be used to design nonclinical and organizational interventions that enhance multidisciplinary decision-making in the context of specific teams, organizations, and health systems. Interventions aiming to enhance the input of psychosocial information are crucial to ensure that MDTM can benefit from their diverse membership to achieve their full potential.

Conflicts of Interest

None declared.

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Abbreviations

MDTM: multidisciplinary team meeting
MOC: multidisciplinary oncology consultation

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Protocol

Self-Management and Self-Efficacy in Patients With Acute Spinal Cord Injuries: Protocol for a Longitudinal Cohort Study

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Abstract

Background: People with recently acquired spinal cord injury (SCI) experience changes in physical, social and psychological aspects of their lives. In the last decades, attention has grown for aspects of self-management and self-efficacy in SCI research. However, we still do not know what the self-management and self-efficacy outcomes of first rehabilitation are and whether utilizing these skills may prevent secondary health conditions (SHCs) and increase participation and psychological adjustment early after SCI.

Objective: To describe the course and determinants of self-management and self-efficacy during and after first SCI rehabilitation; and to determine theory-based associations between self-management and self-efficacy with SHCs, participation and psychological adjustment.

Methods: Multicenter prospective longitudinal cohort study. All people with a newly acquired SCI admitted to one of the 8 specialized SCI rehabilitation centers in the Netherlands will be considered for inclusion in this study. Main assessments will take place during the first and last week of admission and 3, 6 and 12 months after discharge. The target sample is 250 participants. The primary outcomes are self-management (knowledge and execution of self-care) and self-efficacy (confidence in the ability to manage the consequences of SCI and of self-care). Secondary outcome measures are SHCs, participation and psychological adjustment to SCI.

Results: The first results with the complete set of data are expected in June 2019.

Conclusions: This protocol describes the SELF-SCI cohort study investigating self-management and self-efficacy of initial inpatient SCI rehabilitation. Second, associations will be investigated with SHCs, participation and psychological adjustment early after onset of SCI, until 1 year after discharge. The results will be used to test theories about motivation to perform health-promoting behaviors and adjustment to SCI.

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KEYWORDS

spinal cord injuries; self-care; self-efficacy; rehabilitation; complications; social participation

Introduction

Overview

The global incidence of spinal cord injury (SCI) is estimated between 40 and 80 new cases per million population per annum [1]. In the Netherlands, between 400 and 500 people suffer SCI each year and the total number of persons living with SCI is estimated between 10.000 and 15.000 [2,3]. The primary loss of motor, sensory and autonomic function below the level of injury may lead to several secondary health conditions (SHCs) [4-7]. These primary and secondary consequences of SCI may affect the functional independence, participation and quality of life (QoL) of the person involved [8-10].

SHCs are common in people with SCI in the Netherlands [11], and their participation and QoL fall behind those of people without SCI [12,13]. One and 5 years after discharge from initial inpatient rehabilitation, many people with SCI reported urinary tract infections (57-59%), severe neuropathic pain (40-44%), pressure ulcers (29-46%), problematic spasticity (23-36%), and severe muscle or joint pain (22-35%) among other problems [14]. On the long term (>5 years post-injury), people with SCI report an average of 8 SHCs in the previous year [15], their participation in employment is lower compared to society as a whole [16], and more than a third experience mild to severe chronic mental health problems [9]. These findings are similar to results of studies in other countries [17-19].

The high prevalence and the chronic nature of SHCs, can lead to the conclusion that SCI should be seen as a chronic condition, rather than an incidental trauma. This also focuses attention to the crucial role and responsibility persons with SCI themselves have regarding the lifelong maintenance of their health and participation in the society. During first rehabilitation of people with SCI, learning and practicing self-management skills should therefore be a main concern.

Self-management is defined as the individual's ability to manage the symptoms, treatment, physical and social consequences and lifestyle changes in accordance to a life with a chronic disease (Chronic Care Model) [20]. To be able to apply self-management, persons with SCI must have knowledge of their physical condition and how to prevent complications or control them if they do occur [18,21]. The high prevalence of SHCs reported in the SCI literature, however, suggest that at least part of the people with SCI lack sufficient self-management skills or do not use them properly [18,22].

Another concept associated with high prevalence of SHCs, especially psychological SHCs, is self-efficacy [23]. Self-efficacy is defined as the belief that one can successfully execute the behavior required to produce the desired outcomes [24]. Negative associations are found between self-efficacy and depression and anxiety. The negative association between self-efficacy and the occurrence of physical SHCs of people with SCI is still unclear [23]. There is, to date, also limited information about the course of self-efficacy and self-management during and after the SCI rehabilitation. Nor do we know if self-management and self-efficacy may prevent SHCs from occurring.

The SELF-SCI study has been designed to investigate this gap. The aims of the SELF-SCI study are: 1) to describe the course of self-management and self-efficacy during and after the first year of clinical SCI-rehabilitation; 2) to examine determinants of self-management based on the theory of planned behavior (TPB); 3) to examine determinants of adjustment after SCI based on the SCI adjustment model (SCIAM).

Theoretical Background

To understand how people handle the consequences of their SCI, it is not only important to know the aspects involved in health-related behavior, but also the way people adjust to this situation. Therefore we will use two complementary models; the Theory of Planned Behavior (TPB) which has its focus on health-promoting behavior [25], and the SCI adjustment model (SCIAM) [26] which describes the way people adjust after SCI.

According to TPB, the intention of people to perform health-promoting behaviors depends on their attitude, subjective norms and perceived behavior control. The scheme of TPB is depicted in Figure 1. Attitude is the individual's prospective evaluation of self-performance of a particular behavior [25]. Subjective norm refers to the perceived social pressure to perform certain behavior [25]. Perceived behavioral control refers to an individual's belief in their ability to succeed in specific situations or accomplish a task, also called self-efficacy [25,27].

The SCIAM (Figure 2) [26] is based on the notion that adjustment to SCI is influenced by physical aspects, psychological resources and social factors. These aspects interact with each other and influence the person's appraisal of their situation. This will lead to certain ways of coping and levels of motivation. The result will be positive or negative adjustment. Adjustment has a psychological component, reflected in well-being or distress, and a social component, reflected in social engagement/participation.

The continuous process of appraisal and re-appraisal of the situation has a central role within SCIAM. First there is the perception of the current situation, the primary appraisal, then there is the secondary appraisal to what extent the person has sufficient resources to deal with this situation. These beliefs are influenced by the aforementioned physical, social and psychological factors. A variety of psychological resources have been associated with adjustment in the literature [12,28]. Resources with a high potential to predict adjustment and with a minimum of conceptual overlap are: self-efficacy, resilience, personality and meaning in life [12].

In studies on self-efficacy during and shortly after SCI rehabilitation, moderate relationships between self-efficacy with participation and psychological wellbeing were found [23,29,30]. In the chronic stage, moderate to strong relationships between self-efficacy with adjustment variables (especially depression and anxiety) were found [23,31,32]. Self-efficacy can be conceptualized and measured at different levels [23]. General self-efficacy (GSE) refers to the self-beliefs of a person to cope with a variety of difficult commands in general [27,33]. Disability management self-efficacy (DMSE) is defined as the confidence that people have in their ability to manage the

consequences of their chronic condition [34]. Finally, self-care self-efficacy (SCSE) refers to specific beliefs concerning the opportunities to perform appropriate self-care. The specific self-efficacy described within TPB is best categorized at the level of SCSE. The secondary appraisal process in SCIAM is self-efficacy at the level of DMSE. GSE, finally, is considered to be a trait variable that will not change much over time, and therefore is seen as one of the psychological resources as described in SCIAM. DMSE and SCSE are seen as state variables that are more situation-specific and vary over time. From literature as well as from a theoretical point of view self-efficacy seems to play an important role in participation and psychological adjustment.

To investigate the role of both self-management and self-efficacy, TPB and SCIAM were used to design the current study. All the aspects described in both theoretical models were taken into account by measuring each aspect through one or more assessment tools.

Figure 1. Scheme of theory of planned behavior.

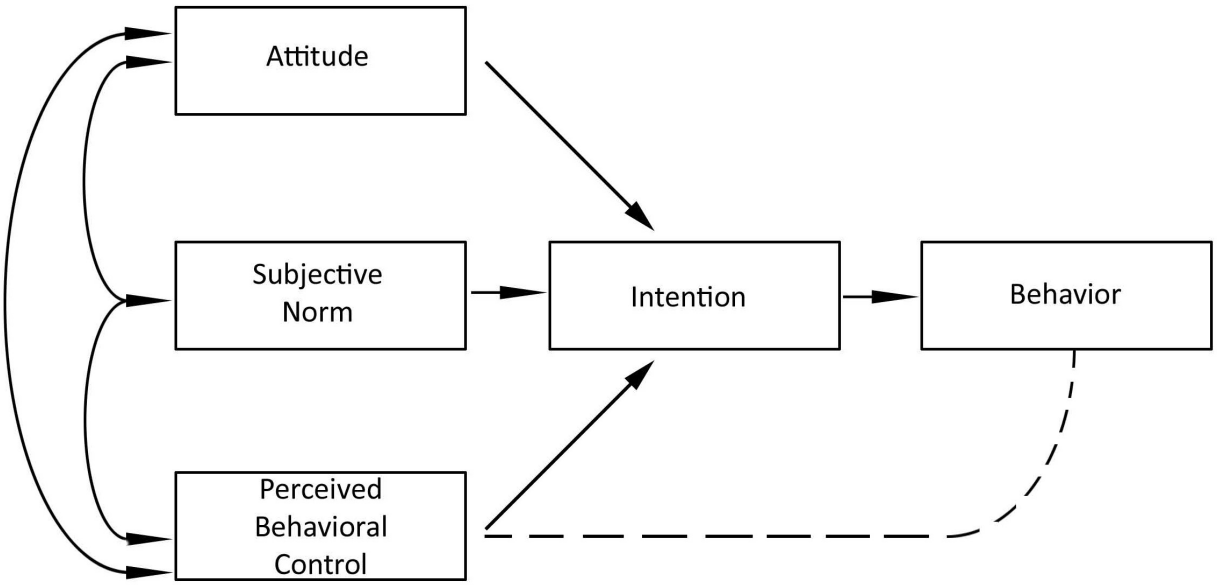
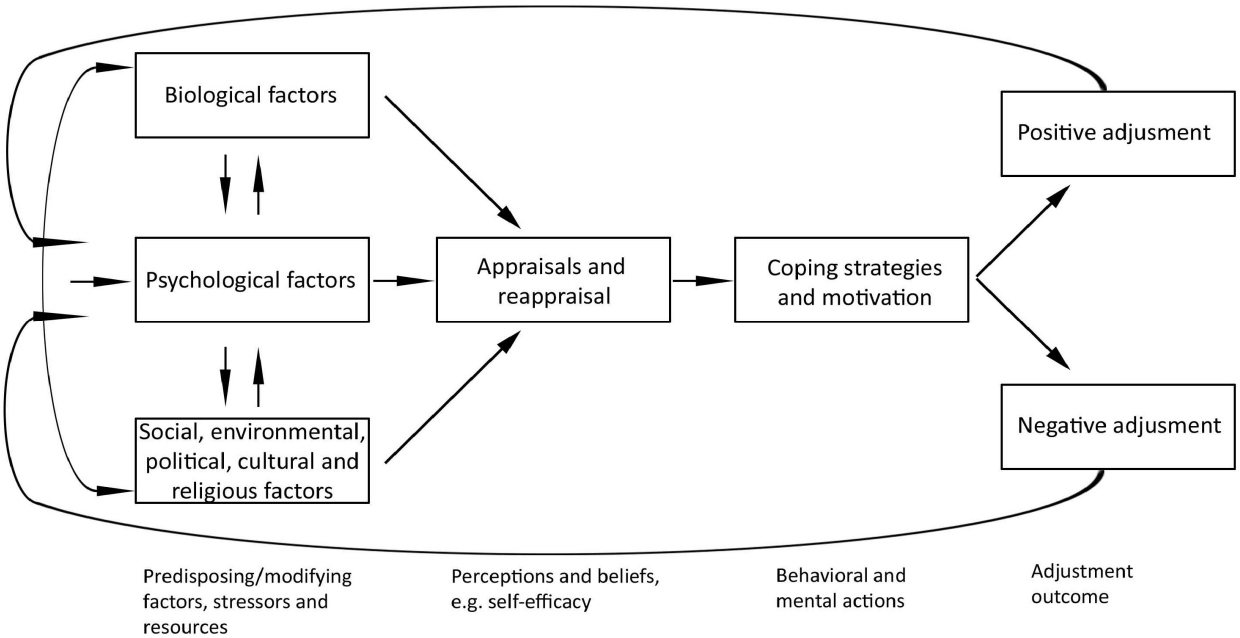


Figure 2. Scheme of spinal cord injury adjustment model.



Methods

Overview

SELF-SCI is a multicenter prospective longitudinal cohort study during the first SCI inpatient rehabilitation until one year after discharge. To describe the course of self-management and self-efficacy, repeated measures of the main outcome variables are used. In this quantitative study all aspects described in the theoretical models (TPB and SCIAM) are investigated, to examine determinants of self-management and adjustment after SCI.

Data Collection tools

First Aim

The main outcome variables of the first aim of this study are self-management and self-efficacy. Self-management is operationalized as knowledge and execution of self-care. Selfefficacy is measured at two levels; the level SCSE and of DMSE.

Self-management will be measured with a questionnaire concerning the knowledge and execution of self-care. The 13 questions about the knowledge of self-care can be answered on a 5-point scale ranging from certainly not true to certainly true. An example of a question is: "I know what to do when confronted with a pressure ulcer." The 14 questions about the execution of self-care can be answered on a 4-point scale ranging from never to always. An example of a question is: "I maintain my physical fitness as good as possible." This list was previously used among community-dwelling people with SCI, with a high internal consistency α=.80 [35]. Because knowledge and execution of self-care must be acquired during rehabilitation, this questionnaire is administered for the first time at discharge.

Self-care self-efficacy will be measured with the Managing Disease in General subscale of the Self-efficacy for Managing Chronic Disease Scale [36]. This subscale consists of 5 items with a 0-10 numeric rating scale (NRS) which indicate to what degree participants have confidence in the asked behavior or judgment. The internal consistency is high α=.87 [36]. Some questions have been adapted to get a better fit with the research question. An example of a question is: "How confident are you that you can do all the things necessary to manage your condition on a regular basis?"

Disease management self-efficacy will be measured with the short version of the University of Washington Self-efficacy Scale [34]. This 6-item version has a 5-point scale ranging from not at all confident to totally confident. This scale has been validated for people with SCI and multiple sclerosis [34,37]. The internal consistency of the short version is high (α=.90) [34]. At admission one question will be added concerning the confidence one has about the increase of DMSE during rehabilitation on a 0-10 numeric rating scale (NRS).

Second Aim

The main outcome variable of the second aim is self-management. Main determinants of self-management are SCSE, attitudes towards self-management and subjective norm.

Attitude to perform health behavior in SCI was, to our knowledge, not studied previously. A new scale was constructed, the Motivation for Health Care Scale. Based on the theoretical background of TPB a total of 6 questions were formulated, covering the subject of attitude to perform health behavior in people with SCI. On each question the participants can point out to what extent the given health behavior is important to them on a 0-10 NRS. An example of a question is: "Do you find it important to have an active role in preventing health problems?" Data of the current study will be used to investigate reliability and convergent validity of this scale.

Subjective norm is operationalized as experienced stimulation from the people close to the participant, with respect to self-care. While no such scale existed, a new scale was constructed for this purpose; the Stimulation to Perform Self-care List. On 6 questions with a 0-10 NRS, the participants can state to what extent they are stimulated to perform self-care and health-promoting behaviors by people in their social environment (eg, "My partner/family stimulate me to take good care for myself?").

Third Aim

The main outcome variable of the third aim is adjustment. Adjustment is operationalized as distress, illness cognitions, life satisfaction and participation. Demographic, physical -, social aspects and psychological resources are taken into account as determinants of adjustment.

Distress will be assessed using the Hospital Anxiety and Depression Scale [38]. This scale is a commonly used measure of distress and contains 14 statements equally divided in two scales; Depressive mood and Anxiety. Participants will be asked to indicate the extent to which they agree with each item, on a 4-point scale [38,39].

Illness cognitions will be assessed using an adapted version of the Illness Cognitions Questionnaire [40,41]. This instrument contains 18 statements divided into three subscales: Helplessness, which measures the aversive cognitive attributions attached to the SCI; Acceptance, which measures neutralizing connotations of the condition; and Disease benefits, which measures the positive meaning given to the SCI. Participants will be asked to indicate the extent to which they agree with each statement, ranging from 1 (not at all) to 4 (completely).

Life Satisfaction will be assessed using 2 Life Satisfaction questions [42]: one question about the QoL at this moment with 6 answer categories (ranging from very unsatisfying to very satisfying), and the second question about the comparison of QoL now with the QoL before the SCI with 7 answer categories (ranging from much worse to much better) [43].

Participation will be measured using the Utrecht Scale for Evaluation of Rehabilitation-P, participation [44,45]. The scope of this 32-question scale is to investigate the frequency of participation in daily activities, experienced participation restrictions due to the SCI and satisfaction with participation. At T1 the questions will somewhat be changed to assess the activity level and the satisfaction with these activities before the SCI, as has been done before [46]. One year after discharge the original scale will be used.

Participation will further be assessed using two questions from the Craig Handicap Assessment and Reporting Technique [47]. These two questions (how many hours a day one is out of bed and how many days per week one gets out of the house) are more often used for this purpose [48].

Determinants of Adjustment

SCI characteristics (time since injury; cause of the lesion: divided into traumatic and non-traumatic; level and severity of injury according to the International Standards for Neurological Classification of Spinal Cord Injury) [49] will be determined by a trained rehabilitation physician at admission and discharge.

Functional independence in self-care and mobility will be measured with the corresponding subscales of the Utrecht Scale for Evaluation of Rehabilitation [50]. This observation scale consists of 7 items for each subscale, that can be scored by a professional on a 5-point scale. Higher scores indicate higher independence.

Experienced pain and fatigue during the past week will be measured with a NRS ranging from 0-10.

Medical consumption will be measured with questions about the amount of visits to health professionals like physicians, physiotherapists, stay in a hospital and the amount of help from family and friends for the past three months. Other questions will be about the occurrence of medical complications: pressure ulcers, incontinence, urinary tract infections and weight gain or loss.

Influence of SHCs will be measured with the Spinal Cord Injury Secondary Conditions Scale [51]. From the original 16 items, 12 were selected, which can be influenced by the participant with health-promoting behaviors. The participants have to rate on a 4-point scale how much each health problem affected their activities and independence in the last three months [51].

The *appraisal of the current situation* will be measured with the Appraisal Life Events Scale [52]. Using 16 adjectives, participants will respond how they appraised their life in the past 3 months on a 6-point scale. The Appraisal Life Events Scale is recently used in a study with community-dwelling people with SCI [32].

The *general self-efficacy* will be measured with the General Competence Scale, the ALCOS-12, the Dutch version of the General Efficacy Scale from Sherer [33]. The ALCOS-12 consists of 12 questions with a 5-point scale, concerning the confidence to solve problems in general.

Resilience will be measured with the Brief Connor-Davidson Resilience Scale. This short version consists of 10 items with a 5-point scale [53,54].

Personality will be measured with the subscale neuroticism of the Eysenck Personality Questionnaire [55]. This scale consists of 12 dichotomous questions. Neuroticism has a strong association with QoL according a systematic review [12].

Meaning in life will be measured with the short version of the Purpose in Life Scale [56]. This scale consists of 4 of the original 20 questions that can be answered on a 7-point NRS.

Coping is operationalized in two different ways, previously be proven to be of influence on adjustment in people post-stroke [57], namely passive coping and proactive coping.

To measure the *passive coping*, the passive reaction pattern subscale of the Utrecht Coping List will be used [58]. This subscale consists of 7 questions with a 4-point scale.

The *proactive coping* style will be measured by the Utrecht Pro-active Coping Competence Scale short version [59]. This scale measures to what extent the participant is proficient to anticipate on difficult situations in the future on a 4-point scale. This short version, consisting of 7 of the original 21 items, is recently developed and had a high internal consistency (α=.90) and a very high intra class correlation (=.96) with the total list (Post in preparation).

Social support will be assessed by the Social Support List-12 [60]. This short version consists of 12 items with a 4-point Likert scale. There are three sub-scales; everyday social support, support in problem situations and esteem support [60,61].

The way participants are *empowered* during the rehabilitation phase will be measured with a selection of questions from the Patient Assessment of Chronic Illness Care [62]. These 8 questions reflect the way in which the participants are involved in decision making during the rehabilitation phase. On a 5-point scale, participants can respond to what extent they were supported by the professionals, in making their own decisions and to perform self-care, during clinical rehabilitation [62].

Demographic variables including age, sex, living with a partner, and educational level will be assessed.

An overview of all measurement instruments is shown in Table 1.

Ethical Considerations

The Medical Ethics Committee of the University Medical Centre Utrecht declared that this protocol does not need formal ethical approval under the Dutch law regulating medical research in human beings (reference number: 15-449/C). The Medical Ethics Committees of all participating rehabilitation centers approved this protocol. The study will be carried out according to the code of conducts formulated by Helsinki code. As part of this code all participants will give written informed consent before entering the study.

Table 1. Measurement instruments on the different test occasions.

Outcome measures	Instrument	T1	T2-T4	T5	T6	T7	T8
Primary outcome measures							
Self-management (first and second aim)	Knowledge and execution of self-care			X			X
Self-care Self-efficacy (first aim)	Self-efficacy for Managing Chronic Disease Scale, Managing disease in General subscale			X			X
Disability management Self-efficacy (first aim)	University of Washington Self-Efficacy Scale-Short Form	X		X	X	X	X
Distress (third aim)	Hospital Anxiety and Depression Scale	X		X			X
Illness cognitions	Illness Cognitions Questionnaire	X		X			X
Life satisfaction (third aim)	Two Life Satisfaction questions	X	X	X	X	X	X
Participation (third aim)	Utrecht Scale for Evaluation of Rehabilitation, participation part	X					X
Participation (third aim)	Craig Handicap Assessment and Reporting Technique, 2 questions				X	X	X
Determinants of second aim							
Stimulation from environment	Stimulation to Perform Self-Care List			X			X
Motivation to prevent health problems	Motivation for Health Care List			X	X	X	X
Determinants of third aim: Biological and functional determinants							
SCI characteristics	—	X		X			
Functional independence	Utrecht Scale for Evaluation of Rehabilitation	X		X			
Experienced pain, fatigue and mood	Numeric Rating Scale	X	X	X	X	X	X
Medical consumption	Questions about received help			X	X	X	X
Experienced complications	Spinal Cord Injury Secondary Conditions Scale			X	X	X	X
Determinants of third aim: Psychological determinants							
Appraisal	Appraisal Life Events Scale	X		X			X
General self-efficacy	General Competence Scale (ALCOS-12)	X					
Resilience	Brief Connor-Davidson Resilience Scale	X					
Personality	Eysenck Personality Questionnaire, neuroticism subscale	X					
Meaning in life	Purpose in Life Scale (short version)	X					
Passive coping	Utrecht Coping List, passive reaction patron subscale	X					
Active coping	Utrecht Pro-active Coping Competence Scale (short version)	X					
Determinants of third aim: Social determinants							
Social support	Social Support List-12	X					
Demographic determinants	Age, sex, level of education, marital status, and other	X					

Study Setting and Participants

In the Netherlands 8 rehabilitation centers are specialized in SCI rehabilitation. All 8 centers participate in this study. In this protocol patients are eligible for this study if they have been admitted for inpatient rehabilitation with a clinically confirmed diagnosis of SCI, this is their first inpatient rehabilitation after the onset of the SCI, and this admission will last for at least 4 weeks. Furthermore the patient must be at least 18 years old and be able (with help if necessary due to hand function problems) to complete the self-report questionnaires. Patients with severe cognitive problems are excluded, as well as patients who have insufficient knowledge of the Dutch language to understand and complete the questionnaires. Patients are also excluded from this study if they have a limited life expectancy, for example in case of cancer-related SCI. There are no restrictions regarding the severity of SCI or maximum age. Decision on in/exclusion is based on the clinical judgment by the rehabilitation physician and will be checked by the research assistant. If the participants are not able to complete the questionnaire because of hand function problems, help is offered by a research assistant.

All eligible patients will be informed about the study by their rehabilitation physician on the first day of admission into

rehabilitation. One or two days later the research assistant will inform the patient more extensively. After informed consent is given, the research assistant will provide the participant with the first comprehensive questionnaire (T1). Next, a short 5-item questionnaire will be administered after 4 (T2), 8 (T3) and 12 weeks (T4), if at that time the participant is still admitted for at least two weeks. In the last week of admission the second comprehensive questionnaire (T5) will be administered. Three (T6) and six months (T7) after discharge a brief questionnaire will be sent to the participants, and one year after discharge the final comprehensive questionnaire (T8) will follow. During inpatient rehabilitation, participants will complete paper/pencil versions of the questionnaires. After discharge, the participants can choose whether they want to complete the questionnaire on paper or online (NetQ package). Before the questionnaire is sent after discharge (T6 to T8), the participants will be contacted by phone, further two reminders will be send in case of no response. Participants will not be offered monetary or non-monetary compensation for their efforts.

A total of 250 participants will be recruited. This target number is chosen to allow regression models with 15 determinants with sufficient statistical power per determinant in the model. An estimated 350-400 people who fit the in- and exclusion criteria are admitted to one of these 8 specialized centers each year. Therefore, it seems feasible to include the desired 250 participants within the two-year inclusion period from January 2016 until December 2017.

Data Analysis

All data will be entered into SPSS statistical program for Windows (version 24). The manually entered data will be checked by a second person. The data from the online questionnaires will be exported and merged with the manually entered data. When all data is entered descriptive statistics will be performed. Outliers and scores out of range of the questionnaires will be double-checked. Next, multilevel analysis, with mixed methods approach, will be performed to estimate differences between the three major assessments (T1, T5 and T8) and between all 8 assessments with a limited number of variables. Next, latent class growth mixture modeling will be used to investigate if there are different trajectories of self-management and DMSE between admission and one year after discharge. Prediction of problems regarding self-management and DMSE on T8 will be analyzed using multivariate regression models. Also relationships between self-management, DMSE and SCSE on the one hand and SHCs, participation and psychological adjustment on the other will be analyzed using multivariate regression analyses and path analysis.

The first aim of this study is to describe the course of self-management and self-efficacy during the first SCI rehabilitation period until one year after discharge. All available data concerning the three main variables will be used. For the second and third aim (examine the determinants of self-management and adjustment) the theory will be tested using a path analysis.

Discussion

The SELF-SCI Cohort study investigates the changes in self-management and self-efficacy of people with a recently acquired SCI during the first initial rehabilitation until one year after discharge. Next, this study determines, based on theories about motivation to perform health-promoting behaviors and adjustment to SCI, to what extent self-management, DMSE and SCSE are predictors of SHCs, participation and psychological adjustment.

There are several reasons why this cohort study is innovative. First its focus on the changes in self-management, self-efficacy over time, from shortly after the occurrence of SCI until one year after inpatient rehabilitation. Traditionally, much research and rehabilitation care has focused on the physical and functional impact of SCI. Research on psychological impact of SCI is most often cross sectional and performed in community-dwelling people with SCI. In addition, this longitudinal study focuses on the post-acute phase until one year after SCI-rehabilitation. Second, this study will investigate the relationship between self-management and self-efficacy on the one hand and SHCs, participation and psychological adjustment on the other. With a growing amount of older people with SCI, these SHCs and reduced participation in society is of major interest for health workers and policy makers. Thirdly, this study is theory driven. The present study will extensively investigates the influence of motivation to perform health-promoting behaviors and adjustment to SCI on self-management and self-efficacy. All the variables within both theories will be taken into account, as much as possible, in order to be able to test these models for the SCI population [31,32]. And lastly, this is a nation-wide study including all 8 rehabilitation centers with a SCI specialization in the Netherlands. This means that a broad range of people, who are recently confronted with SCI, including people with traumatic and non-traumatic SCI and irrespective of age and severity of SCI, will be included in this study.

A limitation of this study could be the fact that the outcomes are only measured with self-assessment questionnaires. However, we do not consider this as a problem, because especially DMSE and SCSE are subjective concepts which we will measure with a validated scale.

In conclusion, the information which will be gathered in the present study, especially about the influence of self-management and DMSE on SHCs and participation, will be used to establish better rehabilitation care and to develop new interventions for SCI patients. This should allow people with SCI to make optimal use of their capacity to deal with their new situation.

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Authors' Contributions

MP developed the idea and procured funding for the study. TvD and ES worked out the details of the study. All authors contributed to the design and the protocol of the study. All authors reviewed the manuscript and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

DMSE: disability management self-efficacy
GSE: general self-efficacy
NRS: numeric rating scale
QoL: quality of life
SCH: secondary health condition

SCI: spinal cord injury
SCIAM: spinal cord injury adjustment model
SCSE: self-care self-efficacy
TPB: theory of planned behavior

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Protocol

Possible Risk Factors for Severe Anemia in Hospitalized Sickle Cell Patients at Muhimbili National Hospital, Tanzania: Protocol for a Cross-Sectional Study

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Abstract

Background: Sickle cell disease (SCD) is the most common inherited disorder worldwide, with the highest burden in sub-Saharan Africa. The natural history of SCD is characterized by periods of steady state interspersed by acute episodes. The acute anemic crises may be transient and are precipitated by treatable factors like infections, nutritional deficiencies, and sequestration. Anemia is almost always present, although it occurs at different levels of severity.

Objective: This paper describes the protocol of a cross-sectional study to determine the prevalence of severe anemia and associated factors among sickle cell patients hospitalized at the Muhimbili National Hospital.

Methods: This is an ongoing, descriptive, cross-sectional, hospital-based study among individuals with SCD, admitted to the Muhimbili National Hospital in Dares Salaam, Tanzania. A minimum sample size of 369 was calculated based on the previous prevalence of hospitalizations due to severe anemia (20%) in the same cohort. We are using a piloted standardized case report form to document clinical and laboratory parameters following informed consent. Data analysis will be performed using Stata software. Severe anemia is defined as Hb<5g/dL. Chi-square or Fisher's exact test will be used to ascertain association between categorical variables, and *t*-test will be used for numerical variables. Regression models for severe anemia against explanatory and confounding variables will be run, and results will be presented as adjusted odds ratio with 95% confidence intervals. A *P* value of <.05 will be considered significant.

Results: Enrolment commenced in January 2015 and concluded in September 2016. Complete data analysis will begin in February 2018. The study results are expected to be published in May 2018.

Conclusions: This protocol paper will provide a useful and practical model for conducting cross-sectional studies in hospitalized patients that cover a wide ranging of clinical and laboratory variables.

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KEYWORDS

severe anemia; sickle cell; hemoglobin; hospital-based surveillance; protocol; Tanzania

Introduction

Sickle cell disease (SCD) is the most common inherited disorder worldwide with the highest burden in sub-Saharan Africa [1]. It is also estimated that between 7800 and 11,000 children with SCD are born in Tanzania every year [2]. Most of these children will not be diagnosed as there are no neonatal screening programs in place, and up to 50% of these children will die before the age of 5 years [1]. It is estimated that 6 million people would be living with SCD in Africa if the average survival of affected children reaches half the African norm [3]. With demographic transition, the survival of SCD beyond childhood is increasing. The survivors will suffer from chronic ill health due to a number of factors including anemia [4].

Anemia is a condition in which the number of red blood cells (and consequently their oxygen-carrying capacity) is insufficient to meet the body's physiological needs. These needs vary with a person's age, sex, residential elevation above sea level (altitude), smoking behavior, and different stages of pregnancy [5]. The World Health Organization has defined very severe anemia as hemoglobin (Hb) levels of <5 g/dL. The progression of SCD is characterized by periods of dormancy coupled with periods of acute crises. Usually transient, the acute anemic crises may be precipitated by treatable causes. In SCD, severe anemia (ie, low hemoglobin, Hb <5 g/dL [3.8 (CI 1.8–8.2); p=.001]) has been shown to be an independent predictor of death [6]. Similarly, a study by Calis and colleagues from Malawi indicated a mortality rate of three folds (95% CI 1.3- 6.9) in SCD individuals with severe anemia compared to those with nonsevere anemia [7].

The major contributors of severe anemia in SCD in Africa are not known. Studies on African children on this topic have reported an association with bacteraemia, malaria, hookworm, HIV, as well as deficiency in vitamins A, B12 and glucose-6-phosphatase dehydrogenase [8-11,12]. Nutritional deficiencies in children with SCD may be due to poor dietary intake and increased requirements [13]. In endemic areas, malaria has been associated with severe anemia and is a major cause of morbidity and mortality [12,14-16]. Hyperhemolysis, sequestration transient red cell aplasia [17] and bacteremia [18], have been implicated in causing severe anemia in SCD cases. Hyperhemolysis may be an independent complication of SCD [19] or may be due to infections (eg, malaria and bacteremia), hemolytic transfusion reaction or drugs. Acute splenic sequestration is a major cause of death although this is often idiopathic [20-22].

Blood transfusion is almost always used to manage severe anemia in SCD [23]. There are, however, concerns for blood transfusion, particularly in Africa, where the risk of transmitting infections including HIV, and hepatitis B and C is still high [24,25]. With multiple transfusions, patients are at risk of hemolytic transfusion reactions, alloimmunization [26-28] and iron overload [23,29]. It is clear that blood supply is inadequate and costly although the blood transfusion requirements for SCD are not known [27].

Although the burden and factors associated with severe anemia have been described in children and pregnant women in sub-Saharan Africa [6,8,11,30,31], detailed characterization of these factors in SCD individuals is lacking. This study, therefore, aims to establish the prevalence and spectrum of factors associated with severe anemia in SCD. The information obtained from this study has the potential to significantly impact the clinical course and survival of SCD individuals in Tanzania.

Methods

Study Design and Site

This is a hospital-based, descriptive, cross-sectional study among SCD individuals hospitalized at the Muhimbili National Hospital (MNH). MNH is the national referral hospital in collaboration with Muhimbili University of Health and Allied Sciences, which is the oldest and largest biomedical university in Tanzania. Muhimbili is located in Dar es Salaam on the eastern coast of Tanzania.

Study Population

The study population consists of individuals with SCD who are already registered in the Muhimbili Sickle Cohort (MSC) and are hospitalized at MNH. The MSC has enrolled 5430 individuals with SCD between 2004 and March 2016. Of these 51.5% and 48.5% are male and female, respectively. The majority (65%) are below the age of 18 years. In this study, we enrolled hospitalized patients who consented and fulfilled inclusion criteria during the 21-monthstudy period (January 2015 to September 2016).

Sample Size Determination

The sample size for this study was estimated to be 369 patients and it was based on the finite population of 800 SCD cases (ie, number of annual SCD hospitalization, from 2014 estimates). This sample has a power of 80% to detect the prevalence of severe anemia of 20% with a 4% margin of error and confidence interval of 95%.

Eligibility criteria

The following inclusion and exclusion criteria were used:

Inclusion criteria

- Confirmed SCD; HbSS by High Performance Liquid Chromatography or Hemoglobin Electrophoresis
- Enrolled in the MSC
- Hospitalization at MNH during the study period

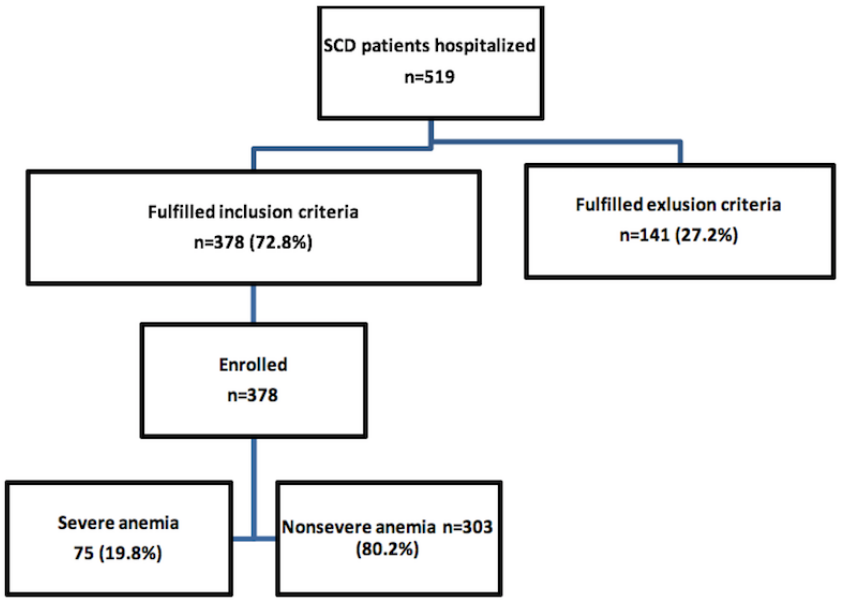
Exclusion criteria

- Individuals on hydroxyurea
- Blood transfusion in the past 4 weeks
- Readmission within the past 4 weeks

Procedures During Hospitalization

The enrolment procedure is illustrated in Figure 1. Clinical surveillance of the adult and pediatric admitting wards to identify individuals admitted with known SCD was maintained throughout the study period. On arrival, SCD patients were admitted following normal hospital procedures.

Figure 1. Enrolment flow chart. SCD: sickle cell disease.



A general examination was performed that included a record of temperature, weight, blood pressure, peripheral oxygen saturation, pulse, and respiratory rate. Detailed clinical history and physical examination were undertaken to determine the events leading to hospitalization. The study procedures were explained to the patients as well. Details of tests to be performed and samples needed were given to the patients by the study clinician. HIV pretesting counseling was done to all eligible patients. Consent was sought after all the information had been given to the patients.

Patient Care and Management

Confirmed SCD individuals admitted and enrolled were managed according to the standardized guidelines on the management of SCD. Additional investigations were requested depending on clinical indications. Clinical outcomes and laboratory results (Textbox 1) of every patient were documented in the hospital case file as well as in the study's case report form (CRF). The results of all the tests done were made known to the patient and the attending doctors to guide patient management and care. We routinely conducted HIV postcounseling to all HIV positive patients, and upon discharge they were referred to the HIV Care and Treatment Centers near them.

Procedures for Collection of Samples

Ten milliliters of blood was collected from all participants under aseptic technique. Of these, 2 mL of blood was collected in a tube with ethylenediamine tetraacetic acid (EDTA) anticoagulant, 2 red tops (serum separator) were filled with 2 mL of blood each, and 4 mL was taken for blood culture. Samples for blood culture were collected in commercially prepared BacTec bottles. In addition, stool and urine samples were collected in empty sterile bottles. All samples were labelled with patients' name, SCD identification number and a special ID number created for the purposes of this study.

Processing and Separation of Samples

Of the EDTA sample, 5µl was used to perform a malaria rapid test (RDT). The remaining sample was used to perform a full blood count. This includes a peripheral blood cell count, both total and differential white cell count, as well as red blood cell indices. These tests were performed immediately after sample collection.

For the serum separated samples, clinical chemistry analysis as well as micronutrient analysis (iron, folate, retinol and B12) were performed on the batched serum samples after enrolment had concluded.

Procedures for Laboratory Investigations

Parasitology

Malaria Rapid Test

Venous blood in a EDTA tube or capillary blood sample via puncture of a finger was required for the malaria test. The malaria device Pf (HRP2) Ag RDT was used and 5µl of blood was applied to the sample using a pipette or micropipette. 60 µl of assay buffer solution (2 drops of the bottle type) was put into the A well. Results were read in 20 minutes. Correction for white cell count was conducted for counting parasite density in thick films. If the test could not be performed immediately, the blood was stored at 2-8˚C for 3 days. All test components were performed at room temperature.

Quality control was used to assure that the malaria Pf cassette test was working properly and that the results being generated are correct. If no lines were visible, or if no control line (C) formed, whether or not a sample line (T) appeared, the assay was deemed invalid and was repeated with a new sample and cassette.

Microscopy for Malaria Parasitaemia

Thick films for malaria diagnosis was prepared from the blood sample at the time of collection or from the EDTA bottle in the laboratory.

Textbox 1. Key variables.

Outcome variable: hemoglobin levels (categorical: Hb <5 g/dL or ≥5 g/dL)
Independent variables
Sociodemographic characteristics
Ethnicity
Residency
Age as continuous and as categorical variable (<18 or ≥18 years)
Sex (categorical: male or female)
Symptoms and signs
Pallor (categorical: Yes [Y] or No [N])
Jaundice (categorical: Y/N), if yes (categorical: tinge, moderate, severe)
O_2 saturation-continuous, hypoxia (categorical: <95% or ≥95%)
Enlarged spleen (categorical: Y/N), size (continuous)
Enlarged liver (categorical: Y/N), size (continuous)
Past medical history
Admissions in the past 12 months (categorical: Y/N), frequency (numerical)
Blood transfusion in the past 12 months (categorical: Y/N), frequency (continuous), units (continuous)
Pain in the past 12 months (categorical: Y/N), frequency (continuous)
Stroke in the past 12 months (categorical: Y/N)
History of heart failure (categorical: Y/N)
Laboratory variables (continuous and categorical); see Table 1)
Hematological: full blood count and reticulocyte count
Parasitology: malaria and hookworm
Microbiology: bacteraemia and HIV infection
Biochemistry: liver and renal function tests, lactate dehydrogenase, C reactive protein, serum folate, vitamin B12, vitamin A and serum iron studies

Thick films were stained using Giemsa staining and examined by microscopy for the presence of malaria parasites using standard methods. The number of parasites (trophozoites) was counted against 200 white blood cells. A slide was reported negative for malaria parasites after at least 100 high-powered microscopic fields were examined. Counting malaria parasites against 200 white blood cells may have resulted in underestimating malaria density as the white cell count in SCD patients tends to be higher due to inflammation and hematology analyzers counting nucleated red blood cells as neutrophils and small lymphocytes. Therefore, ideally, the white cell count should be corrected and “normal” reference values for SCD and non-SCD individuals be calculated and used.

The quality assurance process involved the following: all positive slides were read by a second person. If there were discrepancies between the two readings, then a third person was asked to intervene. For the negative slides, one out of every ten slides was read by a second person .

Hookworm

Fresh stool was collected in a clean container to test for hookworm infection. A portion of fresh stool was taken with a spatula or wooden applicator and placed in a test tube, and then the test tube was filled with normal saline. The mixture was mixed well and centrifuged for 5 min at 3000 rpm (Rotina 46, Germany). The supernatant was discarded and with help of a Pasteur pipette, the deposit (stool) was extracted and a small drop was placed on a slide. The deposit on the slide was covered by the cover slip and immediately observed for the hookworm ova under the microscope at 10x magnification. The counting was performed 20 minutes after collection. This method allows for other egg species to be identified .

We ensured that samples were collected in a clean container so as to avoid any false positive results. A picture of hookworm ova was available to make sure of correct diagnosis.

Hematology

The Sysmex XT2000i–Hematology automated analyzer was used to obtain the full blood count. The machine gives a wide range of hematological indices such as white blood cell count, reticulocyte count, hemoglobin levels and platelet count. 2µl of nonclotted venous blood was collected in EDTA tubes (purple caps). The samples were arranged on the roller mixer ready to be tested. Alternatively, the sample was inverted gently end to end (approximately eight times) until the cell bottom of the tube was completely suspended.

On the standard tools bar, the manual section was selected, the patient details were entered and the enter button was pressed.

Then the sample vial was held to the needle in front of the start button, and the start button pressed. Once the analysis was done, the results were printed out and reviewed for any panic values, which were then reported to the clinician immediately. If the differential values were missing from the printed results, the sample was diluted in a ratio of 1:5 using the cell pack reagent and the percentage values obtained. After the sample had been analyzed, plasma and buffy coat were obtained and stored under –20°C. This was achieved by centrifuging the EDTA blood at 3000 rpm for 10 minutes, thereafter separating the plasma and buffy coat in graduated cryo-preservative tubes.

The controls for Sysmex machine XT2000i were commercially prepared reagents in 3bottles. Tube one contained low ranges of the hematological indices, tube two for normal and tube three for high hematological values. The quality control procedure was performed before running the samples. The controls needed to be at room temperature before the quality control procedure. The sampler mode from the main menu screen was selected and the tubes were arranged on the sample loader tray with their barcode facing the red barcode light. Then the start button was clicked for the analyzer to start analyzing the controls. Once done, one researcher ensured that the controls had been run on the analyzer and that they were within the acceptable limits.

Chemistry

Architect Kits was used for aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, lactate dehydrogenase (LDH), vitamin B12, folate and C reactive protein (CRP). The Retinol Kit was used for retinol binding protein (vitamin A). The analyzer used was Architect Ci 4100, which includes the chemistry analyzer C4000 (for AST, ALT, creatinine, LDH and CRP2) and the immunoassay analyzer i1000SR (for vitamin B12 and folate). Our samples were stored at –80ºC for a maximum of 90 days.

The batched samples that have been collected throughout the study period will be assayed using a chemistry analyzer (Roche Cobas Mira, New York, USA or Abbott Architect, New York, USA) for the following parameters: bilirubin (total and direct); LDH), iron studies (serum ferritin, serum iron and transferrin saturation), CRP, folate, AST, ALT, vitamin A (retinol) and vitamin B12. Quality assurance was done using commercially prepared reagents that are run on a daily basis with the readings documented following laboratory protocol.

Microbiology

Blood Cultures

Blood cultures were processed using standard hospital laboratory procedures. Culture media were prepared in a microbiological laboratory and identification followed conventional techniques.

Blood Culture Methodology

Samples were drawn from patients, stored in the BacTec blood culture bottles, and inserted directly into the instrument as soon as possible to ensure performance efficacy. Before placing vials into the instrument, barcodes were scanned and placed in their assigned stations through the vial entry activity. When scanning barcodes, the vial was placed in the alignment block in front of the scanner with the barcode label facing the scanner. The vial was rotated slightly so that the scanner could read the label. A single beep indicated a successful (good) scan. Station assignments were calculated by the system software to balance the rotor. In order to maintain rotor balance, vials were introduced and placed where the system indicated.

The vial was carefully pushed into the station. In order to ensure that the vial was fully seated in the station, the shoulders were pressed. The vials were not twisted or turned once they were placed in the stations. Vials were not removed except in the following conditions:

- Removal of positive
- Removal of negative
- Identification of anonymous vials

When microorganisms are present, they metabolize nutrients in the culture medium, releasing carbon dioxide, which reacts with a dye in the sensor. The dye modulates the amount of light that is absorbed by a fluorescent material in the sensor. The instrument's photo detectors then measure the level of fluorescence, which corresponds to the amount of carbon dioxide released by any micro-organisms present. This measurement is interpreted by the system in accordance with the preprogrammed positivity parameters.

Sample Handling

Positives

Many positive cultures were detected in the first 24 hours after inoculation. Subculturing the positive cultures was done in blood agar, chocolate agar, MacConkey agar, and in other culture media as appropriate. Gram staining was performed for each positive vial. Preliminary antimicrobial susceptibility and identification procedures were performed from fluid in the culture vials.

Negatives

Ongoing negative vials were kept for 7 days before being discarded as negatives.

HIV Test: Rapid Test (Determine and Unigold)

Serum/whole blood samples were used for this test. The samples were centrifuged at 3000 rpm for 10 minutes. Thereafter, the serum was graduated 1.25 mL tubes for the HIV test. With whole blood samples, the blood was directly tested for HIV test. The test was performed according to the Tanzania National HIV Rapid Test Algorithm.

Data Management

Data Collection

All clinical and laboratory information was collected using a preformatted CRF that was designed specifically for this study. This was piloted for a period of 2 weeks and adjusted accordingly. The CRF was reviewed weekly for the first month of data collection to amend variables and improve the quality of data collected. Tools for collecting anthropometric measurements and vital signs were calibrated according to manufacturer's specifications. All data will be linked to the MSC database, a Web-based system known as MySQL (Sun Microsystems Inc, Santa Clara, California, USA).

Laboratory data is being collected from different sources. For hematology data, the results were printed from hematology analyzers. Results generated from all laboratories were photocopied and the copies were added to the patient's case notes. The original copies of results were attached to the corresponding CRFs.

Data Cleaning

Data verification and cleaning is ongoing following double entry, and inconsistencies are being corrected. Missing data, not obtained during the data collection period, will be collected during subsequent visits or by telephone.

Data Security

The CRFs are stored in filing cabinets and locked, with access only to personnel involved in the study and to a few key personnel who are authorized by the principal investigator. Data backup is done on a daily basis onto 2 storage devices and stored in 2 different physical locations.

Analysis Plan

Data is double entered and validated in a software application developed using MySQL database and PHP, a server-side HTML scripting language.

Statistical Methods

Descriptive statistics will be summarized using cross-tabulation and frequencies for categorical data. For continuous variables, measures of central tendencies will be used after checking for normality and transformation where necessary. All estimates will be presented with 95% confidence intervals. Proportions will be compared using Chi-square test of Fisher's exact test for categorical variables, while continuous variables will be compared using *t*-test or analysis of variance. These will be adjusted for age and sex. Logistic and linear regression models will be used in assessment of the risk factors for severe anemia for the binary and continuous variables, respectively, as well as for controlling for confounders.

Modelling procedures will start with the univariate models where the response variable will be fitted against each explanatory variable. Only sets of explanatory variables with a *p* value <.10 will be included in the multivariate models. Linear and nonlinear relationship between response and explanatory variables as well as the interaction between the explanatory variables and how these change in relation to age groups and sex , will be explored during model fitting. Both forward and backward elimination methods will be used to decide which variables remain in the minimal model based on the likelihood ratio test. We will produce a single, final model combining both laboratory and clinical variables as this will be the best model predicting severe anemia. Data analysis will be performed using Stata software (version 11) and R (version 3.3.2).

Table 1 describes the laboratory variables; these will be compared among those with and without severe anemia.

For univariate and multivariate analyses, it will depend on how the *p* values look like after analysis. We will decide which clinical and laboratory variables are most important and should be included; these may be the most important factors from literature and/or have enough participants in comparison groups to allow for reasonable comparison.

Table 1. Baseline laboratory characteristics of the study population.

Variable	Variable type	Measure of central tendency	Categories
Hemoglobin (g/dL)	Numerical, categorical	Mean ± SD	<5, ≥5
Mean corpuscular volume (fl)	Numerical, categorical	Mean ± SD	<80, 80-96, >96
Mean corpuscular hemoglobin (pg)	Numerical, categorical	Mean ± SD	<27, 27-33, >33
Reticulocyte count (%)	Numerical, categorical	Mean ± SD	<0.5, 0.5-1.5, >1.5
White blood count x 10^3/L	Categorical	Mean ± SD	≥11, <11
Malaria	Categorical		Positive, negative
HIV	Categorical		Positive, negative
Stool hookworm	Categorical		Positive, negative
Alanine aminotransferase (U/L)	Numerical, categorical	Mean ± SD	<17, 17-63, >63
Aspartate aminotransferase (U/L)	Numerical, categorical	Mean ± SD	<18, 18-40, >40
Serum creatinine (µmol/L)	Numerical, categorical	Mean ± SD	<62, 62-115, >115
Folate (ng/mL)	Numerical, categorical	Mean ± SD	< 2.6, ≥ 2.6
Retinol (µg/L)	Numerical, categorical	Mean ± SD	<30, 30-80, >80
Vitamin B12 (pg/mL)	Numerical, categorical	Mean ± SD	< 187, ≥187
C reactive protein (mg/L)	Numerical, categorical	Mean ± SD	<8, ≥8
Lactate dehydrogenase (U/L)	Numerical, categorical	Mean ± SD	<50, 50-200, >200
Bacteraemia	Categorical		Yes/no, type, sensitivity
Serum ferritin (ng/mL)	Numerical, categorical	Mean ± SD	<15, 15-200, >200

Ethics Approval and Consent to Participate

Ethical clearance to conduct the study has been obtained from the Muhimbili University of Health and Allied Sciences and Research and Publication Ethical Committee. A formal written informed consent in Swahili was used for eligible individuals. Nonconsenting patients and those who were not eligible for the study were attended to by the clinical team per SCD management guidelines. Personal, clinical and laboratory information is being kept with utmost confidentiality in keeping with the standards and procedures guiding the organization.

Results

Enrolment commenced in January 2015 and concluded in September 2016. During the study period, 513 SCD individuals were hospitalized, of these 387 (72.8%) fulfilled inclusion criteria and were enrolled. Final results of batched laboratory tests are expected in January 2018. Data analysis is expected to be done in February 2018. The study results will be published in a peer-reviewed journal.

Discussion

Study Rationale

Severe anemia is the most common cause of SCD morbidity and mortality in Tanzania. Although the clinical and laboratory factors associated with severe anemia have been described in the general population of sub-Saharan Africa [6,8,11,26,27], detailed characterization of these factors in SCD individuals is lacking.

Currently available data in the literature list possible causes of severe anemia in SCD cases. These include infections like malaria, bacteraemia and HIV infections as well as hookworm infestation [8-12,18]. Other factors include nutritional deficiencies like iron, vitamins A, B12 and folate [6,13]. Hyperhemolysis has also been shown to contribute to anemic crises [17]. Multiple transfusions increase the risk of hemolytic transfusion reactions, alloimmunization [23,24,26-28] and iron overload [29,30]. Furthermore, severe anemia in SCD patients has been shown to be an independent predictor of death [6].

This protocol describes in detail participant enrolment, and clinical and laboratory procedures. The study involved collecting multiple clinical and laboratory variables during the hospitalization period. No data was collected outside the hospitalization period. Drawing from 12 years' experience in clinical longitudinal surveillance, this protocol will contribute significantly to building a basis for a single-center, multivariable clinical study. It will also contribute towards harmonized inpatient clinical and laboratory procedures. The methodology will ensure the validity and reliability of data on the prevalence of severe anemia and associated factors in hospitalized SCD individuals.

Limitations

This study has several limitations. First, its cross-sectional design precludes us from establishing a cause-effect relationship. There is also potential for patient recall bias, especially in establishing past medical history. In this instance patients were asked to recall events from 12 months prior to hospitalization. Second, although interventions, like the use of antibiotics and/or antimalarial drugs in the days prior to admission were recorded, we have no certain way of knowing if the information provided is accurate. MNH is a national referral hospital; most patients are referred from peripheral facilities where they would have received interventions. Third, in this study, we are using 3 different laboratories to carry out various tests. Although the standard operating procedures for laboratory procedures are present and enforced, we cannot entirely eliminate human errors. Fourth, by the fact that MNH is a tertiary institution, there is a simple selection bias. This methodology paper will provide a useful and practical model for conducting inpatient clinical cross-sectional studies that cover a wide range of clinical and laboratory variables. The results of this study will be published in a peer-reviewed journal and have a potential to guide the management of severe anemia in SCD in order to reduce associated morbidity and mortality.

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Authors' Contributions

FT developed the study proposal and protocol and prepared the data collection tools and analysis plan. FU prepared laboratory procedures and data collection tools. AM undertook proposal development and reviewed the analysis plan. BM and RS reviewed the study design and analysis plan. JM secured funding and reviewed the protocol, analysis plan, and manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ALT: alanine aminotransferase
AST: aspartate aminotransferase
CRF: case report form
CRP: C reactive protein
EDTA: ethylenediamine tetraacetic acid
Hb: hemoglobin
LDH: lactate dehydrogenase
MNH: Muhimbili National Hospital
MSC: Muhimbili Sickle Cohort
RDT: malaria rapid test
SCD: sickle cell disease

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Original Paper

Lessons From Recruitment to an Internet-Based Survey for Degenerative Cervical Myelopathy: Comparison of Free and Fee-Based Methods

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Abstract

Background: Degenerative Cervical Myelopathy (DCM) is a syndrome of subacute cervical spinal cord compression due to spinal degeneration. Although DCM is thought to be common, many fundamental questions such as the natural history and epidemiology of DCM remain unknown. In order to answer these, access to a large cohort of patients with DCM is required. With its unrivalled and efficient reach, the Internet has become an attractive tool for medical research and may overcome these limitations in DCM. The most effective recruitment strategy, however, is unknown.

Objective: To compare the efficacy of fee-based advertisement with alternative free recruitment strategies to a DCM Internet health survey.

Methods: An Internet health survey (SurveyMonkey) accessed by a new DCM Internet platform (myelopathy.org) was created. Using multiple survey collectors and the website's Google Analytics, the efficacy of fee-based recruitment strategies (Google AdWords) and free alternatives (including Facebook, Twitter, and myelopathy.org) were compared.

Results: Overall, 760 surveys (513 [68%] fully completed) were accessed, 305 (40%) from fee-based strategies and 455 (60%) from free alternatives. Accounting for researcher time, fee-based strategies were more expensive ($7.8 per response compared to $3.8 per response for free alternatives) and identified a less motivated audience (Click-Through-Rate of 5% compared to 57% using free alternatives) but were more time efficient for the researcher (2 minutes per response compared to 16 minutes per response for free methods). Facebook was the most effective free strategy, providing 239 (31%) responses, where a single message to 4 existing communities yielded 133 (18%) responses within 7 days.

Conclusions: The Internet can efficiently reach large numbers of patients. Free and fee-based recruitment strategies both have merits. Facebook communities are a rich resource for Internet researchers.

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KEYWORDS

cervical; myelopathy; spondylosis; spondylotic; stenosis; disc herniation; ossification posterior longitudinal ligament; degeneration; disability; recovery; questionnaire; Internet survey; Google Adwords; advertising; social media; electronic survey; Internet; survey

Introduction

Degenerative Cervical Myelopathy (DCM) is a syndrome of cervical cord compression secondary to degenerative disease of the cervical spine [1]. Causative pathology includes disc herniation, osteophyte formation and ligament hypertrophy or ossification. Symptoms are often initially subtle and mislabelled as "old age."

Evidence from radiological series suggest 30%-59% of healthy individuals above the age of 50 show compression of the spinal cord on magnetic resonance imaging scans [2-4], of which up to 34% will develop myelopathy [5,6]. This equates to an estimated prevalence of 5% in patients over 50.

The epidemiology of DCM is poorly characterised at present, therefore such numbers are estimates [1]. The cause for this is multi-factorial but in part due to most research deriving from surgical studies [7], which only capture a sub-population of DCM patients. At present, not all DCM patients will reach specialist services and not all DCM patients will undergo surgery.

The Internet has become an attractive tool for medical research [8-10]. It enables access to individuals from across the globe who are of different ethnicities and socioeconomic backgrounds [11,12]. This access can be achieved in an unrivalled cost- and time-efficient manner. Therefore, for DCM, this presents an exciting opportunity to reach a larger, perhaps more complete, population and advance our understanding of the disease.

At present, most medical Internet research uses online questionnaires for data collection. Questionnaires are a research tool which can be completed by respondents anywhere at any time. Given the recognized significance of Patient Reported Outcome Measures [13], questionnaires, whether online or not, are a mainstay of clinical research.

Health surveys are notoriously difficult to recruit to [9]. Many different techniques have been trialled, including face-to-face events [11,12,14,15], print media [14-16], email [14,15,17,18], paid for Internet [14,18] or social media [12,15,16,18-22] advertising, social media engagement [11,15,17,18,21-25], and the use of incentives [17]. However, an optimum recruitment strategy has not yet emerged [9].

Comparing these studies to identify the most effective strategy is limited as many studies either do not provide a comparison arm or they bundle strategies together. Additionally, the implications of whether different strategies work across health research or are specific to certain conditions is unclear. Regardless, similar themes appear to be emerging; studies are moving away from print media or face-to-face strategies to Internet-based strategies [14,15,17]. Of these Internet strategies, Internet advertising specifically using Google AdWords or Facebook adverts, and/or social media engagement appear most popular and successful [12,20,22-24]. Google AdWords and Facebook Adverts are paid-for services whereas social media is free. A direct comparison of these methods has not been made specifically but cost-free options are clearly attractive if adequately effective.

Our overall objective, therefore, was to investigate whether the Internet could enable us to reach patients with DCM efficiently and on a large scale, and ask them about their disease and its consequences. In the absence of an ideal Internet recruitment strategy [9], we trialled fee-based methods (Google AdWords) and free methods (including social media and development of a condition specific website). We present a comparison of our experience and discuss their implications for others.

Methods

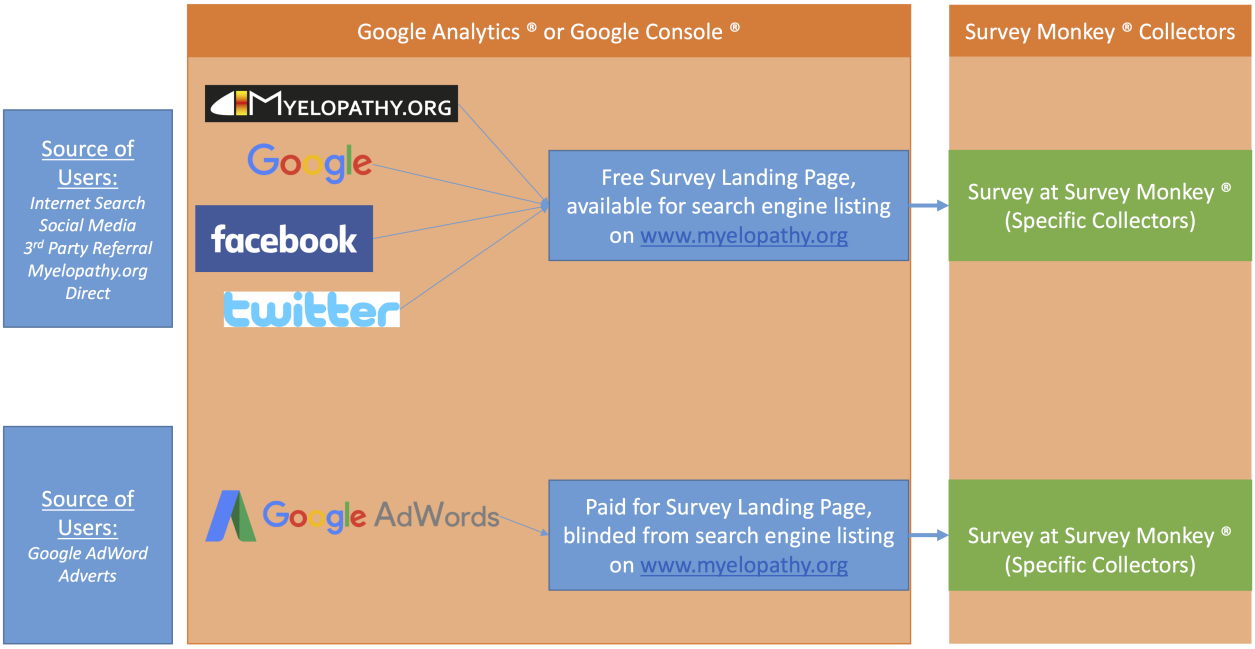
Ethical approval for this survey was granted by the University of Cambridge (Cambridge, UK). The survey was hosted on Survey Monkey (SurveyMonkey, California, USA) and contained 38 questions.

Tracking Recruitment Strategies

The SurveyMonkey advanced pro package was purchased to allow a single survey to have multiple collectors. A collector is a point of entry to the survey, which, in this study, was a custom URL. By using a different collector for each recruitment strategy, their individual performance could be tracked (Figure 1). These URLs were a combination of letters and numbers and were hidden from search engine listings, thus they were unlikely to be accessed directly.

Consequently, access to the survey was limited to landing pages hosted on our newly created DCM Internet platform, myelopathy.org. This enabled all traffic to be monitored precisely using Google Analytics (Google, California, USA). One landing page was accessible directly from the website and open to search engine listing. This was the portal for tracking free recruitment strategies. Google AdWords (Google, California, USA) adverts were directed to blind weblinks for myelopathy.org, hidden from search engine listing (Figure 1).

Figure 1. A flowchart describing the different access points (blue boxes) and flow to the survey, along with how they were tracked (orange boxes). Google AdWords adverts directed individuals to hidden landing page(s) at www.myelopathy.org, where interested viewers could click through to the survey at SurveyMonkey. All alternatives were directed to an open landing page and then to the survey. SurveyMonkey tracked respondents based on the URL used to access the survey. All prior data was tracked using Google Analytics and/or Google Console.



Recruitment Strategies: Fee-Based Methods (Google AdWords)

Google advertising was capped at $15 per day. Other constant settings included using both the "Search Network" (appearing on the Google search engine) and the "Display Network" (appearing on third-party applications, through their embedded Google adverts), and allowing Google to optimize advert choice based on their overall performance (option "optimize for clicks"). Advertisement was limited to an English-speaking audience, prioritizing North America, Australia, and the UK.

Adverts were created within a single group so that they would be displayed against all chosen keywords. Two adverts were developed using Google AdWord advice pages only (Figure 2). The research team had no prior experience with online advertising. Themes taken from these advice pages included using a relevant keyword within the title ("myelopathy"), identifying who you are ("Uni Cambridge" and "www.myelopathy.org"), what you are offering and what makes you unique ("Help Research"). With regards to this latter aspect, the only variations were whether "Please complete our survey" or "Wondering whether surgery is right?" were used. These adverts remained unchanged throughout the period of Google AdWord advertising for comparison.

Keywords were author-selected based on their theoretical relevance. Google Trends (Google, California, USA) was used to suggest related search terms. Chosen keywords were adapted and refined based on performance metrics.

Recruitment Strategies: Free Methods

Website

The website (www.myelopathy.org) was developed using Weebly (Weebly, San Francisco, USA). The intended target audience was patients, so initial content was produced to explain the disease, its symptoms, and its treatments. Each week further content was added, including further generic content, as well as expert articles, patient stories, and blog entries concerning the latest research. The home page opened with an advert for the survey and additional content included links to the survey.

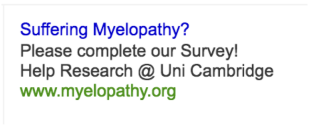
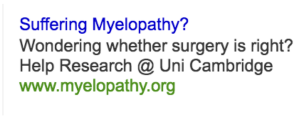
The website was submitted to Google Search Console (Google, California, USA) for indexing, which was completed November 2, 2015. Alongside Google Analytics, Google Search Console was used to track the website's overall performance in Google search returns. This is a relatively new service and data is only available from May 2016.

Social Media

Along with the website, a Twitter (Twitter, California, USA) account (@myelopathyorg) and a Facebook (Facebook, California, USA) page (www.facebook.com/myelopathy) were created. Website content was promoted, including postings and tweets using these accounts.

In addition, active related Twitter users/organizations (such as charities) and Facebook groups were approached to advertise the survey. Users, organizations, or Facebook groups were targeted a maximum of two times, at least 1 month apart. Facebook groups were approached using a researcher's personal Facebook profile, ensuring their privacy settings were optimized (as Facebook does not permit an organization to directly join groups). Permission from group administrators was sought before posting in closed Facebook Groups. The resultant post was made either by the researcher or the group administrator depending on their preference.

Figure 2. Comparison of different Google Advert types. One style advertised a clinical survey whilst another advertised information about surgery. Information about surgery was chosen, as surgery is the only treatment for Degenerative Cervical Myelopathy (DCM) and is the major focus of patient discussion following diagnosis. CTR: click-through-rate; CPC: cost-per-click.

	Advertising a Survey	Advertising Information Resource
Example Advert		
Usage (%)	35.1	64.9
Impressions	398763	738763
Clicks	1199	4439
CTR	0.3	0.6
Spend ($)	405.93	1833.97
CPC ($)	0.34	0.41
Completed Surveys	63	242
Conversions (Impressions per Surveys) (%)	0.02	0.03
Click Conversions (Clicks per Survey Response) (%)	5.3	5.5
Cost per Survey Response ($)	$6.3	$7.6

Potential Facebook groups or organizations and Twitter users or organizations were identified by searching the platforms for "myelopathy" and related disease specific terms. Initial approaches were simply as informal tweets (Twitter) or direct messages (Facebook and Twitter). No specific template was used. Social media links were embedded with Urchin Tracking Module codes to allow Google Analytics to register their impact individually.

Third-Party Websites

Related online content providers were approached to reference myelopathy.org. Google and Yahoo email indexes were not explored given the poor response by Morgan et al (2013)[18].

Study Structure and Analysis

Myelopathy.org went live October 1, 2015. Recruitment strategies commenced November 2, 2015. The initial four-week period was used as a control period to test the platform, register with Google Search Console, and measure any preintervention traffic. The total available budget for Google AdWords was $2200 and this was continued until this budget was exhausted.

The principal outcome to evaluate recruitment strategies was the number of survey responses. Complete survey responses (ie, questionnaires answered in full) were differentiated from incomplete responses. The completion rate was the proportion of fully completed survey responses.

Metrics of Google AdWord advert performance included impressions (number of times the advert or link was displayed), clicks (number of times the advert or link was clicked on), click-through-rate (CTR) (proportion of clicks to impressions), total cost, and cost-per-click (CPC) (cost per advert clicked on).

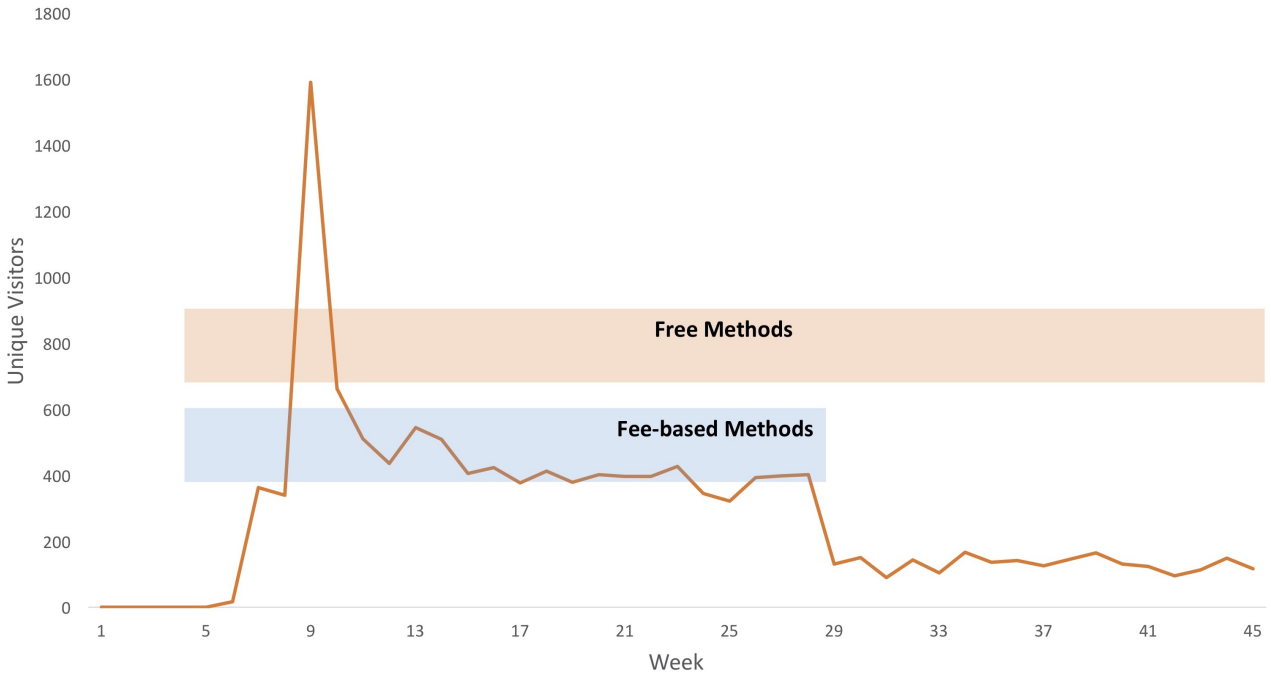
Metrics of user activity, tracked via Google Analytics, included views (number of times a page was viewed), unique visitor views (number of times a page was viewed by different users), and bounce rate (proportion of times a user came directly to a page and then left the website without clicking on any additional links).

Individualised SurveyMonkey collectors allowed the number of responses per intervention to be tracked directly, as the Google Analytics could not assess whether a survey was completed or not. Figure 1 provides an overview of how the free and fee-based recruitment strategies were tracked. The time spent managing interventions by the researcher between week 8 and 12 was logged per action.

Results

As outlined, myelopathy.org went live on October 1, 2015 and the recruitment interventions commenced following a 1-month control period. In total 12,671 unique users have accessed the platform, rising from 0 per week to an average of 454 per week using both fee and free methods, settling at an average of 130 per week with just free methods continuing (Figure 3). Excluding an outlier in week 9, during these two periods, traffic was very consistent; both periods having a relative standard deviation of 17%.

Figure 3. Unique visitors to Myelopathy.org. Active survey recruitment started during week 6 of this study. Google AdWords was used between week 6 and week 28 (blue bar) compared to free recruitment methods which continued throughout (orange bar).



Overall, 760 surveys were completed during the 10-month period of which 513 (68%) were fully completed.

Fee-Based Methods: Google AdWords

Google AdWords was used for 22 weeks (Week 6 -28) at a total cost of $2239.90 and resulted in 5638 users who clicked on adverts, at a CPC of $0.4. Using the fee-based method SurveyMonkey collectors, 305 (CTR 5%) surveys were completed, accessed through Google AdWords 98.5% of the time, of which 195 (64%) of the survey responses were complete.

Adverts attached to Google AdWords were broadly split into two categories; those advertising the DCM health survey and those advertising myelopathy.org as a DCM information resource (Figure 2). Adverts specifically inviting users to participate in a survey (CTR 3%) were less likely to be clicked on than adverts promoting myelopathy.org as an information resource (CTR 6%) (Figure 2). Consequently, Google's "Optimize for Clicks" algorithm favored their presentation. However, the bounce rate for users arriving at the survey page expecting information was higher (90% vs 50%) than those having clicked through for a survey. Despite this, there was an equivocal completion rate of 5.3% and 5.5%, and the survey specific adverts were financially more efficient at a cost of $6.30 per response compared to $7.60 per response.

AdWords were chosen with the help of Google Trends and refined based on performance. In total over 100 keyword combinations were tried. These were typically related to "myelopathy," the causative pathologies, or treatment. The most effective keywords and eventual focus of Google AdWords were terms related to understanding myelopathy, eg, "what is cervical myelopathy?" and "cervical myelopathy symptoms and treatment." There was no relationship between the cost of an advert and its likelihood to yield a survey response. Of the advertisements, 46.7% were placed independently using the Google Display Network, ie, appearing as third-party advertisement on websites it considered related. These adverts performed better than those appearing on Google Search with a lower cost per click ($0.30 versus $0.48) and bounce rate (73% versus 90%). Unfortunately, our analytics design could not differentiate survey responses between these groups.

Free Methods

The survey landing page for free methods was accessed 730 times. This generated 455 survey responses (CTR 62%), of which 312 (69%) were complete. Of these viewers, 40 (5.5%) came from Google AdWords, whereas the majority came from social media (249 [55%]), most notably Facebook (239 [53%]) (Figure 4). Users arriving at the landing page from Facebook had a CTR of 73%, compared to 45% for Twitter.

We identified 9 related patient support groups on Facebook whose membership numbers ranged from 33 to 2137. However, only 4 of these groups appeared to be active. Of the active groups, combined membership exceeded 4000 people. Within 7 days of the initial approach to these groups during week 5, 133 users had accessed and completed the survey. Repeat approaches in week 10 had less significant impacts (Figure 4).

The sharing of new website content on social media, particularly Facebook, was beneficial. Our opening piece, a story of a patient (identified from the active Facebook communities) drew significant attention. It was shared 176 times in 12 hours and lead to our peak website traffic in week 9 of 1591 unique users (Figure 4). However, this story had not been linked to the survey and, as such, only 25 of these users accessed the survey (yielding 3 survey responses). By advertising the survey within subsequent articles, more survey responses were gained even though the articles generated less traffic.

Figure 4. Survey traffic from free recruitment methods, including examples of successful interventions. Social Media (blue) was particularly effective in the early stages.

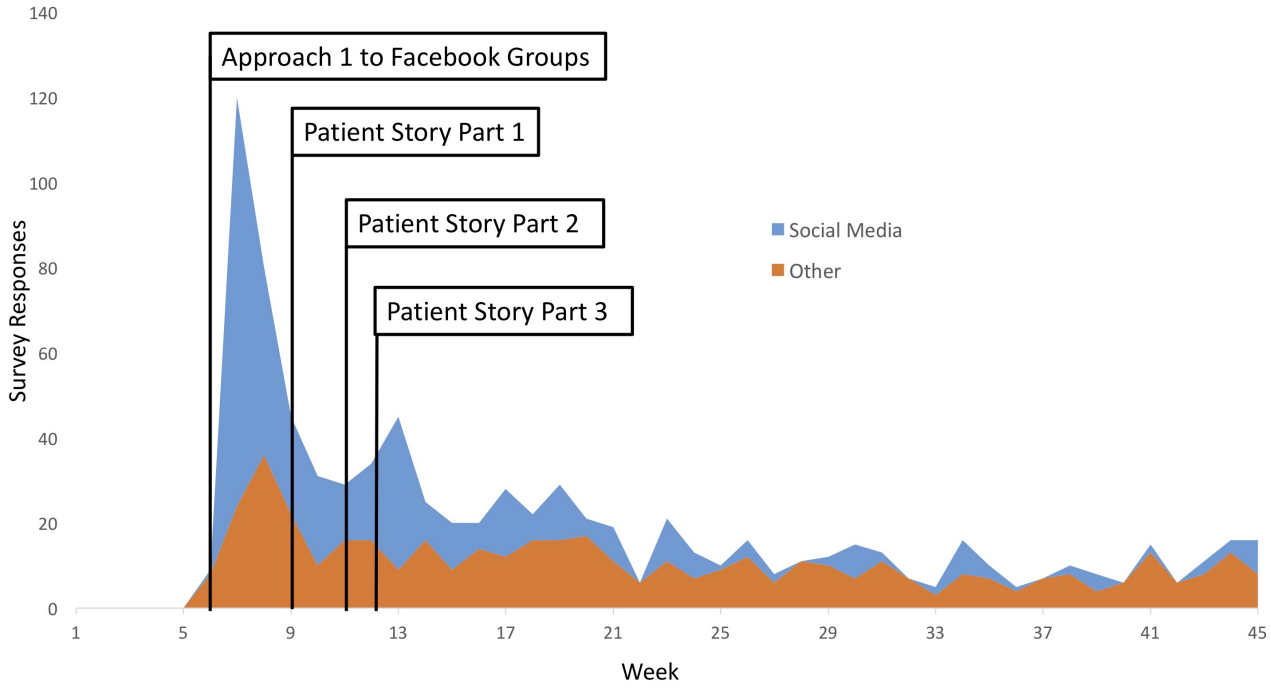


Table 1. Comparison of Free and Fee-based recruitment methods, data from week 6 to 28.

Variable	Fee-based methods (Google AdWords)	Free methods
Survey Responses	305	367
Complete n (%)	195 (64)	250 (68)
Advertising Cost/Response ($)	7.40	0
Click-through-rate (%)	5	57
Time/Response Estimate (mins)	2	16
Total Cost/Response Estimate ($)	7.80	3.20

Twitter was less fruitful in identifying and engaging participants. No existing specific organization or discussion thread or related hashtag were identified. Based on their potential relevance, 22 charities were approached. Of these, 11 (50%) retweeted the survey, yielding 9 survey responses. Keyword searches identified 6 individual users, of which 1 responded to the survey.

Third-party websites also provide a small number of respondents. These websites referred to myelopathy.org as an information source and not the survey page specifically. NHS Choices (www.nhs.uk), where myelopathy.org is listed as a DCM support organization, provided 615 unique user referrals of which 6 (0.1%) completed the survey. Wikipedia provided 70 unique user referrals but no survey responses.

Comparison of Fee-Based and Free Methods

From week 6 to 28 both fee-based and free recruitment methods were used. During this time, free recruitment methods returned 367 survey responses. When directly compared (Table 1), in addition to being free, these methods were more likely to yield a response from the targeted audience (CTR 57% versus 5%). Following initial setup, between week 8 and 12, all activities related to either method were time-logged. In these 4 weeks, free recruitment methods required 10 hours and 21minutes of maintenance by a researcher, compared to just 30 minutes for the Google AdWords. Based on survey responses during these 4 weeks, free methods were estimated to require 16 minutes per survey response compared to 2 minutes for Google AdWords. Using a UK junior postdoctoral research salary of $26,000 to estimate the administrative costs, free recruitment strategies yielded responses at a cost of $3.17 per response, compared to $7.80 for fee-based methods.

Discussion

Over 700 patients with DCM were recruited to an Internet survey in 10 months. This places it amongst the largest clinical DCM data sets based on sample size [7]. Simple, cost-free techniques, particularly approaching Facebook groups, were effective in reaching a motivated audience. However, this was time-consuming and may have a saturation point. Google AdWords was an effective and time-efficient alternative, but its use comes with a price.

Limitations

From the outset, it is important to acknowledge the limitations of this study. This was an adaptive study design, more akin to a quality improvement process. Interventions, therefore, were not prescriptively performed throughout the period and it is not possible to directly compare these individually any further. For example, it is likely Facebook activity targeted the same users on each occasion, therefore the sequence in which interventions occurred will no doubt have contributed to their specific impact, but this cannot be commented on further.

Additionally, Google Analytics shows that fee-based and free collectors had small overlaps. Given the complex URLs for fee-based collectors and their blinding to search engines, it is very unlikely access to the survey could come about by any other means than clicking on the Google AdWord advert. Therefore, for fee-based methods, this is unlikely to be significant. These recorded accesses are instead, most likely to represent maintenance views by the research team and the method of access (direct or via Weebly) on Google Analytics would reflect this. However, for free methods collectors, users may have initially reached the platform via a Google AdWord advert and explored the platform further, before deciding to participate in the survey. Therefore, this may have yielded some survey responses. However, the maximum this would be is 40 responses (assuming 100% completed a survey) and this would not alter the overall conclusions.

Findings in Context

Our findings further demonstrate the power of the Internet to reach patients, either by paid advertisement or free alternatives. At present, no absolute strategy has emerged as the most successful [8,9], and it is likely that any strategy needs to be considered in the context of the individual project as both strategies have their merits. Most recent examples have used a combination of paid advertising and alternative methods, including social media [15,21,22].

In the first quarter of 2016, Google and Facebook held 85% of the global digital advertising market [26]. Their popularity is also reflected in recent recruitment studies, particularly Facebook [8]. The attraction of Facebook advertising for researchers is the ability to specify target demographics. This has been effectively utilised, for example, in sexual health studies [21]. However, Facebook adverts only target the Facebook community. In this study we chose Google AdWords because the demographics of our patients are not so clearly defined and potentially include older individuals less likely to be using Facebook [27]. We also wanted to avoid overlap with our alternative Facebook interventions. This overlap may explain the contrasting findings of Yuan et al (2014) in their recruitment of HIV positive patients to an Internet survey. Their study used very similar recruitment strategies, with the exception that their paid advertising was conducted on Facebook as opposed to Google AdWords. They found only a very weak correlation between social media engagement and survey responses, concluding it was less efficient than Facebook advertising [21]. Likewise, Valdez et al (2014) showed promising, albeit less significant, engagement from social media groups.

Therefore, the significant impact of social media engagement here is a novel finding. This success may stem from several unmeasured factors. Firstly, compared to the very simple one sentence of text allowed by Google AdWords, posts to Facebook could contain a far more detailed overview of the study and its objectives. This may have helped capture an audience and explain their greater motivation to complete the survey fully having accessed it. Additionally, our modifications to Google AdWords were very basic and our relative inexperience with this tool undoubtedly had some influence. Furthermore, the use of Facebook groups led to patient support and promotion of the survey. For example, the Facebook posts often developed into conversation threads, with group users commenting when they had responded. This maintained the post's prominence within the group for some time. This promotion by the users themselves may also explain the similar trends in the efficacy of social media and other free advertising strategies (Figure 4) in weeks 5-9.

In DCM, the Facebook communities are relatively small which may limit their representation and overall number of responses [23]. However, for many conditions this is not the case. A simple search of 'Multiple Sclerosis Group' in Facebook returns many groups, with the top four groups have a combined membership of >22,000. Many alternative free recruitment strategies have been tried, including email, alternative social media, and alternative third-party websites, but as with our findings, their impact has been relatively minor [9,15,21,23,28].

Conclusions

A large number of patients can be efficiently reached using the Internet. Internet advertisements and free alternatives both have their merits. Google AdWords provides a simple and constant stream of traffic, although comes with significant cost. The targeting of existing communities was cheaper and identified a more motivated user. Whilst this exposes the researcher's identity, this is a highly effective and simple strategy.

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Conflicts of Interest

None declared.

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Abbreviations

CPC: cost-per-click
CTR: click-through-rate
DCM: Degenerative Cervical Myelopathy

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Original Paper

Telehealth Rehabilitation for Cognitive Impairment: Randomized Controlled Feasibility Trial

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Abstract

Background: Nonpharmacological interventions are needed to support the function of older adults struggling with subjective cognitive impairment (SCI), mild cognitive impairment (MCI), and dementia due to Alzheimer disease (AD). Telerehabilitation aims to provide rehabilitation at a distance, but cognitive rehabilitation by videoconferencing has not been explored.

Objective: The objective of this study was to compare goal-oriented cognitive rehabilitation delivered in-person with videoconferencing to determine whether telehealth cognitive rehabilitation appears feasible.

Methods: Random assignment to in-person or telehealth videoconferencing cognitive rehabilitation with a combined between-subjects, multiple baseline single-case experimental design, cognitive rehabilitation was delivered by a therapist to 6 participants with SCI (n=4), MCI (n=1), or dementia due to AD (n=1).

Results: Two of the 6 participants randomly assigned to the telehealth condition withdrew before beginning the intervention. For those who participated in the intervention, 6 out of 6 goals measured with the Canadian Occupational Performance Measure improved for those in the in-person group, and 7 out of 9 goals improved for those in the telehealth group.

Conclusions: Delivery of cognitive rehabilitation by telehealth appeared feasible but required modifications such as greater reliance on caregivers and clients for manipulating materials.

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KEYWORDS

cognitive rehabilitation; Alzheimer disease; dementia; telehealth

Introduction

Background

Populations are aging worldwide [1]. In Canada, the rural population is older and is disproportionally aging relative to the urban population [2]. The incidence of dementia increases with age, and formal dementia services are the least accessible in rural and remote communities where the proportion of older adults is the greatest [2,3]. Long travel distances and transportation difficulties further limit accessibility [3]. Telemedicine, or telehealth, is the remote delivery of health care services, where distance is a critical factor, by means of information and communications technology [1]. Expanding telehealth services has been suggested to reduce disparities in urban and rural health care [4]. Interventions to support the function of older adults with cognitive concerns, including dementia, are needed, and it is essential that these interventions are accessible to all families. Cognitive rehabilitation is a promising but understudied nonpharmacological individualized treatment that has been shown to help individuals with mild cognitive impairment (MCI), early stage dementia due to Alzheimer disease (AD), and vascular dementia set [5] and attain personally important functional goals [6-8]. This study investigated the feasibility and acceptability of delivering cognitive rehabilitation to individuals with subjective cognitive impairment (SCI), MCI, and early stage dementia using telehealth videoconferencing.

Telemedicine and Dementia

Research on telemedicine and dementia has primarily focused on diagnosis (eg, [9,10]), clinical consultation, follow-up appointments [11], and support for family caregivers [12-14]. In comparison, relatively little work has studied interventions for individuals diagnosed with dementia, although research in this area has begun to emerge. For example, Dal Bello-Haas et al [15] demonstrated that videoconferencing is a feasible method to deliver an exercise intervention for rural individuals with dementia due to AD. These examples of successfully delivering remote interventions for individuals with dementia suggest that remote cognitive rehabilitation could be feasible.

Telerehabilitation

Telerehabilitation is "the set of instruments and protocols aimed at providing rehabilitation at a distance" [16]. Telerehabilitation has been used to provide a range of interventions to individuals diagnosed with a number of different disorders. For example, telerehabilitation has been used to treat stroke [17], spinal cord injury [18], traumatic brain injury [19,20], multiple sclerosis [21], and cognitive impairment following intensive care [22]. Diverse use of telehealth includes delivering diagnostic assessments, caregiver support groups, individual and group psychotherapy [23], home exercise programs, clinical consultations, and cognitive rehabilitation using information and communications technology [16].

Cognitive Rehabilitation for Dementia

Clare and colleagues have developed a goal-focused approach to cognitive rehabilitation for individuals with early stage dementia due to AD, or mixed AD, and vascular dementia [7,24]. In this approach, cognitive rehabilitation begins with an assessment, which is followed by collaborative goal setting [24]. Typically, functional goals related to everyday memory problems, practical skills, and activities and concentration are set, and improved function in these areas has been reported in multiple studies (eg, [25-31]). Generally, these collaborative goals are addressed in weekly 1-hour sessions using empirically supported techniques such as spaced retrieval, cuing and fading, errorless learning, and external memory aids [24]. Briefly, errorless learning involves training without allowing trial-and-error guessing; cues and supports are given to maximize the probability of guessing the correct response instead [24]. Numerous methods facilitate errorless learning, which includes cuing, gradual fading of cues, and spaced retrieval where recollection occurs over increasing time intervals [24]. Although promising, research evaluating cognitive rehabilitation for individuals with early stage dementia is still emerging [32].

Remotely-Delivered Cognitive Rehabilitation

The majority of literature on remotely-delivered cognitive rehabilitation focuses on interventions with individuals who have a traumatic brain injury (TBI). Early research suggests that remotely-delivered rehabilitation for individuals who have sustained TBI is feasible (eg, [33,34]). For example, Tam and colleagues [35] reported a series of 3 case studies where individuals with TBI participated in cognitive rehabilitation using customized software. This software combined videoconferencing with screen-sharing, and participants completed computer-based activities that targeted word recognition, semantic memory (ie, memory for factual knowledge), and prospective memory (ie, memory to perform something in the future). In other work, Bergquist and colleagues [33] opted to use technology to remotely teach participants who had had a severe TBI to use a calendar as a compensatory memory strategy. They adapted Sohlberg and Mateer's [36] calendar training procedure to an instant messenger format and also taught participants to use a personal diary [33]. Both interventions led to increased use of compensatory strategies and improved mood [33]. Finally, in an approach that is more similar to the type of cognitive rehabilitation reported here, Bourgeois and colleagues [37] had participants with chronic TBI identify three everyday memory problems (ie, forgetting appointments, forgetting day planner at home, and losing items), and they provided either an errorless learning approach, spaced retrieval, or memory strategy instructions over the telephone. Individuals in the spaced retrieval group made greater gains in their target goals than those given strategy instructions, and both groups improved their everyday memory functioning. These studies suggest that traditional, in-person cognitive rehabilitation strategies can be delivered by videoconferencing, instant messaging, or telephone.

Remotely-delivered cognitive rehabilitation has also been demonstrated for persons with dementia. Joltin et al [38] used the telephone to train spaced retrieval, a memory intervention, to help 3 women previously diagnosed with dementia recall target information. The goals addressed using spaced retrieval were set in collaboration with family caregivers, staff at the assisted living facility, and the individual diagnosed with dementia [39]. Two participants set the goal to recall what time to take their medications, and one participant set the goals to recall her grandson's names, her room number, and the year [39]. The first participant (Mini-Mental State Exam, MMSE=17) did not always answer the telephone when the researchers called to provide spaced retrieval training and after 4 sessions, she was still unable to recall the times to take her medication for longer than 2 min [39]. The second participant (MMSE=17) was able to pick up a prompt card listing the times she needed to take her medications across a 5-min interval at the conclusion of the intervention. The third participant (MMSE=13) achieved all three of her goals (grandchildren's names, room number, and year) and was able to recall the target information across 3 sessions [39]. The authors concluded that it is feasible to modify spaced retrieval for remote delivery. To date, no research has explored videoconferencing for remote delivery of cognitive rehabilitation.

Objectives

Telerehabilitation is a developing field with the promise of increasing the accessibility of specialized interventions such as cognitive rehabilitation. To date, remotely-delivered cognitive rehabilitation for persons with dementia has not been systematically studied. Interventions that are included in cognitive rehabilitation, such as spaced retrieval, have been applied in a telerehabilitation format, suggesting that this may be an acceptable and feasible approach to increasing the accessibility of cognitive rehabilitation for dementia for persons

residing in rural and remote areas. The purpose of this study was to investigate the acceptability and feasibility of delivering cognitive rehabilitation to individuals diagnosed with dementia due to AD using telehealth videoconferencing.

Methods

Experimental Design

This small-scale randomized control trial used a combined single-case and between-subjects design. Random assignment to in-person versus videoconferencing conditions occurred by random number generator. Random assignment to condition occurred before recruitment (conditions were determined before the study commenced and hidden in envelopes) and was not stratified by diagnosis or by rehabilitation goal. Regardless of randomized condition, all participants received an in-person initial assessment. At the initial in-person assessment participants selected at least two goals for cognitive rehabilitation. The features of a between-subjects design were combined with the features of a multiple-baseline design. Multiple baselines were measured within-subjects, and treatment modalities were compared across participants. After 3 weeks of baseline assessment, Goal 1 was targeted and baseline assessment for Goal 2 continued. After 3 weeks of Goal 1 intervention, Goal 2 was targeted. In this way, both the in-person and telehealth groups were observed repeatedly during the baseline and treatment phases. The repeated observations over the baseline and treatment phases meet the criteria for a multiple-baseline design (across groups) [39]. In single-case experimental design guidelines, three is the minimum number of data points required to establish a baseline, and the minimum number of data points needed in each phase [40].

Participants

The University of Saskatchewan Behavioural Ethics Review Board provided ethical approval. Participants were recruited through community-based organizations and a hospital-based geriatric assessment program. Initially, the researchers hoped to recruit participants solely from clinical settings, but low enrollment led us to expand the recruitment strategy and inclusion criteria. With the expanded criteria, individuals with SCI and no diagnosis, MCI, early stage dementia due to AD, or mixed AD and vascular dementia, were all invited to contact us if they were interested in participating in the study. Diagnosis was self-reported (ie, participants reported that they had received a diagnosis of dementia due to AD from their neurologist, reported no diagnosis), but all self-reported diagnoses were consistent with the clinical interview, neuropsychological tests, and questionnaires administered in the assessment for the study. Prior to enrolling in the study, participants completed a brief clinical interview where cognitive rehabilitation was reviewed, informed consent was obtained (from participant and caregiver wherever appropriate), and a Mini-Mental State Exam (MMSE; [41]) was administered. All individuals were encouraged to participate with a family member or friend, but this was not mandatory.

Measures

Two sets of measures were used in this study: pre-post measures and weekly measures. A set of measures was administered in-person to all participants before and after the intervention. Second, weekly observational measures and measures of goal performance and satisfaction were collected using the medium of in-person versus telehealth as per the random assignment. The measures were selected to be similar to those used by Clare and colleagues in their 2010 randomized control trial [7].

In-Person Initial Assessment and Posttreatment Measures

All participants completed neuropsychological testing and self-report measures of mood, anxiety, and quality of life. Support persons completed measures of quality of life (self and participant), function (participant), and caregiver burden.

Rivermead Behavioral Memory Test III (RBMT-III)

The RBMT-III was developed to detect memory impairment and change in memory impairment over time [42] and detect problems that may interfere with rehabilitation [43]. The alternate forms reliability of the subtests of the RBMT-III range from r=.58 to r=.68 in a mixed clinical sample [44]. The RBMT-III differentiates between individuals with and without brain injury [44], and the RBMT-III's subtests correlate with other similar cognitive tests, with observations of everyday memory failures, and with subjective ratings of memory performance completed by patients and relatives [44]. There are no RCIs reported in the literature; Wilson et al. [44] reported SEM.

Delis Kaplan Executive Function System (D-KEFS), Verbal Fluency Subtest

The verbal fluency subtest of the D-KEFS includes letter fluency, category fluency, and category switching [45]. The letter fluency condition, where individuals are asked to say words that begin with a particular letter has high (.80-.89) internal consistency [43]. The category fluency condition, where individuals are asked to say words from a particular semantic category (eg, boy's names) has adequate (.70-.79) test-retest reliability. The category switching condition, where individuals are asked to alternate between saying words from two different semantic categories (eg, fruit and furniture) has low (<.59) test-retest reliability. RCI's have been reported by Brooks et al. [46].

Test of Everyday Attention (TEA)

The TEA is a measure of attentional processes, and participants completed elevator counting and elevator counting with distraction subtests [47]. Elevator counting measures sustained attention, and elevator counting with distreaction measures selective attention/working memory [43]. The reliability of the map search, elevator counting, and elevator counting with distraction subtests was adequate (r=.75-.86) [43]. The TEA is a theoretically-based test of attention, and, further evidence of its convergent and discriminant validity and its psychometric properties in clinical samples is needed [43]. To measure change, there are no RCIs reported in the literature.

Quality of Life in Alzheimer Disease (QoL-AD)

The QoL-AD scale is a 13-item questionnaire completed by both the individual diagnosed with AD and his or her caregiver to generate self and informant ratings [48]. The QoL-AD has adequate internal consistency and test-retest reliability, and there is evidence for its validity as a measure of quality of life in persons with AD [48]. A recent review of measures of health-related quality of life for individuals diagnosed with dementia [49] reported good evidence for QoL-AD's internal consistency, test-retest reliability, content validity, convergent validity, and responsiveness.

World Health Organization Quality of Life Assessment, Short Version (WHOQOL-BREF)

Caregivers completed the WHOQOL-BREF, which is a 26-item questionnaire covering the physical, psychological, social, and environmental aspects of quality of life [50]. The measure had good to excellent reliability and there was preliminary evidence for the measure's validity [50], and more adequate psychometric properties were found with older adults [51]. Skevington et al. [50] did not provide an overall internal consistency reliability, but instead they reported for each subscale: these were averaged (average reliability .778; ranging from .82 to .68 for the 4 subscales), and SDs were pooled (ranging from 2.6 to 3.2) based on the sample of 11830 to equal 2.88.

Zarit Burden Inventory (ZBI)

The ZBI is a self-report measure of caregiver burden and the short form of the ZBI has adequate internal consistency (Cronbach alpha=.88-.90), and there is robust evidence for its predictive validity [52,53].

Weekly Measures

Performance and satisfaction ratings on the goals for cognitive rehabilitation were measured with the Canadian Occupational Performance Measure 4th Edition (COPM; [54]). The COPM is a semistructured interview where clients identify problems related to self-care, productivity, and leisure; they rate the importance of each of these identified problems and their satisfaction with each problem from 1 ("not able to do it" or "not satisfied at all") to 10 ("able to do it very well" or "extremely satisfied") [55]. The COPM was designed to measure change in performance and satisfaction with performance, it is responsive to change, and a two-point change has been established as clinically significant [56]. The COPM has demonstrated adequate test-retest reliability (.84-.92), and there is evidence for the measure's content, criterion, and construct validity [54].

The number of learning trials related to a specific goal were observed and recorded. For example, if an individual set the goal to learn the names of the members of a social group or improve recall of personal information this was addressed using vanishing cues and spaced retrieval to reduce errors and be consistent with the principles of errorless learning [24]. The measure was the proportion of items correctly recalled. Or, if an individual set the goal to keep track of the date and the plans for the day, this was addressed using prompting and fading to teach the use of a calendar, and the measure was the level of prompting required.

Intervention Phase

Cognitive rehabilitation followed the procedures outlined by Clare [24] in her manual *Neuropsychological Rehabilitation and People With Dementia.* This manual emphasizes individualized, person-centered goal setting. One participant set goals related to mood and sleep. Here, cognitive behavioural strategies were used to treat insomnia [57] and low mood [58,59]. All of the interviews, assessments, and interventions were completed by a senior doctoral student in clinical psychology (RLB) and supervised by a neuropsychologist (MEO).

Procedure

Assessment

First, all participants participated in an in-person assessment where the pretreatment testing and an interview were conducted. The assessments were carried out over 1 or 2 sessions, based on the scheduling availability of the participants.

Baseline Phase

Following the assessment, goals for cognitive rehabilitation were set collaboratively, and baseline performance and satisfaction was measured using the COPM for all goals during 3 baseline sessions (labeled B1, B2, and B3 on the figures below). Measurement occurred either in-person or through telehealth, depending on the experimental condition. Following 3 weeks of baseline measurement, each participant's first goal was addressed in the subsequent cognitive rehabilitation sessions. Baseline COPM measurement continued for all goals that were not the target of the intervention (ie, Goal 2 and Goal 3).

Intervention Phase

The cognitive rehabilitation intervention followed the guidelines provided by Clare [24] in her text on cognitive rehabilitation for people with dementia. Each participant's first goal(s) were addressed in cognitive rehabilitation on the fourth week, following the baseline phase. A new goal, or set of goals, was introduced every 3 weeks (ie, in CR 4, and in CR 7).

For all participants, the treatment phase was designed to take place over 8 weeks. This decision was based on the procedure reported in Clare and colleagues [7]. Participants attended the Video Therapy Analysis Lab on the University of Saskatchewan campus once a week for a 1-hour session. The setting was the same regardless of in-person versus telehealth condition, but for the telehealth condition, the therapist was not in the same room and videoconferencing was used.

Research Journal

RLB kept a research journal during this study beginning in the recruitment phase. Entries were made in the journal after each assessment, baseline, and intervention session. Journal entries documented what took place in the sessions, reflections on the experience of delivering the intervention, and emphasized any adaptations that were made to make cognitive rehabilitation more amenable to videoconferencing.

Data Evaluation

Evaluation of the Quantitative Data Provided by Participants

The data from the study were evaluated using visual inspection. In single-case research visual inspection is the primary method of data evaluation and, although statistical methods for evaluating single case data are increasingly available, they are not widely used [39]. Visual inspection is based on exploration of changes in the magnitude of the data and changes in the data across phases (eg, from the baseline to the intervention phases). There are two characteristics of single-case data related to magnitude: changes in means across phases and changes in level across phases [39]. A change in means refers to a change in the average of a measure in one phase to another. A change in level refers to a shift, jump, or discontinuity in the data from the end of one phase to the beginning of another. There are also two characteristics related to rate of change: changes in trend and latency. A change in trend is a change in the slope of the data from one phase to the next. A change in latency refers to the period of time that elapses from the time the phase changes (ie, the onset of the intervention) until there is a change in the data.

Visual inspection is a reliable method of data evaluation when the results are strong, and changes from one phase to the next are clear [60]. Therefore, visual inspection encourages researchers to study interventions that have potent effects that are readily observable because weak results are generally not visible under visual inspection [39]. The insensitivity of visual inspection to weak results is often considered to be a strength of this approach rather than a limitation. For example, looking for consistent results that can be easily seen also minimizes the chances of making a Type I error (concluding that the intervention has an effect when the results are because of chance; [39]). In this multiple-baseline study, the researchers were interested in determining whether there was a significant change in performance from the baseline to intervention phase. Changes in level and trend were both of interest.

Evaluation of Qualitative Data Provided in the Research Journal

The journal documenting the experience of adapting cognitive rehabilitation to telehealth videoconferencing was analyzed thematically. Journal entries were organized into a descriptive summary based on the method of qualitative description detailed in Sandelowski [61,62], and the technique of thematic analysis was as described by Braun and Clark [63]. The thematic analysis took a theoretical approach (as opposed to an inductive approach) insofar as the researchers specifically coded responses related to ways in which the videoconferencing-delivered intervention needed to be modified. This method of qualitative description is a low inference qualitative methodology, and it is intended to generate a comprehensive summary of an event in everyday terms [61].

Results

Participants

Eight individuals were recruited to participate in this study, participants were immediately randomly assigned to in-person versus telehealth, and the initial assessment was completed in-person. Two discontinued the study following the initial assessment, and these two happened to be randomly assigned to the telehealth condition. In one case, the family member support person reported that she and the participant did not have time to participate. In the other case, the family member support person reported that initial assessment had been distressing for the participant, and following a family discussion it had been decided that participating in the study was likely to be more distressing than helpful. Demographic and descriptive data for the six individuals who participated are presented in Tables 1 and 2.

Table 1. Participant characteristics.

Participant	Delivery	Age	Years of education	Gender	Recruitment source	Diagnosis	Relationship to support person	Involvement of support person
A	In-person	72	18	Female	Support organization	AD[a]	Husband	Attended all sessions
B	In-person	68	14	Male	Support organization	MCI[b]	Wife	Initial interview and questionnaires
C	Telehealth	80	16	Female	Community	SCI[c]	None available	None
D	Telehealth	66	13	Female	Community	SCI	Husband	Initial interview and questionnaires
E	In-person	77	12	Female	Community	SCI	Husband	Questionnaires only
F	Telehealth	68	16	Female	Community	SCI	Husband	Initial interview and questionnaires

[a]AD: dementia due to Alzheimer disease.

[b]MCI: mild cognitive impairment.

[c]SCI: subjective cognitive impairment.

Table 2. Initial assessment (1st) and postcognitive rehabilitation (2nd) assessment measures for participants and support persons. Initial assessment (1st) and postintervention (2nd) measures for participants randomly assigned to the in-person cognitive rehabilitation group. Participants were all encouraged to participate with a support person, but participants C and E stated that no support person was available to participate, consequently missing data exist for caregiver reported items for these participants. "dc" indicates caregiver data are missing (discontinued).

Measure[a]	Maximum SE_D/RCI[b]	A		B		C		D		E		F	
		In-person		In-person		Telehealth		Telehealth		In-person		Telehealth	
		1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
MMSE	30	17		27		29		27		29		26	
Memory-RBMT-III	194[c]	55	45	101	103	158	151	158	152	152	158	106	144
Memory-RBMT-III	100th percentile, SE_D=7.6[d]	0.2	0.2	4	4	92	82	93	82	84	92	5	63
Executive Function-DKEFS	19[c]												
Letter fluency	RCI=2.7[e]	6	2	11	12	8	9	13	16	14	14	15	16
Category fluency	RCI=3.1[e]	3	3	9	5	10	14	18	16	18	18	16	17
Switching total correct	RCI=5.8[e]	1	1	8	8	14	13	19	18	17	18	15	14
Switching total switch	RCI=5.4[e]	1	1	10	9	15	13	17	14	17	14	15	13
Attention-TEA													
Elevator count	7 raw[f]	6	4	6	7	7	-	7	7	7	7	7	7
Elevator distraction	SE_D=0.8[f]	dc	dc	5	6	dc	-	11	11	13	9	5	6
QoL-AD	52, SE_D=3.8[g]	25	48	34	34	108	109	106	108	28	-	115	118
ADLs-Bristo	60, SE_D=4.0[h]	0	1	3.5	1	0	0	0	0	0	0	-	0
Anxiety-HADS	21, MCID=1.4[i]	4	4	8	5	6	0	6	7	10	10	4	2
Depression-HADS	21, MCID=1.6[i]	0	3	2	2	1	1	2	0	9	7	2	0
Caregiver measures													
Quality of life-WHO-QOL-BREF	130, SE_D=1.9[j]	103	79	86	91	-	-	91	96	-	-	126	110
Quality of Life-AD	52, SE_D=3.8[g]	40	36	30	22	-	-	0	-	-	-	0	0
ADLs-Bristol	60, SE_D=4.0[h]	18	14.5	7.5	2.5	-	-	6	0	-	-	10	0
Caregiver Burden-ZBI	36, SE_D=7.0[k]	35	-	37	51	-	-	13	-	-	-	6	-

[a]Acronyms: MMSE: Mini-Mental State Exam; RBMT-III: Rivermead Behavioural Memory Test III; DKEFS: Delis Kaplan Executive Function System; TEA: Test of Everyday Attention; QoL-AD: Quality of Life in Alzheimer Disease; ADLs-Bristol: Bristol Activities of Daily Living Scale; HADS: Hospital Anxiety and Depression Scale; MCID: Minimum Clinically Important Difference; WHOQOL-BREF: World Health Organization Quality of Life Assessment, short version; ZBI: Zarit Burden Inventory.

[b]Standard error of the difference (SED) is the SD of the expected test-retest difference score if no change has occurred; accounts for standard error in measurement (SEM) at both time points; SED=square root of 2 times the SEM squared. SEM=SD times square root of 1 – reliability. Reliable change indices (RCI) incorporate SED and expected improvement in performance due to practice effects or expected changes due to standard error in prediction and regression to the mean in addition to practice effects, depending on the RCI formula.

[c]Refers to standard score.

[d]No RCIs reported in the literature; [44] reported SEM.

[e]RCIs from [46]; 90th percentile with average practice effect used.

[f]No RCIs reported in the literature, reliability of elevator counting not reported due to ceiling effect, reliability of elevator counting with distraction [43] reliability .857; SD 1.42.

[g]Internal consistency reliability .82; SD 6.3 [64].

[h]Test-retest reliability=.95; SD 12.7 [65].

[i]MCID: Minimum Clinically Important Difference [66] detail changes in HADS scores that were important based on external measures, which is a

suggested method for determining MCID.

[j][50] did not provide an overall internal consistency reliability, but instead they reported for each subscale: these were averaged (average reliability .778; ranging from .82 to .68 for the 4 subscales), and SDs were pooled (ranging from 2.6 to 3.2) based on the sample of 11830 to equal 2.88.

[k]Internal consistency reliability .90; SD 15.64 [52].

Goals and Completion

Participants each collaboratively set between one and five goals for cognitive rehabilitation. Table 3 lists the specific goals and the cognitive rehabilitation strategies used to address them. The study was designed to deliver 8 sessions of cognitive rehabilitation after 3 sessions of the baseline phase. All 3 participants randomly assigned to the in-person intervention completed 8 sessions. In the telehealth group, one individual completed 8 sessions, one individual (Ms D) completed 7 sessions, and one individual (Ms F) completed 6 sessions. Ms D reported that she had decided to go on vacation, and therefore the researchers decided to cancel the final telehealth rehabilitation session and complete posttreatment assessment. Ms F only had one goal for cognitive rehabilitation, and she felt it had been accomplished after 6 telehealth cognitive rehabilitation sessions.

Goal Performance

The primary outcome measure was goal performance as measured by the COPM. Figures 1 to 6 display the COPM scores across the baseline and intervention phases for each of the 6 participants.

Table 3. Participants' goals and cognitive rehabilitation strategies used to address these goals during the intervention.

Participant	Intervention delivery	Goals	Cognitive rehabilitation strategies used to address goals
A	In-person	To remember personally significant life events and accomplishments; To know the names and relationships of important people (eg, grandchildren, siblings, friends).	These two goals were addressed together using an external aid (memory book), which included photos, newspaper clippings, and documents displaying significant people and events. Twenty pages from the memory book were chosen, and these focused on in 2 sets of 10 using spaced retrieval and cuing and fading.
B	In-person	To keep track of date, plans, and activities.	An external aid (day timer) was used to address this goal. Use of the day timer was trained using spaced retrieval and cuing and fading.
		To reduce frustration related to memory and organizational difficulties; feel more engage in activity at hand.	A relaxation exercise and relaxation cues chosen by Mr B were used to address this goal.
C	Telehealth	To recall the names of group members.	Face-name association and spaced retrieval was used to address this goal.
		To improve sleep.	Sleep hygiene, relaxation strategies (eg, deep breathing), and cognitive behavioral (eg, developing alternative thoughts for cognitive distortions) was used to address this goal.
		To remember what was read in a novel or non-fiction book.	External aids and Preview Question Read State Test were used to address this goal.
D	Telehealth	To remember plans and what to bring to club meetings.	External aids (using a single, large day timer), and habits and routines were used to address these goals.
		To keep track of the date and plans for the day.	External aids (using a single, large day timer), and habits and routines were used to address these goals.
		To feel more confident driving and navigating.	Relaxation strategies (eg, deep breathing), external aids (eg, GPS), and habits and routines were used to address this goal.
		To maintain concentration when multitasking at home.	Goal management training was used to address this goal.
		To remember what was read in the newspaper or a novel.	Preview Question Read State Test was used to address this goal.
E	In-person	To remember what was read in bridge books and apply it when playing bridge.	External aids and Preview Question Read State Test were used to address this goal.
		To know what was done from day-to-day and be able to tell friends on the phone.	An external aid (daily journal) and routine was used to address this goal.
F	Telehealth	To keep track of plot and characters when reading a novel.	External aids (eg, notes, sticky tabs, and highlighting) and Preview Question Read State Test were used to address this goal.

Figure 1. Canadian Occupational Performance Measure (COPM) scores and total item recall scores (two sets of 10) for participant A. The first line indicates when training for Recall Set 1 was initiated and the second line indicates when training for Recall Set 2 was initiated. CG: caregiver; B: baseline; CR: cognitive rehabilitation.

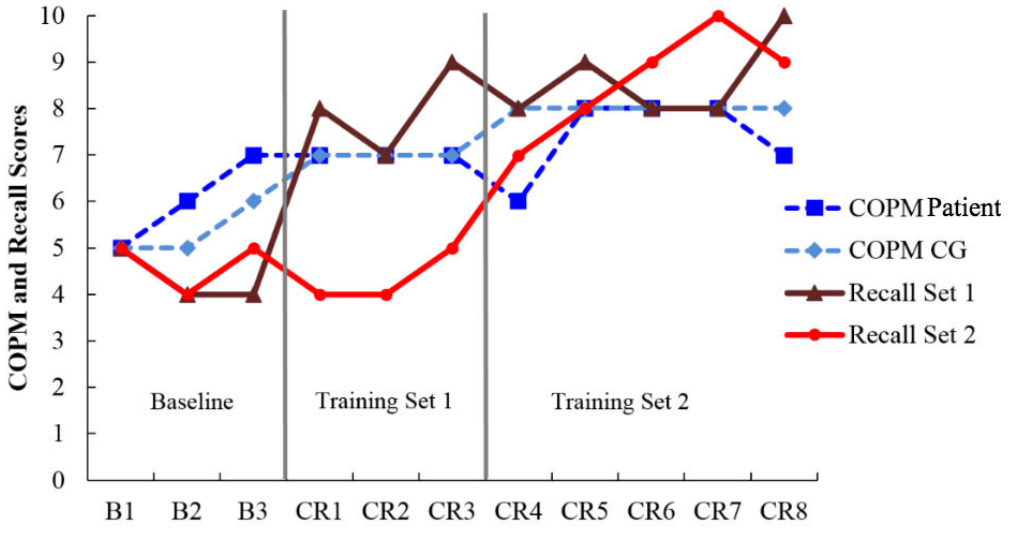
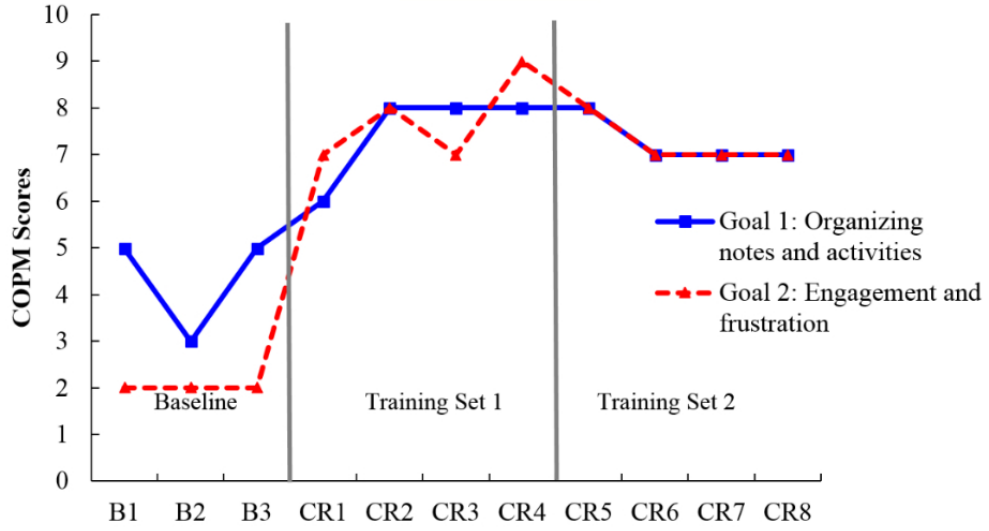


Figure 2. Canadian Occupational Performance Measure (COPM) scores for participant B who attended cognitive rehabilitation sessions in-person. B: baseline; CR: cognitive rehabilitation.



In-Person Intervention (Participants A, B, and E)

Figures 1,2, and 5 display the session-by-session COPM scores for Ms A, Mr B, and Ms E who were all assigned to participate in cognitive rehabilitation in-person.

Ms A (patient) participated in-person with her husband (caregiver; CG), and their data are represented in Figure 1. Ms A's goal was to improve her recollection of personally significant life events. A memory book was compiled by Ms A and her husband, and this book was trained using spaced retrieval and fading and cuing in two sets of 10 memory book pages (ie, 2 sets of 10 pages each). Baseline data from all measures was collected. Set 1 was studied in sessions CR 1, 2, and 3 (indicated by the first vertical line in Figure 1). Sets 1 and 2 were both studied in sessions 4, 5, 6, 7, and 8. Visual inspection of Figure 1 suggests Ms A's (COPM patient) COPM scores were relatively stable across the cognitive rehabilitation, but her husband's scores increased with the number of intervention sessions. Moreover, Figure 1 demonstrates support for spaced retrieval: recall of both memory book sets was at floor during the baseline, and only recall set 1 improved with the initiation of spaced retrieval (first vertical line in Figure 1) and the untrained set 2 remained at baseline, only improving after initiation of training (second vertical line in Figure 1).

Mr B set two goals for cognitive rehabilitation. First, he wanted to keep better track of his daily notes and musings, which were disorganized. Second, he wanted to reduce feelings of frustration when challenged during a task to feel more engaged in his daily activities (eg, attending club meetings, taking his dog for a walk). Figure 2 shows a moderately stable baseline for Goal 1 and robustly stable initial baseline for Goal 2 as measured by the COPM. At the first intervention session (first vertical line in Figure 2), a consolidated notebook strategy was introduced to target Goal 1, and COPM scores for both goals show a change

in level and trend. The change in level is maintained throughout the remainder of the sessions. Although Goal 2 was not explicitly targeted until session CR 4 (the second vertical line in Figure 2) when relaxation techniques and cues were introduced, Goal 2 scores nevertheless appeared to have improved with the intervention targeting Goal 1. Introducing the organizational strategy designed to target Goal 1 had a greater impact on Goal 2 scores than the relaxation exercises designed to address Goal 2. If Mr B's frustration is conceptualized as being a reaction to cognitive lapses that were not mitigated by his previously disorganized memory aide strategy, this "bleeding" of the organizational intervention from one goal to another goal is expected.

Ms E set two goals for cognitive rehabilitation. Following 3 baseline sessions (B1, 2, and 3) the researchers focused on her goal to improve her recall of bridge (a card game) strategies, which she enjoyed studying. This was addressed using the Preview Question Read State Test [67] strategy, a hierarchical strategy for organizing texts, which was trained using spaced retrieval. Ms E also began to use an external aid (note taking) when reading her bridge books. Visual inspection of Figure 3 shows some variability in the baseline, but consistent and sustained improvement one session after initiation of the intervention aimed at this goal (first vertical line in Figure 3). The baseline sessions for goal 2, keeping track of daily activities, also show variability, but COPM scores clearly increase after this goal was the focus of cognitive rehabilitation (second vertical line in Figure 3).

Figure 3. Canadian Occupational Performance Measure (COPM) scores for participant E who attended cognitive rehabilitation sessions through in-person. B: baseline; CR: cognitive rehabilitation.

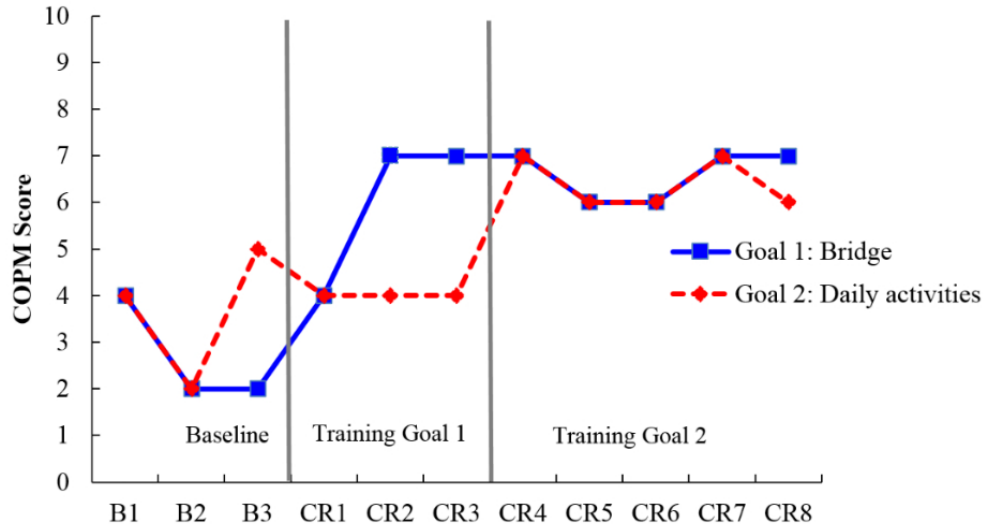
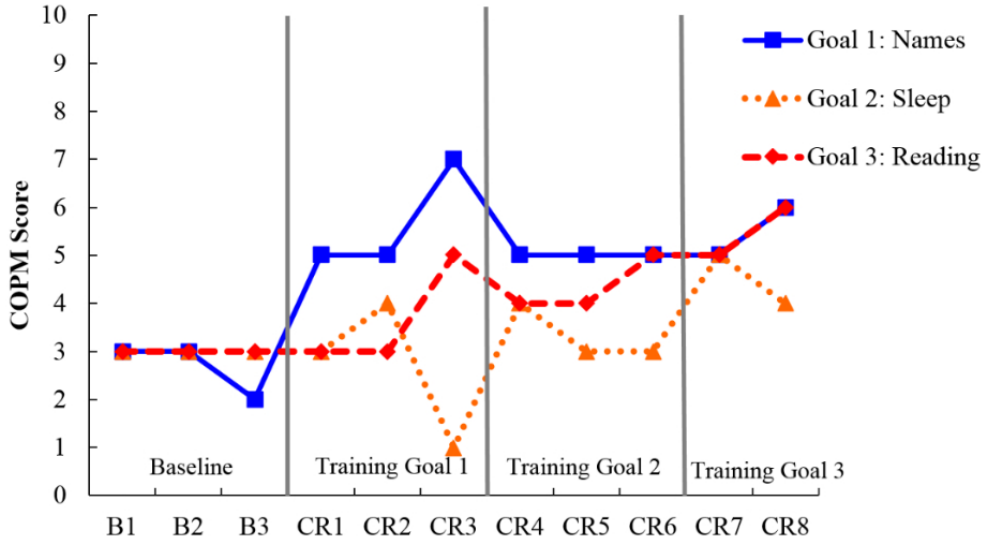


Figure 4. Canadian Occupational Performance Measure (COPM) scores for participant C who attended cognitive rehabilitation sessions through telehealth videoconferencing. B: baseline; CR: cognitive rehabilitation.



Telehealth Intervention (Participants C, D, and F)

Figures 4 to 6 display the session-by-session COPM scores for Ms A, Mr B, and Ms F, who were all randomly assigned to participate in cognitive rehabilitation through telehealth videoconferencing.

Following 3 baseline assessment sessions Ms C's cognitive rehabilitation sessions (CR1, 2, and 3; first vertical line in Figure 4) focused first on strategies for learning and remembering names using cuing and fading of face-name associations and spaced retrieval. Next the researchers targeted her sleep (CR 4, 5, and 6; second vertical line in Figure 4) using strategies from cognitive behavioral therapy for insomnia (CBTi), and finally her ability to recall what she read (CR 7, 8; third vertical line in Figure 4) using external aids and the Preview Question Read State Test [67] strategy. Visual inspection of Figure 3 suggests name recall and reading improved, with sleep showing variability through its baseline sessions (B1-3, CR 1-3) and training sessions. Reading performance improved starting at CR 3 suggesting treatment carry over from training naming strategies, which makes sense considering that the strategies for learning and remembering names (ie, face-name associations) require one to slow down, to focus on the information that is being presented, and to work to encode it in a more rich, elaborative manner.

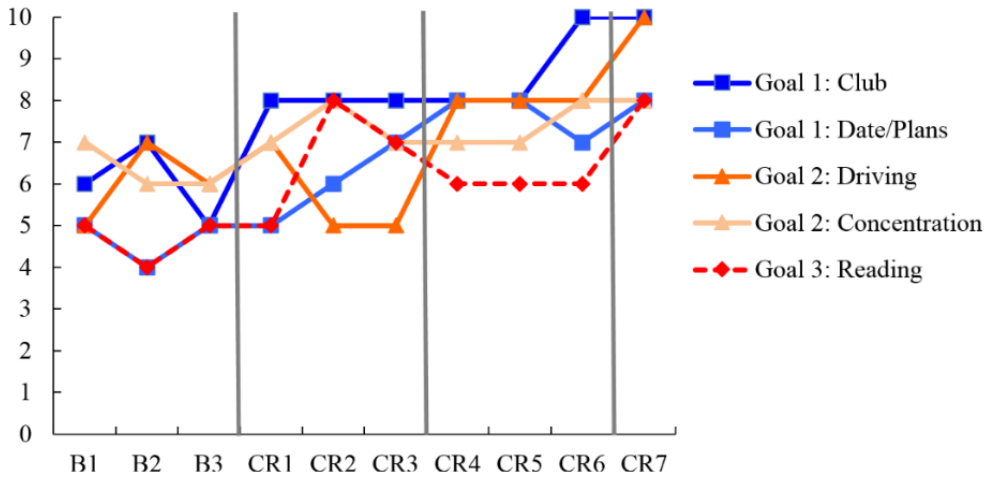
Ms D reported subjective cognitive impairment and set five goals, which were addressed in three training sets (see Table 3). Cognitive rehabilitation was ended after 7 sessions because of a summer vacation for Ms D. Goal set 1 focused on keeping track of day-to-day events, and what to bring to club meetings was addressed using external aids. Ms D was using a number of different systems (cellphone, notebook, day timer), which were consolidated. Visual inspection of Figure 5 suggests that despite some variation in the baseline sessions (B1, 2, and 3), performance on Goal 1 improved by 3 points on the COPM from the highest baseline rating to the highest intervention rating. This increase begins following the first vertical line and is maintained over the course of the remaining sessions. Similarly, performance on Goal set 2, which was concentration and driving, improved when cognitive rehabilitation targeted this goal starting in CR 4 (second vertical line). Goal 3, reading, was targeted only in CR 7 using the Preview Question Read State Test [67] strategy, but performance improved starting in CR 1 and 2, which suggests that the specific training provided during cognitive rehabilitation in CR 7 did not cause the improvements shown in the Figure 5. Rather, the strategies started in CR 1 (external aids) appeared to have supported her goal to recall what she had read. These data suggest that Ms D tended to multitask, and moved quickly from one partially finished task to the next. Using external aids may have reduced the load on her working memory, which would allow her to devote more of her cognitive resources to reading when she picked up a book or newspaper.

Ms F only had one goal for cognitive rehabilitation: she described herself as an avid reader and reported struggling to recall the plot of a novel while reading. Her goal was to be able to keep track of significant characters and their relationships when reading, which was addressed using the Preview Question Read State Test [67] strategy taught through spaced retrieval. This was also combined with external aids including using sticky notes in her books to mark important passages and writing down notes about major characters which she could refer back to. Keeping track of appointments was rated weekly using the COPM as a comparison goal, and served as the second baseline but was never trained. Visual inspection of Figure 6 suggests little variability in this comparison measure, which was, unfortunately likely at ceiling even during the baseline and was therefore never trained. Regarding Ms F's goal, the baseline phase is stable and substantial improvement in performance is present beginning with cognitive rehabilitation in CR 1 (vertical line in Figure 6).

Secondary Outcomes

The pretreatment and posttreatment scores for the secondary outcome measures are presented in Table 2. To facilitate comparisons reliable change indices (RCI) were provided where they were available in the literature. When RCI were not available, standard error of the difference (SE_D) or minimum clinically important differences (MCID) were provided in Table 2.

Figure 5. Canadian Occupational Performance Measure (COPM) scores for participant D who attended cognitive rehabilitation sessions through telehealth videoconferencing. B: baseline; CR: cognitive rehabilitation.



There were few changes in the secondary measures that exceeded these estimates of change, and only changes greater than the SE_D, RCI, or MCID are reported below.

In-Person Intervention (Participants A, B, and E)

Ms A was the only individual with a dementia due to AD diagnosis who participated in the study, and her scores on the memory measure (RBMT-III) and executive function measure (DKEFS letter fluency) declined in the 12 weeks between the initial assessment and posttreatment assessment. This may reflect disease progress or failure to benefit from practice (the DKEFS RCI includes practice effects). She demonstrated an increase (from 0 to 3) on the Hospital Anxiety and Depression Scale (HADS) depression subscale that was greater than the MCID, but her score remained well below cut-off for clinical depression. Although she reported improved quality of life, her husband reported decreased quality of life over the 12 weeks. The second in-person participant, Mr B had decreased category fluency as measured by the DKEFS, and decreased anxiety as measured by the HADS. His wife reported improved quality of life for herself, decreased quality of life for Mr B, improved function for Mr B, and increased caregiver burden. Finally, Ms E had decreased divided attention as measured by elevator counting with distraction, and decreased depression as measured by the HADS. A support person did not accompany her.

Telehealth Intervention (Participants C, D, and F)

Ms C demonstrated improved category fluency and decreased anxiety as measured by the HADS. The second telehealth participant, Ms D, demonstrated improved letter fluency as measured by the DKEFS and decreased depression as measured by the HADS. Her husband reported improved quality of life for himself and improved function for Ms D. Finally, Ms F had improved memory as measured by the RBMT-III and decreased anxiety and depression as measured by the HADS. Her husband reported decreased quality of life for himself and improved function for Ms F.

Findings From the Research Journal

The research journal was used to reflect on the process of conducting this study, to document any challenges and successes that may not have been fully captured by the quantitative measures, and to document modifications that were made to deliver the intervention to the individuals in the telehealth group. The codes that were generated were organized into two major themes: “relationship and therapeutic alliance” and “method and technique.” Text pertaining to how the researcher (RLB) felt working with the participant, comments the participant made regarding comfort, or how they felt in the session were coded in the “relationship and therapeutic alliance category.” “Engagement” (interest in the intervention and attendance), “connection and enjoyment” (partnership with participants and fun during the sessions), and “responsibility” (researcher’s sense of personal accountability) were coded as subthemes. Text pertaining to study design, measurement, or comparisons between in-person and telehealth treatment were coded in the method and technique theme. “Adjustment to telehealth” and “challenges of measurement” were the themes within “method and technique.” The findings of the thematic analysis are summarized in Table 4, and characteristic examples of text from the journal are presented in the table.

The research journal reflects the importance of building rapport and an alliance to carry out the cognitive rehabilitation. Initial codes were organized into the minor themes of “engagement,” “enjoyment and connection,” and “responsibility.” It is notable that these themes were similar irrespective of treatment modality (in-person vs telehealth).

Figure 6. Canadian Occupational Performance Measure (COPM) scores for participant F who attended cognitive rehabilitation sessions through telehealth. Here, only one goal was set to improve recollection when reading. Keeping track of appointments was rated weekly as a comparison measure to provide a second baseline. B: baseline; CR: cognitive rehabilitation.

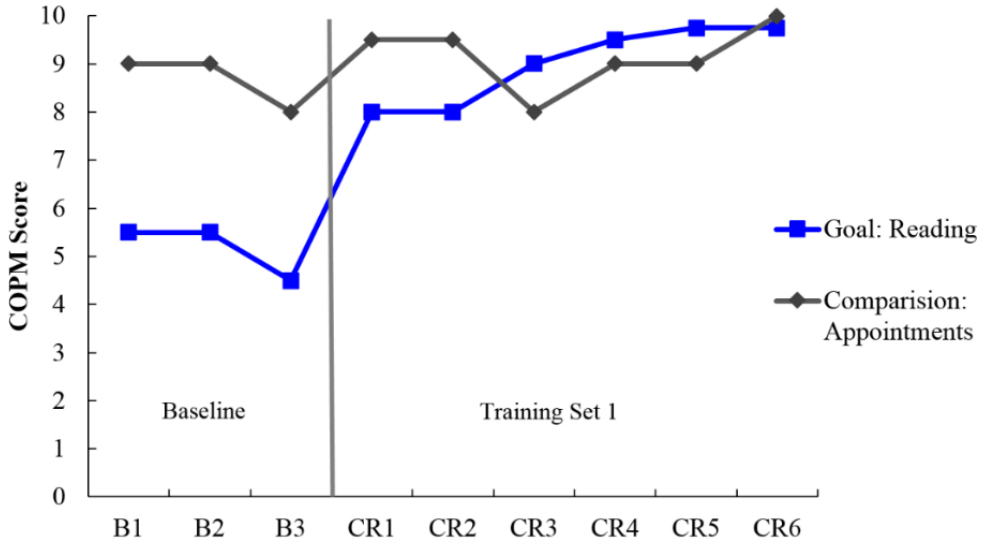


Table 4. Themes from the research journal. Quotes illustrating characteristic examples are observations and reflections made by the researcher (RLB) throughout the study.

Major & minor themes	Characteristic examples
Relationship and therapeutic alliance	
Engagement	*Mr B's wife explained that she preferred not to attend sessions with her husband because she felt so busy with other commitments. It will be important to have at least one session with her where I show her how we have been using the book.*
	Mr and Mrs D are both highly engaged. Megan and I discussed the self-selection that is taking place in my recruitment process.
	Ms E called me this morning to ask if it would be alright if her husband did not attend. When she arrived she explained the he "doesn't really believe in mental things" and didn't think she needed to participate in the study.
Connection and enjoyment	*I really enjoyed working with her and found her bright, perceptive, and easily engaged.*
	He seems to enjoy attending our sessions. Specifically, we laugh and joke a little. He always attends. I am enjoying working with him...some things are a bit challenging/ frustrating. He talks a lot and it can be challenging to interrupt and redirect him to the task at hand.
	She is friendly and easy going, and it's highly enjoyable to work with her.
	Ms E commented that participating has been "very interesting and I've enjoyed coming."
Responsibility	*This is a deeply personally challenging research project. It is so much more difficult than using archival data because of the personal connection and responsibility I feel towards the research participants.*
	I have to manage the expectations and the hopes of the participants.
Method and technique	
Adjustment to telehealth; different but not worse	*She noted that she was disappointed to be assigned to the telehealth videoconferencing condition but would participate.*
	The volume was too loud and it hurt Ms C's ears. She easily turned down the volume using the remote control.
	I could hear a delay between when I spoke and when my voice played in the testing room which was distracting.
	Ms C said it was fine to see and talk to me through videoconferencing. In fact, it was better than expected.
	Ms D said it [telehealth] was just fine. Mr D commented that he preferred when we talked face to face and I was in the same room as them. That being said, he agreed with his wife that it was perfectly feasible to work with me through videoconferencing and the goal-setting session had gone well.
	There is a bit of overlap in us speaking. Conversing is not quite as natural. Ms F compared it to talking on a cell phone, and not being sure when it was her turn to talk.
Greater reliance on verbal description	*I noticed that it was more difficult to see if her chest and abdomen were rising and falling as we practiced diaphragmatic breathing. To compensate, I asked her to describe any spots where she was struggling verbally.*
	I could not see what was written, so she read what was written to me.
Challenge of measurement	*It has been very challenging to balance meeting their goal of developing Ms A's ability to discuss important autobiographical events with the need to have measureable outcomes.*
	...it starts to feel "like a test and that's never fun."
	I have observed marked "spillage" from the intervention items to the baseline items. Ms A now recalls pieces of information about the photos that she could not previously tell me. It will be very difficult to describe whether improvements in Ms A's descriptions of the pages of her memory book are due to spaced retrieval and prompting and fading, or whether they are due to reminiscence and increased familiarity with the pages in the book.
	I am noticing that it is very challenging to address goals purely and there is contamination between goals.

The theme of "method and technique" is comprised of journal entries that comment on the adaptation of cognitive rehabilitation to telehealth videoconferencing. Participants adjusted easily and quickly to working through telehealth videoconferencing. Journal entries were organized into the subtheme of "different but not worse." Participants commented that although they might have preferred to meet in-person, the telehealth sessions ran smoothly. As a clinician, the researcher (RLB) noted challenges because of not being able to physically interact with materials. For example, the researcher was unable to pick up a day timer and read through what the participant had written. Therefore, the researcher had to cue participants to read out written notes or from worksheets. Initial codes in the research journal were organized into the minor theme "greater reliance on verbal description." Lastly, journal entries comment on working to adjust and modify goals and sessions to make the intervention measureable and adhere to the multiple baseline design. Initial codes were organized into the subtheme "measurement challenges."

Discussion

Principal Findings

The results of this study cautiously suggest cognitive rehabilitation can be adapted to telehealth videoconferencing for older adults with subjective and objective memory impairment. The study also adds to the growing body of literature that suggests goal-oriented cognitive rehabilitation delivered in-person is a promising nonpharmacological intervention for older adults with SCI, MCI, and early stage dementia due to AD. For participants who completed the initial assessment and baseline sessions, participation was excellent with all in the in-person group completing 8 out of 8 sessions. Although two in the telehealth group completed fewer than 8 sessions, one terminated because of the goal having been attained and the other terminated because of scheduling conflict with vacation. Both groups demonstrated high completion rates, however the lower rate of session completion for the telehealth group may suggest that telehealth-delivered treatment is less acceptable to participants or something about this modality of treatment (such as the virtual nature of the interpersonal connection, or added challenge of describing steps and materials verbally rather than physically interacting or handing something in to be read) delivery made completion of the sessions less motivating. Despite this caveat, the high completion rates over 12 weeks (3 baseline and 8 intervention sessions) suggest participating through either delivery modality was acceptable to participants. The themes from the research journal also support this conclusion; although some participants assigned to telehealth were initially apprehensive or even disappointed to be assigned to the telehealth condition, as sessions progressed the theme “different but not worse” as a description of videoconferencing-delivered sessions emerged from the research journal entries. These qualitative data revealing apprehension about telehealth could have interacted with the decision to withdraw made by the 2 participants initially assigned to telehealth, but who withdrew after the initial assessment and before the intervention. In order of theme of “different but not worse” to be created, an individual needed to first interact through telefhealth to discover that expectancies regarding apprehension of technology were unfounded.

Importantly, the results suggest participants’ goal performance improved across both treatment delivery modalities. Of the 15 goals set in this study, performance on only two goals (sleep set by Participant C, and concentration set by Participant D) did not improve by 2 or more points on the COPM. Participants C and D were both assigned to the telehealth group, so this raises the possibility that telehealth may reduce the efficacy of cognitive rehabilitation for older adults with SCI. It may also be the case that these goals are less amenable to cognitive rehabilitation. Improved sleep, in particular, is not a typical goal for cognitive rehabilitation, however, improving sleep and managing daytime sleepiness were both reported as goals set in Clare and colleagues’ [26] study (goal attainment was not reported goal by goal). In the sleep intervention literature more generally, CBTi is an effective treatment, demonstrates efficacy that is similar to pharmacological interventions with better long-term outcomes, and has been recommended as a standard treatment for insomnia [68]. Importantly, a full course of CBTi, which is typically between 6 and 8 sessions was not delivered here (Ms C participated in 5 sessions that focused on her goal to improve her sleep). Overall, the results of this study suggest that it is worthwhile to pursue adapting cognitive rehabilitation to telehealth videoconferencing. This is consistent with previous research that has explored remotely-delivered cognitive rehabilitation (ie, [37]) as well as remotely-delivered psychotherapy (ie, [14,23]).

The importance of establishing a strong therapeutic relationship was a major theme that emerged from the research journal. This aspect of cognitive rehabilitation has perhaps not been emphasized enough in the literature, and clinicians who are providing the intervention (whether or not they have been trained as psychotherapists) may benefit from attending to the research on the common factors of psychotherapy (see [69] for a recent summary of the common factors literature based on meta-analyses). This is not to suggest that the therapeutic relationship has been ignored in the cognitive rehabilitation literature, but to highlight the importance of not emphasizing technique (ie, errorless learning and spaced retrieval) at the expense of developing an alliance. One imagines that telehealth videoconferencing could impact developing an alliance, however, this was not noted in the research journal and psychotherapy noninferiority trials (ie, [23]), and other videoconferenced work [14] detail how the therapeutic relation can be established and maintained remotely. Future researchers might consider adding a formal measure of alliance to their protocols.

Limitations

In carrying out this study, the researchers learned a number of things that may be helpful for future researchers. First, the researchers were surprised by how challenging it was to recruit research participants with MCI or early-stage AD. Those recruited and retained in the study were highly motivated and engaged, which is a self-selection bias. This recruitment challenge and the way in which participants were randomly assigned to the in-person or telehealth videoconferencing limits the conclusion the researchers can draw about delivering cognitive rehabilitation through videoconferencing to individuals with MCI or dementia due to AD (the 3 telehealth participants were individuals with subjective memory impairment). The researchers were also surprised to find that the majority of the participants in this study opted to participate without a support person. This was either because no support person was available (Ms C), because a support person was not interested in participating (Mr B and Ms E), or because it was decided that the support person was not needed (Ms D and Ms F). Only Ms A’s husband accompanied her to every session. This is noteworthy because Ms A was the only participant with a diagnosis of dementia due to AD. Previous research (ie, [8]) has recommended that a support person always be included in the intervention. The results of this study suggest that for individuals with SCI a support person is not necessary, but for individuals with dementia due to AD or MCI, the researchers continue to recommend a support person.

The researchers also came to reconsider the experimental design. The multiple baseline design was chosen to be able to infer that any improvements in COPM scores were due to cognitive rehabilitation interventions rather than common therapeutic factors such as establishing a positive relationship with the researcher delivering the treatment. As the study progressed, it became apparent that skills being taught for one goal carried over to other goals, and in some cases (Participant D in particular), participants spoke explicitly about generalizing strategies from a goal that was being trained to a goal that was not being trained. Of course, this is excellent for that individual, but it does limit the usefulness of within-person multiple baselines for cognitive rehabilitation. Therefore, this type of experimental design is not recommended, at least not for similar goals. Furthermore, in this study the researchers chose to rely on visual inspection to examine these data. This has the advantage of highlighting strong effects, which are more likely to be functionally relevant. The limitation of this approach is that subtle trends such as serial dependency are not readily observable using visual inspection, visual inspection is unreliable when effects are not large, and for these reasons, statistical methods of analyzing single-case data have been increasingly studied and used [60].

Conclusions

The findings presented in this study support developing goal-oriented cognitive rehabilitation delivered both in-person and expanding the accessibility of this intervention by adapting it to videoconferencing. Further research is needed to replicate the results presented here. Additionally, this data does not fully explore the adaptation of cognitive rehabilitation to videoconferencing for individuals with cognitive impairments consistent with MCI or dementia due to AD. Given the increasing prevalence of cognitive impairment in late life in both urban and rural areas, interventions aimed at supporting the personally relevant functional goals of these individuals are clearly needed.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

CONSORT - EHEALTH checklist (V 1.6.1).

[PDF File (Adobe PDF File), 550KB - resprot_v7i2e43_app1.pdf]

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Abbreviations

AD: Alzheimer disease
ADLs-Bristol: Bristol Activities of Daily Living Scale
CBTi: cognitive behavioral therapy for insomnia
CG: caregiver
COPM: Canadian Occupational Performance Measure 4th Edition
D-KEFS: Delis Kaplan Executive Function System
HADS: Hospital Anxiety and Depression Scale
MCI: mild cognitive impairment
MCID: minimum clinically important differences
MMSE: Mini-Mental State Exam
QoL-AD: Quality of Life in Alzheimer Disease
RBMT-III: Rivermead Behavioral Memory Test III
RCI: reliable change indices
SCI: subjective cognitive impairment
SED: standard error of the difference
SEM: standard error of measurement
TBI: traumatic brain injury
TEA: Test of Everyday Attention
WHOQOL-BREF: World Health Organization Quality of Life Assessment, short version
ZBI: Zarit Burden Inventory

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Protocol

Understanding the Impact of Childhood Sexual Abuse on Men's Risk Behavior: Protocol for a Mixed-Methods Study

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Abstract

Background: Childhood sexual abuse (CSA) remains a critical public health issue among black and Latino men who have sex with men (MSM), as it is associated with multiple negative outcomes including substance misuse, poor mental health, revictimization, and high-risk sexual behavior. Most CSA research with MSM relies on quantitative assessment that often precludes consideration of cultural variations in how formative sexual experiences are understood and is based on inconsistent or overly restrictive definitions of abuse, and therefore may fail to detect certain abusive experiences (eg, those involving female perpetrators), which can have harmful health consequences if they remain unrecognized.

Objective: The objective of this study is to overcome existing limitations in the literature by drawing on perspectives of black and Latino MSM and men who have sex with men and women (MSMW), as well as relevant service providers to better understand the role of, and the need to include, sexual abuse histories (eg, CSA) in treatment and counseling settings, with the long-term goal of improving assessment and health outcomes.

Methods: We will conduct mixed-methods interviews, framed by an intersectionality approach, with 80 black and Latino men (40 MSM and 40 MSMW) in New York City (NYC), exploring appraisals of their formative sexual experiences, including those described as consensual but meeting criteria for CSA. We will also interview 30 local service providers representing substance abuse treatment, mental health care, and HIV prevention and outreach.

Results: The study was launched in May 2017.

Conclusions: This formative research will inform testable approaches to assessing and incorporating sexual abuse history into substance abuse treatment and other health and mental health services used by men with such histories.

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KEYWORDS

protocol; childhood sexual abuse; MSM

Introduction

Background

Childhood sexual abuse (CSA) is nearly five times greater among men who have sex with men (MSM) than in the general male population [1], with prevalence as high as 27% according to findings from a meta-analysis [2]. Yet, society has scarcely recognized sexual abuse among boys outside of institutional settings [3-5]. MSM with CSA history are more likely to be black or Latino [6-10], or less likely to be white [11]. Although men who engage in same-sex encounters and have a history of CSA tend to be behaviorally bisexual or less likely to identify

as gay [9-11], it is unclear whether and how the formative sexual experiences of men who have sex with men and women (MSMW) differ from those of MSM only. CSA is associated with adverse consequences among MSM and MSMW including substance use [2,8,9,12-14], poor mental health [8,9,11,13-19], high-risk sexual behavior [11,13,14,19-23], and revictimization [11,15,24]. Yet, investigating these histories is often confounded by underreporting [22,25-27] and varied definitions of abuse [2,27-31]. Moreover, large scale quantitative studies that confront participants with questions about unwanted or coercive sexual encounters during childhood are not likely to account for experiences perceived as consensual or normative that would otherwise meet criteria for abuse—that is, unrecognized by the victim [27,32-34]. Recognizing men's own appraisals and interpretations of their childhood sexual experiences (hereafter referred to as CSE) may lead to a better understanding and assessment of abuse and its consequences [12,32,35-37].

Appraisals of CSE (eg, desired, unwanted, coercive, abusive) are influenced by social environmental factors including gender and culture. Men may be less likely than women to define certain CSE as abusive because their socialization into masculine gender roles leads them to fear that they will be perceived as homosexual or as victims [25,38,39]. Black and Latino MSM and MSMW may be under additional pressure to deny unwanted CSE as abusive or to appraise abusive experiences as consensual, including those with female perpetrators, as black and Latino cultures stress the most traditional forms of masculinity [29,32,40,41]. Indeed, these cultural forces may also pressure black and Latino men to conceal same-sex behavior [29,42-45] and to not identify themselves as gay or homosexual [29,46-48]. For these men, CSE with an older male and/or same-sex behavior may be sources of shame and social isolation [44,46,47,49-51]. Furthermore, research suggests that men with histories of sexual abuse are less comfortable with their same-sex attraction than men without such histories [13], and several studies have found that some black and Latino men who were sexually abused as children experience sexual identity confusion [41,52] or establish a link between their abusive experiences and current same-sex desire [32,50,52].

This study recognizes female perpetrators in the early sexual experiences of MSM and MSMW. To our knowledge, this is the first study to investigate formative sexual experiences of black and Latino MSM/W involving older female partners relative to their sexual identity development, adult sexual relationships, masculine and cultural norms, and psychosocial health outcomes. The majority of CSA research with men, specifically gay and bisexual men, would suggest that perpetrators are typically male. Female perpetrators are rarely accounted for in either research designs or analyses. Indeed, several studies have failed to report the gender or sex of perpetrators [8,12,17,21,29,33,53]. Others have omitted female perpetrators from their analysis and discussion [11,20,22,23]. In most of these studies, participants were asked to report incidents they perceived as abusive. If some men normalize early sexual experiences with older female partners, including those where conditions were coercive or there was an obvious age difference between the child/adolescent and partner, they are less likely to appraise—let alone report—such experiences as abusive [27]. Thus these studies will fail to detect situations of abuse that may have affected men's sexual identity development, mental health, substance abuse, and adult sexual relationships.

However, there are a few exceptions [9,32,35]. In a recent study of MSM with a history of CSA, 42% reported at least one incident of abuse by an older female [9]. Another study found that 20 cases (out of 43) involved a female perpetrator, out of which only 4 men initially defined their experiences as abusive [35]. By recruiting and interviewing adult men who experienced their first sexual encounter(s) as a child or adolescent (with an older male, female, or both), the proposed study will overcome this limitation of prior research by increasing knowledge about female perpetrators, particularly, the way men consider these experiences as being influential to their sexual development, psychological and emotional functioning, and current risk-taking behaviors. Moreover, it responds to recent calls for research with black and Latino MSM/W to explore differences in appraisal and meanings of sexual abuse by perpetrator gender [29,52].

There is a need for qualitative research on CSE of black and Latino MSM/W. An in-depth qualitative exploration can yield a better understanding of the meanings that individuals assign to CSE [32,33] and the impact they believe those experiences have on their lives, particularly later substance use, mental health, and sexual behavior. As discussed above, much of the research on sexual abuse among MSM has been quantitative. Moreover, although several of these studies included sizable samples of black and Latino men [9,20,21,29,35,54], most included small percentages of MSMW.

Few studies have explored CSE with MSMW beyond quantitative assessment [10,32,37,50,52,55]. The findings from these qualitative studies are promising, suggesting that men perceive connections between abuse and their current same-sex behavior [32,37,50,52], including high-risk exploration of their sexuality [37], that abusive experiences may result in negative mental health consequences and coping strategies [10,32,50], and that being coerced into same-sex encounters by older men led to intense internal debate about their sexual identity and coming to terms with the combined pain and pleasure they derived from these experiences [55]. Nevertheless, these studies are limited; they had small sample sizes (Ns=13-33), some of which focused exclusively on black men, the original study aims were broader than childhood sexual experiences, and/or only a few included in-depth interviews. Therefore, it is critical to further explore through in-depth interviews how black and Latino MSM and MSMW perceive connections between their formative sexual experiences, cultural attitudes and masculinity norms, same-sex and opposite-sex attractions, and adult health and risk behavior. This study will also be critical in addressing shame, internalized homophobia, and fear of provider insensitivity, all of which may impact the disclosure of CSE (and potential detection of CSA by competent providers) and same-sex behavior and can reduce men's willingness to seek substance abuse treatment and other health services [56-59].

Service Provider Perspectives

Service providers, including substance use counselors and HIV outreach workers, may not be adequately prepared to recognize or safely address CSA with male clients. Male survivors of CSA, often overlooked as health care consumers, have unique clinical and psychological needs that warrant critical scientific inquiry [60]. Knowing that CSA history among gay and bisexual men is associated with negative outcomes (eg, revictimization, substance use, mental health, high-risk sexual behavior), researchers have called for interventions to incorporate CSA history into health services used by these men [2,29,37,50,56,61]. Recent evidence suggests that doing so can achieve reductions in psychological symptoms and sexual risk taking [62]. Yet, there is reason to believe that black and Latino MSM/W may be reluctant to access health services and substance abuse treatment due to fears of being stigmatized, potential exposure of their same-sex behavior, general provider mistrust, and perceptions that providers lack training in sexuality [56,63,57,64]. Furthermore, service providers may not be equipped to recognize the need for safe trauma-informed care, particularly as it relates to sexual abuse [65-70]. Currently, the inclusion of CSA in treatment and health-related service settings is nonexistent or hindered by assessments that use language assuming an experience is appraised as abusive, inadequate provider training, or lack of provider preparedness [65-70] that potentially places clients at risk of retraumatization. Thus, we need to understand attitudes and expectations of the providers and their potential clients regarding the inclusion of sexual histories in treatment and other health care settings, and how this should be done. We also need to account for the perceived level of preparedness among providers to address issues of abuse and sexuality among racial and ethnic minority men.

Study Objective and Aims

To our knowledge, very few studies focus specifically on understanding formative sexual histories, particularly those experiences occurring before the age of 16 years (ie, CSE), of black and Latino MSM and MSMW. We are conducting mixed-methods interviews with 80 black and Latino men (40 MSM and 40 MSMW) in New York City (NYC), exploring appraisals of their formative sexual experiences, including those described as consensual but meeting criteria for abuse (Multimedia Appendix 1). We are also interviewing 30 local service providers representing substance abuse treatment, mental health care, and HIV/sexually transmitted infection (STI) prevention and outreach.

To address the need for better recognition of CSA at multiple levels, we will do the following: (1) investigate appraisals of CSE among black and Latino MSM and MSMW and evaluate these experiences using established criteria for defining sexual abuse; (2) examine appraisals of CSE relative to sexual identity formation, adult sexual relationships and behaviors, concealment of same-sex behavior, alcohol and drug use, psychological and emotional functioning, and cultural ideologies of masculinity among black and Latino MSM and MSMW; and (3) examine perspectives of black and Latino MSM and MSMW and relevant service providers to understand the role of, and the need to include, sexual history in treatment and counseling settings and to determine service providers' preparedness to address CSE in treatment and counseling settings.

Methods

Intersectionality Framework

This study employs an intersectionality framework to examine appraisal and interpretation of CSE. Multiple social identities (eg, race, ethnicity, gender, sexual orientation) "intersect at the micro level of individual experience to reflect interlocking systems of privilege and oppression at the macro level" [71-73]. This framework holds that no one social identity is more important than others, and is ideally suited to qualitative or mixed-methods research as it is not intended to predict behaviors, health, or mental processes. It was included as a conceptual perspective for advancing lesbian, gay, bisexual, and transgender (LGBT) research in the Institute of Medicine Committee on LGBT Health report [74].

Through an intersectionality lens, and relying on an indirect approach to assessing CSE, this study will use mixed methods to consider how current appraisals of first sexual experiences are shaped by intersecting social identities (Multimedia Appendix 2). These include gender and perceptions of masculinity, black or Hispanic racial or ethnic identification, level of cultural estrangement, and sexual orientation. Measuring cultural estrangement and masculinity norms will help to specify racial and ethnic identity factors that may have particular salience for men's appraisals of their CSE. Examining these factors using mixed methods permits data triangulation, enabling us to assess their reliability and validity. We further conceptualize that one's appraisal of a childhood sexual encounter (or multiple encounters), together with these social identities, influences adult sexual relationships (including disclosure or concealment of same-sex behaviors), current and past use of alcohol or drugs, current psychological distress and emotional functioning, and whether or not an individual perceives a need for (or has attempted to access) substance use, mental health, or other health services. As has been suggested [75], attention will be paid to within- and between-group differences and similarities.

Study Overview

This cross-sectional study will include in-person interviews with 80 black and Latino men (40 MSM and 40 MSMW) with a history of CSE, and interviews with 30 service providers about their preparedness to address issues of abuse with clients.

Interviews With Black and Latino MSM and MSMW in New York City (NYC)

Inclusion Criteria

Participants of any HIV status must: (a) be biologically male and identify himself as male; (b) be 18-50 years of age; (c) be black non-Hispanic or Hispanic/Latino; (d) have had sex with a man within the past 12 months; (e) have had at least one sexual experience before age 16 with a man or woman who was at least 18 years of age at the time; (f) be fluent in English; and (g) live in the NYC area.

Sampling Quotas

The study team will recruit a minimum of 30 men (38%) with a history of CSE with older female partners. This quota falls between estimates from our work with black MSMW (24% CSA by a female partner) [32] and those reported in 2 prior studies (CSA range 42%-47%) [9,35]. Furthermore, we will recruit 40 participants (20 black, 20 Latino) who have had sex with a woman (ie, MSMW) within the past 12 months. Finally, we will oversample by 5 to allow for incomplete interviews and/or unusable data.

Recruitment Strategy

We employ multiple recruitment methods (ie, internet advertising, community-based organizations) based on our experience in working with stigmatized populations [49,76-78]. Recruitment materials indicate that we are conducting a study on the sexual history of black and Latino men and their relationships with men and women, and that participants are compensated. Interested men are directed to the study website for more information and to be screened for eligibility. The research team has successfully used these methods in past research with MSM and MSMW [49,76,79-81].

Internet Advertising

The research team is utilizing social (eg, Facebook) and sexual networking websites to recruit participants who may or may not openly identify as having sex with men. Advertisements target users in our study population. Facebook has been used to recruit MSM [80,82] and young adults with a history of child maltreatment [83] for internet surveys. The research team purchased an email blast targeting local users of a sexual networking website for black and Hispanic MSM. We also intend to advertise through mental health services websites that provide support to men with a history of unwanted or abusive sexual experiences in childhood.

Community-Based Organizations

We are using relationships with local organizations to generate participant referrals [49] by posting or distributing recruitment materials and providing in-service presentations to staff members and clients. These organizations provide diverse services such as substance abuse, counseling and treatment, mental health services, medical care, and HIV/STI testing.

Screening Procedures

We screen for eligibility via a brief internet and mobile survey (Table 1). The study team has conducted numerous internet and mobile surveys in past research with MSM [79,80,84,85] and substance-using populations [86,87]. Eligible men interested in participating are asked to provide contact information (ie, email, phone) so that study staff can schedule an in-person interview.

Interview Meeting

After providing informed consent, participants complete a short interviewer-administered questionnaire to verify information collected during screening (ie, history of CSE, sociodemographics). Participants also complete a short series of survey measures to assess sexual orientation, concealment of same-sex behavior, HIV and STI testing history, substance use, psychological distress, suicidality, post-traumatic stress symptoms, cultural estrangement, masculinity, and history of intimate partner violence (estimated time is 25 min), see Table 1). The remainder of the meeting (estimated time is 1 h 35 min) is used to conduct the audio-recorded qualitative interview. Participants receive US $50 in compensation plus reimbursement for transportation costs.

Qualitative Interviews

We conduct semi-structured (focused) interviews [100] using a nondirective approach, whereby the interview trajectory is largely determined by participants. This provides them with an opportunity to explore their formative sexual experiences relative to matters of personal significance with the interviewer remaining attentive to issues of sexual identity and orientation, adult sexual relationships, identification with masculinity norms, substance use, emotional functioning, and concealment of same-sex behavior. We use an interview guide (Multimedia Appendix 3) that reflects a preliminary framework of factors expected to be important in understanding appraisal of CSE. As data are collected and the Principal Investigators (PIs) conduct initial analyses, elements of the guide may require revision and any important issues that emerge will be added. Interviewer training focused on skills for putting participants at ease, remaining neutral, establishing rapport, and eliciting rich data using an interview guide. Throughout data collection, the PIs will review randomly selected interviews to monitor their quality. The PIs also conduct regular debriefing sessions with the interviewers to review field notes and discuss concerns or unanticipated issues. This gives interviewers an opportunity for catharsis and allows for a preliminary examination of study aims within the context of each interview. Regular interaction of the PIs with the data and with field staff also serves as a verification step to ensure reliability and validity of the data [101].

Indirect Approach to Assessing Childhood Sexual Experiences

Researchers have called for more in-depth exploration of CSE among MSM and MSMW [29,32,37,50], with particular emphasis on how men perceive these experiences (eg, unwanted, consensual) [32]. Knowing that cognitive appraisal and interpretation of sexual abuse is associated with adjustment and coping strategies [29,39,102,103], it is critical that men be able to reflect on their experiences in their own terms. A major strength of this study is that it will differentiate experiences that men appraise as being abusive from those appraised as being consensual but meeting criteria for sexual abuse. We know from past research that this process allows for emerging connections among CSE, adult sexual relationships, and substance use behavior that may not be revealed in a quantitative assessment reliant on preimposed CSA definitions [32].

This is not to deny the value in definitions of CSA generated by quantitative research. On the contrary, a framework of agreed-upon variables to reinterpret men's narratives of their experiences enables investigators to detect discrepancies that can be further addressed.

Table 1. Screening and interview measures (M).

M #	Phase	Measure
1a-1j	S[a]	Sociodemographics: (1a) sex at birth, (1b) gender identity and expression, (1c) age, (1d) ethnicity (Hispanic or non-Hispanic), (1e) race, (1f) income, (1g) education, (1h) religion and spirituality, (1i) housing, (1j) reside in NYC
2	I[b]	Klein Sexual Orientation Grid [88]: 21 items to assess past, present, and ideal sexual attraction, behavior, and fantasies; emotional, social, and lifestyle preferences; and self-identification
3a,b	S	Sexual partners: (3a) relationship status, (3b) gender of sexual partners in the past 12 months
3c	I	Sexual behavior in the past 6 months
4	I	Concealment of same-sex behavior: 7-item modified version [76] of the Self-concealment Scale [89]
5	I	HIV and sexually transmitted infection testing history: ever tested, when was the most recent test, results of most recent test
6a-6d	S, I	Childhood sexual experiences [32]: (6a) age at first sexual experience with a female (if applicable), (6b) age at first sexual experience with a male, (6c) age of female partner, (6d) age of male partner
7	I	Recent substance use [90,91]: 21 items to assess recent alcohol use, drug use, and related problems
8	I	Addiction Severity Index lite version [92]: Two items to assess substance use history
9	I	Mental Health Inventory[93]: 18-item measure to assess symptoms of psychological distress
10	I	Suicidality [94]: Single item to assess if participant ever seriously considered or tried to commit suicide
11	I	Post-traumatic stress symptoms [95]: 6-item screening tool
12	I	Cultural estrangement [96]: 4-item scale to assess perceived differences between one's ideas or opinions and those of individuals in one's primary and secondary groups
13	I	Male Role Norms Inventory-Short Form [97]: 21-item measure of traditional masculinity ideology
14	I	Intimate partner violence (IPV) [15]: three items to assess past year IPV and perpetrator
15	I	Resilience [98,99]: 2-item modified version of resilience
16	S	Provider interactions: Six items to assess perceptions of service in health care settings

[a]S implies administered as part of study screening.

[b]I implies administered as part of study interview.

Our approach: (1) allows men to discuss formative sexual experiences occurring before age 16 without imposing terminology that is commonly associated with abuse; (2) allows men to discuss why they appraise these experiences as abusive or consensual; and (3) allows researchers to systematically (re)appraise certain experiences as abusive based on details provided by the participant (ie, age differential, evidence of coercion, penetration) without influencing the narrative [32,34]. This strategy can be particularly useful for providers working with stigmatized populations, including black and Latino MSM/W who may be motivated by normative heterocentric pressures from within their respective communities to conceal abusive same-sex experiences. Indirect questioning has been used to elicit more accurate responses in screening for substance abuse [104], HIV risk [105], and intimate partner violence [106].

Interviews With Service Providers

For Aim 3, we are interviewing 30 NYC-based service providers (concurrently with the MSM and MSMW interviews) recruited through provider training networks and local organizations that specialize in substance abuse treatment, HIV prevention and counseling services, and mental health and other health-related services. Interviews are audio-recorded and take approximately 1.5 hours; providers receive $30 compensation. We begin with a few structured questions (eg, time in the profession, educational background, types of services offered to MSM and MSMW, courses and training in sexual education and crisis counseling); estimated time is 15 min. The remainder of the meeting focuses on perceived preparedness to incorporate sexual history and issues of sexuality into treatment or counseling and issues of trauma-informed care, including whether and how providers screen for CSA and what they do with this information as they learn it from clients. We present vignettes (of hypothetical clients) derived from previous research [32] to ascertain whether and how providers recognize potentially abusive sexual experiences. Follow-up (probing) questions ask how the provider would proceed with each client presented in the vignettes. We have also modified several topics from the interview guide used with black and Latino MSM/W (IG12-IG15) to examine provider perspectives on the need to incorporate sexual history (and how) in treatment and other counseling settings.

Data Analysis and Interpretation

Qualitative Analysis

Interviews with black and Latino MSM/W will be transcribed before coding and thematic analysis [107,108]. The investigators will extract and examine interview text as it relates to the study aims. Using qualitative data analysis software (ATLAS.ti v. 8.0), the study team will be able to search for and extract text by combining codes: for example, "Appraisal of CSE with Male" AND "Concealment of Same-Sex Behavior." In this example, retrieved segments of text will show only those interview sections where men discuss their appraisal of CSE

with an older male partner and whether/how they conceal same-sex encounters. This process will be replicated throughout the analysis to examine each of the aims. The investigators will evaluate participant appraisals [32] of their CSE using established criteria for sexual abuse (*Aim 1*) [12,35,50]. The following will be coded for each of the narratives and validated with study measures: participant's age at the time of his experience(s); age of sexual partner(s); and the nature of the relationship or encounter (eg, power differential, evidence of coercion). Whenever possible, we will consult information regarding age of consent laws to further determine whether descriptions of sexual experiences are consistent with those of abuse. Furthermore, this process will allow us to consider how the intersection of social identities may influence appraisals of CSE (*Aim 2*)—for example, current relationships with women (IG8), identification with masculinity norms (IG7), and CSE with an older female (IG3).

Analysis of Service Provider Interviews (Aim 3)

Interviews with service providers will be transcribed and coded before analysis. We will analyze and integrate provider data in several ways. First, using data from both providers and MSM/W, we will compare perceptions of the need to incorporate sexual history into treatment and counseling settings. We will also examine acceptable intervention formats with sexual abuse issues from the perspectives of potential clients and providers (IG13-IG15). Second, provider responses to vignettes will reveal patterns in perceived abuse and preliminary findings as to the acceptability of using an indirect approach to assessing CSE (and ultimately, abuse). Third, using provider accounts of their experiences with client sexual histories, in conjunction with how they respond to the vignettes, we will derive a preliminary assessment of the level of preparedness to address issues of abuse and sexuality in diverse treatment and counseling settings.

Quantitative Analysis (Aims 1 and 2)

The study aims will be primarily addressed through qualitative analyses. However, the proposed sample (N=80 black and Latino MSM and MSMW) will allow for some supplemental quantitative analyses [109]. Validity of self-reported data will be assessed by comparing eligibility survey information, survey measures administered during the interview meeting (see Table 1), and the qualitative interview [110]. For statistical analyses, we will use the conventional alpha level (.05). For Aims 1 and 2, we will run all frequencies to describe sample characteristics (eg, age, sexual orientation, HIV status) and conduct chi-square or analysis of variance tests to compare key characteristics (eg, differences [racial/ethnic, sexual orientation, concealment of same-sex behavior, perpetrator gender, and perpetrator age] between men who perceive their experiences as abusive versus those who do not). We will also examine potential differences between those participants who described consensual experiences that met conditions for CSA and those who reported abusive experiences.

Appraisals of CSE are a critical outcome of the proposed study. Power calculations for this outcome (example below) are based on estimates from our previous study with nongay-identified MSMW [32]. In that study, 27.5% of men reporting a sexual experience during childhood perceived it as abusive. Estimated power for a two-sample paired proportions test is based on the following: proportion of experiences appraised as abusive by the participant and proportion of experiences (re)appraised as abusive by the study investigators. Assuming an alpha of .05 and a conservative change (increase) of 30% in abuse appraisals [32], the proposed sample sizes (N=80; n=40 per subgroup [MSM, MSMW; black, Latino]) have sufficient power (>.90) to detect a difference.

Data Integration

We will employ "Best Practices" for mixed methods research [111] to integrate quantitative and qualitative data. Quantitative data will be used to identify subgroups to compare emergent qualitative themes. For example, cases of problematic substance use will be identified before reviewing the qualitative data pertaining to IG9 (coping with CSE) and IG10 (alcohol or drug initiation). Quantitative and qualitative data will be used to assess multiple social identities expected to influence appraisal (Multimedia Appendix 2). Thus, we will be able to examine, for example, how black MSM who identify themselves as gay understand their CSE with an older male compared with heterosexually-identified black MSMW who actively conceal same-sex behavior. We will also analyze potential cultural similarities in CSE appraisal and interpretation—for example, Latino and black MSMW with low levels of cultural estrangement and high identification with traditional masculine norms. Attention will be paid to similarity and diversity within and between groups throughout the analysis [75]. Finally, employing both qualitative and quantitative analyses can enhance the validity of study findings [110,111].

Results

The study received Institutional Review Board approval and was launched in May 2017. Data collection is underway and results are forthcoming.

Discussion

Limitations

We recognize that this formative study will not have sufficient resources to recruit a truly representative sample. For example, nonspeakers of English will not be included. Moreover, recruitment methods favor those with internet access, but this may be somewhat offset by recruitment from community-based organizations. Much of the data will be retrospective and despite measures that we have incorporated to minimize recall bias, the possibility remains that some accounts may suffer from memory suppression.

Practical Significance

Findings will inform an R01 proposal to develop and test an alternative CSA instrument accompanied by a training curriculum for use in health services and research settings. Specifically, data from black and Latino MSM/W will be translated into a preliminary set of testable questions to indirectly detect sexual abuse perpetrated against male participants or clients. Study findings from service providers will offer insight into how qualitative assessments of sexual

history can be used in conjunction with substance use measures and mental health screenings to better understand the impact of abuse; inform strategies to improve linkage to care; elucidate the degree of acceptability, preparedness, and potential discomfort among service providers in taking childhood sexual histories; and inform training in the use of this alternative instrument.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

NIH summary statement (peer-review report).

[PDF File (Adobe PDF File), 172KB - resprot_v7i2e62_app1.pdf]

Multimedia Appendix 2

Intersecting social identities and their influence on CSE appraisal and interpretation.

[PDF File (Adobe PDF File), 161KB - resprot_v7i2e62_app2.pdf]

Multimedia Appendix 3

Qualitative interview guide topics.

[PDF File (Adobe PDF File), 84KB - resprot_v7i2e62_app3.pdf]

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Abbreviations

ASI: Addiction Severity Index
CSA: childhood sexual abuse
CSE: childhood sexual experience
IPV: intimate partner violence
LGBT: lesbian, gay, bisexual, and transgender
MSM: men who have sex with men
MSMW: men who have sex with men and women
NYC: New York City
STI: sexually transmitted infection

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