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Protocol

Telerehabilitation Versus Traditional Care Following Total Hip Replacement: A Randomized Controlled Trial Protocol

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Abstract

Background: Total hip replacement (THR) is the gold standard treatment for severe hip osteoarthritis. Effectiveness of physical rehabilitation for THR patients following discharge from hospital is supported by evidence; however, barriers such as geographical location and transport can limit access to appropriate health care. One solution to this issue is using an alternative model of care using telerehabilitation technology to deliver rehabilitation programs directly into patients' homes. A telerehabilitation model may also have potential health care cost savings for health care providers.

Objective: This study aims to determine if a telerehabilitation model of care delivered remotely is as effective as face-to-face rehabilitation in the THR population and cost effective for health care providers and patients.

Methods: A total of 70 people undergoing THR will be recruited to participate in a randomized, single-blind, controlled noninferiority clinical trial. The trial will compare a technology-based THR rehabilitation program to in-person care. On discharge from hospital, participants randomized to the in-person group will receive usual care, defined as a paper home exercise program (HEP) targeting strengthening exercises for quadriceps, hip abductors, extensors, and flexors; they will be advised to perform their HEP 3 times per day. At 2, 4, and 6 weeks postoperatively, they will receive a 30-minute in-person physiotherapy session with a focus on gait retraining and reviewing and progressing their HEP. The telerehabilitation protocol will involve a program similar in content to the in-person rehabilitation program, except delivery will be directly into the homes of the participants via telerehabilitation technology on an iPad. Outcomes will be evaluated preoperatively, day of discharge from in-patient physiotherapy, 6 weeks and 6 months postoperatively. The primary outcome will be the quality of life subscale of the hip disability and osteoarthritis outcome score, measured at 6 weeks. Both intention-to-treat and per-protocol analyses as recommended in the extension of the Consolidated Standards for Reporting Trials (CONSORT) guideline for noninferiority trials will be performed.

Results: Recruitment commenced in September 2015 and is expected to be completed by June 2017. Data collection will be completed by December 2017. It is anticipated the results from this trial will be published by July 2018.

Conclusions: Previous research investigating telerehabilitation in postoperative orthopedic conditions has yielded promising results. If shown to be as effective as in-person care, telerehabilitation after THR could be helpful in addressing access issues in this population. Furthermore, it may help reduce the cost of health care provision by enabling patients to take a more independent approach to their rehabilitation.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12615000824561; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=364010 (Archived by WebCite at http://www.webcitation.org/6oWXweVfI)

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KEYWORDS

total hip replacement; total hip arthroplasty; telerehabilitation; telehealth; physiotherapy; physical therapy; rehabilitation

Introduction

Total hip replacement (THR) is the gold standard treatment for severe hip osteoarthritis. A rising trend has seen an increase of approximately 40% in procedures over the last decade, with over 40,000 and 85,000 THRs being performed in Australia and the United Kingdom, respectively, in 2014 [1,2]. This trend is even more pronounced in the United States where the number of THRs performed in patients aged 45 years and over rose from 138,700 in 2000 to 310,800 in 2010 [3]. Optimizing acute postoperative care for THR patients through enhanced and rapid recovery programs has been effective [4-9]. Such programs include preoperative consultation, multimodal analgesia, and early physiotherapy intervention and can decrease length of stay and improve patient outcomes.

Optimal care beyond discharge from hospital remains unknown. Effectiveness of physical rehabilitation for THR patients following discharge from hospital is supported by evidence [10-14]; however, the quality of existing trials prevents robust conclusions on the optimal content of rehabilitation programs. Recommendations regarding content include arm ergometer interval exercise [10], aerobic type dance routines [15], various strength and range of motion (ROM) exercises with and without resistance [11-13,16,17], and walking programs [13,17]. Existing literature also varies with respect to the quantity, timing to commencement, and frequency of physiotherapy rehabilitation [10-13,15-23]. Frequency ranges from twice daily [21] to twice weekly [15], and timing to commencement from immediately following hospital discharge [11] to greater than 6 months after [15,21]. This variability presents difficulties in determining usual physiotherapy care for THR patients after discharge from hospital.

We conducted a national survey of Australian physiotherapists to establish usual physiotherapy care for THR patients following discharge from hospital in Australia. Of 151 physiotherapists representing both public and private facilities and metropolitan and rural areas, 116 (76.8%) responded to the questionnaire. Usual care programs for physiotherapy in Australia consist of 1 to 5 sessions of physiotherapy commencing within 2 weeks of hospital discharge and lasting 4 to 8 weeks. Commonly, physiotherapy sessions included strengthening of hip abductors and extensors and hip and knee flexors; education on hip precautions and exercise progression; gait retraining; stairs practice; and ROM exercises for hip abduction, extension, and flexion. Physiotherapy sessions are complemented by a home exercise program (HEP).

One alternative model of care is the use of telerehabilitation technology to deliver rehabilitation programs directly into patients' homes. This has the potential benefit of addressing access issues for patients living in rural and remote areas and patients living in urban areas with transport difficulties. Many THR patients find it difficult to access health care once discharged from hospital. The elderly demographic coupled with the risk of THR dislocation postoperatively can make driving and transportation difficult [24]. Access to rehabilitation programs is compounded with the financial cost to the patient [25] and health systems to provide domiciliary services in conjunction with or in lieu of center-based care. For patients living outside urban areas, access issues become magnified due to traveling distances and time for either the patient or treating clinician [26,27]. The use of technology-mediated HEPs may also encourage patients to exercise more frequently, potentially addressing strength deficits documented in the literature in THR patients postoperatively [28]. In addition to addressing access issues, there are potential savings in the cost of health care provision.

Previous research investigating telerehabilitation in postoperative orthopedic conditions has yielded promising results. The majority of research in this area has been focused on the total knee replacement (TKR) population. Multiple randomized controlled trials have compared telerehabilitation programs to conventional programs for postoperative rehabilitation in TKR patients [29-31]. Russell et al [29], Tousignant et al [30], and Piqueras et al [31] all demonstrated the efficacy of telerehabilitation programs compared to in-person programs in the TKR population. In addition to achieving comparable outcomes to conventional rehabilitation, patients participating in telerehabilitation reported high levels of satisfaction with their program [32,33].

This study aims to determine if delivery of usual physiotherapy care via telerehabilitation is as effective as in-person usual physiotherapy care in the THR population and cost effective for health care providers and patients.

Methods

Experimental Design

A randomized, single-blinded, controlled noninferiority clinical trial [34] will be conducted comparing a technology-based THR rehabilitation program to in-person care. The trial protocol has been developed conforming to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.

Ethical approval was obtained from the Metro South Human Research Ethics Committee (HREC No. HREC/14/QPAH/628) and University of Queensland Medical Research Ethics Committee.

Participants

All patients undergoing primary THR at Queen Elizabeth II (QEII) Jubilee Hospital, Brisbane, Australia, will be approached by a physiotherapist for consent to participate in the study. Consenting patients will have preoperative outcome measures collected. Patients will formally enter the study and be randomized to a group following their operation providing they satisfy the following inclusion and exclusion criteria.

Participants will be eligible for inclusion if they are undergoing primary elective THR, can attend 5 in-person appointments (outcome measure assessment preoperatively, physiotherapy

rehabilitation sessions at weeks 2, 4, and 6 postoperatively, and a final outcome measure assessment at 6 months postoperatively), and are able to independently provide signed informed consent.

Participants will be excluded if they have comorbidities preventing participation in rehabilitation (eg, severe obstructive pulmonary disease, hemiplegia following stroke), are undergoing revision THR, experience intraoperative complications that prevent participation in the Queensland Health THR clinical pathway, or are unable to mobilize full weight-bearing in a bipedal manner with or without a walking aid.

Sample size calculations were conducted based on existing data for the subscales of the Hip disability and Osteoarthritis Outcome Score (HOOS) [35]. Required data was available for the pain, symptoms, and quality of life (QOL) subscales. Sample size was calculated using the noninferiority power calculation described by Jones [36] and shown in Figure 1.

Three separate calculations were undertaken for each of the pain, symptoms, and QOL subscales. In the absence of existing delta values from comparable studies, the minimal clinically important improvement (MCII) values determined by Paulsen [37] were applied as our noninferiority delta margin (QOL 17, pain 24, symptoms 23). We argue that if the difference between the groups is less than what has been established as the minimum improvement that matters clinically, we are willing to accept the new intervention as equivalent. Standard deviation values were taken from Duivenvoorden [38], who applied the HOOS to a THR population and reported the standard deviation of the change in HOOS pain, symptoms, and QOL scores from preoperatively to 12 months postoperative (QOL 26.3, pain 22.8, symptoms 14.9). Calculations were based on 80% power and an alpha value of .05. QOL values yielded the largest sample size of 30 per group. Symptoms and pain produced sample sizes of 6 and 12, respectively. Accounting for a 15% dropout rate, a sample size of 35 participants per group equating to a total of 70 participants will be recruited.

Figure 1. Sample size formula.

$$n = 2\left(\frac{SD^2}{delta^2}\right)\left(Z_{(1-alpha)} + Z_{(1-beta)}\right)^2$$

Randomization

Randomization will be performed using a computer random numbers generator to allocate participants to either the in-person (control) group or the telerehabilitation (intervention) group. Randomization will be restricted by a permuted block design of size 4 which will be generated by an independent administrative officer. Randomization codes will be sealed in sequentially numbered opaque envelopes that will be assigned to participants in their order of recruitment by an independent administrative officer.

Interventions

Interventions will be performed by registered physiotherapists employed by the QEII Jubilee Hospital, Brisbane, Australia. All physiotherapists performing interventions will receive training in the delivery of a standardized exercise program that participants will commence on discharge from hospital. The program will be progressed by the treating physiotherapist based on their assessment and participant progression throughout the 6-week intervention period.

On discharge from hospital, participants randomized to the in-person group will receive usual care, defined as a standardized paper HEP targeting strengthening exercises for quadriceps, hip abductors, extensors, and flexors; they will be advised to perform their HEP 3 times per day and provided with an exercise diary to record exercise compliance. At 2, 4, and 6 weeks postoperatively they will attend QEII Jubilee Hospital physiotherapy outpatient department for a 30-minute in-person physiotherapy session with a focus on gait retraining and reviewing and progressing their HEP.

The telerehabilitation protocol will involve a program similar in content to the in-person rehabilitation program, except delivery will be directly into the homes of the participants via telerehabilitation technology on an Apple iPad. Two apps will be used to deliver this program. Participant's standardized HEPs will be facilitated using the Wellpepper clinic (Wellpepper Inc, Seattle, WA) app. Wellpepper is an app enabling health care professionals to create exercise programs that patients can follow on a tablet device. The app will provide notifications to complete the exercises and prerecorded videos and instructions of their exercises and enables the patient to record pain levels and difficulty at the conclusion of the exercise. Patients can contact their health care provider through a messaging system built in to the app. The health care professional has a clinic version of Wellpepper installed on an iPad that enables them to review and adjust exercises and communicate with all patients under their care. Real-time video-based physiotherapy consultations will be conducted with the patient via the eHAB app (NeoRehab, Brisbane, Australia). eHAB is a clinically validated telerehabilitation system that allows clinicians to provide services to their patients via real-time videoconferencing into the home.

On discharge from hospital, participants randomized to the telerehabilitation group will be provided an iPad with Wellpepper and eHAB installed. They will undergo training in the use of both apps. All iPads will be enabled with prepaid mobile data.

Participants allocated to the telerehabilitation arm of the trial will receive 3 notifications per day via the Wellpepper app reminding them to perform their exercise program. At the conclusion of each exercise they will be prompted by the app to record pain and difficulty levels experienced during the exercise. Once recorded, this information becomes available to the physiotherapist. The physiotherapist will review the Wellpepper clinic app weekly to review participant's progress, adjust exercises as required, and respond to any communication via the messaging system. Patients who have not accessed the app and recorded exercises in Wellpepper will be contacted via telephone to discuss their progress. At 2 weeks following hospital discharge, participants will receive a physiotherapy session via real-time videoconferencing using the eHAB app. This session will enable analysis and advice regarding gait retraining and exercise progression. Following this session,

participants will continue to use the Wellpepper app to facilitate their rehabilitation until 6 weeks postoperatively. Telerehabilitation participants may receive additional eHAB appointments following their 2-week review if deemed appropriate by the physiotherapist.

Participants from both groups will have outcome measures collected in an in-person assessment at 6 weeks postoperatively. If at this session it is deemed they require further physiotherapy input, they will be booked for an in-person physiotherapy session. The requirement of further physiotherapy will be based on the outcome measures collected by the blinded assessor. The main determinant of additional physiotherapy will be reliance on a walking aid during the timed Up and Go test when participants had mobilized unaided preoperatively. Participants will be instructed not to advise the assessor which group they were randomized to or ask clinical questions of the assessor. Likewise, the assessors will not seek this information from the participant.

Outcome Assessment

Outcome measures will be collected at 4 time points: preoperatively, day of discharge from in-patient physiotherapy, and 6 weeks and 6 months postoperatively. Following the final physiotherapy session of the 6-week intervention period, 6-week assessments will be conducted. Not all outcome measures will be collected at each time point (Table 1). All assessors will receive training in standardized methods of collecting outcomes. Assessors will conduct blinded assessments of participants from both groups to minimize any assessor effects.

Table 1. Summary of outcome measures per time point.

Outcome measure	Time point collected				
	Preoperatively	Discharge from physiotherapy	6 weeks in-person	6 weeks telerehabilitation	6 months
HOOS[a]	x		x	x	x
SF-12[b]	x		x	x	x
EQ-5D-5L[c]	x	x	x	x	x
System usability scale				x	
Patient satisfaction questionnaire			x	x	
Technology preferences	x			x	
Timed Up and Go	x	x	x	x	x
Muscle strength	x		x	x	x
Step test	x		x	x	x
HEP[d] compliance			x	x	

[a]HOOS: Hip disability and Osteoarthritis Outcome Score.

[b]SF-12: Short Form-12.

[c]EQ-5D-5L: EuroQol 5 dimensions questionnaire.

[d]HEP: home exercise program.

The primary outcome will be the QOL subscale of the HOOS, measured at 6 weeks. The HOOS is a self-administered questionnaire that assesses participants' opinion about their hip and associated problems and evaluates symptoms and functional limitations related to the hip during a therapeutic process [35]. The HOOS consists of 5 subscales; pain, other symptoms, function in daily living, function in sport and recreation, and hip-related QOL. The last week is taken into consideration when answering the questions. Standardized answer options are given (5 Likert boxes), and each question receives a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. The HOOS has established content validity in a THR population and has high test-retest reproducibility (intraclass correlation coefficient >0.78) [35,39]. Secondary outcome measures include the following series of questionnaires and physical outcomes.

Questionnaires

The Short Form-12 (SF-12) is a multipurpose, short-form health survey with 12 questions that measures functional health and well-being from the patient's point of view. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group [40].

The EuroQol 5 dimension 5 level questionnaire (EQ-5D-5L) is a standardized instrument for use as a measure of health outcome. Participants answer questions regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems [41].

Participants will complete a satisfaction questionnaire pertaining to the rehabilitation program they received. This questionnaire is based off the validated health care satisfaction questionnaire developed by Gagnon et al [42].

Participants will complete a self-report questionnaire pertaining to their preferences, access to, and use of technology.

Physical Outcomes

The timed Up and Go test is a reliable and valid test for quantifying functional mobility and can also be used to follow clinical change over time. The participant rises from an arm chair, walks 3 meters, turns, walks back and sits down again [43].

Hip strength (flexion, extension, abduction, adduction, internal rotation, and external rotation) and knee strength (extension) will be measured (kgs) using a Lafayette 01165 manual muscle tester. All persons performing manual muscle testing will be trained using standardized methods for each muscle group.

The step test involves stepping one foot on, then off, a block as quickly as possible in a set time period. It was originally developed to assess dynamic standing balance in stroke patients [44]. Subsequent studies have proven it a reliable balance outcome measure in both the hip osteoarthritis and postsurgical hip fracture populations [45,46].

Other Outcomes

The system usability scale is a reliable tool for measuring the usability of a system. Participants are asked to score 10 items with 1 of 5 responses ranging from Strongly Agree to Strongly Disagree. Only participants assigned to the telerehabilitation group will complete the system usability scale [47].

HEP compliance will be collected during the period from hospital discharge to 6 weeks postoperatively. The telerehabilitation group will have this information automatically collected via the Wellpepper app. Participants from the in-person group will be provided with a paper-based exercise diary to complete.

Blinding

Participants and treating physiotherapists will not be blinded to the allocation. The physiotherapists assessing outcomes at each time point will be blinded. Multiple physiotherapists will be trained in performing outcome assessments to enable compliance with blinding. Physiotherapists who have provided rehabilitation to a participant in either group will not be involved in the outcome assessment of that patient.

Economic Outcomes

Data will be collected at 4 time points to enable analysis of both patient and health care provider costs: 2 weeks, 4 weeks, 6 weeks, and 6 months postoperatively.

Data relating to patient-associated costs will include time per physiotherapy appointment including travel and associated carer time, cost of travel to and from appointments using distance traveled and per kilometer values provided by the Australian taxation office for private vehicle use or patient-reported public transport and taxi fares if not using a private vehicle, gap fees associated with health care visits related to their hip surgery, and cost of time off work related to their hip surgery using the median Australian wage.

Data relating to health care provider costs will include cost per appointment using standardized government charges for in-person physiotherapy appointments, clinician time multiplied by hourly pay rate for telerehabilitation appointments and time spent monitoring the telerehabilitation system, cost of THR-related health care visits using standardized government charges, and cost of software subscriptions to Wellpepper Inc and eHAB.

Data Management and Monitoring

Data will be collected directly from participants via paper questionnaires and forms. These will be stored in a locked cabinet within the physiotherapy department at QEII Jubilee Hospital. Data from paper forms will be periodically entered into an electronic spreadsheet in a reidentifiable form. Electronic files will be password protected and stored in secured databases for access by research members only. Information will be kept in a reidentifiable format during data collection. This will enable reviewing of data as required to ensure complete and accurate data sets. On completion of data collection, all information will be converted to a nonidentifiable format.

There will be no external data and safety monitoring board. Data and safety monitoring will be the responsibility of the principal and associate investigators.

Harms

Participation in this trial will not entail additional risks beyond those associated with standard care. If any adverse events (ie, THR dislocation, deep vein thrombosis) are identified, participants will be advised to attend the emergency department as per usual management of THR patients. Participants will be asked regarding adverse events at each physiotherapy session and outcome assessment. Any adverse events identified by treating physiotherapists or outcome assessors during the 6-month trial period will be reported to the primary investigator. Details of these events will be documented in a logbook. Adverse events will be reviewed on completion of the trial to investigate any trends. Additionally, any participant who is unable to attend a physiotherapy session or outcome assessment appointment will have the reason for being unable to attend recorded.

Statistical Analysis

All missing data within surveys will be managed as per developer guidelines. Both intention-to-treat and as-treated analyses as recommended in the extension of the Consolidated Standards of Reporting Trials (CONSORT) guideline for noninferiority trials will be performed [48]. Prior to statistical analysis, data will be tested for compliance with the assumptions of parametric statistics (normality, skewing, kurtosis, etc). If failing to meet these assumptions, data transformation will be attempted to achieve compliance. Nonparametric equivalents will be employed if parametric assumptions are not met. Covariance will be determined and incorporated into analyses as appropriate. The treatment effect of each intervention will first be computed by comparing the pre-to-post intervention measures. Our primary analysis of noninferiority will be implied if the lower limit of a 1-sided 95% confidence interval of the difference between the telerehabilitation and control group is

within the prestated MCII values [37]. Secondary analysis with a linear mixed model (LMM) will be used to ensure no statistically significant differences exist between groups. LMM is appropriate for comparing means in independent samples and has the added advantage of adjusting for baseline differences and being tolerant of missing data. Because baseline differences are adjusted for with this approach, it is possible to compare pre- and posttreatment scores between groups, rather than their change scores. The statistic will be computed with observed outcomes as the dependent variables and with fixed factors of treatment group (telerehabilitation, in-person) and assessment time (preoperatively, day of discharge, 2 weeks, 6 weeks, and 6 months postoperatively). Interactions among these factors will also be assessed. Fixed predicted values and residuals from these analyses will be used for data inspection purposes. The outcome of primary interest is the interaction effect between group and time. An alpha level of .05 will be used for the analysis.

Economic Evaluation

Concurrently undertaking an economic evaluation with a randomized controlled trial allows for efficient and simultaneous collection of relevant clinical and economic outcomes to be included in both analyses [49]. Given that a noninferiority research hypothesis is proposed, the planned economic evaluation will be a cost-minimization analysis. This analysis answers the question of which health program uses the lower quantity of resources to achieve the same health outcome. Direct costs to the health system and total direct costs (including non–health care costs and out of pocket costs) will be considered in this evaluation. However, an incremental cost-utility analysis (CUA) will be undertaken if a difference in clinical outcomes between groups is determined. The EQ-5D scores will be used to generate quality-adjusted life year scores for the purpose of the CUA. Multivariate sensitivity analyses will be conducted to confirm stability of results and adjust for uncertainty in clinical and economic data [49]. The time horizon for this economic evaluation will be the 6-month follow-up during which each participant is involved in the study, and the base year will be 2015.

Results

This trial received a Aus $10,000 grant from the Queensland Orthopaedic Physiotherapy Network to fund the infrastructure required to conduct the trial. The trial is being conducted by means of an in-kind contribution from the QEII Jubilee Hospital Physiotherapy Department. Recruitment commenced in September 2015 and is expected to be completed by June 2017. Data collection will be completed by December 2017. It is anticipated the results from this trial will be published by July 2018.

Discussion

THR is a high-volume surgery with good success rates. Evidence suggests physical rehabilitation is an important component of recovery; however, access to rehabilitation is often limited. This study will investigate the effectiveness of a telerehabilitation program for THR patients once discharged from hospital. It will compare self-reported and physical outcomes from the intervention group to a control traditional-care group. The intervention group will undertake their rehabilitation at home using 2 existing rehabilitation apps (Wellpepper and eHAB) via an iPad. The control group will receive traditional in-person rehabilitation.

The positive results from TKR telerehabilitation studies suggest that similar results could be achieved in the THR population where rehabilitation programs have a focus on functional activities, exercise, and education. If shown to be as effective as in-person care, telerehabilitation for THR patients could help solve an access issue that exists for many of the population. Furthermore, it may help reduce the cost of health care provision by enabling patients to take a more independent approach to their rehabilitation.

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Authors' Contributions

MN, MB, KC, and TR were involved in the conception and organization of the research and the review and critique of the manuscript. MN wrote the first draft of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CUA: cost-utility analysis
HEP: home exercise program
HOOS: Hip disability and Osteoarthritis Outcome Score
LMM: linear mixed model
MCII: minimal clinically important improvement
QEII: Queen Elizabeth II
QOL: quality of life
ROM: range of motion
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
THR: total hip replacement
TKR: total knee replacement

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Protocol

Bioengineered Temporomandibular Joint Disk Implants: Study Protocol for a Two-Phase Exploratory Randomized Preclinical Pilot Trial in 18 Black Merino Sheep (TEMPOJIMS)

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Abstract

Background: Preclinical trials are essential to test efficacious options to substitute the temporomandibular joint (TMJ) disk. The contemporary absence of an ideal treatment for patients with severe TMJ disorders can be related to difficulties concerning the appropriate study design to conduct preclinical trials in the TMJ field. These difficulties can be associated with the use of heterogeneous animal models, the use of the contralateral TMJ as control, the absence of rigorous randomized controlled preclinical trials with blinded outcomes assessors, and difficulties involving multidisciplinary teams.

Objective: This study aims to develop a new, reproducible, and effective study design for preclinical research in the TMJ domain, obtaining rigorous data related to (1) identify the impact of bilateral discectomy in black Merino sheep, (2) identify the impact of bilateral discopexy in black Merino sheep, and (3) identify the impact of three different bioengineering TMJ discs in black Merino sheep.

Methods: A two-phase exploratory randomized controlled preclinical trial with blinded outcomes is proposed. In the first phase, nine sheep are randomized into three different surgical bilateral procedures: bilateral discectomy, bilateral discopexy, and sham surgery. In the second phase, nine sheep are randomized to bilaterally test three different TMJ bioengineering disk implants. The primary outcome is the histological gradation of TMJ. Secondary outcomes are imaging changes, absolute masticatory time, ruminant time per cycle, ruminant kinetics, ruminant area, and sheep weight.

Results: Previous preclinical studies in this field have used the contralateral unoperated side as a control, different animal models ranging from mice to a canine model, with nonrandomized, nonblinded and uncontrolled study designs and limited outcomes measures. The main goal of this exploratory preclinical protocol is to set a new standard for future preclinical trials in oromaxillofacial surgery, particularly in the TMJ field, by proposing a rigorous design in black Merino sheep. The authors also intend to test the feasibility of pilot outcomes. The authors expect to increase the quality of further studies in this field and to progress in future treatment options for patients undergoing surgery for TMJ disk replacement.

Conclusions: The study has commenced, but it is too early to provide results or conclusions.

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KEYWORDS

temporomandibular joint disorders (TMD); temporomandibular joint bioengineered disk implants; temporomandibular randomized preclinical trial protocol

Introduction

The temporomandibular joint (TMJ) is the most frequently used joint in the human body. The TMJ opens and closes 1500 to 2000 times daily and is essential for everyday functions of the mouth, such as mastication, speech, deglutition, yawning, and snoring, involving special mandatory synergy of both articular sides [1]. The TMJ disk is an essential component in the normal TMJ and has the following functions: (1) it distributes the intra-articular load, (2) it stabilizes the joints during translation, and (3) it decreases the wear of the articular surface [2,3]. The majority of TMJ disorders (TMD) are successfully treated with reversible, conservative, and low-tech treatments such as education and counseling, therapeutic exercises, splint therapy, and pharmacotherapy [4,5].

When the TMJ disk is displaced, malformed, or damaged, it can induce serious internal pathologic processes and/or osteoarthritis [6,7]. Currently, patients suffering from severe TMD have limited validated treatment options. Most surgical approaches, such as TMJ discectomy, do not restore the structural or biological properties of the articulation and disk. This procedure may not be ideal because the TMJ is left without an important functional structure. A variety of interpositional materials have been used to replace the removed disks, including synthetic materials manufactured from silicone, Teflon, polytetrafluoroethylene, and biological interpositional grafts taken from different anatomic sites [8-11]. These interpositional materials do not take in consideration the anatomy and biochemical and biomechanical characteristics of the TMJ native disk [12], and some of them have been associated with serious complications for the patients [8,13,14]. In the late 1980s, Proplast/Teflon TMJ (synthetic interpositional implant) were found to be harmful in many patients. The breakdown of the material, probably caused by TMJ high biomechanical forces, lead to fragmented particles that resulted in an immune foreign body response that caused problems ranging from severe cutaneous inflammatory reaction in the preauricular and cheek areas [15] to severe degenerative joint disease with perforation into the middle cranial fossa [16,17]. The result was a dramatic clinical spectrum of failures for these implants [10]. In December 1991, the US Food and Drug Administration's Bulletin recommended immediate removal of all previous TMJ Proplast/Teflon implants because of the mechanical failures, many resulting in progressive bone degeneration [18]. In a 1992 workshop, the American Academy of Oral and Maxillofacial Surgery instructed the discontinuation of Proplast/Teflon [18].

The absence of efficacious options to substitute the TMJ disk can be related to difficulties in the translation of animal evidence to the clinical practice in humans. These limitations are likely related to:

1. the use of heterogeneous animal models with conflicting results, possibly due to variable anatomy and intra-articular loading between species [19,20];

2. the use of the contralateral TMJ as control, which may be associated with contralateral overloading [21];

3. the biomaterials used to replace the disk do not account for the morphologic and biomechanical characteristics of the native disk;

4. absence of randomized controlled trials with blinding of outcomes' assessors; and

5. lack of multidisciplinary teams involved in the project.

Preclinical research should promote the effective translation of knowledge into practice. The previously mentioned aspects can limit the effective translation of quality scientific knowledge into clinical practice and these may present potential issues to patients, clinicians, and scientific progress.

The contemporary absence of successful options to substitute the TMJ disk is still a major issue for public health. Little has changed in the past decade regarding study designs for TMJ investigation, and the treatment for patients with severe TMD remains controversial. The main objective of the Temporomandibular Joint Interposal Material Study (TEMPOJIMS) is to develop a new, reproducible, and effective study design for preclinical research in the TMJ field. The second goal is to progress in bioengineering and regenerative medicine evaluating the benefits of a TMJ bioengineering implant to substitute the damaged native TMJ disk. This preclinical exploratory study is divided into two phases. Phase 1 of this study is a blinded randomized preclinical trial, designed to investigate if the TMJ undergoes important injury in bilateral discectomy, bilateral discopexy, and sham surgery. Phase 2 intentions are to evaluate the safety and efficacy of three different TMJ bioengineering implants using the same rigorous method of phase 1.

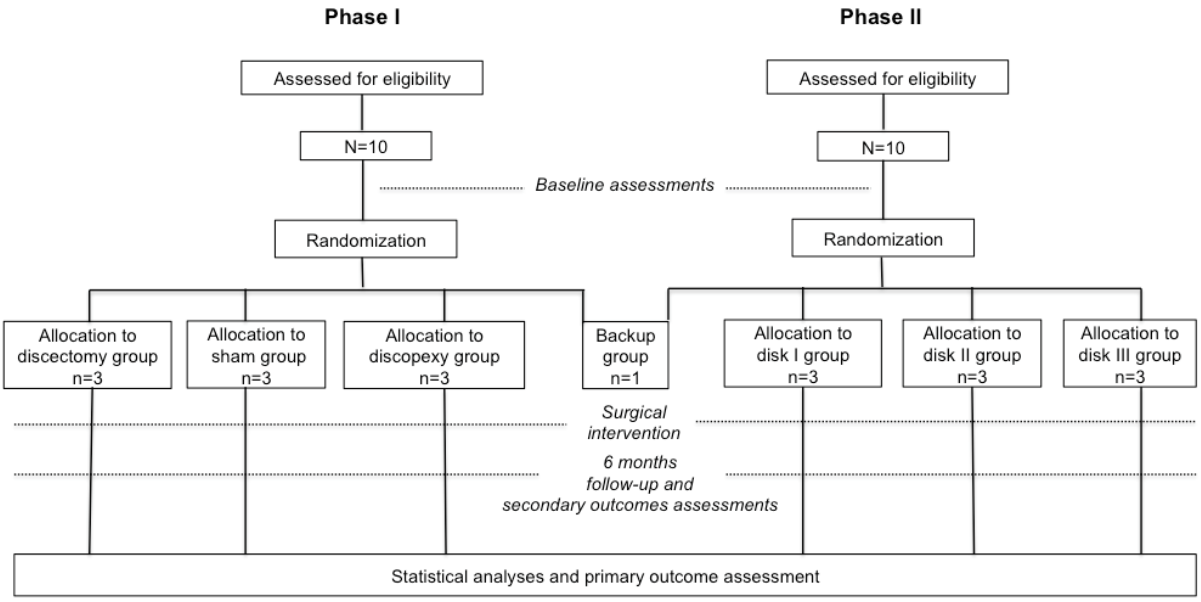
Methods

Study Design

The TEMPOJIMS is a two-phase exploratory randomized controlled preclinical trial planned to gather preliminary information to (1) evaluate a new study design for TMJ investigation; (2) evaluate the black Merino sheep animal model for TMJ investigation; (3) evaluate TMJ behavior under bilateral surgical intervention (discectomy and discopexy) using a histologic primary outcome (microscopic scoring of destructive changes in TMJ using a modified Mankin scoring system [22]), secondary imaging outcome (imaging scoring of TMJ); (4) testing the applicability of pilot secondary outcomes predominantly for ruminant kinetics; and (5) obtain a baseline for interpretation of TMJ disk bioengineering implants results. Phase II is aimed to test safety and efficacy of three different bilateral TMJ bioengineering disk implants (Figure 1). Outcome evaluators and analysts are blinded for surgical assessments.

Major institutions involved in this study are (1) Lisbon Faculty of Medicine for study design, coordination, and statistical analysis; (2) Interdisciplinary Centre of Research in Animal Health in Faculty of Veterinary Medicine for histological preparation and veterinary support of all animals; (3) Centre for Rapid and Sustainable Product Development for bioengineered disk implants (disks I and II); (4) Bioengineering, Surgery, Chemical Engineering, Mechanical Engineering and Materials Science, University of Pittsburgh, for bioengineered disk implants (disk III); (5) Department of Oral and Maxillofacial-Head and Neck Surgery, University Hospital Infanta Cristina, Badajoz, Spain, for surgical support; (6) Institute of Bone and Joint Research-Northern Sydney Local Health District-Sydney Medical School Northern, University of Sydney, Australia, for histological analysis; and (7) Radiology Department of Santa Maria Hospital, Lisbon, Portugal, for imaging analysis.

Figure 1. Study design.



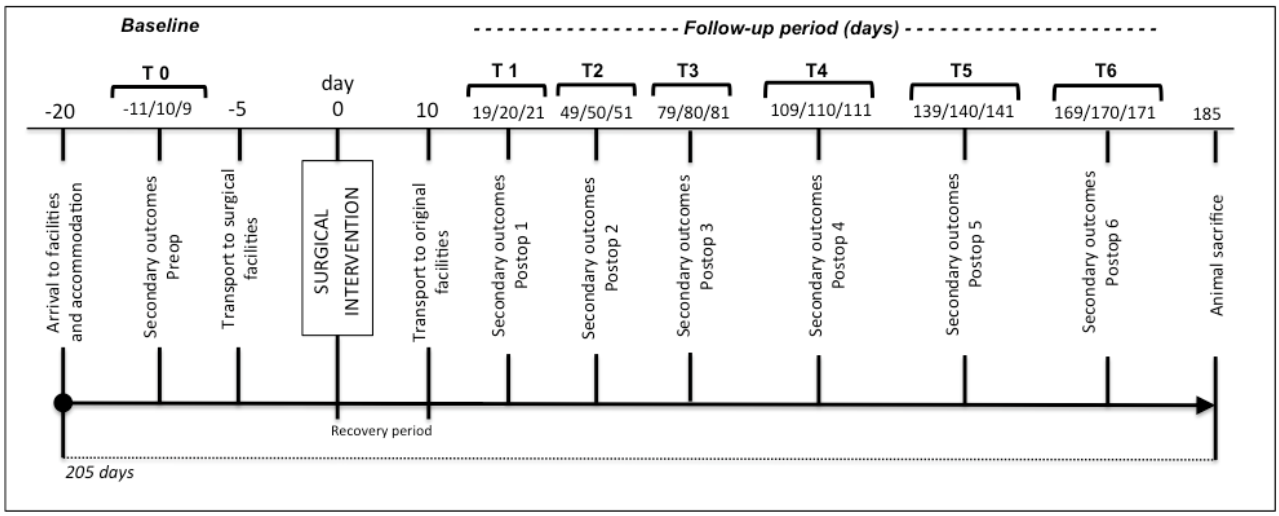
Animal Model

A variety of strains/breeds of sheep have been used in TMJ investigations. To decrease biological variability, the authors recommended black Merino sheep as the animal model to conduct the study [20]. As recommended, the authors proposed to use “sheep skeletally mature” at ≥2 years of age [23]. The inclusion criteria are certified black Merino sheep, adult (age 2-5 years), female, and in good health condition (veterinary check-up is performed on all animals). Regarding the animal ethical considerations, the study design was approved by the Portuguese National Authority for Animal Health registered with number 026618. The study design and organization respect the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines.

Baseline and Follow-Up Evaluation

The baseline and follow-up evaluations are outlined at particular time points (Figure 2). Pilot secondary outcomes and weight are measured at days 11, 10, and 9 before surgery (details on secondary outcomes are reported in outcomes measures). Transportation to surgical facilities is performed 5 days before surgery to avoid animal stress and allow familiarization to the temporary facilities. Head computerized tomography (CT) scan is performed on the day of surgery taking advantage of preanesthesia sedation. Ten days after surgery, animals are transported to TEMPOJIMS main facilities. Days 19, 20, and 21 after surgery, the follow-up secondary outcomes start to be recorded every 30 days for 6 months (Figure 2). At the end, animals are sacrificed and a new CT scan is performed to measure the imaging outcome and to begin the histologic preparation.

Figure 2. Study flowchart.



Randomization, Allocation, and Blinding

The randomization is performed by a statistical group not involved in the outcome assessments, managed by Lisbon Faculty of Medicine. Allocation to each randomized group is performed preoperatively by sealed envelope and separately for phase 1 and phase 2 of the study. The surgical team is not blinded to treatment allocation given the type of intervention; however, surgical team members are not involved in outcome assessments. All outcome evaluators are blinded to intervention. In phase 1, 10 sheep are allocated to the intervention group: sham surgery group (n=3), discectomy group (n=3), discopexy group (n=3), and backup group (n=1). The backup sheep is planned to be used if death occurs due to anesthesia or another complication not related to the surgical intervention. In phase 2, 10 sheep are randomly assigned to disk I group (n=3), disk II group (n=3), disk III group (n=3), and backup group (n=1) (Figure 1).

Intervention Phase

Anesthesia Protocol

Fasting and water restriction are required 24 hours before surgery. Sedation is performed with diazepam (0.5 mg/kg iv), followed by anesthesia induction with ketamine (5 mg/kg iv). Oral intubation is performed and anesthesia is maintained with isoflurane (1.5% to 2%). To assure animal analgesia, meloxicam (0.5 mg/kg iv, bid) is administered on surgery day and during 4 days postoperatively. Antibiotic prophylaxis with amoxicillin and clavulanic acid are used for 5 days.

Surgical Intervention Protocol for Phases 1 and 2

Phase 1

Bilateral discectomy (n=3): under general anesthesia, the surgical team perform a preauricular skin incision and a blunt dissection of the soft tissue covering the joint. The joint area is disclosed and the articular capsule is incised. The disk and its attachments are identified. The medial, anterior, posterior, and lateral disk attachments are detached and discectomy is performed. The wound is closed in layers.

Bilateral discopexy (n=3): under general anesthesia, the surgical team perform a preauricular skin incision and a blunt dissection of the soft tissue covering the joint. The joint area is disclosed and the articular capsule is incised. The disk and its attachments are identified. The lateral and posterior disk attachments are detached and sutured with poly- *p*-dioxanone (PDS) 3/0. The wound is closed in layers.

Sham surgery (n=3): under general anesthesia, the surgical team will perform a preauricular skin incision and a blunt dissection of the soft tissue covering the joint. The capsule is not incised. The wound is closed in layers.

Phase 2

Disk I (n=3): under general anesthesia, the surgical team perform a preauricular skin incision and a blunt dissection of the soft tissue covering the joint. The joint area is disclosed and the articular capsule is incised. The disk and its attachments are identified. The medial, anterior, posterior, and lateral disk attachments are detached and discectomy is performed. The disk I is introduced into the articular space and sutured in the lateral attachments. The wound is closed in layers. Disk I will be an alternative biomaterial and for intellectual reasons cannot be revealed in this paper.

Disk II (n=3): under general anesthesia, the surgical team perform a preauricular skin incision and a blunt dissection of the soft tissue covering the joint. The joint area is disclosed and the articular capsule is incised. The disk and its attachments are identified. The medial, anterior, posterior, and lateral disk attachments are detached and discectomy is performed. The disk II is introduced into the articular space and sutured in the lateral attachments. The wound is closed in layers. Disk II will be a porous poly(glycerol sebacate) (PGS) scaffold reinforced with polycaprolactone (PCL).

Disk III (n=3): under general anesthesia, the surgical team perform a preauricular skin incision and a blunt dissection of the soft tissue covering the joint. The joint area is disclosed and the articular capsule is incised. The disk and its attachments are identified. The medial, anterior, posterior, and lateral disk attachments are detached and discectomy is performed. The

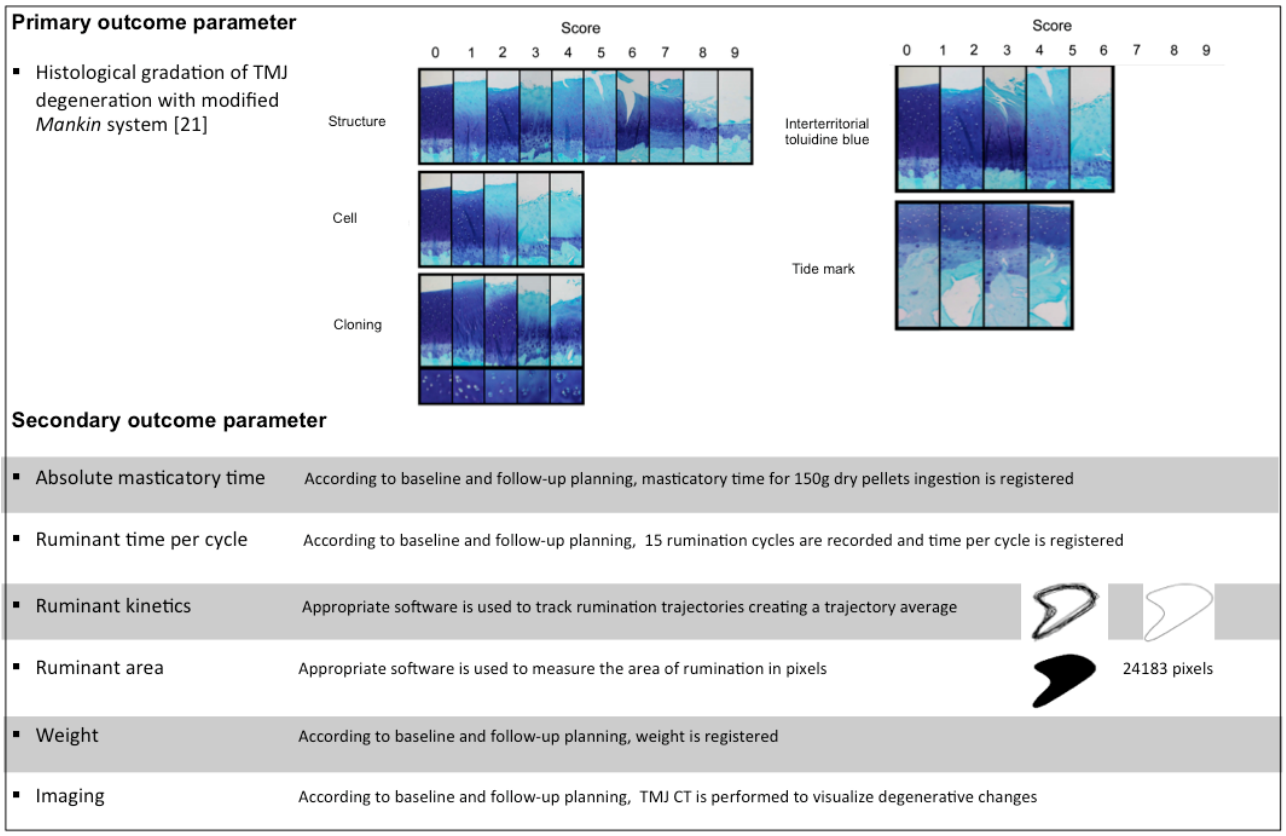
disk III is introduced into the articular space and sutured in the lateral attachment. The wound is closed in layers. Disk III will be a porous PGS scaffold prepared by a modified salt fusion method. Briefly, ground salt particles (150 mg) with a size range of 25 to 32 µm will be placed into a 3-D printed mold. The mold will be transferred to an incubator at 37°C and 90% relative humidity for 1 hour. The fused templates of salt particles will dry in a vacuum oven at 90°C and 100 millitorr (mTorr) overnight, removing salt cake carefully from the mold before further processing. Fresh-made PGS dissolved in tetrahydrofuran (THF; 20 wt%, 380 µL, salt:PGS=2:1) added to the salt cake, and the THF is allowed to evaporate completely in a fume hood for 30 minutes. The salt cake is transferred to a vacuum oven and cured at 150°C and 100 mTorr for 24 hours. The resultant PGS-impregnated salt templates are soaked in deionized water for 4 hours, and then replaced with water for 4 hours, with water exchange every 4 hours during the first 12 hours. After the 12-hour water bath, scaffolds are transferred to deionized water for another 24 hours with water exchange every 8 hours. The resultant scaffolds are frozen down at –80°C and then the lyophilization process is applied.

Ten days for recovery is contemplated for wound care and postoperative medication (see Figure 2).

Outcome Measures

The primary outcome is the microscopic scoring of destructive changes in the TMJ using a modified Mankin scoring system [22]. Secondary outcomes are imaging scoring of TMJ destructive changes, absolute masticatory time, ruminant time per cycle, ruminant kinetics, ruminant area, and sheep body weight. Primary and secondary outcome parameters are outlined in more detail in Figure 3.

Figure 3. Primary and secondary outcome parameters.



Primary Outcome

The goal is to evaluate histologic gradation of TMJ destructive changes. The time point is 6 months following surgical intervention.

Six months after surgery, the TMJ is removed using a necropsy bone oscillatory saw according to the following anatomic references: cranial (cranial aspect of coronoid process in the union region of the zygomatic process), caudal (external to acoustic meatus), dorsal (reference is established to the squamous temporal bone), and ventral (reference is fixed 2 cm below the acoustic meatus in the zone of stylohyoid angle). The joints are fixed in 10% buffered formalin for 24 hours and stored in 70% ethanol. Decalcification is obtained by immersion in 10% formic acid in 5% formalin for up to 20 days, after which the articulations are cut sagittally through the whole condyle. After decalcifying, TMJ articulations are immersed in three graded methyl salicylate/paraffin mixtures and cut sagittally through the lateral into the central part of the TMJ. Histological sections are sent to Sydney Institute of Bone and Joint Research for histological scoring using a modified Mankin scoring system [22]. This assessment is performed and classified independent by two histologists who will be blinded to intervention. A third histologist will act as arbiter in case of disparity.

Secondary Outcomes

The features evaluated are imaging analysis, absolute masticatory time, ruminant time per cycle, ruminant kinematics, ruminant area, and sheep weight (see Multimedia Appendices 1 and 2). Time point is every month following surgical intervention for a total of 6 months.

To measure secondary outcomes, a specific cage (see Figure 4) was built with a frontal window and a feeder.

Imaging analysis: preoperative CT is performed on all sheep. After animal sacrifice, TMJ blocks are scanned by CT and imaging evaluation is performed using the criteria and score described in Table 1.

Table 1. TEMPOJIMS imaging evaluation criteria.

Items	Criteria	0 (no change)	1 (mild change)	2 (moderate change)	3 (severe change)
Shape	Change of joint form	May include reformed joint	Small changes; this change may include ≤2 osteophytes	Moderate changes; multiple osteophytes	Severe changes and outgrowth; marginal proliferation
Condyle erosion	Concavity in cortical	This stage includes normal joint with no signs of condyle erosion	Erosion in one-third of joint surface	Erosion in two-thirds of joint surface	Erosion over all joint surface
Temporal erosion	Concavity in cortical	This stage includes normal joint with no signs of temporal erosion	Erosion in one-third of joint surface	Erosion in two-thirds of joint surface	Erosion over all joint surface
Condyle sclerosis	Cortical thickening of condyle	This stage includes normal joint with no signs of condyle sclerosis	Sclerosis in one-third of joint surface	Sclerosis in two-thirds of joint surface	Sclerosis over all joint surface
Temporal sclerosis	Cortical thickening of temporal fossa	This stage includes normal joint with no signs of temporal sclerosis	Sclerosis in one-third of joint surface	Sclerosis in two-thirds of joint surface	Sclerosis over all joint surface
Condyle marrow	Change of underlying trabecular bone	This stage includes normal joint with no change of condyle trabecular bone	Sclerosis in less than half of trabecular bone	Sclerosis in half of trabecular bone	Sclerosis in all trabecular bone
Temporal marrow	Change of underlying trabecular bone	This stage includes normal joint with no change of temporal trabecular bone	Sclerosis in less than half of trabecular bone	Sclerosis in half of trabecular bone	Sclerosis in all trabecular bone
Calcification	Development of calcification across joint space	No calcification across joint space	Calcification in one-third of joint surface	Calcification in two-thirds of joint surface	Bony fusion across joint space
Global appreciation		Normal joint	In general, mild changes	In general, moderate changes	In general, severe changes

This assessment is performed and classified independently by two experienced radiologists who will be blinded to intervention. A third radiologist will act as arbiter in case of disparity.

Absolute masticatory time: respecting the flowchart (Figure 2), at 9:00 am the animals are placed in individual cages. A dose of 150 grams of dry pellets (Rico Gado A3) are introduced in the feeder and the time until they eat all the pellets is measured with a chronometer (see Multimedia Appendix 1).

Ruminant time per cycle: respecting the timetable (Figure 2), we record 15 ruminatory cycles approximately 4 hours after 150 gram feeding. We use a Canon 7D video camera and images with 25 frames per second. Then, the number of frames per cycle are divided by 25 to obtain time in seconds per cycle (see Multimedia Appendix 2).

Ruminant kinetics: we use the software Foundry Nuke (2D tracking) to perform the ruminatory tracking and to obtain the ruminatory cycle average. With the software After Effects , we convert the 2-D tracking into a geometric form (see Multimedia Appendix 2).

Ruminant area: we determine the average of 15 cycles and create a geometric form. Using the software Image J , we perform a quantitative measure in pixels of the ruminant area average.

Weight: according to the timetable, after eating 150 grams of dry pellets the sheep are weighed (see Multimedia Appendix 1).

All assessments are performed by researchers who are blinded to surgical intervention.

Figure 4. TEMPOJIMS main facilities.

Statistical Analyses

All statistical analyses will be performed using the SPSS version 22 (IBM Corp, Armonk, NY, USA). A cross-sectional analysis will be performed to compare the outcome variables in the three levels of the independent variable before and after the randomized treatment group assignment. In the cross-sectional analyses, one-way analysis of variance (ANOVA) will be performed, after testing all the assumptions. For longitudinal analysis, one-way ANOVA with repeated measures will be performed taking as within-subjects effects observations after surgery (months 1 to 6). Fisher least significant difference will be performed as post hoc tests to check for significant differences for the different treatments.

Reporting of Adverse Events

Adverse events related to the study will be considered, including (1) anesthesia events: idiopathic death, pneumothorax, other complications related to anesthesia; (2) surgical technique: massive bleeding, condylar fracture, other complications related to surgical technique; and (3) postoperative events: TMJ infection, suture dehiscence, decreased appetite, facial paresis, decreased rumination, decreased weight.

Discussion

This study investigates the effects and adverse effects of (1) bilateral discectomy, (2) bilateral discopexy, and (3) bioengineered disk implants. Although this preclinical study will primarily serve as a pilot study, we expect to gain a better understanding of the morphologic and histologic changes in TMJ and implications in masticatory kinetics.

So far, results on discectomy are conflicting. Previous preclinical studies in this field [24-33] have used the contralateral unoperated side as a control and different animal models ranging from mice to a canine model. Using the contralateral side as a control can be inappropriate considering contralateral overload influence. Theoretically, we expect to reduce this bias using a bilateral approach. Animal variability in the different studies is a warning about the importance of using the same animal model in further studies regarding TMJ implant investigations. Therefore, our group performed a previous study considering black Merino sheep as a promisor animal model for studies regarding TMJ disk implants investigation, TMJ prosthesis, and TMJ osteoarthritis model. To increase the quality of TEMPOJIMS the authors will use a sham surgery control group.

We expect to obtain valuable information related to the phase 1 discopexy group regarding if the surgical approach promotes intra-articular damage. This can improve future conclusions about attributing possible damage to the intervention itself instead of the TMJ implant. This question is important considering that a surgical approach to place TMJ implants in phase 2 will be required. Again, using a bilateral intervention could reduce a possible bias.

Most preclinical studies have focused on gross morphological/histological assessments and were not designed

to characterize the fundamental altered joint movement (kinetics) or functional consequences. In this study, we include pilot secondary outcomes to evaluate changes in ruminant kinetics. We expect to correlate the primary with the secondary outcomes to understand if they can be used in future TMJ studies. It may be interesting to understand several items:

1. Are there differences regarding masticatory time in the disk groups versus discectomy and discopexy?

2. Is there a correlation between histologic and imaging and kinetics results?

3. Does the ruminant area and geometry change when performing different interventions?

4. Is there a difference regarding ruminant kinetics in the disk groups versus discectomy and discopexy?

5. Do TMJ implants accelerate osteoarthritis?

Concerning phase 2, the choice of biomaterial is critical. The TMJ implant will be exposed in a mechanical, stressful environment with a limited blood supply that can limit cell migration and in situ regeneration. Testing three different bioengineering discs in vivo and correlating in vitro with in vivo behavior can seriously improve bioengineering strategies to achieve a safe and efficacious TMJ disk implant for humans.

The main strength of this study is the animal model proposed; the conventional and pilot outcomes described; the study design with a randomized, blinded, and placebo control group; and the use of bilateral surgical procedures. Potential limitations of the study include the relatively small sample size. If this study confirms the feasibility of the proposed protocol and initial efficacy of the TMJ disk implants planned, a larger preclinical trial would be warranted to further determine the effectiveness of these discs and promote translation of animal evidence to clinical practice in humans.

Trial Status

At the time of submission, the surgical interventions of phase 1 were ongoing at Faculdade de Medicina Veterinária de Lisboa and TEMPOJIMS facilities in Portugal.

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Authors' Contributions

The contributors, with input from the other investigators, conceived this study protocol. JF, RF, NG, AT, NG, and DA developed the protocol and study materials with input from all investigators. NG, AT, and DA participated in the randomization process. LM will conduct the statistical analyses. FM, RG, and SF will participate in the surgical interventions. CB and SC are the coordinators of the veterinary staff and responsible for the animal anesthesia and animal welfare. DC participated in organization support and was study advisor. PM, NA, and MC are dedicated to disk implants 1 and 2. WY, JE, and GJ are dedicated to disk implant 3. SR will coordinate the imaging evaluation. MP and FB are responsible for processing the histologic samples and preparing sections. LC group will coordinate histologic scoring system. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Outcomes assessments in TEMPOJIMS main facilities, absolute masticatory time and weight.

[MP4 File (MP4 Video), 230MB - resprot_v6i3e37_app1.mp4]

Multimedia Appendix 2

Outcomes assessments in TEMPOJIMS main facilities. After recording 15 ruminant cycles with a Canon 7D Video Camera we used the software Foundry Nuke (2D tracking) to make the ruminant tracking to obtain the ruminant cycle average in each time period.

[MP4 File (MP4 Video), 4MB - resprot_v6i3e37_app2.mp4]

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Abbreviations

CT: computerized tomography
PCL: polycaprolactone
PDS: poly-p-dioxanone
PGS: poly(glycerol sebacate)
TEMPOJIMS: Temporomandibular Joint Interposal Material Study
THF: tetrahydrofuran
TMD: temporomandibular joint disorders
TMJ: temporomandibular joint

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Protocol

Home-Based Intervention Program to Reduce Food Insecurity in Elderly Populations Using a TV App: Study Protocol of the Randomized Controlled Trial Saúde.Come Senior

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Abstract

Background: The limited or uncertain access to adequate food in elderly people includes not only economic restrictions but also inability of food utilization due to functional or cognitive impairment, health problems, and illiteracy.

Objective: The aim of this work is to present the protocol of the randomized controlled trial Saúde.Come Senior, an educational and motivational television (TV)-based intervention to promote healthy lifestyles and decrease food insecurity in elderly people.

Methods: A randomized controlled study will be conducted in subjects aged 60 years and older with food insecurity, identified at 17 primary care centers in the Lisboa e Vale do Tejo health region in Lisbon, Portugal. The primary outcome will be the changes in participants' food insecurity score (evaluated by the Household Food Insecurity Scale) at 3 months. Change in other outcomes will be assessed (dietary habits, nutritional status, physical activity, health status, and clinical outcomes). Subjects will be followed over 6 months; the intervention will last 3 months. Data collection will be performed at 3 different time points (baseline, end of intervention at 3 months, and follow-up at 6 months). The intervention is based on an interactive TV app with an educational and motivational program specifically developed for the elderly that has weekly themes and includes daily content in video format: (1) nutrition and diet tips for healthy eating, (2) healthy, easy to cook and low-cost recipes, and (3) physical exercise programs. Furthermore, brief reminders on health behaviors will also be broadcasted through the TV app. The total duration of the study will be 6 months. The intervention is considered to be effective and meaningful if 50% of the individuals in the experimental group have a decrease of 1 point in the food insecurity score, all the remaining being unchanged. We expect to include and randomize 282 (141 experimental and 141 control) elderly with food insecurity. We will recruit a total of 1,128 subjects considering that 50% of the target individuals are food insecure (based on INFOFAMÍLIA Survey) (567) and about 50% of those will adhere to the study (282).

Results: The randomized controlled trial with the 12-week home-based intervention with a comprehensive program on healthy eating and physical activity delivery is planned to start recruiting participants at the end of 2017.

Conclusions: This study will assess the efficacy of this innovative tool (Saúde.Come Senior) for disseminating relevant health information, modifying behaviors, and decreasing food insecurity in an easy, low-cost, and massive way.

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KEYWORDS

information and communication technology; new technologies; TV app; healthy lifestyle promotion; food insecurity

Introduction

The world is facing a situation without precedent: soon there will be more older people than children and more people at extreme old ages than ever before [1]. In fact, by 2025 more than 20% of Europeans will be aged 65 years or over, with a particularly rapid increase in the number of over 80s [1]. Portugal has a high proportion of elderly persons and is one of the European countries with the lowest birth rate [2]. As both the proportion of older people and the length of life increase throughout the world, some key questions arise. Will population aging be accompanied by a longer period of good health, a sustained sense of well-being, and extended periods of social engagement and productivity, or will it be associated with more illness, disability, and dependency? What are the consequences of the European economic distress on the health of the elderly?

The impact of an economic crisis may be particularly acute for older people, mainly for those who are physically vulnerable, living in poverty, or dependent on private pensions, leading to adverse lifestyles and health outcomes. Adverse lifestyles and health outcomes include increasing food insecurity; use of tobacco, alcohol, and drugs; increasing depression and anxiety; and a general neglect of overall health [3]. In fact, elderly people with food insecurity report reduced quality, variety, or desirability of diet which leads to higher morbidity through decompensated chronic noncommunicable diseases (diabetes mellitus, hypertension, dyslipidemia), low muscle strength with less mobility, higher mortality, and higher health care costs [4,5]. Many have significant cognitive, psychiatric, and physical problems yet do not seek assistance. Assessment and intervention in these cases requires an interdisciplinary approach. An understanding of risk factors, the clinical evaluation process, competency issues, and basic management strategies is integral to good care.

According to the internationally recognized definition, “food security is the situation that exists when all people, at all times, have physical and economic access to sufficient safe and nutritious food that meets their dietary needs and food preferences for an active and healthy life” [6]. In contrast, food insecurity is a broad concept that includes attributes related with the uncertainty or worry about food, inadequate quality of food, inadequate quantity of food, food acquired through socially unacceptable means, and lack of consistent access to adequate food [7]. Food insecurity is often associated with economic constraints. The rates of food insecurity have been rising worldwide [7]. While the United States is one of the wealthiest nations in the world with a rich and abundant supply of food and resources, 14.3% of US households were food insecure at some point during 2013 [8]. A study of Portuguese primary care center attendees in 2013 showed that 50.7% were food insecure [9]. Furthermore, more than one-third of Portuguese adults with food insecurity are overweight (41.0% in moderate food insecurity and 37.7% in severe food insecurity categories) [10]. This situation needs particular attention if we consider that Portugal is one of the Organization for Economic Cooperation and Development countries with highest levels of income inequalities [11].

Food insecurity has been shown to be associated with poor self-rated health and several noncommunicable diseases such as diabetes, hypertension, fibromyalgia, and osteoporosis [12,13].

In general, food insecurity has been less well studied in the elderly. Data from the United States suggested that food insecurity decreases as age increases. The prevalence of food insecurity was 20.4% among US adults aged between 40 to 49 years and 15.7% among older adults aged between 60 to 69 years [14]. The same trend was observed for Canada: the prevalence of food insecurity was lower in elderly people (16% vs 29% for the total sample) [15]. However, the nutrition and health consequences might be potentially more severe for older adults. In elderly populations, food insecurity might occur as a result of other factors rather than constraints of financial resources. There is evidence that food insecurity among the elderly can be associated with health or mobility problems (functional impairment), which can also compromise the access to healthy food.

Indeed, the concept of food insecurity in elderly persons also includes nutritional deficits and other relevant aspects related with limited or inability to use food due to functional impairments and health problems [16,17]. For older adults, who generally require special attention for optimal nutrition, food insecurity has been a risk factor for poor nutritional status and low muscle power especially in those with physical disabilities, increasing hospitalizations and death [4,5].

Information and communication technology (ICT) solutions can be used as a personalized cost-effective smart model of health empowering subjects to take more responsibility for their own health and quality of life. Moreover, ICTs have the potential to make a major contribution to improve access to quality services while controlling costs. Elderly people spend a significant amount of time watching television (TV) [18], which can be used as a tool to improve health literacy and a vehicle for promoting health lifestyles. Promoting healthy lifestyles in elderly populations is crucial to slow physical decline and

improve well-being, delay the deterioration of health, and reduce the risk of mortality [19].

For this study, we hypothesized that a home-based intervention program on dietary and physical activity through a TV app will improve food security as well as clinical endpoints such as nutritional status, body composition, balance, strength, and quality of life in the elderly population. Considering the broad definition of the food insecurity concept and its 4 main dimensions (availability of food, physical and economic access to food, food utilization, and stability of the other dimensions) [20], our intervention program will be focused on the dimension of food security related to the use or utilization of food, which might be affected by literacy in food and health. Our hypothesis is that a TV-based intervention might have a large potential in promoting healthy lifestyles among low socioeconomic status groups and for people with low literacy, since TV is the most frequently used ICT by low literacy people.

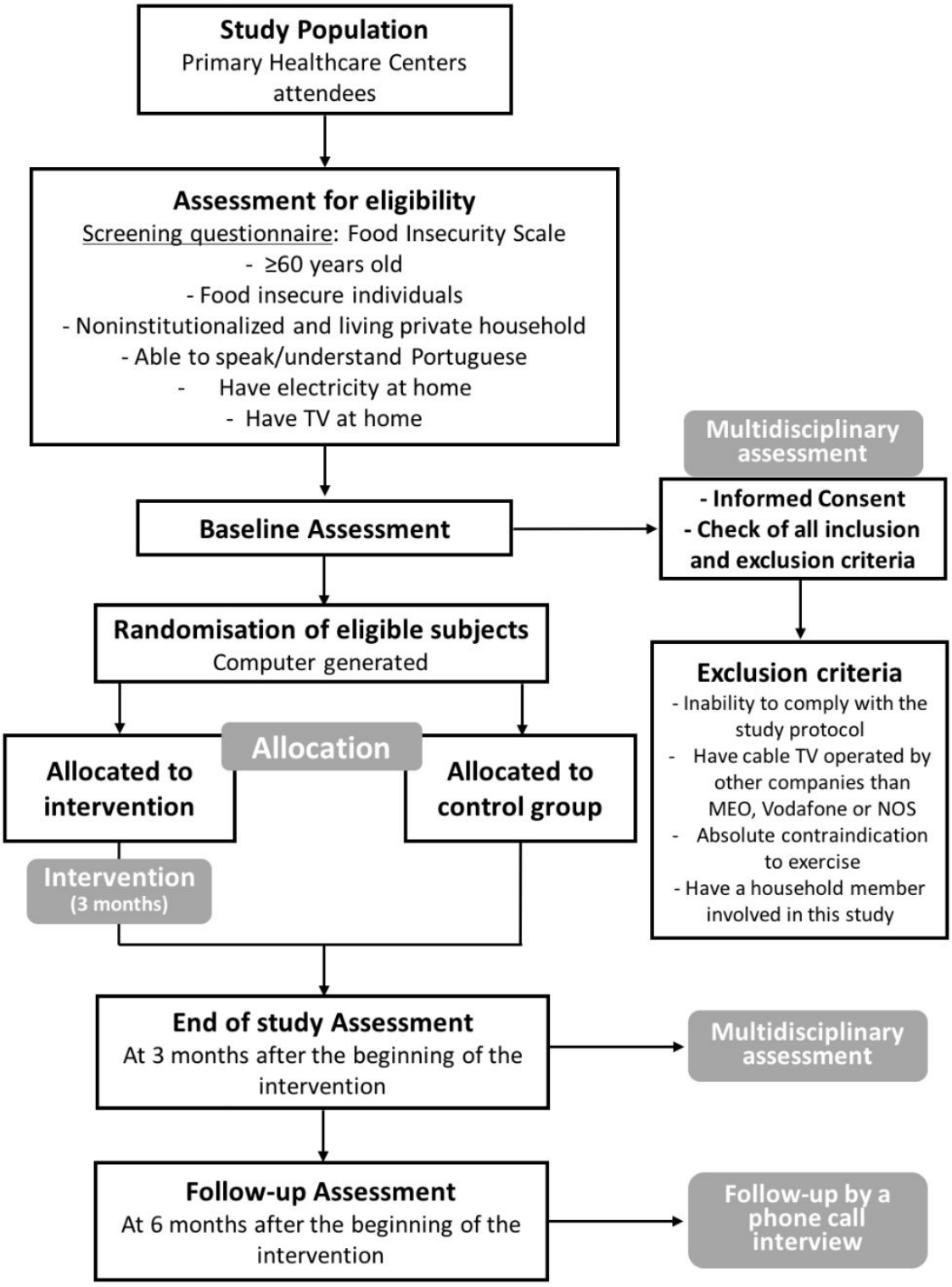
This paper describes the study protocol of a home-based randomized controlled trial aimed at evaluating the impact of a TV-based intervention on healthy lifestyle promotion in elderly subjects in food insecurity reduction.

Methods

Design Overview

This is a randomized controlled study based on an intervention program on diet and physical activity that uses a TV app in about 282 elderly subjects aged 60 years and older with food insecurity identified at 17 primary care centers in the *Lisboa e Vale do Tejo* health region in Portugal. Subjects will be followed over 6 months after the beginning of intervention, which will last 3 months. The research protocol of this study is illustrated in the study design flowchart depicted in Figure 1.

Figure 1. Study design flowchart.



Study Population and Recruitment Plan

A convenience sample of food-insecure elderly people from 17 primary care centers of *Lisboa e Vale do Tejo* health region will be enrolled in this study. All elderly subjects who attend health services in the selected primary care centers during the recruitment period will be approached by our research team and asked to complete a questionnaire for the initial screening. The questionnaire includes a food insecurity scale to identify food-insecure elderly persons, and an authorization request form

will be provided to obtain consent for a further contact. All elderly subjects identified as food insecure will be invited to participate in this study. The baseline assessment will be performed during an appointment at the primary care center with a multidisciplinary team that includes a medical doctor, nurse, nutritionist, and physiotherapist. The medical doctor will ask for informed consent and check inclusion and exclusion criteria.

Eligibility

To be eligible for this randomized controlled study, subjects must fulfill all of the following inclusion criteria: (1) aged 60 years or older, (2) identified as food insecure in the recruitment [21], (3) able and willing to give written informed consent and phone number contact and comply with other requirements of the study protocol, (4) Portuguese speaker or able to understand Portuguese, (5) noninstitutionalized and living in a private household in Portugal, (6) have electricity at home, and (7) have cable TV with box at home. The exclusion criteria are as follows: (1) inability to comply with study protocol (hearing/visual loss, cognitive impairment, etc); (2) absolute contraindication to exercise; (3) have cable TV operated by other companies than MEO, Vodafone, or NOS; and (4) have a household member involved in this study.

Description of the Intervention

Our intervention program is based on a cognitive behavioral strategy for promoting lifestyle behavior changes, combining sets of different strategies that will be important to the learning process as well as to behavioral changes.

This tool was developed based on the transtheoretical model [22] that conceptualizes the process of intentional behavior change in 5 stages, from precontemplation to maintenance. This intervention program accompanies the participants through all these phases. At T0 clinical appointments, doctors, nutritionists, physiotherapists, and nurses lead the participant through the stages of precontemplation and contemplation. In the preparation and action phases—when the subject intends to change behaviors and in fact does change them—the intervention program offers them all the cognitive and behavioral tools to achieve the changes. In addition, the intervention promotes helping relationships, since participants have at their disposal the telephone number and the possibility to contact the team as regularly and as often as they wish. The program also considers the phases of maintenance and prevention of relapse in the T1 clinical appointment and 3 months after the program.

The contents of the intervention program using a TV app were developed closely regarding Kolb's experiential learning model [23,24]: videos on physical exercise and recipes (reflective and active experimentation); videos with tips on nutrition and healthy lifestyles (abstract conceptualization); queries; reminders; and the option to contact the medical doctor, nutritionist, nurse, and physiotherapist.

We designed an interventional program using an interactive TV app to improve dietary habits and physical activity levels among elderly populations with food insecurity. Of the several ICTs available, we have chosen the TV app because the majority of elderly people with food insecurity watch TV [25]. Unpublished data from our group have shown that TV is the most important source of health information for this group.

Our intervention consists of a 12-week home-based intervention with a comprehensive program on healthy eating and physical activity, specially designed for the elderly. This program is an innovative interactive TV app for healthy lifestyle promotion and was designed taking into account (1) the need to educate elderly people about the importance of a healthy diet and exercise, (2) the need to explain that low household income is not a barrier to healthy lifestyles and it is possible to have a healthy diet and physical activity habits at low cost, and (3) the importance of motivating individuals to eat healthier and engage in more physical activity in order to reduce noncommunicable diseases. This interventional program is composed of 3 parts: nutrition and diet tips for healthy eating, low-cost healthy recipes, and physical exercise programs. The nutrition tips content was adapted for people who have economic difficulties in accessing food. In fact, all of the contents were based on a book published by the Portuguese Directorate-General of Health, developed with the main aim of improving dietary habits of low-income people. For example, we promote the consumption of eggs as one of the most economical choices among the good sources of protein, we promote the consumption of vegetarian sources of protein (pulses), and we promote the consumption of seasonal fruit and vegetables because fresh produce often costs less and is a nutritious option. The recipes were developed in order to show how to prepare healthy, tasty, and low-cost recipes. Finally, the physical activity video shows that is possible to do some physical activity at home without spending money.

All of the contents were disseminated on a dedicated channel through a TV app in a video format. As part of the motivation approach of our intervention program, brief reminders on health behaviors will also be diffused weekly through the TV app. These brief reminders will be powerful in recalling and stimulating study participants to adhere, encouraging lifestyle changes. Moreover, frequent contacts with participants are a relevant aspect of successful behavior change intervention programs [26], and follow-up monitoring is included in our program in order to monitor changes in specific behaviors and knowledge during the intervention period. With that purpose, short questionnaires will be delivered weekly through the TV. Thus, the interactive app will be used to collect data (short questionnaires) to evaluate the program compliance and learning. With these short questionnaires we aim to capture lifestyle changes and evaluate the learning along the intervention period. These questionnaires can easily be answered by pushing TV remote control buttons.

This 12-week TV-delivered program is composed by thematic weeks, and all of the contents ("nutrition and diet tips for healthy eating" videos, "healthy recipes" videos, brief reminders, and short questionnaires) developed for each week were specially designed to take into account the thematic week (Table 1).

Table 1. Theme of each week of the interventional TV app on healthy eating and physical activity.

Week	Theme	Content
1	**Vegetable week**	
		Health benefits of vegetable consumption
		Recommendations for vegetable intake
		How to increase the daily intake of vegetables
2	**Water week**	
		Water, hydration, and health
		Recommendations for water intake
		Food resources that contain water
3	**Milk week**	
		Health benefits of consumption of milk and other dairy products
		Recommendations for milk intake
4	**Olive oil week**	
		Olive oil as a healthy cooking oil option
		Adequate amounts for using olive oil for food preparation and cooking
5	**Fruit week**	
		Health benefits of fruit consumption
		Recommendations for fruit intake
6	**Salt week**	
		Health risks of salt intake
		Recommendations for salt intake
		Foods with high and low salt content
		Strategies to reduce salt intake
7	**Meat, seafood, and eggs week**	
		Importance of consuming adequate amounts of meat, seafood, and eggs
		Adequate portions of meat, seafood, and eggs
		Healthier food options within the different foods of this group
8	**Vegetable soup week**	
		Health benefits of vegetable soup consumption
		Standard recipe for a healthy vegetable soup
9	**Vegetable and fruit week**	
		Health benefits of vegetable and fruit consumption
		Recommendations for vegetable and fruit intake
		Meeting vegetable and fruit intake recommendations
		How choose the low cost options for these foods
10	**Healthy cooking week**	
		How to cook healthy food
11	**Sugar week**	
		Health risks of sugar intake
		Recommendations for sugar intake
		Foods with high and low sugar content
12	**Pulses week**	

Week	Theme	Content
		Health benefits of pulses consumption
		Recommendations for pulses intake
		How to include pulses in your diet daily intake

The themes for each week and consequently the contents of each video on nutrition and diet tips for healthy eating were chosen considering the main concerns on diet, in particular the main risk factors for noncommunicable diseases that are associated with unhealthy diets and the nutritional requirements for elderly people [27-29]. The low-cost healthy recipes are chef-created recipes and were specifically developed for our program by a popular Portuguese TV chef with a consulting nutritionist. The physical activity program was developed by physical exercise experts with the main goal of encouraging at least 30 minutes of physical exercise at home 3 times per week [30].

The delivery of these contents through the TV app will be scheduled for specific days of each week in order to develop a routine and constant program over the intervention period. Each day, 1 program will be available (Table 2). The TV app was developed by an external company, and the main TV cable operators agreed to disseminate this app.

Table 2. Weekly schedule of the intervention delivery.

Weekday	Hour	Program delivery
Monday	2:00 PM	Nutrition and diet tips for healthy eating
Tuesday	12:00 PM	Healthy and low-cost recipes
Wednesday	9:00 AM	Physical exercise program
Thursday	2:00 PM	Brief reminder
Friday	Not fixed	Questionnaire
Saturday	Not fixed	Questionnaire
Sunday	—	—

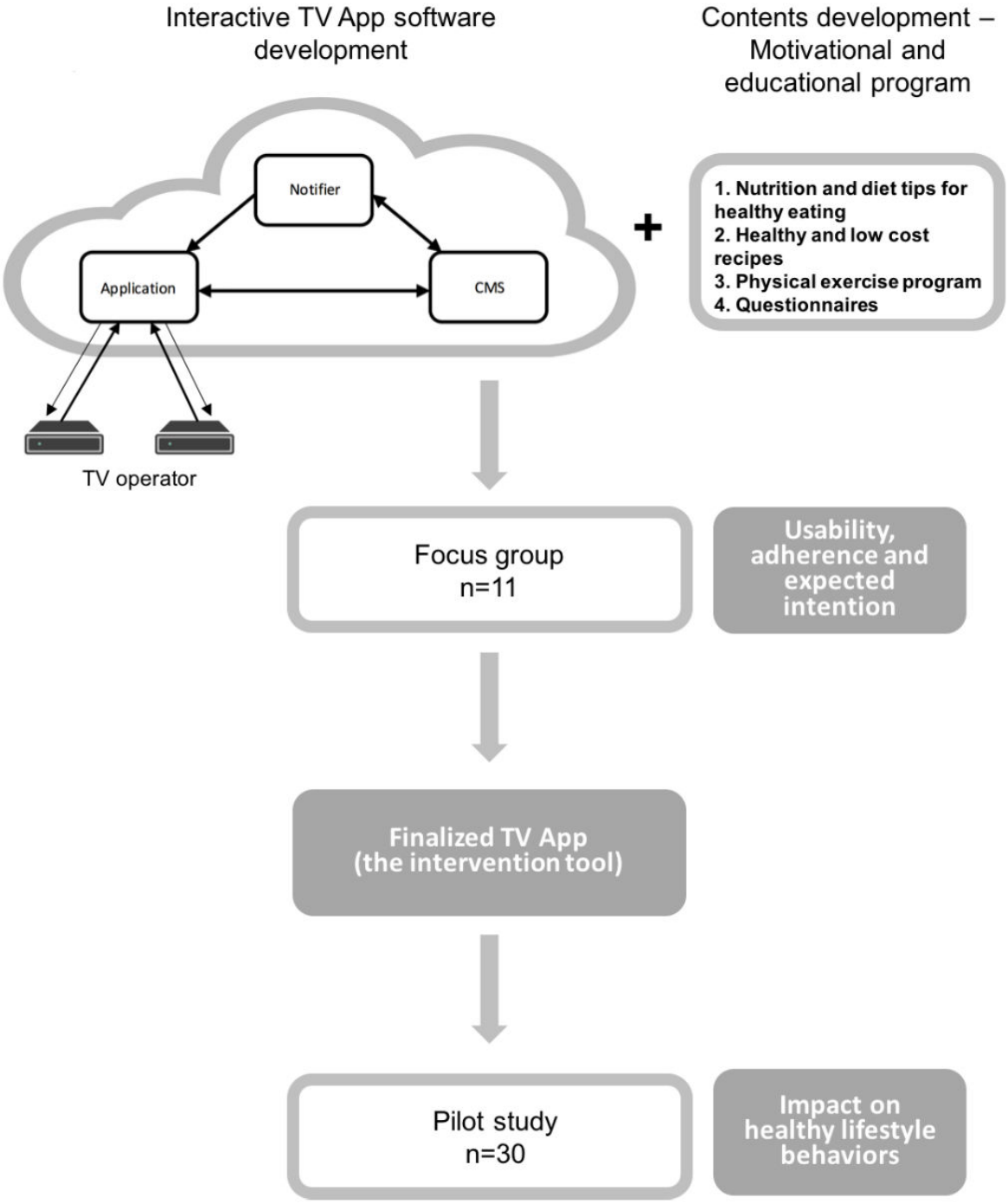
During the development of the TV app, a focus group was conducted by a trained psychologist using a semistructured interview to assess the concept of the TV app, its usability, the adherence intention, and the expected impact on behavior modification. To this end, 11 subjects (6 women and 5 men) with similar characteristics to the study population were enrolled. In terms of the concept of a "TV-based intervention on healthy lifestyles promotion in the reduction of food insecurity in elderly subjects," the members of the focus group generated immediate, very positive, and homogeneous reactions in respondents. The unsolicited comments were many and denoted a strong reception of the concept by all respondents. On the other hand, there was a clear projective identification with the tested app, since it addresses some of the issues that most concern this group: healthy lifestyles, diet, nutrition, and exercise.

Regarding the sense of usability, participants pointed out that the TV is a familiar device and, for that reason, considered the TV app easy to use. On the other hand, little sensitivity in the fingers to handle the remote control and the lack of vision to distinguish a few keys and buttons were stated as likely barriers to its use. Concerning the adherence intention, all respondents were willing to have this app in their homes and report feeling motivated to use it because it is a targeted tool for them.

The TV app seemed to have the potential to generate a positive impact on changing behaviors of seniors. This focus group reported general satisfaction and motivation. Nevertheless, the impact assessment will only be possible at a later stage of use. By using this cognitive behavioral strategy, we reinforce elderly learning and behavioral modifications for promoting lifestyle behavior changes.

After the TV app is completed, a pilot study will be performed in order to test (1) the TV app diffusion conditions by the TV cable operators, (2) TV app user experience, (3) subjects' adherence to the TV app, and (4) subjects' behavioral changes through qualitative analysis. For this study a small sample (n=30) of elderly people with and without food insecurity will be recruited (Figure 2).

Figure 2. Television app development process.



Data Collection

During the study, 3 different collection points are planned: baseline assessment, end of intervention assessment (at 3 months after the beginning of the intervention) and follow-up assessment (at 6 months after the beginning of the intervention). Clinical assessments will be performed by a multidisciplinary team (medical doctor, nurse, nutritionist, and physiotherapist) at primary care centers involved in this study. Structured evaluations will be conducted with a computer-assisted personal interview (CAPI) system. Each assessment will start with the medical doctor evaluation, followed by the nutritionist, physiotherapist, and nurse evaluation. As explained above, before the baseline assessment, the medical doctor will obtain the informed consent and check the eligibility of the participant.

During the baseline assessment, the following sociodemographic data and socioeconomic profile variables will be recorded: age, sex, ethnicity, education, marital status, measures of wealth (used to generate income quintiles), and household income. Also, medical history and physical examination will be performed by the medical doctor. In addition, the following

data will be collected: health care resource consumption (number and type of outpatient clinic visits, hospitalizations, home care assistance, and other needs for health care services in the previous 12 months), health-related quality of life (European Quality of Life questionnaire with five dimensions and three levels [EQ-5D-3L] and the Functional Assessment of Chronic Illness Therapy–Fatigue [FACIT-F]), lifestyle behaviors (alcohol and coffee consumption, smoking habits, and regular physical activity), physical function (Health Assessment Questionnaire [HAQ]), anxiety and depression symptoms (Hospital Anxiety and Depression Scale [HADS]), self-reported chronic diseases (high cholesterol level, high blood pressure, allergy, gastrointestinal disease, mental disease, cardiac disease, thyroid and parathyroid disease, urolithiasis, pulmonary disease, hyperuricemia, malignancy, neurologic disease, and rheumatic and musculoskeletal diseases), and information regarding pharmacological and nonpharmacological therapies.

A nutrition and physiotherapy assessment will be performed at baseline and end of intervention assessment (at 3 months). The nutritionist will collect data regarding food insecurity (Household Food Insecurity Scale [HFIS] adapted from the US Department of Agriculture Household Food Security Survey Module [21]), dietary habits (2-day 24-hour diet recall, Prevención con Dieta Mediterránea [PREDIMED] index [31], and food frequency questions), anthropometric data (height, weight, and waist circumference), body composition data obtained by bioimpedance (fat mass, fat-free mass, total body water), attitudes and barriers on diet, food expenses, and other resources for food. Regarding the dietary habits assessment, a second 24-hour diet recall will be performed by phone call interview performed within 1 week.

Physiotherapy assessment will be conducted aiming at collect data regarding physical activity (Elderly Mobility Scale [EMS] [32] and International Physical Activity Questionnaire [IPAQ]) and muscle strength (hand grip, knee extension, and hip flexion by using a dynamometer). The assessment scales used in the study are all Portuguese-validated versions, and the average time for the evaluation will be 90 minutes.

The nurse will perform a structured questionnaire in order to capture baseline knowledge on healthy lifestyles. This questionnaire will be repeated during the 3-month and 6-month follow-up assessments.

Blood samples will also be collected in order to obtain data regarding the nutritional status and serological biomarkers of cardiovascular risk (albumin and prealbumin levels, insulin resistance, cholesterol levels, hemoglobin A_{1c}, adipocytokines, high sensitivity C-reactive protein, interleukin 1, interleukin 6, and tumor necrosis factor).

At the 6-month follow-up time point, the assessment will be telephonically performed with the assistance of a CATI system (an in-house software platform) by a team of research assistants. These data will be collected in a standardized form; database access is protected by unique username and password for each research team member. In this telephone interview, we will collect data regarding food insecurity (HFIS [21]), dietary habits (2-day 24-hour diet recall, PREDIMED index [31], health-related quality of life and health status (E-5D-3L and FACIT-F), physical activity (IPAQ), consumption of health care resources (inpatient admissions and outpatient appointments), functional disability (HAQ), anxiety and depression symptoms (HADS), and lifestyle behaviors (see Multimedia Appendix 1 for a schedule of all collected data). Finally, the intervention group data regarding the adherence to the program will be monitored using the TV interactive data.

Outcome Measures

The primary outcome assessed will be the changes in participant food insecurity score (evaluated by the HFIS) from baseline to 3 months. Secondary outcomes at 3 months will be changes in dietary habits (evaluated by 2-day 24-hour recall, PREDIMED index [31], and food frequency questions), changes in indicators of nutritional status (body mass index [BMI] and albumin and prealbumin levels), changes in muscle strength improvement (evaluated by dynamometer), changes in quality of life (EQ-5D-3L) [33], changes in fatigue scale (FACIT-F) [34], changes in serological markers of cardiovascular risk (insulin resistance, cholesterol levels, hemoglobin A_{1c}, high sensitivity C-reactive protein, adipocytokines, interleukin 1, interleukin 6, and tumor necrosis factor), changes in physical activity (EMS [32] and IPAQ [35]); changes in body composition balance evaluated by bioimpedance, changes in inpatient admissions and outpatient appointments, changes in falls, and changes in knowledge regarding healthy lifestyle.

The secondary outcomes at 6 months will be changes in participant food insecurity score, changes in dietary habits (2-day 24-hour recall, PREDIMED index [31], and food frequency questions), changes in quality of life (EQ-5D-3L) [33], changes in fatigue scale (FACIT-F), changes in physical activity (IPAQ) [35], changes in inpatient admissions and outpatient appointments, changes in falls, and changes in knowledge regarding healthy lifestyle.

Sample Size

Sample size was estimated considering a *t* test (independent samples) for comparing the mean change in food insecurity score from baseline to the end of study between group 1 (intervention) and group 2 (control). The intervention is considered to be meaningful if 50% of the individuals in group 1 have a decrease of 1 point in the food insecurity score, all the remaining being unchanged. This results in a difference of –0.5 between the mean changes of the 2 groups. Standard deviation of the change is assumed to be 1.5. Power is set at 0.80 and α=.05. We expect to include and randomize 141 experimental and 141 control elderly people with food insecurity (n=282) equally distributed among the 17 primary care centers. We are prepared to recruit around 70 individuals in each primary care center (a total of 1128 subjects are needed) because we assume that 50% (based on the INFOFAMÍLIA [National Survey on Food Insecurity in Portugal] survey) [36] of the target individuals are food insecure and that 50% of those will adhere to the study.

Of note, the standard approach to sample size calculation based on a clinically important difference was not possible to use in this study because data on interventions in food insecurity are

scarce. We have considered the referred effect size based on the INFOFAMÍLIA survey data. In this study, the majority of Portuguese food-insecure households are in low food insecurity level (39.8%), and about 80% of those in the low food insecurity level obtained just 1 point in the food insecurity score, which means that if our intervention decreases the food insecurity score by 1 point we will be able to see a change from the low food insecurity level to the food security level.

Randomization, Allocation, and Blinding

Randomization will be computer generated. Randomization will be stratified according to gender and food insecurity level (low/moderate vs severe) with permuted blocks of six. Subjects will be allocated to the study group versus control with a probability of 1:1.

We will ensure researchers taking follow-up outcome measures will be blinded to group allocation; after randomization, the intervention group will be informed that they will have access to the intervention program (TV app) by an independent assessor (single-blind).

Data Analysis

Analysis will be performed with Stata software (StataCorp LLC). Continuous variables will be reported as mean and standard deviation (or in case of nonnormal distribution as median and interquartile range). Categorical variables will be displayed as frequencies or proportions. The association between food security status, dietary data, and health outcomes will be assessed through chi-square analysis of baseline data.

To assess the effect of the interventional program on food security, dietary intake, nutritional status and body composition, quality of life, muscle strength, fatigue scale, physical activity habits, and serological markers of cardiovascular risk, 2-tailed *t* tests will be used to compare the amount of change within each group (baseline, end of study [at 3 months] and follow-up [at 6 months]). Independent sample *t* tests will be used to compare the intervention group and control group on the same outcomes.

Dietary intake assessed with 2-day 24-hour recall will be analyzed according to the recommended number of servings from each food group of the Portuguese Food Wheel [37]. Intakes of micronutrients that tend to be low in vulnerable population groups (iron, calcium, folate, and vitamins A, C, and D) will be also analyzed. The percentage of individuals meeting the Estimated Average Requirement or Adequate Intake for iron, calcium, folate, and vitamins A, C, and D will be calculated [38]. Food Processor Nutrition Analysis software (ESHA Research) will be used to estimate the intakes of energy, macro-, and micronutrients.

The association between each outcome and the candidate covariables will be performed using generalized models. We will use multivariate logistic and linear (according to the outcome) regression models. The candidate covariates will be first analyzed by univariate regression. Covariates will enter the multivariate models if their *P* value is less than .25 in univariate analysis or considered clinically relevant in this setting. The selection of covariates will be stepwise by backward selection, according to the level of significance (<.05). Multilevel analysis and sensitive analysis will be performed when appropriate.

Ethical Considerations

Study design was performed according to the principles established by the Declaration of Helsinki. The protocol was reviewed and approved by the NOVA Medical School Ethics Committee, by the National Committee for Data Protection (*Comissão Nacional de Proteção de Dados*), and by the Ethical Committee of the Regional Health Authority of *Lisboa e Vale do Tejo.*

The details of the protocol, including the study aims, methods, procedures, and measurements performed during the study, will be provided in written format and discussed with each potential subject. Written informed consent will be obtained for all subjects before any project-related procedure is performed. A copy of the signed and dated consent form will be given to the subject. Participants will also be informed about ethical issues such as confidentiality, the right to ask any questions during the study, and their right to withdraw at any time. The risks associated with participation in this study are minimal; they do not constitute a threat to confidentiality and are not expected to harm the participants.

Data protection is assured by a data encryption process, ensuring the confidentiality and anonymity of each study subject. Decryption is possible with a secure password known only to the principal investigator.

During the multidisciplinary assessments (baseline and end of study assessment), all participants with a new diagnosis of a chronic disease will be referred to their primary care physician for follow-up. Participants will receive laboratory test results by letter. If a clinically significant abnormality was depicted in the laboratorial results, the participant will also be advised to see his or her doctor for further investigation.

Results

The present project was granted by the Public Health Initiatives Programme (PT06) and financed by European Economic Area (EEA) Grants Financial Mechanism 2009-2014. The pilot study with 30 elderly people to test user adherence, TV app diffusion conditions, and subjects' behavioral changes through qualitative analysis has already been performed; results are being analyzed and the TV app is being adjusted according to the participants suggestions.

The randomized controlled trial with the 12-week home-based intervention with a comprehensive program on healthy eating and physical activity delivery is planned to start recruiting participants at the end of 2017.

Discussion

This article describes the protocol of an interventional study aimed to evaluate the effect of a TV-based intervention on healthy lifestyles promotion in the reduction of food insecurity in elderly subjects. We aim to improve health literacy and empower subjects with food insecurity using new ICTs. By

conducting this study, we will add an interventional tool that will promote healthy lifestyles in food insecure subjects.

The growth of new information and communication technologies represents a clear opportunity to develop and implement health interventions using these new tools. In the literature, different advantages of the use of these tools in health interventions have been described, such as the convenience for users and the fact that, with these type of tools, it is possible to reach a large number of individuals in an easy and cost-effective way [39].

Furthermore, the use of a TV app as an informative and motivational tool for healthy lifestyles behaviors in elderly populations will have potential success, since TV plays an important role in their day life. Indeed, data from a national study we performed in Portugal showed that the average Portuguese elderly person spends approximately 3 hours per day watching TV. However, until now, few studies have evaluated the efficacy of these new approaches in healthy lifestyle promotion, in particular their clinical impact and cost-effectiveness [40]. Inconsistent results were found in studies that evaluated the impact of interactive TV programs on quality of life in patients with several comorbidities [41-43]. Evidence in this field is even more scarce if we take into consideration the effectiveness of interventions among disadvantaged populations groups, such as food-insecure individuals.

With this study we expect to provide important information about the impact of an innovative tool such this educational and motivational TV app for healthy lifestyle promotion in food insecure elders. The knowledge and insights gained from this study will be potentially useful for the identification of new and effective models of intervention for the promotion of healthy lifestyle behaviors and consequently better prevention of noncommunicable diseases in food insecure subjects. We expect to prove the effectiveness of this innovative tool for disseminating relevant health information in an easy, low-cost, and massive way.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Measures and data collection points.

[PDF File (Adobe PDF File), 59KB - resprot_v6i3e40_app1.pdf]

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Abbreviations

BMI: body mass index
CAPI: computer-assisted personal interview
EEA: European Economic Area
EMS: Elderly Mobility Scale
EQ-5D-3L: European Quality of Life questionnaire with 5 dimensions and 3 levels
FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue
HADS: Hospital Anxiety and Depression Scale
HAQ: Health Assessment Questionnaire
HFIS: Household Food Insecurity Scale
ICT: information and communication technology
IPAQ: International Physical Activity Questionnaire
PREDIMED: Prevención con Dieta Mediterránea
TV: television

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Protocol

Writing for Health: Rationale and Protocol for a Randomized Controlled Trial of Internet-Based Benefit-Finding Writing for Adults With Type 1 or Type 2 Diabetes

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Abstract

Background: Diabetes mellitus is Australia's fastest growing chronic disease, and has high comorbidity with depression. Both subthreshold depression and diabetes distress are common amongst people with type 1 or type 2 diabetes, and are associated with poorer diabetes self-care. A need exists for low-intensity self-help interventions for large numbers of people with diabetes and diabetes distress or subthreshold depression, as part of a stepped-care approach to meeting the psychological needs of people with diabetes. Benefit-finding writing is a very brief intervention that involves writing about any positive thoughts and feelings about a stressful experience, such as an illness. Benefit-finding writing has been associated with increases in positive affect and positive growth, and has demonstrated promising results in trials amongst other clinical populations. However, benefit-finding writing has not yet been examined in people with diabetes.

Objective: The aim of this randomized controlled trial (RCT) is to evaluate the efficacy of an Internet-based benefit-finding writing (iBFW) intervention for adults with type 1 or type 2 diabetes (compared to a control writing condition) for reducing diabetes distress and increasing benefit-finding in diabetes, and also improving a range of secondary outcomes.

Methods: A two-arm RCT will be conducted, using the online program Writing for Health. Adults with type 1 or type 2 diabetes living in Australia will be recruited using diabetes-related publications and websites, and through advertisements in diabetes services and general practitioners' offices. Potential participants will be referred to the study-specific website for participant information and screening. All data will be collected online. Participants will be randomized to either iBFW about diabetes, or a control writing condition of writing about use-of-time. Both conditions involve three daily sessions (once per day for three consecutive days) of 15-minute online writing exercises. Outcome measures will be administered online at baseline, one-month, and three-month follow-ups.

Results: This trial is currently underway. The primary outcomes will be diabetes distress and benefit-finding in diabetes. Secondary outcomes will be depression, anxiety, diabetes self-care, perceived health, and health care utilization. We aim to recruit 104 participants. All stages of the study will be conducted online using the Writing for Health program. Group differences will be analyzed on an intention-to-treat basis using mixed models repeated measures. Linguistic analyses of the writing exercise scripts, and examinations of the immediate emotional responses to the writing exercises, will also be undertaken.

Conclusions: This RCT will be the first study to examine iBFW for adults with type 1 or type 2 diabetes. If iBFW is found to be efficacious in reducing diabetes distress and improving diabetes self-care and other outcomes, iBFW may offer the potential to be a low-cost, easily accessible self-help intervention to improve the wellbeing of adults with diabetes.

Trial Registration: Australia and New Zealand Clinical Trials Registry (ACTRN12615000241538)

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KEYWORDS

type 1 diabetes; type 2 diabetes; diabetes-related distress; writing; Internet intervention; randomized controlled trial

Introduction

Background

Need for Cost-Effective Psychological Interventions for People with Diabetes

Diabetes mellitus is a global public health challenge. Diabetes is a leading cause of disease burden worldwide [1] and is increasing in prevalence, with an estimated 422 million adults having diabetes in 2014 [2]. The cooccurrence of diabetes and depression is common, with the prevalence rates of depression and anxiety at least twice as high in patients with type 1 or type 2 diabetes compared to the general population worldwide [3-5]. Depression is associated with poor diabetes self-management [6,7] and increased disease severity, complications, and mortality [8,9]. Subthreshold depression (clinically significant symptoms of depression that do not meet diagnostic criteria for a major depressive episode or dysthymia) is more common in people with diabetes than major depression, with approximately half of all adults with type 2 diabetes experiencing at least one episode of subthreshold depression over five years [9]. Even subthreshold depression in diabetes is associated with poorer quality of life [10] and reduced adherence to diabetes self-care (including exercise, diet, and medication) [11], in addition to being a risk factor for future major depression [12].

Diabetes distress is a construct partly overlapping with depression in people with diabetes, and includes negative thoughts and emotions towards diabetes and its treatment [13]. Approximately 10-30% of people with diabetes experience severe diabetes distress [14,15], yet many of these people are not clinically depressed. Approximately 70% of people with type 2 diabetes display high levels of diabetes-related distress without meeting criteria for major depressive disorders [16,17]. Diabetes distress is associated with poor glycemic control, acting as a unique contributor to poor self-care adherence [18]. Diabetes distress is also a risk factor for the incidence and persistence of depressive symptoms [19].

Thus, international guidelines for diabetes management now recognize the importance of psychological care, not only to improve quality of life, but also diabetes self-management and medical outcomes [20]. Screening for both depression and diabetes distress, followed by appropriate interventions, has been recommended [21,22]. A stepped-care approach to the management of depression in people with diabetes has been suggested, with mild or subthreshold symptoms of depression managed within primary care, utilizing evidence-based self-help interventions [23]. This approach is in line with recommendations by the UK National Health Service, and Diabetes UK, for low-intensity psychological interventions to be used for people with diabetes with lower-level depression or distress [24].

Given the large numbers of people affected by diabetes globally, accessibility and cost-effectiveness are key issues in their psychological care. The Internet is an increasingly popular and cost-effective method of increasing access to evidence-based psychological interventions, and overcomes several of the traditional barriers to accessing mental health care, such as cost and concerns about stigma and privacy [25]. The Internet offers great potential for public health and prevention interventions [25]. For people with diabetes, Internet-based programs have demonstrated user acceptability and potential efficacy for improving diabetes self-management [26,27], and efficacy in reducing depression, anxiety, and diabetes distress [28-30]. Therefore, brief, Internet-based interventions have the potential to offer low-cost assistance to large numbers of people with diabetes who are experiencing mild or subthreshold psychological symptoms, as part of a stepped-care approach.

Evolution of Expressive Writing as a Brief Intervention

Therapeutic writing is a brief intervention that aims to improve physical or mental health [31]. The most common form of therapeutic writing is expressive writing (EW), in which thoughts and feelings regarding a stressful event are disclosed in writing, typically for 15-20 minutes for three to four days within a short period of time [32]. EW has been examined in over 250 studies investigating its effects on physical and/or mental health in a wide range of populations, including healthy participants, people with psychological problems, or people with long-term health conditions such as chronic pain, asthma, cancer, cystic fibrosis, or arthritis [31,33]. Mental health benefits of EW have included reduced symptoms of depression [34,35], anxiety [36], and posttraumatic stress [37,38]. Physical health benefits of EW have included improved lung function in asthma patients [39], improved immune function in patients with human immunodeficiency virus infection [40], and reduced fatigue and pain in adults with lupus or rheumatoid arthritis [41]. Evidence for behavioral change following EW also exists, such as decreased health care utilization [32,42], reduced aggression in adolescents [43], and improved exam performance [44]. Several reviews and meta-analyses of EW studies are available [31,33,39,45,46].

However, there are limitations to EW. Results of EW studies are quite variable, and effect sizes are often small. Meta-analyses of the effects of EW have found overall small effects of EW for distress (r=.102) [33] and physical health in medically ill populations (Cohen d=.21) [45]. The mechanisms of EW remain

unclear [31], and tend to differ depending on the exact instructions that are used [47]. Furthermore, EW often involves an immediate increase in negative mood [31], even when followed by longer-term psychological benefits [46]. Thus, it has been suggested that EW in vulnerable populations is best undertaken with therapist support and follow-up [46].

Indeed, pilot trials of EW in people with diabetes have yielded mixed results. A pilot trial of 22 participants with type 1 diabetes randomized to either an EW group (instructed to write about an emotional or stressful topic *related to diabetes* for 20 minutes each day over four consecutive days) or a control group (instructed to write about factual topics related to diabetes) found that, at three-months follow-up, the EW group experienced less depressive symptoms and fewer incidences of physical illness [48]. The difference between the two groups in mean self-recorded blood glucose levels (effect size r=.236) was in the direction of benefit to the EW group, although this difference was not statistically significant [33]. However, a pilot trial of 41 adults with type 2 diabetes randomized to either EW or neutral writing found that EW was associated with a *worsening* in depressive symptoms, with no change in diabetes distress [49]. Of note, in the latter study the EW task involved writing about any stressful experience over the past month rather than a diabetes-specific task.

These findings have led researchers to investigate other variations of therapeutic writing, to maximize benefits and increase positive affect (and reduce distress) during the intervention. By modifying writing instructions, researchers can attempt to increase the likelihood that participants engage in desired cognitive processes, and thereby aim to increase the benefits gained from the writing task [38,47].

Benefit-Finding Writing

Benefit-finding writing involves participants writing about any *positive* thoughts and feelings about a stressful experience, such as an illness. Until recently, research has largely overlooked the utility of positively-focused writing following stressful events or illness [50]. However, there is emerging evidence that the experience of a medical illness often has sequelae that patients view as positive or beneficial [51]. Increased recognition has been given to the concept of *benefit-finding*, defined as, “identifying positive life changes resulting from adversity and negative life stressors, including illness” [52]. Correlated with posttraumatic growth (positive changes in individuals following traumatic life events) [53], benefit-finding has been associated with increased psychosocial wellbeing and decreased depression in a range of clinical populations [52,54], including people with diabetes [55]. Benefit-finding has also been linked with increased optimism, positive affect [56], self-efficacy, and adaptive coping strategies [57]. Benefit-finding in diabetes has been associated with lower symptoms of depression, increased adherence to diabetes self-care, and greater perceived coping effectiveness [55]. Furthermore, benefit-finding amongst parents of children with diabetes has also been associated with better glycemic control in their children [58]. It has therefore been suggested that interventions could be developed to increase benefit-finding in people with diabetes [55].

Benefit-finding writing aims to improve other outcomes by facilitating increased ongoing benefit-finding in relation to a medical condition or stressor. However, this concept has not yet been examined in people with diabetes. To date, benefit-finding writing has been examined in student and community samples [47,59-61], bereaved undergraduate students [62], participants who had recently experienced a relationship dissolution [50], breast cancer patients [42], and adults with lupus or rheumatoid arthritis [41].

Trials in nonclinical populations have found that benefit-finding writing results in less distress and increased positive affect immediately postwriting, compared to EW [60,61]. Benefit-finding writing is associated with greater increases in posttraumatic growth [47], and greater use of cognitive-insight words, compared to standard EW [61].

Two trials in clinical populations have compared benefit-finding writing with EW, with promising results [41,42]. In women with early-stage breast cancer, both benefit-finding and expressive-writing groups had significantly fewer medical appointments for cancer-related morbidities, relative to the control group [42]. In adults with lupus or rheumatoid arthritis, both benefit-finding writing and EW groups had lower fatigue at three months, relative to a control writing group [41]. An interaction with trait anxiety was also found; benefit-finding appeared to be more useful in reducing pain for those with high trait anxiety [41]. Furthermore, the authors noted that all 27 participants in the benefit-finding group were able to write some, “positive thoughts and feelings” about their illness experience [41]. Thus, the limited research on benefit-finding writing to date suggests that it may have the same longer-term health benefits as EW, but with the added advantage of immediate increases in *positive* affect

Rationale for Current Study

EW is a brief, low-cost intervention that can be delivered via the Internet [63-65]. These factors potentially make EW suitable as a short-term, low-intensity intervention to supplement treatment-as-usual for people with diabetes who have lower-level psychological needs [49]. While the results of pilot trials of EW in diabetes are mixed [48,49], benefit-finding writing is a more recent variation of therapeutic writing, which aims to facilitate increased perceptions of positive life changes resulting from adversity and negative life stressors. As outlined above, the limited research on benefit-finding writing suggests that it leads to increases in positive affect and posttraumatic growth, and may have the same physical health benefits as EW in populations with medical conditions. However, benefit-finding writing has not yet been examined in people with diabetes (type 1 or type 2).

Therefore, the current study aims to examine the feasibility and efficacy of an Internet-based benefit-finding writing (iBFW) intervention for adults with type 1 or type 2 diabetes. We seek to evaluate the efficacy of iBFW (compared to a control writing condition) in reducing diabetes distress and increasing benefit-finding in diabetes, and also in reducing symptoms of depression and anxiety, improving diabetes self-care and self-rated health, and improving health-care utilization. This

paper presents the study protocol for this randomized controlled trial (RCT), using the online program *Writing for Health*.

Study Aims and Hypotheses

The primary outcomes of this RCT will be the impact of the iBFW, compared to a control writing condition, on diabetes distress and benefit-finding in diabetes. Our primary hypotheses are that adults with type 1 or type 2 diabetes randomized to receive iBFW will demonstrate significantly reduced diabetes distress and significantly increased benefit-finding for diabetes, compared to the control condition, at both one-month and three-month follow-ups.

Secondary outcomes will include symptoms of depression, symptoms of anxiety, diabetes self-care, health care utilization, and perceived self-health. Our secondary hypotheses are that compared to those in the control condition, the iBFW group will demonstrate significant: (1) reductions in depression symptoms; (2) reductions in anxiety symptoms; (3) increased diabetes self-care; (4) reduced number of visits to health professionals; and (5) improved perceived health, at both one-month and three-month follow-ups.

This study also aims to examine validation of the intervention instructions by investigating immediate emotional responses to the writing tasks, and the number of positive emotion words and cognitive insight words used in the writing tasks. It is hypothesized that compared to those in the control condition, the iBFW group will (1) show greater increases in positive affect postwriting, and (2) use more positive emotion words and more cognitive insight words than the control group.

Methods

Study Design

A 2 (conditions) x 3 (time) RCT design is planned. A flow diagram for the trial is shown in Figure 1. Participants will be randomized to either iBFW or an Internet-based control writing condition. Both conditions involve an intervention of 3 days of online writing. Outcomes will be assessed at 3 time points for both groups: baseline, one-month, and three-months postintervention. We will also assess self-rated current mood immediately prior to and following each writing session, and administer three survey questions (assessing how personal, meaningful, and distressing the writing exercise was) after each writing task. An online *Feedback Questionnaire* to assess user satisfaction and perceived helpfulness will also be administered postintervention.

Figure 1. Study flow chart.

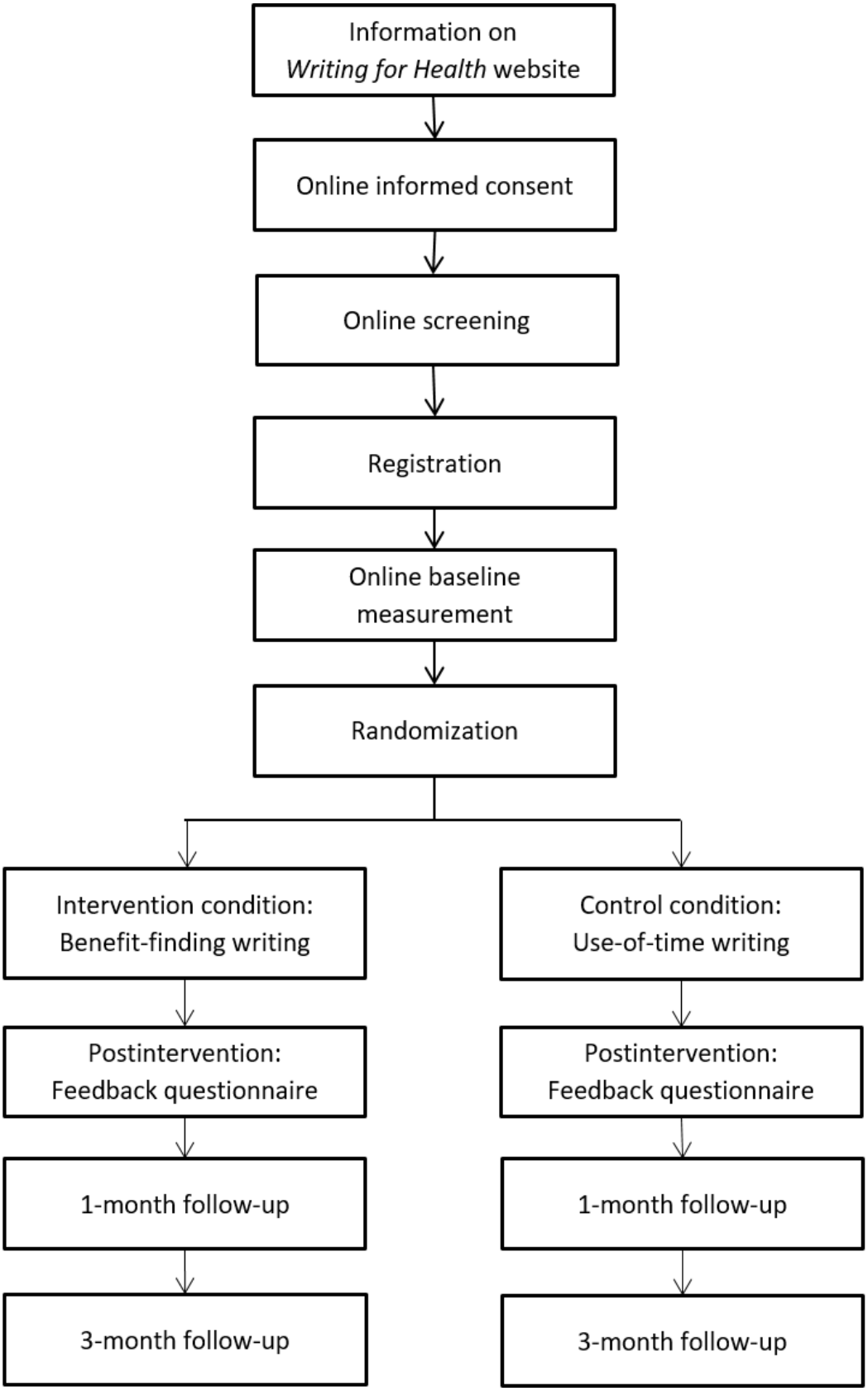
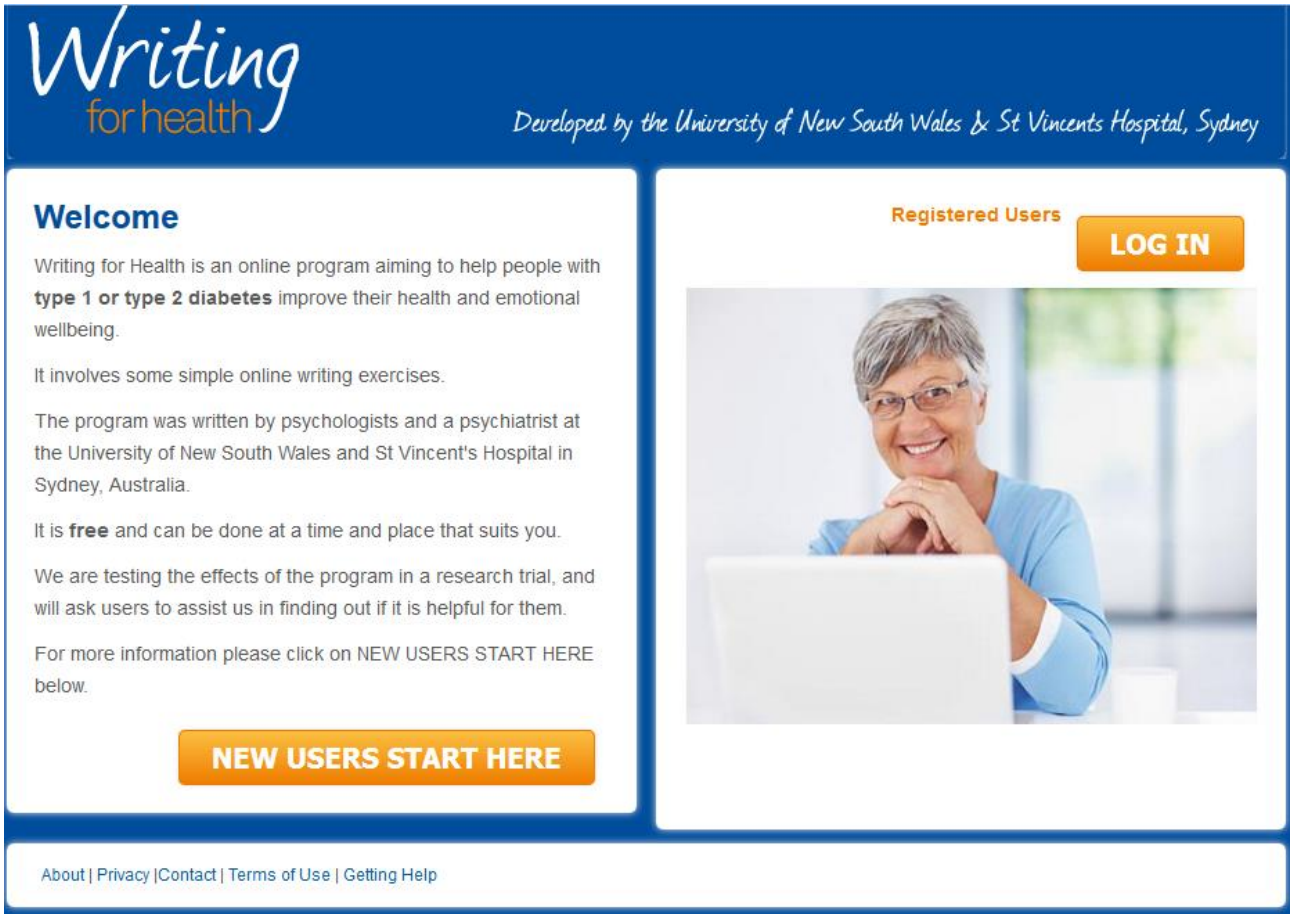


Figure 2. Screenshot of the homepage of Writing for Health.



Participants

Recruitment

Participants will be recruited online from Australian diabetes-related websites and publications, and from advertisements in waiting rooms of diabetes services and general practitioners (GPs) throughout Australia. Participants will apply for the study via the *Writing for Health* website [66], where they will complete an automated screening questionnaire (which also provides baseline data) after reading the study information and provide informed consent. Excluded applicants will immediately receive an onscreen message that informs them that the program is not suitable for them, and will provide links to appropriate resources. All potential participants will be provided with feedback on the severity of their depression and anxiety symptoms. Participants who meet eligibility criteria will proceed to online registration with the program, complete further online questionnaires (for further baseline data), be automatically randomized, and then complete the first writing session.

Eligibility

The inclusion and exclusion criteria and summarized in Textbox 1. Screening will be conducted online in the *Writing for Health* program. If any responses indicate ineligibility, screening will be automatically stopped and the next onscreen page will provide appropriate feedback (including links to relevant resources).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Consent to participate
- Aged 18 years or older
- Living in Australia
- Type 1 or type 2 diabetes, diagnosed by a general practitioner or endocrinologist
- Email address and access to the Internet

Exclusion criteria:

- Inability to read or write in English with ease
- Patient Health Questionnaire-9 (PHQ-9) score >10 and/or Generalized Anxiety Disorder-7 (GAD-7) score >8
- Diagnosis of bipolar disorder or a psychotic disorder
- Diagnosis of dementia or another cognitive disorder
- Current psychological therapy

Ethics

This study protocol has been approved by the Ethics Committee at St. Vincent's Hospital, Sydney, which is certified by the National Health and Medical Research Council in Australia (HREC/13/SVH/379). This trial was prospectively registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12615000241538).

Intervention and Control

Writing for Health

This RCT will be conducted using the online program *Writing for Health* [66], which was developed for this study by mental health researchers (including psychologists and a psychiatrist) at St. Vincent's Hospital, Sydney, and the University of New South Wales. All stages of this study will be conducted online through *Writing for Health*, including information about the study, consent to participate, screening questionnaires with automated feedback, participant registration, randomization to one of two conditions, the writing intervention, and follow-up questionnaires. Automated reminder emails will be sent by *Writing for Health* to participants on each day of the intervention, and when it is time to complete their follow-up questionnaires.

Writing for Health provides minimal clinician assistance. Direct contact between participants and the clinicians will not occur in the standard course of the trial. Psychologists will monitor participant responses and distress levels throughout the intervention, and in accordance with the risk management protocol, will correspond with participants by email and phone to assess any support needed, and refer to appropriate services if required.

Participants registered with *Writing for Health* will be randomized to one of two conditions: iBFW or Internet-based use-of-time writing (control condition). Participants from both conditions will continue to receive usual care from their health services. Following randomization, both conditions involve participants writing online (in the *Writing for Health* program) for 15 minutes once a day, according to instructions provided. There will be three daily 15-minute online writing sessions (once per day for three consecutive days.) A timer on the screen counts down from 15 minutes, to allow participants to keep track of time during their writing session.

Information provided to participants in *Writing for Health* describes the aim of this study as investigating whether the writing exercises in the *Writing for Health* program improve the mental and physical wellbeing of people with diabetes. Participants will be informed that they will be randomized to one of two types of writing exercises, and both types of writing exercises will be described. However, research hypotheses will not be revealed.

Intervention Condition - Internet-Based Benefit-Finding Writing for Diabetes

Participants in the iBFW condition will be asked to write about any *positive* thoughts and feelings that they have had about their experiences with diabetes. The instructions (see Multimedia Appendix 1) are adapted from those used by Stanton and colleagues (2002) in benefit-finding writing for women with breast cancer [42]. The same instructions will be provided for all three of the writing sessions, consistent with previous studies of benefit-finding writing [41,42].

Control Condition - Internet-Based Use-of-Time Writing

Participants in the control condition will be asked to write in detail about how their time was spent that day (first writing session) and plans for how their time will be spent the following day (second writing session) and week (third writing session). Participants will be instructed to be as objective as possible, and to focus on the facts and details of how their time was spent (or will be spent), and not to focus on their emotions or opinions. Writing about use-of-time is a neutral topic that has been previously used as an active control condition in a trial of EW, and was found to be associated with reduced physical and mental health symptoms [63].

Procedure

Potential participants will visit the *Writing for Health* website [66], read the participant information, and indicate their consent to participate by checking a box. Potential participants will complete screening questionnaires with automated feedback, and if eligible, can then register to participate. Following completion of further online questionnaires, participants will be automatically randomized to one of two conditions: iBFW or control writing. Participants can then proceed to the first session of their 3-day writing intervention (either iBFW or control writing). Immediately before and after each of their three 15-minute writing sessions, participants will be asked to rate their current mood. In addition, following each writing session, participants will be asked to rate how personal, meaningful, and distressing their writing session was that day, and can comment on the writing session if they wish. At the completion of their three-day writing intervention, participants will be asked to complete the online *Feedback Questionnaire*, to assess user satisfaction and perceived helpfulness. Outcome measures will be administered in the online *One-Month* and *Three-Month Follow-Up Questionnaires* (in addition to baseline).

Participants will be sent automatic reminder emails by *Writing for Health* on day 2 and day 3 of their writing intervention, and also one-month and three-months postintervention, prompting participants to complete their follow-up questionnaires. All participants will be provided with automatic feedback of the range in which they scored on depression and anxiety measures, at baseline, one-month, and three-month follow-ups.

Risk Management Protocol

Psychologists will monitor participant responses and distress levels throughout the intervention. Although direct contact with participants will not occur during the standard course of the trial, a psychologist or psychiatrist will contact participants by email and/or telephone in certain circumstances, as outlined below. After each writing session, participants will be required to rate how distressing the writing session was on a 6-point scale. If participants indicate that a writing session was at all distressing (by responding 1 or greater), then the *Writing for Health* program will automatically display a feedback page outlining strategies to manage distress and suggest that they contact their GP if further support is needed. This page also includes the telephone number of a 24-hour telephone mental health helpline available in Australia (Lifeline). If the participant responds with a distress rating of 5 or 6 after any writing session, they will also be emailed by a psychologist, with further telephone contact based on the clinical discretion of study psychologists and psychiatrist.

Participants' depression and anxiety scores on the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7), respectively, will also be monitored. If a participant's score is in the severe range for depression or anxiety at one-month or three-month follow-up and/or the participant indicates possible suicidal thoughts by responding 1 or greater on item 9 of the PHQ-9 ("Over the past two weeks, have you been bothered by… thoughts that you would be better off dead, or of hurting yourself in some way?"), the participant will be emailed and then telephoned by a *Writing for Health* psychologist to assess the supports the participant is receiving, and provide contact details or referrals to appropriate services. In addition, the *Writing for Health* program will provide automatic feedback pages at the end of the follow-up questionnaire sessions for participants who have scored in the above ranges, providing information on how to access mental health support, including the recommendation to contact their GP and the telephone number for Lifeline. Similarly, at the final three-month follow-up, the same procedure will apply to participants who score in the moderate or greater range for depression or anxiety on the PHQ-9 or GAD-7, respectively.

Randomization

Randomization to the two groups will be automatically generated by the *Writing for Health* content management system after participants have registered with the program. Randomization is therefore concealed to the researchers.

Primary Outcome Measures

Diabetes Distress

The Diabetes Distress Scale (DDS17) [67] is a 17-item self-report measure of psychosocial stress associated with diabetes, with four reliable subscales: emotional burden (feeling overwhelmed by diabetes), physician-related distress (worries about access, trust, care), regime-related distress (concerns about diet, physical activity, medications), and interpersonal distress (not receiving understanding and appropriate support from others). Cut-off points on the DDS17 have been established for little or no distress, moderate distress, and high distress [68].

Benefit-Finding

The 17-item Benefit Finding Scale [51] was developed to investigate benefit-finding in women with early stage breast cancer. In the current study, the stem question is modified from, "Having had breast cancer has…" to, "Having had diabetes has…" Participants are asked to respond to each of the 17 perceived benefits, such as, "has lead me to be more accepting of things" and, "has brought my family closer together" on a five-point scale with labels of *not at all* (1), *a little* (2), *moderately* (3), *quite a bit* (4), and *extremely* (5). This scale has previously been adapted for use in diabetes (with one item removed) and found to have one large factor and good internal consistency (Cronbach alpha=.89) in a population of adolescents with type 1 diabetes [55]. Table 1 provides an overview of all measurement tools and administration time-points.

Table 1. Measurement tools and questions at each time-point.

		Questionnaires	Baseline	Pre-writing session	Post-writing session	Post-final session	1-month follow-up	3-month follow-up
Demographics			✓					
Primary outcomes								
	Diabetes distress	Diabetes Distress Scale	✓				✓	✓
	Benefit finding	Benefit Finding Scale	✓				✓	✓
Secondary outcomes								
	Depression	Patient Health Questionnaire-9	✓				✓	✓
	Anxiety	Generalized Anxiety Disorder-7	✓				✓	✓
	Diabetes self-care	Summary of Diabetes Self-Care Activities Measure (Revised)	✓				✓	✓
	Self-rated health	Single item	✓				✓	✓
	Health care utilization	Single item	✓				✓	✓
	Positive and negative affect	International Positive and Negative Affect Schedule Short Form		✓	✓			
	Experiences during writing session	Questions assessing how personal, meaningful, and distressing the writing session was			✓			
	User satisfaction	Feedback Questionnaire				✓		

Secondary Outcome Measures

Depression Symptoms

The PHQ-9 [69] is a brief, widely used, reliable, and valid 9-item self-report that measures both the severity of depression over the preceding two weeks and diagnosis of depression based on criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4thEdition (DSM-IV). This questionnaire has established cut-off scores of 5, 10, 15, and 20, representing *mild*, *moderate*, *moderately severe*, and *severe* depression. The total score ranges between 0 and 27, with scores equal or above 10 having a sensitivity of 88% and a specificity of 88% for major depression [69].

Anxiety Symptoms

The GAD-7 [70] is a brief, widely used, reliable, and valid 7-item self-report that measures the severity of anxiety. Scores on the GAD-7 range from 0 to 21; scores of 5, 10, and 15 represent *mild*, *moderate*, and *severe* anxiety symptoms. A total score of 8 on the GAD-7 has been identified as an important threshold for identifying the presence of an anxiety disorder [71].

Positive and Negative Affect

The International Positive and Negative Affect Schedule Short Form (I-PANAS-SF) [72] is a reliable and valid 10-item measure of positive and negative affect, which is comprised of 10 words that represent positive and negative affect. The correlations that this scale has with the positive and negative affect scales of the full 20-item form of the Positive and Negative Affect Schedule (PANAS) are .92 and .95, respectively [72]. Instructions were modified to assess state rather than trait affect, using the instructions of the 20-item PANAS-Immediate Version [73]. Participants will be instructed to indicate the degree of specific affect they feel, “right now, at the present moment”, on a scale of 1 to 5 (1=very slightly/not at all; 5=extremely).

Diabetes Self-Care

The Summary of Diabetes Self-Care Activities Measure (Revised) [74] is an 11-item self-report measure of self-care of diabetes mellitus (including diet, exercise, blood sugar testing, foot care, and smoking) that is widely used both clinically and in research. Items in the revised version were selected based on their psychometric properties, sensitivity to change, and ease of scoring and interpretation [74]. In a critical appraisal of 26 different measures of diabetes outcomes, the Summary of Diabetes Self-Care Activities Measure (Revised) was one of only three measures to meet all criteria of suitability, validity, reliability, and sensitivity to change [75].

Self-Rated Health

Self-rated health will be assessed by the question, “In general, how would you rate your health at present?” The five response options are *very good*, *good*, *fair*, *poor*, and *very poor*. Responses to this question have previously been found to be significantly associated with blood glucose indicator hemoglobin A1c (HbA1c; with poorer self-rated health associated with

higher HbA1c levels) and number of self-reported diabetes-related symptoms in patients with type 2 diabetes [76].

Health Care Utilization

Participants will be asked to answer the question, "In the past month, how many times have you visited a doctor or other health care professional?" This same question will be administered at three time-points: baseline, one-month follow-up, and three-month follow-up.

Additional Measurements

We will collect sociodemographic information (age, gender, education, and occupation), diabetes-related information (type, duration of illness, management, and complications), and participant feedback about the program.

Experiences During Writing Session

Immediately after each writing session, participants will be asked to rate how meaningful, personal, and distressing their writing exercise was, on a 7-point scale (0=not at all; 6=extremely). Similar questions have been used as manipulation checks in previous studies of therapeutic writing [42,77]. In addition, participants in the iBFW intervention condition will be asked immediately after each writing session if they were able to identify *any* positive thoughts or feelings about living with diabetes in their writing session.

Feedback Questionnaire

A 12-item self-report questionnaire was developed to assess participants' experiences and perceptions of the *Writing for Health* program. Item content was informed by self-report measures from other evaluations of Internet-based interventions. Items 1 to 6 ask participants to rate responses on a 5-point scale (from *not at all* to *very*) regarding aspects of usability and perceived helpfulness of the *Writing for Health* program, including how easy to use it was. Items 1 to 3 are taken from the Internet Intervention Evaluation Questionnaire [78]. Items 4 and 5 are modified from items previously used to assess credibility of writing interventions (asking participants to rate how logical the writing exercises seemed and how confident they would be in recommending it to a friend) [79]. Item 6 examined the perceived helpfulness of the writing exercises in reducing stress. Item 7 examined technical difficulties with the online program, and items 8-12 were open-ended questions examining the most helpful and least helpful aspects of the program, and any suggested improvements.

Results

Sample Size

EW studies have typically had modest effect sizes, with meta-analyses reporting small effects of EW for distress (r=.102) [33], and for physical health in medically ill populations (Cohen d=.21) [45]. However, of the few benefit-finding writing studies published, effect sizes appear to be greater than those for EW. Benefit-finding writing has been found to have large within-group effect sizes (Cohen d=.64-1.22) and small-to-moderately large between-group effect sizes (Cohen d=.20-0.66) for improving symptoms of complicated grief, posttraumatic stress disorder, and physical health in bereaved adults (calculated based on means and standard deviations reported in Lichtenthal et al 2010) [62]. Such interventions have also been found to have large between-group effect sizes (Cohen d=.68-2.4) for improvements in somatic symptoms and reduction in medical appointments in women with breast cancer (calculated based on means and standard deviations reported in Stanton et al 2002) [42].

A recent review of therapeutic writing called for future studies to conduct feasibility or pilot studies in new clinical populations, prior to full evaluations with sufficient statistical power to detect modest effect sizes [31]. Given that no previous studies have examined benefit-finding writing in people with diabetes, it would be prudent to first conduct a pilot RCT to examine its feasibility and a preliminary investigation of its efficacy. Other pilot trials of therapeutic writing in clinical populations have taken a similar approach [64,65,80]. Thus, a very large sample required to detect a small effect size is beyond the scope of this initial study.

Given that this study is partially exploratory, we therefore decided to recruit a sample size with sufficient power to detect a moderately large between-groups effect size (Cohen d=.7). Based on statistical power of 0.8 and probability level of P<.05, a sample size of 26 per group (that is, 52 for each of the two groups) will be needed for one-tailed tests. Given the expected attrition rate of up to 50% [81], our target total sample size is therefore 104 individuals.

Statistical Analyses

Statistical analyses will be conducted using SPSS 22 software. Group differences in demographic data, diabetes-related variables, and baseline measures will be analyzed using one-way analysis of variance (continuous variables) and chi-square tests (categorical variables). Similar analyses will be conducted to compare participants who do (nondropouts) and do not (dropouts) complete all questionnaires at each of the time-points, to explore possible biases in study attrition. Analyses will be conducted to validate the writing intervention instructions in several ways:

To examine immediate emotional responses to the writing interventions, scores on the I-PANAS-SF [72] administered immediately before and after each writing session will be analyzed using a 2 (group) x 3 (session) x 2 (positive affect and negative affect) repeated measures multivariate analysis of variance. This test will be used to investigate the hypothesis that the benefit-finding group will have greater increases in positive affect postwriting, relative to the control group.

The content of the written scripts in both groups will be assessed using the Linguistic Inquiry Word Count 2007 software program [82], to examine differences in positive emotion words and cognitive insight words. This validated method provides a content analysis of the language used in the scripts, and quantifies the number of words used from specific categories (eg, emotions, cognitive processes). This approach will be used to investigate the hypothesis that the benefit-finding group will use more positive emotion words and more cognitive insight words than the control group.

Scores on the feedback questionnaire, a measure developed to assess user satisfaction and perceived usefulness of the intervention, will be compared between the two groups using analyses of variances. These tests will be used to examine the hypothesis that the participants in the benefit-finding group will have higher levels of user satisfaction and perceived helpfulness of the writing tasks, relative to the control group.

Outcome data at the one-month and three-month follow-up time-points will be analyzed on an intention-to-treat basis using linear mixed modelling, with time-points as a within-group factor and intervention as a between-group factor. The interaction of time and study condition will be examined in each analysis, as a significant interaction will indicate a group difference in the pattern of change over time in the outcome of interest. Significant interactions will be explored using Bonferroni adjusted comparisons of the two groups at one-month and three-month follow-ups. All effects will be tested at $P<.05$. Within-group and between-group Cohen *d* effect sizes will be calculated.

Trial Status

The trial is currently in the data collection phase. Recruitment to the study commenced in February 2015. Results are expected by July 2017.

Discussion

This study will be the first to examine benefit-finding writing for adults with type 1 or type 2 diabetes. The feasibility and efficacy of this brief intervention will be evaluated in a two-arm RCT, with a three-month follow-up period, in which iBFW for diabetes is compared to an active control condition (use-of-time writing). The participants in this study will be adults with type 1 or type 2 diabetes who may be experiencing diabetes distress and/or mild symptoms of depression or anxiety. Participants with both type 1 and type 2 diabetes will be included in this study, as perceived benefits of living with diabetes have previously been reported by both people with type 1 diabetes [55] and type 2 diabetes [83]. Outcomes assessed will include multiple psychological and diabetes-specific variables, including the primary outcomes of diabetes distress and benefit-finding for diabetes, and secondary outcomes of symptoms of depression and anxiety, diabetes self-care, perceived health, and health care utilization. Furthermore, we will investigate validation of the intervention by examining immediate emotional responses to the writing tasks and conduct linguistic analyses of the writing scripts.

Results from this trial will contribute to the growing body of knowledge about a more recent form of therapeutic writing, known as benefit-finding writing. The limited research on benefit-finding writing to date suggests that it may have the same health benefits of the more commonly researched EW, but with the advantage of increased positive affect immediately following the intervention.

Limitations to this study include the brevity of the follow-up period (three months) and the reliance on self-reported data. Physiological data, such as HbA1c or other indicators of blood glucose level, are not included in this study. The included outcome of health utilization has limitations itself, as participants may not visit health professionals frequently enough for any changes to be detected in the follow-up period of three months. Furthermore, it is unclear as to whether decreased health care utilization is a positive outcome, given that going to an appropriate health professional when a need exists is a good thing [84]. Nevertheless, we have included assessment of this outcome as any changes in health care utilization in people with diabetes would be of interest, and previous trials of EW and benefit-finding writing have reported reductions in health care utilization [42,84].

Similar to many RCTs, the generalizability of our results is restricted by the exclusion criteria. For example, adults with diabetes currently experiencing depression of moderate or greater severity will be excluded from this trial; hence the results will not be able to be generalized to people with diabetes who are currently depressed. Furthermore, the sample size (N=104) will enable the detection of a moderately large effect size, in line with some previous studies of benefit-finding writing [42], but will not allow for the detection of small effect sizes reported in meta-analyses of writing interventions. However, as recommended in a recent comprehensive review of therapeutic writing [31], when investigating new writing interventions in new clinical populations, it is prudent to first conduct feasibility studies and pilot trials. Thus, this novel study will enable a preliminary investigation of the feasibility and efficacy of benefit-finding writing for adults with diabetes.

If the iBFW is found to be helpful for people with type 1 or type 2 diabetes, this intervention will offer the potential to be a low-cost, easily accessible public health intervention to improve the well-being of large numbers of diabetic patients with lower-level psychological needs. Furthermore, benefit-finding writing may also have the potential to assist other populations with chronic conditions.

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Authors' Contributions

JC, KW, and JP conceived of the study and initiated the study design and protocol. JC managed the trail implementation and drafted this paper. LR assisted with implementation of the trail and contributed to this paper. All authors approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Instructions for Internet-based benefit-finding writing (iBFW) for diabetes.

[PDF File (Adobe PDF File), 22KB - resprot_v6i3e42_app1.pdf]

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Abbreviations

DDS17: Diabetes Distress Scale
EW: expressive writing
GAD-7: Generalized Anxiety Disorder-7
HbA1c: hemoglobin A1c

iBFW: Internet-based benefit-finding writing
I-PANAS-SF: International Positive and Negative Affect Schedule Short Form
PANAS: Positive and Negative Affect Schedule
PHQ-9: Patient Health Questionnaire-9
RCT: randomized controlled trial

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Protocol

Automated Adherence Reminders for High Risk Children With Asthma: A Research Protocol

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Abstract

Background: The use of inhaled corticosteroid (ICS) medications has been shown to improve asthma control and reduce asthma-related morbidity and mortality. Two recent randomized trials demonstrated dramatic improvements in ICS adherence by monitoring adherence with electronic sensors and providing automated reminders to participants to take their ICS medications. Given their lower levels of adherence and higher levels of asthma-related emergency department (ED) visits, hospitalizations, and death, urban minority populations could potentially benefit greatly from these types of interventions.

Objective: The principal objective of this study will be to evaluate the feasibility, acceptability, and limited efficacy of a text message (short message service, SMS) reminder intervention to enhance ICS adherence in an urban minority population of children with asthma. We will also assess trajectories of ICS adherence in the 2 months following asthma hospitalization.

Methods: Participants will include 40 children aged 2-13 years, who are currently admitted to the Children's Hospital of Philadelphia (CHOP) for asthma, and their parent or legal guardian. Participants will be assigned to intervention and control arms using a 1:1 randomization scheme. The intervention arm will receive daily text message reminders for a 30-day intervention phase following hospitalization. This will be followed by a 30-day follow-up phase, in which all participants may choose whether or not to receive the text messages. Feasibility will be assessed by measuring (1) retention of the participants through the study phases and (2) perceived usefulness, acceptability, and preferences regarding the intervention components. Limited efficacy outcomes will include percent adherence to prescribed ICS regimen measured using Propeller Health sensors and change in parent-reported asthma control. We will perform an exploratory analysis to assess for discrete trajectories of adherence using group-based trajectory modeling (GBTM).

Results: Study enrollment began in December 2015 and the intervention and follow-up phases are ongoing. Results of the data analysis are expected to be available by December 2016.

Conclusions: This study will add to the literature by providing foundational feasibility data on which elements of a mobile health text-message reminder intervention may need to be modified to suit the needs and constraints of high-risk urban minority populations.

Trial Registration: Clinicaltrials.gov NCT02615743; https://www.clinicaltrials.gov/ct2/show/study/NCT02615743 (Archived with WebCite at http://www.webcitation.org/6ji59rAXN)

(JMIR Res Protoc 2017;6(3):e48) doi:10.2196/resprot.6674

KEYWORDS

asthma; pediatrics; child; child, preschool; adolescent; metered dose inhalers; medication adherence; text messaging; pilot projects; randomized controlled trial; clinical protocols

Introduction

Asthma is the most common chronic medical condition in children in the United States, with 8.3% of children affected [1]. Racial disparities have long existed in both asthma prevalence and morbidity. Several reports from the last few years have demonstrated progress in narrowing the disparities gap in both asthma prevalence [1] and morbidity [2]. Despite this progress, black children with asthma still suffer significantly higher rates of asthma emergency department (ED) visits, hospitalizations, and death compared with their white peers [2].

Use of inhaled corticosteroid (ICS) medications has been shown to improve asthma control and reduce asthma-related exacerbations and hospitalizations [3-5]. Despite this evidence, average adherence to prescribed regimens for ICSs in childhood asthma is only around 50% of prescribed doses [6]. Several studies have demonstrated that adherence rates in urban minority populations in the United States are substantially lower, ranging from 11-37% [7-10]. Yet average rates may be misleading, as research from other studies indicates that patterns of day to day medication adherence are highly variable and these patterns change over time [11-13]. These studies capture the inter- and intra-individual variation in medication use and provide valuable information on the kinetics of different adherence trajectories [11-13]. Such studies may help identify the reasons behind adherence lapses, which, in turn, would allow providers to enhance and better tailor adherence intervention strategies.

Prior interventions to enhance daily medication adherence in children with chronic disease have generated modest, at best, improvements in adherence to recommended regimens [14-17]. However, 2 recent randomized trials from Australia and New Zealand demonstrated dramatic improvements in ICS adherence by monitoring adherence with electronic sensors and providing automated messages to remind participants to take their ICS medications [18,19]. Given their lower levels of adherence, urban minority populations could potentially benefit greatly from these types of interventions. Whether reminder-based interventions are feasible and effective in vulnerable urban populations in the United States, however, is unknown. The factors that drive nonadherence in inner city children with asthma appear more complicated than "just forgetting" [6,20,21]. For this reason, dedicated study of the feasibility and efficacy of automated reminder-based interventions may provide valuable information on how to design and tailor future interventions for this population.

The principal objective of this study will be to evaluate the feasibility, acceptability, and limited efficacy of daily text message (short message service, SMS) reminders as a means to improve adherence to ICS prescriptions in urban minority children with asthma in Philadelphia. We will also assess the longitudinal trajectories of ICS use following hospitalization and explore associations with factors previously associated with nonadherence.

Methods

Overview of Study

This is a pilot randomized controlled trial to assess the feasibility, acceptability, and limited efficacy of text message reminders for daily ICS medication use in high risk children with asthma. Subjects will include children seen in the ED or hospitalized for asthma at the Children's Hospital of Philadelphia (CHOP) and their families. Propeller Health electronic sensors will be placed on ICS metered dose inhalers (MDI) at the time of ED or hospital discharge to measure subsequent medication use in both the intervention group and the regular care control group. The intervention group will receive text message reminders delivered to the caregiver's mobile phone for 30 days following hospitalization. The protocol for the conduct of this study was approved by the CHOP institutional review board and is registered on ClinicalTrials.gov (NCT02615743).

Setting

Subjects will be recruited from the ED and general pediatrics inpatient units at CHOP. CHOP is a large, free-standing, tertiary care children's hospital that also serves as a community hospital for the children of Philadelphia, particularly in the west and southwest regions of the city. There are nearly 6000 ED visits and 2500 inpatient admissions for asthma at CHOP each year.

Participants – Inclusion and Exclusion Criteria

Participants will include 40 children aged 2 to 13 years and their parent or legal guardian. To be enrolled in the study, children and their parent or legal guardian must meet the following eligibility criteria: (1) they must be receiving care for asthma on the ED or inpatient asthma pathways; (2) they must have been prescribed a daily ICS or combined ICS or long-acting beta agonist (LABA) in the year prior to the current admission and the ICS prescribed on discharge must be an MDI compatible with the electronic monitoring sensor (compatible ICS and ICS or LABA medications include Flovent [fluticasone], QVAR [budesonide], Advair MDI [fluticasone-salmeterol], Dulera [mometasone-formoterol], and Asmanex [mometasone-furoate]); (3) children and families must live or receive primary care in Philadelphia ZIP codes with the highest child asthma morbidity (greater than 100 pediatric asthma hospitalizations per year, according to Pennsylvania Health Care Cost Containment Council [22] hospitalization data); and (4) the parent or legal guardian must have a mobile phone plan with unlimited text messages.

Children will be excluded from the study if they are prescribed a controller inhaler to which the electronic device cannot affix (eg, any dry powder inhaler, Symbicort [budesonide or formoterol], or Seretide [fluticasone-salmeterol]) as their primary controller medication. Children with comorbid conditions that may influence the treatment of asthma (such as chronic lung disease, structural heart disease, or cystic fibrosis)

will be excluded. Families will be excluded from the study if they have active state social services involvement or if they are non-English speaking. Subjects with significant developmental delays will also be ineligible.

Outcome Measures

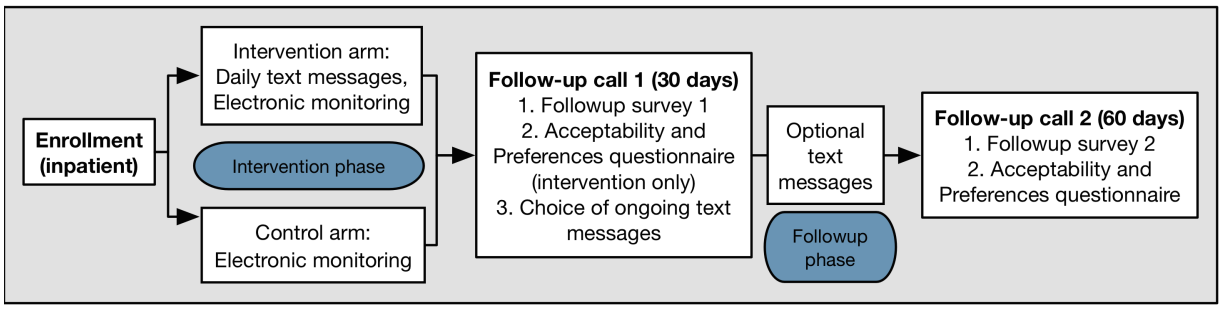
Given that this is a pilot study to assess the feasibility of a text message–based electronic adherence intervention in a vulnerable population, the primary outcomes will be feasibility oriented [23]. Feasibility outcomes will include (1) passive retention through the study and (2) perceived usefulness, acceptability, and preferences regarding the intervention components. Limited efficacy outcomes will include change in parent-reported asthma control and difference in average ICS adherence between the intervention and control conditions. Thirty-day readmissions and parent-reported adherence will be included as secondary outcome measures. Finally, medication use trajectories following hospitalization will be assessed using group-based trajectory modeling.

Feasibility

Feasibility will be assessed in 2 ways: (1) passive retention of participants in the intervention and follow-up phases, indicated by ongoing electronic sensor syncing and (2) text message and its usefulness, acceptability, and preferences, assessed via questionnaire. To assess passive retention, we will monitor duration of the interval that the electronic sensor synced with its receiver (either a mobile phone app or cellular hub). In order to sync effectively, the Bluetooth-enabled sensor must be within range of a functioning (plugged in) cellular hub or an open mobile phone app with Bluetooth enabled. Thus, passive retention represents whether the receiver was capable of transmitting MDI actuations from the sensor during the intervention and follow-up phases of the study. Reasons for missing actuation data will be collected during the follow up calls and during individual calls for participants whose sensors fail to sync within the first 2 days of the intervention phase of the study.

Perceived usefulness, acceptability, and intervention preferences will be measured using a 14-item questionnaire developed de novo for this study and delivered to those who receive the intervention either at follow-up call 1 or 2 (See Figure 1). This survey focused primarily on usefulness and acceptability of the daily text messages, as our prior work in a similar population found electronic sensors to be generally acceptable [24] (see Multimedia Appendix 1).

Figure 1. Study flow diagram.



Limited Efficacy

Limited efficacy outcomes for this study will include (1) percent ICS adherence, as measured by electronic monitoring and (2) average change in parent-reported asthma control, assessed using the parent-reported portion of the child Asthma Control Test [25]. Inhaled controller medication use will be measured in both groups using electronic sensors (see description below) affixed atop of the MDI canister. ICS adherence will be calculated from the daily medication use data as the average percent adherence (observed actuations or prescribed actuations) for the intervention group versus the control group for the 30-day intervention phase. The average change in the parent-reported portion of the child Asthma Control Test score between enrollment and the 30-day follow-up call will be calculated for the intervention and control groups.

Adherence Trajectories

Finally, we will perform an exploratory analysis to assess for discrete trajectories of adherence using group-based trajectory modeling (GBTM). This analysis will include data from both the intervention and follow-up phases of the study. If no significant differences exist in limited efficacy outcomes between the intervention and control groups, data from both groups will be combined to produce pooled trajectory outcomes.

Covariates

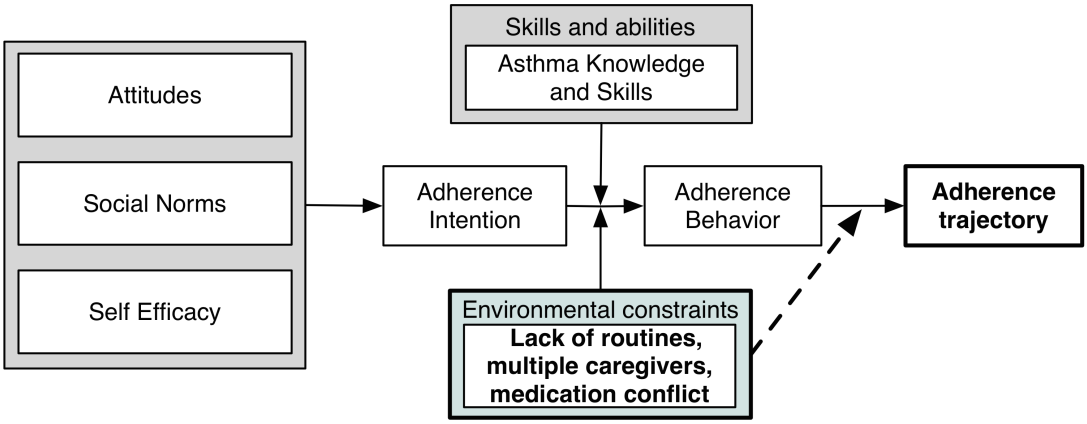
Factors previously shown to be associated with adherence will be assessed using surveys administered to the caregiver upon enrollment and at 30 and 60 days. We adapted a version of the Integrated Behavior Model [26] as a unifying conceptual framework to contextualize these factors that may be influencing adherence patterns. These include medication beliefs, social norms, self-efficacy, intention to adhere to controller medications, asthma knowledge and skills, environmental

constraints (routines, responsibility, and conflict over medication taking), and demographics (see Figure 2).

The Beliefs About Medicines Questionnaire [27] will be used to assess medication beliefs (perceived necessity and concerns regarding ICS use). Descriptive and injunctive social norms will be assessed with separate questions. We will use question blocks from the Caretakers Expectation Scale [28] to assess perceived importance of asthma-related tasks and self-efficacy for each task. The caregiver will be asked to estimate both prior adherence in the previous four weeks, as well as adherence intention for the next 4 weeks. The Asthma Knowledge Questionnaire [29] will assess a basic caregiver understanding of asthma symptoms, triggers, and treatments. The Asthma Routines Questionnaire [30] will measure the strength of routines surrounding asthma care. The Asthma Responsibility Questionnaire [31,32] will assess the degree to which children and caregivers share responsibility for managing asthma. Parent-child conflict over medication use will be measured with 2 questions developed by the study team (see Multimedia Appendix 2).

Demographics will include the caregiver's relationship to the child, age, marital status, family income level, education level, and whether or not he or she is the child's primary caregiver. Child demographic information will include the child's race, ethnicity, age, and number of nights per week he or she typically stays with the primary caregiver.

Figure 2. Conceptual framework adapted from the Integrated Behavioral Model.



Intervention

Enrollment

Potential subjects will be screened through the daily census listings for the ED and general pediatrics inpatient units at CHOP, using the protocol inclusion and exclusion criteria. Parents of eligible participants will be approached for informed consent, screening, and enrollment prior to the patient's discharge from the hospital. Child assent will be obtained from children ages 7 years and older, unless the child is judged to be incapable of assent. If subjects provide consent and enroll, they will complete the initial study visit prior to hospital or ED discharge. As part of enrollment, caregivers will complete an initial 30-minute survey on the Way to Health (WTH) platform (see below for description). Prior to survey completion, participants will be randomized into either the control or intervention group using a 1:1 randomization scheme, stratified by location (ED or inpatient). Each participant will be compensated US $20 through a reusable debit card following completion of each survey, for a total of US $60 for those completing the entire study.

Following the baseline survey, a study team member will attach an electronic sensor to the participant's ICS inhaler. If the participants do not have a currently filled ICS prescription with them in the hospital room, they will be instructed on how to attach the sensor to the child's inhaler when they get home. Participants whose sensors are not attached to the inhaler at discharge will be contacted by phone to achieve an initial sync. Participants who have mobile phones will download the Propeller mobile phone app for data transmission purposes, but the participants will not have access to any information from the app. Preferences for the text messages, which are delivered to the parents' mobile phone via the Way to Health platform (time of day and preferred phone number), will be collected for all participants. Participants will be instructed to use the inhaler as directed by their physician and that they may begin to receive automated text message reminders regarding their child's medication use.

Intervention Phase

The randomized intervention begins the day of discharge from the hospital and lasts 30 days. During this time, the intervention group will receive daily automated text message reminders from the WTH platform at a time of their choosing. In addition to daily text message reminders for the intervention group, both the intervention and control groups will receive programmed text messages when they reach milestones in the study, such as survey or intervention completion. These text messages will also serve as prompts to contact study staff and complete their

next survey. The research team will also program text messages reminding participants to continue syncing their electronic monitoring sensor with its receiver by turning on their Bluetooth, if they are using a mobile phone, or by making sure that their hub is plugged in, if not. A total of 3 syncing reminders will be sent over the course of the intervention. Study staff will send individualized text messages or call participants if the sensor fails to sync in the first 2 days of the intervention phase. Researchers will walk the participant through the syncing process and record any reasons for missing data.

At the end of the 30-day period, families will receive a text message instructing them to set up a follow-up call within the next few days. If the participants don't call within 2-4 days, they will be contacted by the research team. The first follow-up call includes a 10-minute survey for all participants and the questionnaire assessing acceptability and preferences for participants in the intervention arm. After completing the surveys, participants will be asked to choose whether or not to receive text message reminders during the follow-up phase of the study. Automated text messages will be turned on or off for each individual through WTH. All participants will be asked whether they have run out of ICS medication and if they had any problems using the electronic sensor. Any problems that may lead to missing data will be recorded. The participant will then be reminded to transfer the electronic sensor to their new inhaler if or when the prescription is refilled.

Follow-up Phase

The follow-up phase begins the day the first follow-up call is completed and continues until 60 days following the start of the randomized intervention. The follow-up phase lasts up to 30 days. Participants will be given 2 weeks following the end of the follow-up period to complete the second follow-up call.

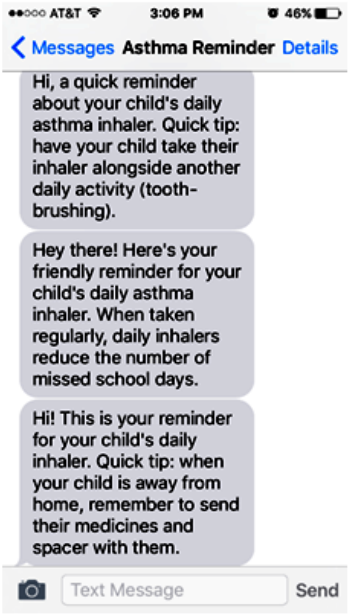
At 60 days, medication adherence monitoring and optional text message reminders will cease and families will receive a message from the study team to set up a second follow-up call (the study completion call) within the next few days. If the participants don't call within 2-4 days, the research team will contact them. The second follow-up call includes a 10-minute survey for all participants. Participants will be asked again whether they have run out of ICS medication or if they had any problems using the electronic sensor and responses will be recorded. Participants initially assigned to the control group who elected to receive text messages during the follow-up phase will also complete the acceptability and preferences questionnaire.

Way to Health Platform

Way to Health (WTH) is a Web-based behavioral intervention toolbox, which automates many of the research functions necessary for conducting randomized controlled trials (waytohealth.org). For this study, the WTH platform will be customized to enroll participants, automate randomization and text message delivery, and complete and store survey data. For participants in the intervention arm, 7 rotating text messages will be programmed into WTH. Each text message will include a reminder to administer the ICS inhaler as well as an asthma-related tip or fact (Figure 3). Each family will be able to customize the time the text message reminders are sent based on caregiver preference.

The Way to Health Platform protects patient information by using a secured firewall accessible only to study research, analysis, and IT staff by use of a password.

Figure 3. Examples of intervention text messages.



Propeller Health System

We will use Propeller Health electronic monitoring sensors to monitor ICS medication use (propellerhealth.com). Propeller Health sensors record the date, time, and number of inhaler actuations. The Propeller Health sensors have been validated and used in previous studies [33,34].

Families with a mobile phone will use the sensor in conjunction with a research "control" version of Propeller Health's mobile app, which receives the medication use data from the sensor through the mobile phone's Bluetooth functionality. Unlike the full Propeller Health mobile app, which provides medication usage summaries, adherence, control status, air quality information, education and personalized trigger information to the participant, the research version provides only medication use and timing data to an encrypted server accessible to the research team alone. Families without a mobile phone will be provided an electronic monitoring device with a paired cellular hub. The hub transmits medication use data from the device to the encrypted server through cellular networks and must be plugged into an electrical outlet for transmission.

The communication between the electronic monitoring sensors and the Propeller Health server is referred to as syncing. Syncing transmits data on inhaler actuations, which refers to medication usage recorded by the sensor. One actuation translates to one single use or puff of the participant's daily controller medication. The Propeller Health research app allows study staff to see when each participant's electronic monitoring sensor last synced with the server. However, it does not display data on device actuations. Thus, study staff will know if a participant's sensor is syncing, but will be blind to each participant's medication

usage data until the end of the intervention interval. The Propeller Health platform will not be used to store protected health information.

Data Analysis

Feasibility

Response rate will be defined as number of participants who complete enrollment, out of the total number of eligible patients who we approach. Passive retention will be evaluated using the median number of days for which the sensor syncs with its mobile phone or hub. Qualitative reasons for missing actuation data (eg, logging out of the app, failing to plug in the hub, or prescription changes) will be recorded if described by the caregiver during follow up or syncing issue calls described above. We will use summary statistics (mean, interquartile range) to describe Likert-based usability, acceptability, and preferences question responses. Qualitative responses regarding what participants liked most about the study and what would make it better will be evaluated for the most common responses.

Limited Efficacy

Bivariate testing will be conducted to assess whether the intervention and control groups are balanced on key characteristics, including demographics, baseline asthma control (based on Child Asthma Control Test score on enrollment), and baseline medication adherence. If the groups are balanced, differences in 30-day adherence proportions and parental perceptions of asthma control between the intervention and control groups will be assessed using *t* tests or Wilcoxon Mann-Whitney tests depending on the distribution of the data. If the groups are unbalanced, regression models will be used to adjust for the unbalanced measured confounders.

Trajectories

We will use GBTM to explore daily longitudinal adherence data for different adherence patterns over time. We will specify several models with the best fit using 3, 4, 5, and 6 group solutions, based on quadratic trajectories and a normal probability distribution. We will compare the models to identify the model and number of groups that best fit the data based on the lowest Bayesian information criterion (BIC) and group percentages that are sufficiently large (eg, >5% of the population). These trajectory groups will be used to assess qualitative trends in medication use that may merit further study.

Results

Study enrollment began in December 2015 and the intervention and follow-up phases are ongoing. Results of the data analysis are expected to be available by December 2016.

Discussion

Contribution to the Literature

This pilot study will evaluate the feasibility, acceptability, and limited efficacy of a text message reminder intervention to improve ICS adherence in an urban minority population of children with asthma. The study will also assess trajectories of ICS adherence in the 2 months following asthma hospitalization to explore how, when, and why ICS use decays following an acute exacerbation and how this may vary between different families.

While there is a substantial body of literature investigating the reasons for poor adherence to asthma controller medications [3-5], traditional approaches to improving adherence have demonstrated inconsistent results [14-17]. New reminder systems that leverage mobile technology have demonstrated promise in improving adherence in certain populations [18,19,35], but how these technologies and interventions may work in cohorts with the highest levels of asthma morbidity and death has not been thoroughly investigated. This study will add to the literature by providing foundational feasibility data on which components of a mobile health text-message reminder intervention are acceptable and useful and which components may need to be modified to suit the needs and constraints of high risk populations.

Limitations

We anticipate several limitations of this study. Since the study is oriented to feasibility, the study is not powered to detect between-groups differences in adherence or adherence trajectories. Differences in actuation data, parent perception of asthma control, and medication use trajectories will be evaluated to assess trends for future efficacy testing.

Given the vulnerable nature of the patient population, researcher's ability to contact caregivers for follow-up calls will limit both completion of the intervention and follow-up surveys and ongoing syncing. Many parents have changing work schedules that make it difficult to predict availability for follow-up calls in advance. Parents also frequently change their primary phone numbers, which limits follow-up and may affect whether they receive the text message intervention for the entire study period. We will reduce this limitation by asking participants for multiple contact numbers and recording preferred times to receive calls.

Most families in this study will go home with a new ICS prescription at discharge, however, the prescription is not always filled at the on-site pharmacy, so the sensor will not always be applied by study staff. In this circumstance, the caregiver must successfully fill the prescription at their pharmacy and correctly attach the electronic sensor themselves in order for actuation data to be available. To address this concern, research staff will conduct reminder calls in the few days following discharge. As a result of this limitation, actuation data at the front end of the intervention phase may be missing for some participants.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Acceptability and preferences questionnaire.

[PDF File (Adobe PDF File), 107KB - resprot_v6i3e48_app1.pdf]

Multimedia Appendix 2

Parent child conflict survey items.

[PDF File (Adobe PDF File), 83KB - resprot_v6i3e48_app2.pdf]

Multimedia Appendix 3

EHealth Consort checklist version 1.6.1.

[PDF File (Adobe PDF File), 725KB - resprot_v6i3e48_app3.pdf]

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Abbreviations

BIC: Bayesian information criterion
ED: emergency department
GBTM: group-based trajectory modeling
ICS: inhaled corticosteroid
LABA: long-acting beta agonist
MDI: metered dose inhalers
SMS: short message service
WTH: Way to Health

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Protocol

Effectiveness of a 16-Week Multimodal Exercise Program on Individuals With Dementia: Study Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: The increasing prevalence of dementia in the next decades is accompanied by various societal and economic problems. Previous studies have suggested that physical activity positively affects motor and cognitive skills in individuals with dementia (IWD). However, there is insufficient evidence probably related to several methodological limitations. Moreover, to date adequate physical activity interventions specifically developed for IWD are lacking.

Objective: This study aims to investigate the effectiveness of a multimodal exercise program (MEP) on motor and cognitive skills in IWD in a high-quality multicenter trial.

Methods: A multicenter randomized controlled trial with baseline and postassessments will be performed. It is planned to enroll 405 participants with dementia of mild to moderate stage, aged 65 years and older. The intervention group will participate in a 16-week ritualized MEP especially developed for IWD. The effectiveness of the MEP on the primary outcomes balance, mobility, and gait will be examined using a comprehensive test battery. Secondary outcomes are strength and function of lower limbs, activities of daily living, and cognition (overall cognition, language, processing speed, learning and memory, and visual spatial cognition).

Results: Enrollment for the study started in May 2015. It is planned to complete postassessments by the beginning of 2017. Results are expected to be available in the first half of 2017.

Conclusions: This study will contribute to enhancing evidence for the effects of physical activity on motor and cognitive skills in IWD. Compared to previous studies, this study is characterized by a dementia-specific intervention based on scientific knowledge, a combination of motor and cognitive tasks in the intervention, and high standards regarding methodology. Findings are highly relevant to influence the multiple motor and cognitive impairments of IWD who are often participating in limited physical activity.

Trial Registration: German Clinical Trials Register DRKS00010538; https://drks-neu.uniklinik-freiburg.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00010538 (Archived by WebCite at http://www.webcitation.org/6oVGMbbMD)

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KEYWORDS

physical activity; dementia; postural balance; gait; activities of daily living; cognition; exercise

Introduction

Dementia is one of the most frequently occurring diseases in the elderly [1], and the World Health Organization has declared dementia a public health priority [2]. The current prevalence of dementia is estimated at 47 million worldwide [3] and will presumably increase because of expected demographic changes [4]. This increasing prevalence (expected 135 million in 2050 [5]) will be accompanied by several societal and economic problems including rising disease-related costs and increasing demands for caregiving [2].

Dementia is a syndrome which comprises several different types of usually chronic and progressive diseases of the brain (eg, Alzheimer disease or vascular dementia) [6]. It encompasses diverse impairments and symptoms which affect individuals with dementia (IWD) in different ways depending on dementia type [7]. According to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Edition* (ICD-10) [6], a diagnosis of dementia minimally requires the following symptoms: an impaired memory, further cognitive disturbances, and noncognitive disorders such as disturbed emotional control. These impairments potentially influence activities of daily living (ADL) [6] accompanied by an increasing loss of independence to a greater or lesser extent [8]. In addition, IWD suffer from motor and functional impairments such as affected gait and balance performance as well as transfer movements, which are not only reported in advanced stages [9-11].

To date, there is no cure for dementia, and commonly used medications for treating the symptoms of dementia have side effects emphasizing the urgent need for nonpharmacological interventions [12]. For instance, there is evidence that physical activity positively affects motor and cognitive skills of cognitively healthy elderly people [13]. Moreover, the number of studies analyzing this issue in IWD has increased [14-18]. For this sample, there are also systematic reviews and meta-analyses examining the effects of physical activity on balance, mobility, and gait as well as strength and ADL. Regarding balance, 3 of 5 reviews reported no or no clear benefit of physical activity [19-21] with largely varying effect sizes from small negative to large positive values [22,23]. Even if a positive effect of physical activity on mobility can be reported [19,21,24], the overall conclusion is inconsistent [20] with effect sizes ranging from small negative to large positive values [22,23]. Only a few reviews have considered specific aspects of gait function. One review has shown no to medium effect sizes for normal gait speed [22]. Reviews focusing on strength of lower limbs and ADL mainly reported improvements [19-26]. However, the small number of high-quality studies and the large heterogeneity in methods used in these studies represent insufficient evidence regarding the effects of physical activity [22,26].

Reviews and meta-analyses examining the effects of physical activity on cognitive skills in IWD mainly assess overall cognition. Of 6 reviews and meta-analyses, 3 found no evidence for the benefit of physical activity on cognition in IWD [20,26,27] while the others found a positive overall effect [12,19,28]. Groot et al [12] stated that overall effects of physical activity on cognition are comparable to the effect size observed in meta-analyses examining the effectiveness of pharmacotherapy in IWD [29-31].

Most of the systematic reviews and meta-analyses suggest even if evidence is lacking that physical activity positively affects IWD, for example, in balance, mobility, and cognition. Their conclusions are that there is an urgent need for high-quality intervention studies [12,20,22,23,27]. In their opinion, methodological shortcomings including insufficient reporting of methods and results and small samples as well as the use of inadequate outcome measures [12,22,27,28] could be responsible for the lack of conclusive evidence. Furthermore, Hauer et al [32] discussed that low effectiveness of existing physical activity interventions may explain negative or inconsistent findings in previous studies. It can be speculated that the effectiveness of existing training interventions is limited by inappropriate intensity, duration, type of training, lack of specific interventions, or individualization of training [32].

This study will investigate the effects of a physical activity intervention on motor and cognitive skills. The intervention focuses on dementia-specific motor deficits and aims to influence the underlying motor performance, which depends on complex cognitive processes like integrating sensory information, central processing, or efferent motor output [33]. This reflects the close connection between cognitive and motor functions and could provide insights in disease progression [34]. It is highly relevant for IWD to counteract and possibly reduce dementia-related motor deficits which typically result in distinct constraints of mobility-dependent quality of life as well as loss of independence and higher risk for falls [35-37]. Hence, primary outcomes are based on 3 considerations: dementia-specific motor deficits, relevance for everyday life, and measurement quality (direct and feasible measurements). Balance, gait, and mobility fulfill all requirements and influence quality of life [9,10,38,39]. ADL are defined as secondary outcomes because they are considered an entire construct related to several motor and cognitive skills. Thus, measuring ADL is more difficult and less objective than measuring balance, mobility, and gait. Further, we chose strength and function of lower limbs and cognition as secondary outcomes because of their expected influence on primary outcomes.

Aiming to overcome the above mentioned methodological limitations, we will realize a high-quality multicenter trial with a sustainable intervention close to everyday life. The following aims will be addressed.

Primary aim: to determine the effect of a multimodal exercise program (MEP) compared to conventional treatment (eg, medication, care, therapeutic applications) on balance, mobility, and gait. We hypothesize that a 16-week MEP in addition to conventional treatment affects balance, mobility, and gait in IWD more than the conventional treatment. Additionally, we will compare different subgroups (eg, according to sex, stage of dementia, or attendance).

Secondary aim: to investigate the influence of mediator and moderator variables on primary outcome measures. We assume that the effects of physical activity on balance, mobility, and

gait are caused or influenced by changes in underlying motor and cognitive skills.

Comparably, we will investigate the effect of MEP on the secondary outcomes strength and function of lower limbs, ADL, and cognition as well as the effect of mediator and moderator variables on ADL. By addressing these aims, this study contributes to enhancing evidence concerning the effects of physical activity on motor and cognitive skills in IWD.

Methods

Study Design

The study design has been primarily defined to address the primary aim of the study on the effectiveness of a 16-week MEP. For this reason, we will perform a multicenter randomized controlled trial with baseline and postassessments and an allocation ratio of 2:1 for intervention (IG) and control group (CG), respectively. Ethical approval has been obtained from the ethics commission of the Karlsruhe Institute of Technology. The study is retrospectively registered in the German National Register of Clinical Trials [DRKS00010538]. This study protocol considers guidelines and recommendations of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [40,41] and Consolidated Standards of Reporting Trials (CONSORT) statements [42-44].

Participants

Participants for this study will be recruited in public, private, and charitable care facilities in southwestern Germany, in particular in the metropolitan region Rhein-Neckar and the district around Karlsruhe. All randomly selected care facilities offer inpatient care for approximately 60 to 300 residents and provide a common room where the intervention will be performed. A total of 3 recruitment periods with consecutive sampling within each care facility are planned.

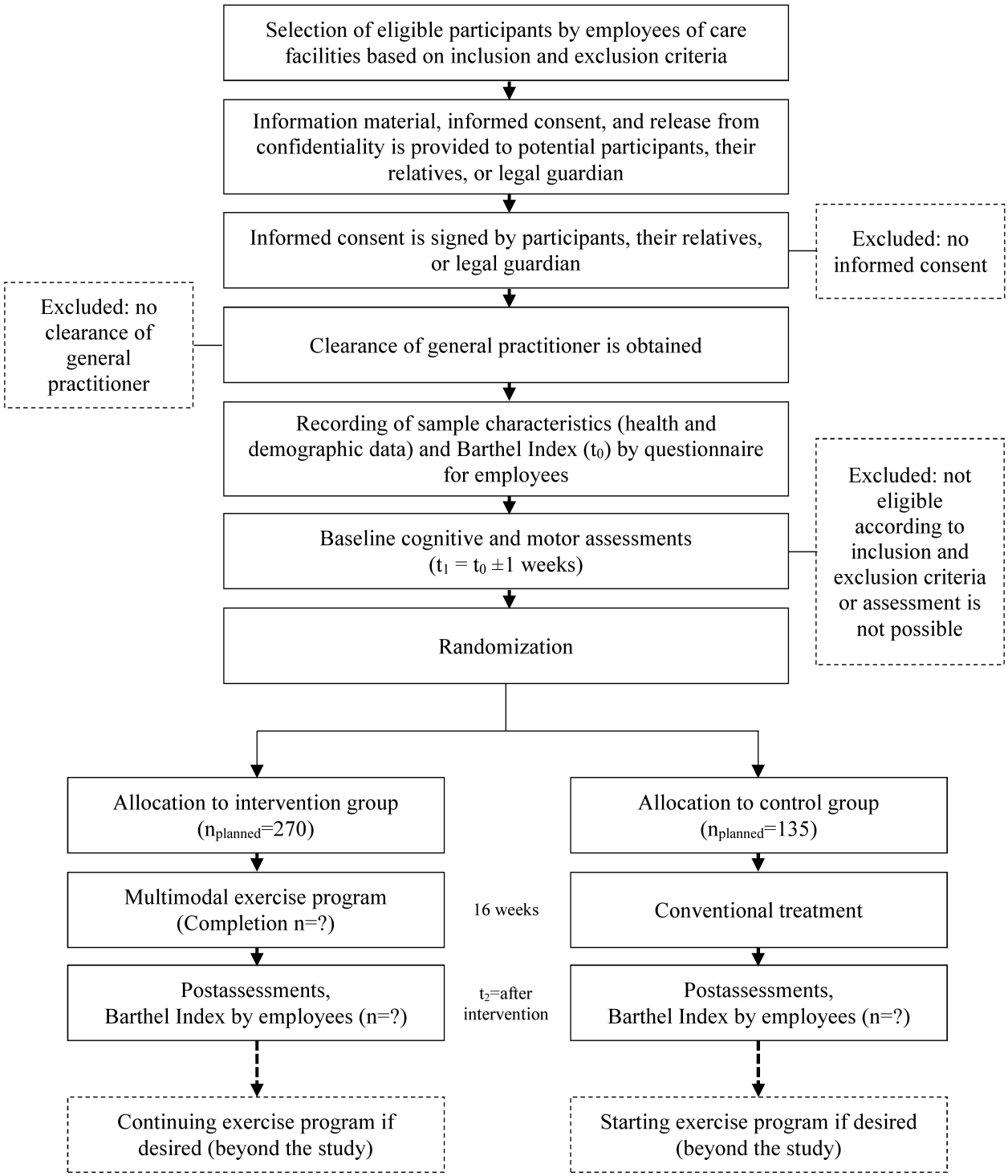
Employees of care facilities will identify possible participants with the purpose to fulfill selection criteria.

Inclusion criteria include (1) diagnosis of dementia or suspected dementia (based on the assessment of the objective ICD-10 criteria by employees and the examination of cognitive abilities with Mini-Mental State Examination [MMSE][45]), (2) Alzheimer disease, vascular dementia, or other primary dementia (all types caused by neurodegenerative or vascular diseases: eg, lewy body dementia or frontotemporal dementia [46]), (3) mild to moderate stage of dementia (MMSE 10-24), (4) age above 65 years, (5) walking ability of approximately 10 meters with or without walking aid, and (6) clearance by general practitioner.

Exclusion criteria include (1) secondary dementia (all types resulting from organic illness or injury: eg, toxic substances or brain injuries [46]), (2) other severe cognitive impairments, (3) other severe neurological disease, (4) other severely acute diseases, and (5) severe motor impairments.

Potential participants will receive a comprehensive information letter and an informed consent form, which will be signed by individuals or their legal guardians prior to the study. The informed consent along with clearance of participant's general practitioner allow scheduling of baseline assessments where eligibility will be verified according to the inclusion and exclusion criteria. Flow of participants is illustrated in Figure 1.

Figure 1. Flow of participants.



Intervention

The intervention is specifically developed for this study based on theoretical considerations, results of a pilot study [47], and a literature review [48]. The combination of motor and cognitive tasks used in the MEP aims to enhance the effectiveness of physical activity on cognition. This is theoretically supported by findings in healthy older adults showing that the combination of both yields larger effects on cognition than using each alone [49]. The pilot study (n=19) aimed to prove feasibility of the intervention and allowed first insights regarding the effectiveness. After a 10-week intervention, IG showed no significant changes in Alzheimer Disease Assessment Scale–Cognitive Subscale (ADAS-Cog, German version) [50] sum score but significant improvements in subscore orientation/praxis. In contrast, we found a significant decline in ADAS-Cog sum score of CG [47]. Moreover, IG showed significant improvements in get-up-and-go test whereas CG did not significantly improve (unpublished results). The literature review aimed at giving recommendations for designing interventions for IWD. Analyzed studies showed that a physical activity intervention for IWD should at least last 4 months with

2 to 3 sessions of 45 to 60 minutes per week. Moreover, interventions focusing on several motor skills (eg, endurance, strength, balance) seemed to be more effective than interventions with only 1 task [48]. Hence, the 10-week intervention of the pilot study has been revised for the current study. The revision, which aimed to provide a balanced MEP with specific, adequate, and intensity-demanding tasks, comprises adjustments of contents (motor qualities as well as connection between motor and cognitive tasks) and intervention duration (extension to 16 weeks).

The MEP will be guided by 2 skilled instructors with experience in sports science and performed as group training mainly in a seated position. A group will consist of a maximum of 12 participants and will be joined by familiar caregivers to support the instructors if needed. The underlying didactic concept focuses on specific needs and characteristics of IWD and includes increased supervision realized by 2 instructors, adaptation to the cognitive level of participants, adjusted communication (eg, simple language, nonverbal aspects), ritualization to give orientation and familiarity, and adequate complexity by simple and well-structured cognitive and motor tasks.

To ensure high standards and comparability, each session is planned in detail and all instructors participate in a special training focusing on structure and contents of MEP as well as special demands resulting from the characteristics of IWD. A detailed training manual is provided for instructors, and the adherence to this manual will be emphasized. To ensure standardization, all tasks are described precisely and photographs are provided.

Providing a sense of security is an important aspect realized by ritualization. To satisfy this ritualization, the general sequence is identical for all sessions including an imagination of experienced journeys. Each session is divided into 3 parts: arrival, destination, and departure. Whereas arrival and departure remain consistent over the whole intervention period, a new travel destination is selected every time. A total sample session of MEP is found in Multimedia Appendix 1.

The arrival as beginning ritual of each training session takes about 5 to 7 minutes and aims to prepare participants for the following main part. Tasks for mobilization and stimulation of the cardiovascular system are linked to cognitive activation.

The main part of MEP is the destination (about 35 minutes) which includes tasks for strength (43%), balance (25%), endurance (16%), flexibility (13%), and not further specified tasks (3%) (see Figure 2). In addition, cognitive tasks are incorporated to stimulate memory, attention, language, and executive functions. Tasks are carried out with medium to submaximal intensity. Throughout the intervention, there will be a progression concerning intensity as well as motor and cognitive requirements. Examples of different motor and cognitive tasks as well as examples for their progression are given in Table 1.

Table 1. Examples of motor and cognitive tasks of the multimodal exercise program and their progression.

		Simple performance	Progressive performance developed within the 16 weeks
Strength			
	Imagination/journey	Mediterranean cruise – aquafitness on the deck of the ship	Circus – task after tightrope dance
	Starting position	Seated, arms stretched above head	Standing upright behind chair, arms stretched above head
	Motor task	Lateral flexion with pool noodle	Lateral flexion with rope
	Sets and repetitions	3 sets with 2 repetitions for each side	2 sets with 3 repetitions for each side
	Muscle activity	Upper limbs and core	Upper limbs, core, and lower limbs
	Cognitive task	No additional cognitive task	Answering questions about circus performances (eg, Have you ever been to a circus? If yes: Which was the best circus act? If no: What do you think would be the most interesting thing if you visited a circus?)
Balance			
	Imagination/journey	Safari in Namibia – washing an elephant	World trip – washing an elephant
	Starting position	Seated, 1 arm is horizontally stretched, flexion in hip joint to shift body weight forward	Standing upright behind chair, one arm is horizontally stretched, flexion in hip joint to shift body weight forward
	Motor task	Slow and large arm movements in horizontal plane holding a small sandbag while leaning to left and right sides	Slow and large arm movements in horizontal plane holding a small sandbag while leaning to left and right sides
	Cognitive task	Answering questions about elephants (eg, Have you ever seen an elephant? Are there different kinds of elephants? What are the differences?)	Counting to 180 in steps of 6 (change hands at 90)
	Duration/repetitions	1 minute/approximately 10 repetitions per side	Approximately 1:30 minutes/15 repetitions per side
Endurance			
	Imagination/journey	Soccer World Cup – walking to the soccer training	On a treasure island – walking downhill through the jungle
	Starting position	Seated	Standing upright behind chair
	Motor task	“Walking” in seated position – lifting legs with active use of arms	“Walking” on the spot – lifting legs with active use of arms (if possible)
	Duration	1 minute	3 minutes
	Cognitive task	Answering questions about soccer and its rules (eg, Who knows some soccer rules? Do you know how many referees there are during a game?)	Naming animals living in the jungle. If a participant repeats an animal he or she is asked to name another one
Flexibility			
	Imagination/journey	Safari in Namibia – wood chopping for a campfire	Olympic Games – laola wave of the audience
	Starting position	Seated	Standing upright behind chair

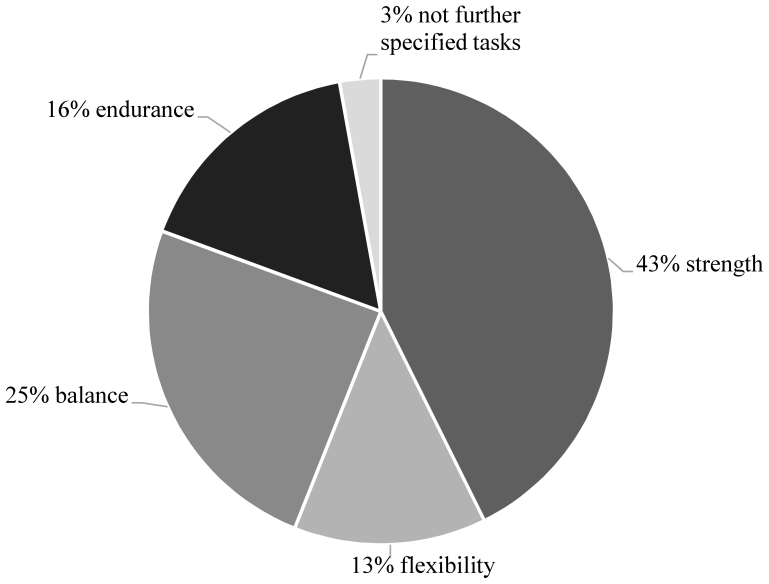
		Simple performance	Progressive performance developed within the 16 weeks
	Motor task	Extention and flexion of the trunk, bringing arms in extention with maximal personal range of motion	Extention and flexion of the trunk, bringing arms in extention with maximal personal range of motion (try to increase range of motion)
	Set and repetitions/duration	3 sets with 10 repetitions (5 repetitions slow, 5 repetitions fast)	No repetitions defined, duration 3 minutes
	Cognitive task (example)	Performing in the same rhythm synchronous with other participants, 5 slow hits, 5 faster hits	Learning 3 different signals: 1= moving fast, 2= moving slow, 3= change direction of laola wave, performing according to signals

The departure takes about 5 minutes and aims to cool down and relax the body while leading participants out of imagination and back into reality. Similarly to the arrival, instructors guide participants through fixed sequences.

The MEP takes place twice a week on nonconsecutive days over a period of 16 weeks. Each session lasts 60 minutes with motor and cognitive tasks taking about 45 minutes to ensure sufficient time for rests and explanations. Prior to the first session, a social gathering session is held aiming for an initial familiarization and information acquisition with regard to participants and care facilities. Attendance and adherence of participants will be documented by instructors for each session. Adherence will be assessed using a short formula to rate attention, participation, motivation, and behavior of each participant.

Conventional treatment comprising, for instance, medication, care, or therapeutic applications is individually tailored and will be continued in all included participants of CG as well as IG.

Figure 2. Distribution of motor qualities within the main parts of the multimodal exercise program.



Outcomes

Determination of Outcomes

Primary outcomes refer to the motor qualities balance, mobility, and gait. Secondary outcomes are other motor variables such as strength and function of lower limbs and ADL as well as cognitive variables assessing overall cognition, language, processing speed, learning and memory, and visual spatial cognition. All outcome parameters are listed in Table 2. The aim of this study is to investigate changes in outcomes between IG and CG. Furthermore, the focus is on differences in all outcome variables between baseline and 16-week postassessment.

Table 2. Primary and secondary outcome parameters.

	Outcome	Assessments (at baseline and 16-week postassessment)
Primary outcomes		
	Balance	Frailty and Injuries: Cooperative Studies of Intervention Techniques 4 (FICSIT-4) [51]
	Mobility	
		Timed Up and Go test [52]
		6-meter walk test [53]
	Gait	Gait analysis using GAITRite: temporal and spatial gait parameters (gait speed, cadence, cycle time, step length, step width, gait variability, single support, and double support)
		- Walking with normal speed
		- Walking with normal speed and the task counting backwards from 50
		- Walking with normal speed and the task naming animals
Secondary outcomes		
	Lower limb strength	Modified 30-second chair-stand test [54,55]
	Lower limb function	Short physical performance battery [56]
	Activities of daily living	
		Barthel Index (German version according to Hamburger Einstufungsmanual [57,58])
		Erlangen Test of Activities of Daily Living (E-ADL-Test) [59]
		7-item physical performance test [60]
	Overall cognition	Mini-Mental State Examination (MMSE) [45]
	Language	
		Verbal fluency “category animals”
		Phonemic fluency “S-words”
	Processing speed	Trail Making Test A [61,62]
	Learning and memory	
		California Verbal Learning Test, short version 1 [63]
		Digit span forward and backward [64]
	Visual spatial cognition	Clock drawing test [65]

The primary and secondary outcomes have been discussed in an international expert panel consisting of 14 scientists from 7 institutions in 3 countries (Germany, Australia, and Netherlands) with the disciplines sports science (especially focusing on locomotion research, sports therapy, kinesiology, biomechanics, training science, physical education and health, diagnostics, evaluation, and sports psychology), geriatrics/gerontology, psychology, and physiology. Among these experts, a standardized testing procedure has been determined focusing on relevance of outcomes as well as validity, reliability, objectivity, and feasibility of recording methods. The selected outcomes and recording methods are common in geriatric assessments and have been frequently used in previous studies examining IWD. However, it must be pointed out that most of recording methods regarding the motor qualities have not been developed for IWD. Feasibility of the test battery and recording procedure was tested in a sample of 20 participants prior to the current study. This pilot study proved feasibility of planned assessments in IWD.

Trained investigators with experience in sports science guide the baseline and postassessments in the care facilities. Prior to assessments, investigators participate in a special course to get detailed information about testing procedure and measurements. To standardize testing procedure and ensure comparability, a detailed testing manual is provided to which investigators are urged to strictly adhere. Accordingly, a detailed description of performing each assessment is given in Multimedia Appendix 2. Moreover, investigators will be educated about specific aspects of working with IWD.

Primary Outcomes

Static balance will be determined using the Frailty and Injuries: Cooperative Studies of Intervention Techniques 4 scale (FICSIT-4) [51]. Mobility will be assessed using the timed Up and Go test [52] and 6-meter walk test [53]. The 6-meter walk test aims to capture normal gait speed. To reduce bias caused by the testing situation, participants are not explicitly informed about time keeping.

Temporal and spatial gait parameters will be analyzed using the electronic gait analysis system GAITRite (CIR Systems Inc, Franklin, NJ) with an active length of 4.88 meters, a spatial resolution of 1.27 centimeters, and a scan rate of 120 hertz. The following parameters are of special interest: gait speed, cadence, cycle time, step length, step width, gait variability, single support, and double support (as percentage of cycle time). Gait parameters are recorded for 3 different conditions: walking with normal speed, walking with normal speed and the task of counting backwards from 50, and walking with normal speed and the task of naming animals.

Changes in gait parameters caused by dual task will be calculated using the equation seen in Figure 3. The generated value represents dual-task costs indicating the better performance under dual-task condition the lower this value is [66,67].

Figure 3. Calculation of changes in gait parameters caused by dual task.

$$\frac{dual\ task - single\ task}{single\ task\ x\ 100}$$

Secondary Outcomes

Strength of lower limbs will be determined by modified 30-second chair-stand test. In this modified version participants are allowed to use their arms [54,55], and the time to perform 5 repetitions is additionally measured. After a rest, fit participants complete a second trial without using arms with the same recording procedure as for the modified 30-second chair-stand test (including time for 5 repetitions). Function of lower limbs will be evaluated using the short physical performance battery, consisting of standing balance (Romberg, semitandem, tandem), gait speed, and 5 times sit-to-stand without using arms [56].

ADL will be determined using the Barthel Index (German version according to Hamburger Einstufungsmanual [57,58]), Erlangen Test of Activities of Daily Living (E-ADL-Test) [59], and 7-item physical performance test [60]. The Barthel Index will be completed by employees of the care facilities. To ensure standardized answers, employees receive a manual with detailed information. The E-ADL-Test and the 7-item physical performance test aim to practically examine ADL. Although the revalidation of the E-ADL-Test [59,68] showed that the tasks are too easy for mild dementia, for our target sample this test is considered as appropriate substantiated by the development for IWD. Furthermore, the E-ADL-Test is regarded as a valid and reliable instrument for assessing ADL of individuals with moderate to severe dementia [59,68].

Cognitive outcomes will be assessed using some subtests of the neuropsychological test battery Consortium to Establish a Registry for Alzheimer's Disease–Plus (CERAD-Plus) [69]. Overall cognition will be determined using MMSE [45]. Language will be examined regarding verbal fluency “category animals” and phonemic fluency “S-words.” The first fluency task provides information about verbal rate and fluency, semantic memory, language, executive function, and cognitive flexibility [70,71]. The second task examines fluency in a more strategic manner rather than the semantic memory. Processing speed and visual scanning will be determined using the Trail Making Test A [61,62]. In addition to CERAD-Plus, the California Verbal Learning Test, short version 1 (except forced choice recognition) [63], and digit span forward and backward [64] will be performed to assess learning and memory. Visual spatial cognition will be assessed using the clock drawing test [65].

Moreover, body mass and height will be measured using a Seca 813 Robusta scale and Seca 213 stadiometer (Seca, Hamburg, Germany) with an accuracy of 0.1 kilogram and 0.1 centimeter, respectively.

Sample Characteristics

Further possible influencing variables including age, medication, or other diseases are recorded chronologically close to baseline assessments. Employees of the care facilities will be asked to complete the health and demographic data questionnaire and the Cumulative Illness Rating Scale [72] for each participant. The questionnaire includes sex, year of birth, diagnosis of dementia, severity of dementia, type of dementia, date of diagnosis, depression, severity of depression, number of medications, medications for dementia, antidepressants, and walking aids. A written consent to collect these data by employees of the care facilities will be obtained from participants or their legal guardian.

Sample Size

The required sample size was calculated via G*Power version 3.1.9.2 (Heinrich Heine University of Dusseldorf) [73], taking into account the following parameters: analysis of variance (ANOVA) for repeated measures, within-between interaction, small effect size (²=0.01, d=0.2) [74], 2-sided α-error of .05, power of .80 (1-β), and 2 groups and 2 measurements. The small effect size used for the calculation of required sample size is based on literature review and assumptions of relevant changes for IWD. Previous studies have reported high variation in the effect sizes of the primary outcomes balance, mobility, and gait. In their review, Blankevoort et al [22] reported small negative to large positive effect sizes for balance (d=–0.24 to d=3.59) and functional mobility (d=–0.25 to d=2.37) as well as no to medium effect sizes for normal gait speed (d=–0.11 to d=0.50). These reported variations do not allow determining actual effect sizes. Thus, the magnitude of relevant changes has to be considered to further support the selection of a small effect size. Because dementia is characterized by rapid progression linked to multiple impairments, it is assumed that even small effects are relevant. The calculation of sample size results in a required sample size of 100 participants for each group (total sample size of 200 participants). Considering reasons for dropout, the sample is set to 405 participants.

Dropout

We assume 3 reasons for dropout: (1) withdrawal from the study, (2) missing data, and (3) low attendance or adherence to MEP. Possible reasons for withdrawal are death, hospitalization, serious deterioration in state of health, refusal to participate, etc. Based on the literature review of Blankevoort et al [22], a dropout rate of 20% caused by withdrawal is expected. Missing data occur if participants are not able to complete the entire test

battery because of motivational aspects or multiple motor and cognitive impairments. In addition, some participants will not participate at all in postassessments because of illness or other appointments. We assume a missing data rate of 15%. A total target number of 200 participants (100 per group) for the analysis and an assumed dropout rate (withdrawal and missing data) of 35% requires enrolling 270 participants into the study. Unfortunately, attendance and adherence are often not stated in previous studies [26]. Hence, we decided to double the sample of IG to ensure the required sample of 100 participants in this group. Low attendance and adherence may be caused by illness, motivation, other appointments, disinterest, or other reasons. Hence, a total sample size of 405 participants is required.

All participants will be asked at least twice if they are willing to participate in the assessments to reduce missing data. A familiar caregiver is asked to invite the participant if appropriate. If participants are not willing to complete all measures they are offered to choose assessments they are willing to complete. Moreover, all possible participants will be included in the data collection regardless of whether they discontinued or deviate from the intervention protocol. Caregivers will be asked to support the participants to get to training sessions to improve attendance. If participants miss a session, they are personally invited to the next training session.

Allocation

Group allocation to IG and CG will be performed by minimization to obtain randomized groups with minimum group differences. Subjects rather than care facilities will be randomized to avoid confounding effects of the geographic location, and minimization will be done separately for each care facility based on the baseline criteria MMSE, sex, age, and baseline performance of modified 30-second chair-stand test. Minimization will be performed with the program MinimPy version 0.3 [75], which includes a random element. The first participant is allocated randomly to IG or CG. Subsequent participants are allocated to each group correspondingly to achieve the least imbalance between groups. Including a random element, participants will be allocated to the better fitting group with a probability of 70%. An allocation ratio of 2:1 is selected because of above-mentioned assumptions regarding dropouts. The input order of participants for allocation will be randomly defined by an assigned number for each participant given prior to minimization.

Blinding and Pseudonymization

Investigators will be blinded to allocation wherever possible. It is not possible to blind participants or employees of care facilities regarding group allocation.

All data is stored in a strictly pseudonymous form. This is achieved by separating personally identifiable information of participants from data collected during baseline and postassessments. Collation of data is only possible with considerable effort at any time of the study. Thus, individual confidentiality will be ensured before, during, and after the study. Only selected team members have access to coded data.

Statistical Analysis

All statistical analysis will be done with SPSS version 23 (IBM Corp). Trained and experienced investigators will evaluate and enter data. Investigators evaluating and entering data are not the same as investigators assessing outcomes. The number of investigators is limited to 2 per assessment method. Prior to actual analysis, interrater reliability (Cohen kappa [76], intraclass correlation coefficient [77]) will be calculated and plausibility (eg, considering range and distribution) will be checked to minimize errors caused by data evaluation and entry.

Because of expected large dropout rate, which can lead to a critical amount of missing data, 2 separate analysis sets are planned: an intention-to-treat analysis and a per-protocol analysis. In the intention-to-treat analysis, all randomized participants regardless of protocol adherence will be included and missing data will be substituted by multiple imputation. Participants with sufficient attendance and adherence to the intervention as well as complete assessments of primary outcomes will be included in the per-protocol analysis, where missing data will not be considered.

Baseline values of participant characteristics will be compared between IG and CG using chi-square tests for categorical data, Mann-Whitney-U tests for nonparametric variables, and *t* tests for continuous and normally distributed parameters. For all normally distributed data (checked by Shapiro-Wilk test), mean and standard deviation will be calculated, and medians and interpercentile ranges will be calculated for not normally distributed data. Treatment effects will be analyzed using 2-factor ANOVA with repeated measurement. A 2-sided *P* value less or equal to .05 will be considered to indicate statistical significance. In addition, 95% confidence intervals and partial Eta^2 will be calculated. Changes in motor and cognitive function are possible mediators and moderators. These mediating and moderating effects on primary outcomes will be analyzed using multiple linear regression models. Additional explorative data analysis exceeding the proposed planned analyses will be performed. Depending on data structure, adequate analysis methods will be defined. These analyses aim to consider further influencing factors or subgroup analysis as well as the development of forecast models.

Results

Enrollment for the study started in May 2015. It is planned to complete postassessments by the beginning of 2017. Results are expected to be available in the first half of 2017.

Discussion

Summary

Previous studies have discussed the use of physical activity as additional therapy strategy, and predominately positive effects have been reported. However, the results of these studies are not consistent and they have several methodological limitations. With respect to these limitations, the current study has been carefully designed and thus reflects the following strengths.

Strengths

The overall strength is the strong effort to conduct a high-quality trial characterized by a standardized study design, theoretical considerations, an intervention specially designed for IWD, assessments adequate for IWD, a large sample size, and detailed and accurate reporting of methods according to the CONSORT [42-44] and SPIRIT [40,41] statements.

The MEP, which is characterized through dementia-specific methodology and a combination of motor and cognitive tasks, is a major strength of this study. Because of its theoretical foundation and based on primary recommendations of the review by Scharpf et al [48], initial guidelines for designing physical activity interventions for IWD can be derived if results support efficiency.

Bearing in mind that most motor assessments are not developed for IWD and their psychometric properties have hardly been systematically established in this specific population [55,78], we took several efforts to construct an adequate test battery considering all relevant primary and secondary outcomes. The international expert panel with members from different disciplines where we have discussed possible and adequate measurements as well as general information on performing cognitive and motor measurements in IWD has been an important attempt to enhance quality. In comparison to previous studies, the large sample size is an outstanding feature of this study. To the best of our knowledge, there is no other study with a comparable sample size. Based on studies analyzed for the Cochrane review [26], sample sizes vary between 12 and 148 participants.

This study is designed as a multicenter trial with a sustainable intervention close to everyday life. For instance, the MEP is established on everyday activities such as getting up, walking, or picking things up (see Multimedia Appendix 1). Performing a field study reflects reality in participating care facilities, and results can be more easily transferred to daily routine. Considering sustainability is an important concern of this study and we intend to continue physical activity interventions after study is finished. Thus, employees of care facilities will be educated to guide the MEP. Furthermore, this approach ensures the opportunity for CG to participate in the MEP, which is an important ethical aspect.

Challenges

There are several challenges in performing intervention studies in IWD. These are related to the selected study design as well as its target group and thus cannot be avoided. However, it is important to deal with these challenges to minimize their impact.

A big challenge in performing intervention studies with IWD is maintaining blinding to group allocation. Although all investigators will be blinded to group allocation, there is a potential risk that participants will disclose their group allocation during assessments. To minimize this risk, investigators will be asked not to talk about the intervention during assessments.

Working with IWD entails several general challenges as they are often suffering from frailty and multimorbidity. According to different motor and cognitive impairments in IWD, it is not possible to develop an intervention completely suitable for all participants. Hence, some adaptions of the intervention cannot be avoided. However, instructors are asked to minimize such adaptions and adhere to the manual as strictly as possible. Besides this, IWD are vulnerable in relation to attendance, adherence, and missing data. For instance, multiple motor and cognitive impairments partially prevent IWD from participating in all subassessments. Thus, attempts to enhance attendance and adherence as personal communication, support, or repeated invitation are planned.

Further challenges are seen in cooperation with care facilities. Employees assume important responsibilities, such as suggesting potential participants, assessing ADL and state of health, or supporting assessments and intervention. Restricted time or missing expertise is a potential risk for limitations. To reduce such limitations, employees will be provided detailed information on how to report required data and support for further problems.

Implications and Perspectives

Findings of this study will be disseminated through publications and presentations (including information about important protocol modifications). Improving the defined primary outcomes is highly relevant considering the consequences of dementia-related motor deficits as stated in the introduction [35-37]. Insufficient amounts of physical activity also expedite existing motor and functional impairments in IWD [32,79]. Therefore, developing adequate physical activity interventions for IWD and offering guidelines is essential. We plan on publishing the MEP and communicating the underlying didactic concept of the training in a detailed manual if it proves to be effective.

This study will contribute to enhance scientific evidence and takes a first look at relations between motor and cognitive skills in IWD. The findings can also be directive for further investigations in the field of prevention, diagnosis, and therapy of dementia.

Conclusions

There is a clear need for high-quality studies investigating the effectiveness of physical activity on motor and cognitive skills in IWD. Our study is mainly characterized by a dementia-specific intervention based on scientific knowledge, the combination of motor and cognitive tasks, and a large sample. Findings are highly relevant to influence the multiple motor and cognitive impairments of IWD often participating in limited physical activity. If the MEP proves to be effective, positive influences on everyday life are expected justifying its permanent implementation in care facilities.

Multimedia Appendix

Multimedia Appendix 1. Sample session of the multimodal exercise program.

Multimedia Appendix 2. Description of the assessments.

Acknowledgments

All authors are members of the research team and participated in the implementation of the study. AW conceived the idea of this study along with ST and AS. All authors contributed to the conception and design of the study. ST coordinates the study under direct supervision of AW. ST and AS are responsible for the implementation of the study. AS developed and supervises the multimodal exercise program. All authors were involved in planning and writing the study protocol. ST and BB wrote the study protocol. AS and CN helped draft this manuscript. All authors provided critical feedback and approved the final manuscript.

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Ethical approval has been obtained from the ethics commission of the Karlsruhe Institute of Technology (11.03.2015, reference number: 7712.14-0508-0). An informed consent will be signed by participants or their legal guardians prior to the study.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Sample session of the multimodal exercise program.

[PDF File (Adobe PDF File), 475KB - resprot_v6i3e35_app1.pdf]

Multimedia Appendix 2

Description of assessments.

[PDF File (Adobe PDF File), 79KB - resprot_v6i3e35_app2.pdf]

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Abbreviations

ADAS-Cog: Alzheimer Disease Assessment Scale–Cognitive Subscale
ADL: activities of daily living
ANOVA: analysis of variance
CERAD: Consortium to Establish a Registry for Alzheimer's Disease
CONSORT: Consolidated Standards of Reporting Trials

CG: control group
E-ADL-Test: Erlangen Test of Activities of Daily Living
FICSIT-4: Frailty and Injuries: Cooperative Studies of Intervention Techniques 4
ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Edition
IG: intervention group
IWD: individuals with dementia
MEP: multimodal exercise program
MMSE: Mini-Mental State Examination
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Protocol for Combined Analysis of FOXFIRE, SIRFLOX, and FOXFIRE-Global Randomized Phase III Trials of Chemotherapy +/- Selective Internal Radiation Therapy as First-Line Treatment for Patients With Metastatic Colorectal Cancer

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Abstract

Background: In colorectal cancer (CRC), unresectable liver metastases are associated with a poor prognosis. The FOXFIRE (an open-label randomized phase III trial of 5-fluorouracil, oxaliplatin, and folinic acid +/- interventional radioembolization as first-line treatment for patients with unresectable liver-only or liver-predominant metastatic colorectal cancer), SIRFLOX (randomized comparative study of FOLFOX6m plus SIR-Spheres microspheres versus FOLFOX6m alone as first-line treatment in patients with nonresectable liver metastases from primary colorectal carcinoma), and FOXFIRE-Global (assessment of overall survival of FOLFOX6m plus SIR-Spheres microspheres versus FOLFOX6m alone as first-line treatment in patients with nonresectable liver metastases from primary colorectal carcinoma in a randomized clinical study) clinical trials were designed to evaluate the efficacy and safety of combining first-line chemotherapy with selective internal radiation therapy (SIRT) using yttrium-90 resin microspheres, also called transarterial radioembolization.

Objective: The aim of this analysis is to prospectively combine clinical data from 3 trials to allow adequate power to evaluate the impact of chemotherapy with SIRT on overall survival.

Methods: Eligible patients are adults with histologically confirmed CRC and unequivocal evidence of liver metastases which are not treatable by surgical resection or local ablation with curative intent at the time of study entry. Patients may also have limited extrahepatic metastases. Final analysis will take place when all participants have been followed up for a minimum of 2 years.

Results: Efficacy and safety estimates derived using individual participant data (IPD) from SIRFLOX, FOXFIRE, and FOXFIRE-Global will be pooled using 2-stage prospective meta-analysis. Secondary outcome measures include progression-free survival (PFS), liver-specific PFS, health-related quality of life, response rate, resection rate, and adverse event profile. The large

study population will facilitate comparisons of low frequency adverse events and allow for more robust safety analyses. The potential treatment benefit in those patients who present with disease confined to the liver will be investigated using 1-stage IPD meta-analysis. Efficacy will be analyzed on an intention-to-treat basis.

Conclusions: This analysis will assess the impact of SIRT combined with chemotherapy on overall survival in the first-line treatment of metastatic CRC. If positive, the results will change the standard of care for this disease.

Trial Registration: FOXFIRE ISRCTN Registry ISRCTN83867919; http://www.isrctn.com/ISRCTN83867919 (Archived by WebCite at http://www.webcitation.org/6oN7axrvA). SIRFLOX ClinicalTrials.gov NCT00724503; https://clinicaltrials.gov/ct2/show/NCT00724503 (Archived by WebCite at http://www.webcitation.org/6oN7lEGbD). FOXFIRE-Global ClinicalTrials.gov NCT01721954; https://clinicaltrials.gov/ct2/show/NCT01721954 (Archived by WebCite at http://www.webcitation.org/6oN7vvQvG).

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KEYWORDS

colorectal neoplasms; liver; neoplasm metastasis; radiation oncology; survival analysis; meta-analysis

Introduction

The 5-year overall survival (OS) of metastatic colorectal cancer (mCRC) patients, who constitute 21% of all CRC diagnoses, is approximately 13% [1]. The liver is the dominant site of metastases in CRC; liver metastases are the most common cause of death for patients with CRC [2,3]. To improve outcomes in mCRC, efforts have been made to increase the proportion of patients eligible for surgical resection, which is currently 20% [4-8]. The use of down-staging neoadjuvant chemotherapy in clinical studies has suggested that 10%-20% of patients with inoperable liver disease may be converted to candidates for curative resection [9]. Furthermore, a statistical correlation between tumor response and resection rates has been found across clinical studies [10].

Among the liver-directed therapies that may control liver metastases, selective internal radiation therapy (SIRT) is one option for patients with liver-only or liver-dominant disease [11,12]. SIR-Spheres (Sirtex Medical Limited) containing the β-emitter, yttrium-90, are delivered into the arterial supply of the liver under fluoroscopic guidance. The delivery of the resin microspheres into branches of the hepatic artery, which supplies the majority of blood to liver tumors, results in selective targeting of the tumor by high-dose radiotherapy, whereas the healthy liver is supplied predominantly by the portal venous system and is therefore relatively spared from radiation treatment [12].

The FOXFIRE (an open-label randomized phase III trial of 5-fluorouracil, oxaliplatin, and folinic acid +/- interventional radioembolization as first-line treatment for patients with unresectable liver-only or liver-predominant metastatic colorectal cancer), SIRFLOX (randomized comparative study of FOLFOX6m plus SIR-Spheres microspheres versus FOLFOX6m alone as first-line treatment in patients with nonresectable liver metastases from primary colorectal carcinoma), and FOXFIRE-Global (assessment of overall survival of FOLFOX6m plus SIR-Spheres microspheres versus FOLFOX6m alone as first-line treatment in patients with nonresectable liver metastases from primary colorectal carcinoma in a randomized clinical study) clinical trials were designed to study SIRT in combination with chemotherapy, specifically the modified fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimen, compared with FOLFOX alone as first-line therapy for mCRC [13,14]. Eligibility criteria and trial designs were similar for the 3 trials so that they could be prospectively combined. The primary and some secondary endpoints of SIRFLOX have been published, representing the largest published, randomized, multicenter trial of any liver-directed therapy in patients with mCRC [15]. The results showed increased progression-free survival (PFS) in the liver with the addition of SIRT but no effect of SIRT on overall PFS [15].

The primary objective of the combined analysis is to report the planned meta-analysis (MA) of individual participant data (IPD) from the FOXFIRE, SIRFLOX, and FOXFIRE-Global studies for the primary endpoint, OS, and for secondary outcomes including PFS, liver-specific PFS, quality of life measures, response rate, resection rate, and adverse event profile. The IPD-MA will assess the treatment effects on clinical outcomes in the entire subject group and in key subgroups.

Methods

Study Design

As the results on survival benefits for each of the 3 studies are still blinded, the statistical design is a prospective MA based on randomized IPD from the FOXFIRE, SIRFLOX, and FOXFIRE-Global clinical trials.

The protocols of the FOXFIRE [13] and SIRFLOX [14] trials have been previously published. All 3 clinical trials were open-label multicenter, randomized, 2-arm trials comparing chemotherapy plus SIRT with chemotherapy alone as first-line treatment for patients with mCRC. The design of the 3 trials is summarized in Table 1 and Figure 1.

Table 1. Characteristics of studies included in the meta-analysis: FOXFIRE [13], SIRFLOX [14], and FOXFIRE-Global.

	FOXFIRE[a]	SIRFLOX[b]	FOXFIRE-Global[c]
Start of recruitment	Nov 13, 2009	Oct 11, 2006	May 20, 2013
End of recruitment	Oct 31, 2014	Apr 25, 2013	Dec 23, 2014
End of follow-up	Oct 31, 2016	Apr 25, 2018	Dec 23, 2019
Number of recruiting centers	28	87	69
Primary objective	Overall survival	Progression-free survival	Overall survival
Secondary objectives	Progression-free survival	Overall survival	Progression-free survival
	Progression-free survival in the liver	Progression-free survival in the liver	Progression-free survival in the liver
	Toxicity and safety	Toxicity and safety	Toxicity and safety
	Tumor response rate	Tumor response rate	Tumor response rate
	Quality of life	Quality of life	Quality of life
	Liver resection rate	Liver resection rate	Liver resection rate
	Health costs/economics	Hepatic and extrahepatic recurrence rate	Hepatic and extrahepatic recurrence rate
	Proportion of patients receiving second line treatment		Health economics
	Time to second line treatment		
Sample size accrued	364	530	209
Accrual period	November 2009–October 2014	October 2006–April 2013	May 2013–December 2014
Follow-up period	November 2014–October 2016	April 2013–April 2018	December 2014–December 2019
Randomization	1:1 with minimization	1:1 with minimization	1:1 with minimization
Minimization factors	Liver only versus extrahepatic metastases	Liver only versus extrahepatic metastases	Liver only versus extrahepatic metastases
	Extent of tumor involvement of the liver (≤25% or >25% determined by CT[d] scan)	Extent of tumor involvement of the liver (≤25% or >25% determined by CT scan) and based upon the tumor involvement groupings used by Gray et al [16]	Extent of tumor involvement of the liver (≤25% or >25% determined by CT scan) and based upon the tumor involvement groupings used by Gray et al [16]
	Planned use of biological agent (from March 2011 on)	Planned use of bevacizumab with chemotherapy	Planned use of bevacizumab with chemotherapy
	Investigational center	Investigational center	Investigational center
Recruiting countries/regions	United Kingdom (England, Northern Ireland, Scotland, Wales)	Australia, Europe, Israel, New Zealand, and United States	Australia, Europe, Israel, Korea, New Zealand, Singapore, Taiwan and United States

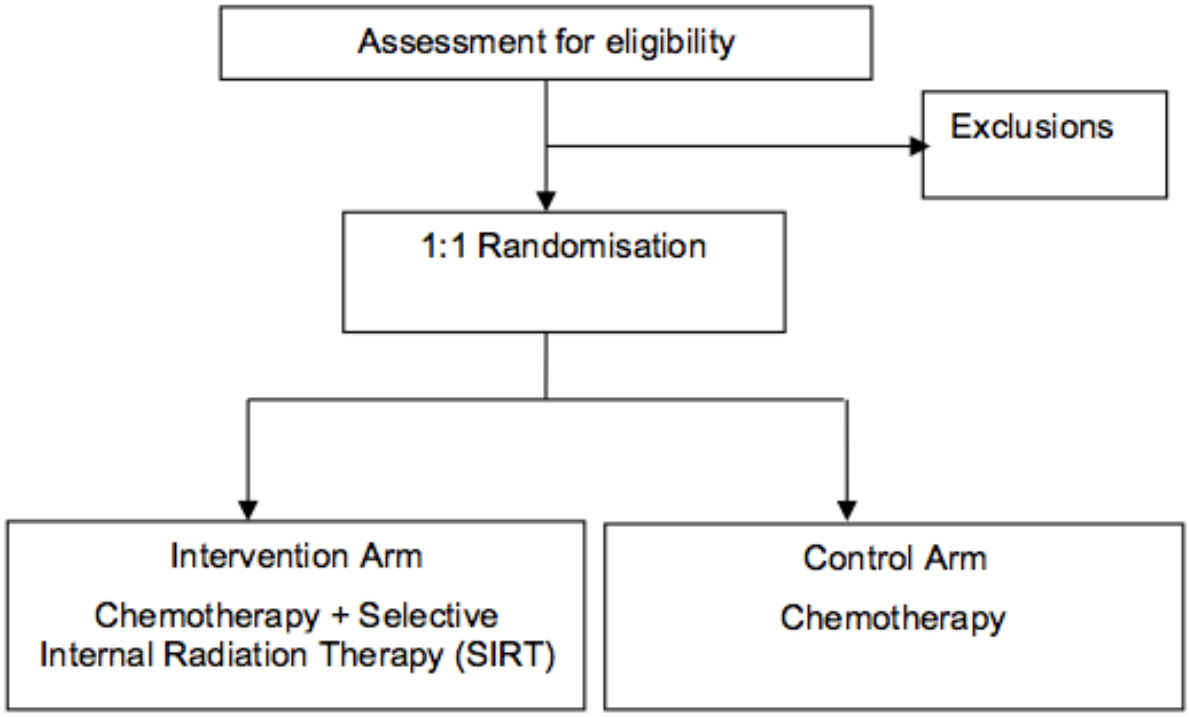
[a]An open-label randomized phase III trial of 5-fluorouracil, oxaliplatin, and folinic acid +/- interventional radioembolization as first-line treatment for patients with unresectable liver-only or liver-predominant metastatic colorectal cancer.

[b]Randomized comparative study of FOLFOX6m plus SIR-Spheres microspheres versus FOLFOX6m alone as first-line treatment in patients with nonresectable liver metastases from primary colorectal carcinoma.

[c]Assessment of overall survival of FOLFOX6m plus SIR-Spheres microspheres versus FOLFOX6m alone as first-line treatment in patients with nonresectable liver metastases from primary colorectal carcinoma in a randomized clinical study.

[d]Computed tomography.

Figure 1. Schema for the FOXFIRE, SIRFLOX, and FOXFIRE-Global trials.



Patients and Treatment

All randomized patients from the SIRFLOX, FOXFIRE, and FOXFIRE-Global clinical trials will be included in the combined analysis.

Inclusion Criteria

- Histologically confirmed CRC with liver-only or liver-dominant metastases not amenable to surgical resection, primary tumour in situ permitted (FOXFIRE); histologically confirmed CRC with liver-only or liver-dominant metastases (SIRFLOX); histologically confirmed adenocarcinoma of the colon or rectum with or without primary tumor in situ (FOXFIRE-Global)
- Unequivocal and measurable computed tomography (CT) evidence of liver metastases not treatable by surgical resection or local ablation with curative intent at time of trial entry
- Chemotherapy-naïve for mCRC, but previous adjuvant systemic chemotherapy for primary CRC or neoadjuvant chemoradiotherapy to the pelvis more than 6 months before recruitment is permitted (SIRFLOX, FOXFIRE-Global); eligible for systemic chemotherapy as first-line treatment for metastatic CRC (FOXFIRE)
- Additional limited extrahepatic metastases in the lung or lymph nodes permitted (SIRFLOX, FOXFIRE-Global); patients are permitted to have limited extrahepatic disease (FOXFIRE)
- Age ≥18 years
- World Health Organization performance status of 0-1
- Life expectancy >3 months
- Adequate hematological, renal, and hepatic function
- Female patients must be postmenopausal or using adequate contraception if premenopausal, and male patients must be using an appropriate method of contraception if with a premenopausal partner (FOXFIRE); female patients must either be postmenopausal, sterile (surgically or chemically or radiation-induced) or if sexually active using an acceptable method of contraception, and male patients must be surgically sterile or if sexually active and have a premenopausal partner must be using an acceptable method of contraception (SIRFLOX, FOXFIRE-Global)
- Suitable for all aspects of treatment determined by clinical assessment undertaken by investigator
- Willing and able to provide written informed consent

FOXFIRE-Global and SIRFLOX:

- All imaging evidence used as part of the screening process must be within 28 days prior to randomization

Exclusion Criteria

- Evidence of ascites, cirrhosis, portal hypertension; tumour involvement of, or thrombosis leading to occlusion of the main portal vein
- Previous radiotherapy delivered to upper abdomen or upper lumbar spine (FOXFIRE); previous radiotherapy delivered to the upper abdomen (SIRFLOX); previous radiotherapy delivered to the liver (FOXFIRE-Global)
- Nonmalignant disease that would render patient ineligible at the discretion of the investigator
- Dose-limiting toxicity associated with previous 5-fluorouracil or oxaliplatin chemotherapy

- Peripheral neuropathy higher than grade 1 (National Cancer Institute–Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 3)
- Pregnant or breastfeeding
- Previous chemotherapy for any malignancy; adjuvant chemotherapy for colorectal cancer is not an exclusion criterion provided that it was completed more than 6 months prior to entry into the study (SIRFLOX, FOXFIRE-Global). Previous chemotherapy for metastatic colorectal cancer; adjuvant chemotherapy for colorectal cancer is not an exclusion criterion provided that it was completed more than 6 months prior to entry into the study (FOXFIRE)
- Concurrent or prior history of cancer other than adequately treated nonmelanoma skin cancer or carcinoma in situ of the cervix (SIRFLOX, FOXFIRE-Global); other active malignancy within last 5 years excluding colorectal cancer and other nonmelanoma skin cancers (FOXFIRE)

SIRFLOX and FOXFIRE-Global:

Allergy to nonionic contrast agents

FOXFIRE only:

- Liver metastases amenable to curative resection at time of study entry
- Equivocal, immeasurable, or nonevaluable liver metastases
- Unequivocal evidence of bone metastasis

All patients received first-line chemotherapy for mCRC. In FOXFIRE, the chemotherapy received was oxaliplatin, 5-fluorouracil, and leucovorin/folic acid in the OxMdG regime [17]. In SIRFLOX and FOXFIRE-Global, the chemotherapy consisted of the same drugs in the mFOLFOX6 regime [18]. Patients were randomized 1:1 to the addition of SIRT using yttrium-90 resin microspheres, using minimization. The minimization factors are given in Table 1. Biological agents (cetuximab or bevacizumab in FOXFIRE; bevacizumab in SIRFLOX) were permitted to be added to chemotherapy at the treating investigators' discretion. Protocol treatment in each study was commenced within 28 days of randomization. Further details on randomization by minimization and treatment regimens for FOXFIRE and SIRFLOX have been published previously [13,14]. FOXFIRE-Global used the same randomization method and treatment regimen as that used for the SIRFLOX study.

In all 3 trials, patients were assessed every 2 weeks during chemotherapy treatment. In SIRFLOX and FOXFIRE-Global, patients were assessed every 12 weeks during the postprogression follow-up period. FOXFIRE patients were assessed every 8 weeks following completion of treatment up to 18 months and then every 12 weeks thereafter. In all 3 trials, patients were followed until death or for a period of at least 2 years after randomization. Patients undergoing surgical resection after trial entry were also followed up until trial closure or until death.

Screening and follow-up assessments included clinical assessment and laboratory analyses, recording concurrent medications, CT scan of the chest/abdomen/pelvis with or without magnetic resonance imaging, recording adverse events, assessment for resection or ablation, and questionnaire-based assessments of quality of life.

Study Outcomes

Primary Outcome of the Combined Analysis

The primary outcome of OS is the time from randomization to death from any cause, with patients still alive being censored at their last known follow-up date.

Secondary Outcomes of the Combined Analysis

The secondary outcomes are PFS at any site, liver-specific PFS, health-related quality of life (HRQoL), response rate, resection rate, and the safety profiles. PFS is defined as the time from randomization to radiological progression according to Response Evaluation Criteria In Solid Tumors (RECIST version 1.0) or death from any cause, whichever is sooner. Patients who are not observed to progress or die during the course of the trial will be censored at last known progression-free follow-up date. Patients who withdraw from study treatment prior to documented progression will be censored at the time they commence nonstudy treatment. Patients who become eligible for resection will be considered as still being on study until progression is documented or last follow-up. Scans and tumor response will be centrally reviewed in FOXFIRE and SIRFLOX.

Liver-specific PFS is defined as the time from randomization to radiological progression in the liver (hepatic progression) according to RECIST version 1.0. Progression outside the liver (extrahepatic progression) and deaths prior to progression will be considered as competing risks for failure in the liver. Hepatic progression will be assumed to have occurred immediately before extrahepatic progression in patients who have identical hepatic and extrahepatic progression dates. Patients who withdraw from study treatment prior to any documented progression will be censored at the time they commence nonstudy treatment. Patients who become eligible for resection will be considered as still being on study until progression is documented or last follow-up.

HRQoL will be assessed using the EuroQol 5 dimensions questionnaire (EQ-5D). The EQ-5D comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the 5 dimensions is scored, generating a profile. A single index score or utility value, representing population-derived preferences for different health states, will be attached to each profile.

The response rate (objective response) is defined as the number of patients achieving a complete or partial response according to RECIST version 1.0 divided by the number of patients in each treatment arm. Early death by any cause and unknown responses will be included in the denominator. Response will be assessed over 2 time periods: within 12 months of randomization and over follow-up.

The resection rate in each treatment arm is defined as the number of patients undergoing resection of their liver metastases divided by the number of patients randomized in each arm. Patients undergoing treatment are assessed by an experienced liver multidisciplinary team or equivalent for eligibility for resection at the discretion of the treating physician.

The safety profile is assessed by the collection of adverse events (AEs) and serious adverse events (SAEs) at any time during treatment with grading using the NCI-CTCAE version 3.

Sample Size Calculation

For the primary combined OS analysis, the FOXFIRE study protocol details a calculated 1075 patients required using a protocol-specified hazard ratio (HR) of 0.8, a 36-month accrual period, and 18-month minimum follow-up with 2-sided 5% significance, 80% power, and allowing for noncompliance. A total of 710 deaths are expected. The required sample size had been previously calculated to be 1022 [13] but was updated to reflect an estimated increase in median OS in the control group. As the intervention is a local treatment to the liver only, it is anticipated that even if there is no OS benefit in the whole population, a demonstrated survival benefit in the liver-only subgroup would be clinically meaningful and could change practice. It is anticipated that, with a 6-month increase in OS in the SIRT treated liver-only patients compared to those randomized to chemotherapy only, this would require 463 events in the liver-only subgroup.

Closure of Study

The final analysis will be undertaken when a minimum of 710 deaths overall and 463 deaths in the liver-only subgroup have been observed in the pooled dataset and there has been a minimum follow-up of 2 years since the last patient was randomized into the 3 trials.

Data Monitoring Committee and Interim Analyses

The independent data and safety monitoring committee (IDSMC) consisted of the same representatives for the FOXFIRE, SIRFLOX, and FOXFIRE-Global clinical trials. Formal interim monitoring of the accumulating data was performed at regular intervals (approximately every 6 months) by the IDSMC for each trial separately. This information included results from other relevant trials but not the analysis of primary or secondary objectives or outcomes by treatment groups apart from the prespecified interim analyses. As part of the review, the IDSMC was asked to justify continued recruitment of further patients or further follow-up. The IDSMC advised on the frequency of future reviews of the data on the basis of accrual and event rates.

The IDSMC reviewed the combined safety data from FOXFIRE and SIRFLOX at the interim analyses. The following planned interim analyses were undertaken using combined data from the FOXFIRE and SIRFLOX trials:

- Analysis of toxicity and safety: 8 months after at least 80 patients were randomized in total (a minimum of 40 per trial)
- Analysis of toxicity and safety: 8 months after at least 300 patients were randomized in total (a minimum of 120 patients per trial)

The 3 clinical trials that constitute this MA were conducted in accordance with the Declaration of Helsinki and current Good Clinical Practice guidelines, and all participating centers obtained the relevant ethics committee approval before patient enrollment. FOXFIRE was approved by the National Research Ethics Service Committee South Central – Berkshire Research Ethics Committee reference 09/H0505/1 and sponsored by the University of Oxford. SIRFLOX and FOXFIRE-Global were approved by the relevant ethics committees for each center and sponsored by Sirtex Technology Pty Ltd.

Statistical Analysis

Descriptive Summaries

Summaries of baseline factors, including minimization factors, and percentages of missing data will be reported. Losses to follow-up will be reported for each trial and combined. Median follow-up time will be calculated using the reverse Kaplan-Meier method. Dose of trial-specific treatment delivered and treatment received subsequent-to-trial treatment will be described.

Efficacy

All efficacy analyses will be performed on an intention-to-treat (ITT) basis. OS and PFS estimates will be obtained using Kaplan-Meier survival curves, unadjusted log-rank tests, and survival models. A 2-stage inverse-variance weighted IPD-MA will be performed for both OS and PFS, with the first stage consisting of trial-specific analyses to obtain efficacy estimates (HRs) and the second stage being a pooled analysis of the separate trial-specific HRs. As a sensitivity analysis, a 1-stage IPD-MA using regression models stratified by study will be performed to confirm the results obtained from the 2-stage IPD-MA. For each outcome, multivariable models will be used in the 1-stage IPD-MA to account for baseline covariates.

Liver-specific PFS will be analyzed using cumulative incidence curves, Gray's test, and competing risks regression. This analysis will be performed on the pooled dataset with models stratified by trial. For OS, PFS, and liver-specific PFS, the potential treatment benefit in those patients who present with disease confined to the liver will be investigated. This prespecified subgroup analysis will be performed on the pooled dataset. The analysis strategy will include calculating HR for the effect of treatment in the liver-only subgroup using survival models stratified by trial.

A separate landmark analysis of OS will start at the 15-month time point (after randomization) and therefore exclude those who have died/withdrawn within 15 months of randomization. This time point has previously been considered of value in clinical trials of the treatment of mCRC [19]. Based on expert opinion, it is anticipated that 15 months from baseline allows sufficient time for events to occur in those with both diagnosed extrahepatic metastases and subclinical extrahepatic metastases at baseline, and therefore this analysis may be of value in detecting any differential survival impact of SIRT in patients with liver-only metastases.

The EQ-5D data will be merged across all 3 trials and summary data prepared on the mean EQ-5D utility score in each trial arm by time period, with appropriate tests for difference. Resection rate and response rate will be analyzed using chi-square tests and odds ratios (ORs) for the individual trials and a 2-stage IPD-MA.

Safety

Safety analyses will be performed on patients who received at least 1 dose of chemotherapy in either arm and on an as-treated basis (safety population). AEs experienced up to 28 days after the end of trial treatment or 7 months postrandomization, whichever was earlier, will be included. Descriptive summaries of the frequency and severity of AEs and the numbers of patients experiencing AEs of grade 3 or higher between treatment arms will be presented overall and by system organ class. The Medical Dictionary for Regulatory Activities version 16.1 is used to categorize the AEs. Univariate comparisons will be made.

All hypothesis tests will be 2-sided. A significance level of .05 will be used to indicate statistical significance. No missing data imputation is intended. Missing days in dates may be appropriately imputed.

Results

Data from the final data lock will become available in January 2017. Data analysis will take place in 2017 with results being disseminated via peer-reviewed journals in 2017 and 2018.

Discussion

Optimizing outcomes of treatment in patients with nonresectable liver metastases was identified in an international consensus expert statement as a key clinical need to be addressed [20]. This is the first extensive investigation of SIRT in the first-line setting for liver metastases from mCRC adequately powered to address an overall survival endpoint.

This prospective MA of 3 phase III studies will provide comprehensive evidence of the safety and potential efficacy of SIRT in the first-line setting for patients with liver metastases from mCRC. The results of the SIRFLOX trial published so far have suggested that the addition of SIRT to chemotherapy can improve liver-specific PFS [15]. The number of patients included in this combined analysis and the long-term follow-up, unprecedented in the field of interventional oncology, will provide adequate power to address a survival endpoint.

Although the SIRFLOX trial reported that liver-specific PFS was longer in the SIRT arm than in the control arm, the PFS at any site was similar between the SIRT arm and the control arm [15]. This can be accounted for by the fact that SIRT is a locoregional treatment to the liver only and therefore will not influence the progression of extrahepatic metastases or extrahepatic subclinical micrometastases.

It is generally accepted that successful resection of liver metastases correlates with improved overall survival, particularly in the context of neoadjuvant or adjuvant chemotherapy [21,22]. Surgery and perioperative chemotherapy are therefore routinely offered to patients with mCRC if the liver metastases are resectable. Similarly, the addition of radiofrequency ablation of liver metastases to standard chemotherapy appears to improve clinical outcomes for patients compared to those patients receiving standard chemotherapy alone [23,24]. These findings with liver-directed therapies suggest that improvement of liver-specific PFS in patients with liver metastases may correlate to improvement in OS, an important hypothesis to be tested for SIRT for the first time in this combined MA of the SIRFLOX, FOXFIRE, and FOXFIRE-Global trials.

The use of an IPD rather than an aggregate data approach to systematic review and MA of randomized controlled trials enables the standardization of outcomes across trials and detailed data checking, providing a more in-depth exploration and more robust MA results [25]. The proposed MA, by prospectively combining IPD from 3 trials, goes beyond classical MA aims and overrides drawbacks from single trials. The prospective approach allows for consistent inclusion and exclusion criteria between studies. The statistical analysis is going to be standardized across studies, and using IPD-MA will provide sufficient statistical power to draw conclusions from subgroup analyses that are generally undermined by low sample size. The use of the 2-stage approach for the main analyses of OS and PFS is prespecified, as the 2-stage approach might produce different parameter estimates to the 1-stage approach, although the estimates are usually similar [26,27].

The results from the combined analysis of the SIRFLOX, FOXFIRE, and FOXFIRE-Global trials will provide valuable clinical information on the efficacy and toxicity profile of SIRT combined with chemotherapy as a first-line regimen for liver metastases from mCRC that will guide clinicians in the use of this technology to treat their patients. The IPD-MA will allow comparisons of less common AEs that would not be possible in a smaller population. Furthermore, this prospective MA provides sufficient power to determine whether SIRT provides a significant survival benefit for patients with metastases confined to the liver and no clinically detectable extrahepatic disease, an important research question among clinicians treating mCRC. When reported, the results of this combined analysis will define the use of SIRT in the treatment of mCRC.

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Authors' Contributions

RAS and HSW conceived the FOXFIRE study and secured the funding for the investigator-initiated study. SBL and JM provided statistical advice. All authors read and approved the final draft of the manuscript for submission. PG, VG, and GVH were substantially involved in the conception and design of the SIRFLOX and FOXFIRE-Global studies. EAF coordinated the FOXFIRE study during the patient follow-up period. All authors were involved in critically reviewing the manuscript for important intellectual content, and all authors read and approved the final draft of the manuscript for submission.

Conflicts of Interest

RAS has received research funding, honoraria, and consultancy fees from Sirtex Medical Ltd. PG has received honoraria from Sirtex for participation in advisory boards and for giving presentations. VG and GVH have received compensation for participation in advisory committees from Sirtex. PSV, JM, HSW, EAF, and SBL declare no competing interests.

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Abbreviations

AE: adverse event
CRC: colorectal cancer
CT: computed tomography
EQ-5D: EuroQol 5 dimensions questionnaire
FOLFOX: modified fluorouracil, leucovorin, and oxaliplatin regimen
FOXFIRE: An open-label randomized phase III trial of 5-fluorouracil, oxaliplatin, and folinic acid +/- interventional radioembolization as first-line treatment for patients with unresectable liver-only or liver-predominant metastatic colorectal cancer
FOXFIRE-Global: Assessment of overall survival of FOLFOX6m plus SIR-Spheres microspheres versus FOLFOX6m alone as first-line treatment in patients with nonresectable liver metastases from primary colorectal carcinoma in a randomized clinical study
HR: hazard ratio
HRQoL: health-related quality of life
IDSMC: independent data and safety monitoring committee
IPD: individual participant data
IPD-MA: Individual participant data meta-analysis
ITT: intention-to-treat
MA: meta-analysis
mCRC: metastatic colorectal cancer
NCI-CTCAE: National Cancer Institute–Common Terminology Criteria for Adverse Events
OR: odds ratio
OS: overall survival
PFS: progression-free survival
RECIST: Response Evaluation Criteria In Solid Tumors
SAE: serious adverse events
SIRFLOX: Randomized comparative study of FOLFOX6m plus SIR-Spheres microspheres versus FOLFOX6m alone as first-line treatment in patients with nonresectable liver metastases from primary colorectal carcinoma
SIRT: selective internal radiation therapy

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Protocol

Supporting the Delivery of Total Knee Replacements Care for Both Patients and Their Clinicians With a Mobile App and Web-Based Tool: Randomized Controlled Trial Protocol

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Abstract

Background: Total knee replacement (TKR) surgeries have increased in recent years. Exercise programs and other interventions following surgery can facilitate the recovery process. With limited clinician contact time, patients with TKR have a substantial burden of self-management and limited communication with their care team, thus often fail to implement an effective rehabilitation plan.

Objective: We have developed a digital orthopedic rehabilitation platform that comprises a mobile phone app, wearable activity tracker, and clinical Web portal in order to engage patients with self-management tasks for surgical preparation and recovery, thus addressing the challenges of adherence to and completion of TKR rehabilitation. The study will determine the efficacy of the TKR platform in delivering information and assistance to patients in their preparation and recovery from TKR surgery and a Web portal for clinician care teams (ie, surgeons and physiotherapists) to remotely support and monitor patient progress.

Methods: The study will evaluate the TKR platform through a randomized controlled trial conducted at multiple sites (N=5) in a number of states in Australia with 320 patients undergoing TKR surgery; the trial will run for 13 months for each patient. Participants will be randomized to either a control group or an intervention group, both receiving usual care as provided by their hospital. The intervention group will receive the app and wearable activity tracker. Participants will be assessed at 4 different time points: 4 weeks before surgery, immediately before surgery, 12 weeks after surgery, and 52 weeks after surgery. The primary outcome measure is the Oxford Knee Score. Secondary outcome measures include quality of life (Short-Form Health Survey); depression, anxiety, and stress (Depression, Anxiety, and Stress Scales); self-motivation; self-determination; self-efficacy; and the level of satisfaction with the knee surgery and care delivery. The study will also collect quantitative usage data related to all components (app, activity tracker, and Web portal) of the TKR platform and qualitative data on the perceptions of the platform as a tool for patients, carers, and clinicians. Finally, an economic evaluation of the impact of the platform will be conducted.

Results: Development of the TKR platform has been completed and deployed for trial. The research protocol is approved by 2 human research ethics committees in Australia. A total of 5 hospitals in Australia (2 in New South Wales, 2 in Queensland, and 1 in South Australia) are expected to participate in the trial.

Conclusions: The TKR platform is designed to provide flexibility in care delivery and increased engagement with rehabilitation services. This trial will investigate the clinical and behavioral efficacy of the app and impact of the TKR platform in terms of service satisfaction, acceptance, and economic benefits of the provision of digital services.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12616000504415; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370536 (Archived by WebCite at http://www.webcitation.org/6oKES0Gp1)

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KEYWORDS

orthopedic; TKR; rehabilitation; physiotherapy; mHealth; eHealth

Introduction

Overview

Rates of total knee replacement (TKR) procedures have been rising steadily worldwide in recent years [1]. There has been an 80% increase in TKR procedures in Australia since 2003 [1-3], with increasing incidence and prevalence likely to continue due to factors such as the aging population, an increase in obesity and joint injury, and expectations of a continued physically active lifestyle, as well as higher demand for surgery at a younger age [1,4,5]. The mean age of TKR patients in Australia is 69 years; however, the demand for the surgery in the younger population (less than 65 years) has been increasing and is expected to double in the next decade [3,6-8].

Research has shown that a number of interventions prior to TKR surgery can improve outcomes or patient's satisfaction [9,10]. Physiotherapy undertaken before TKR is effective in improving postoperative outcomes [10]. Quadriceps muscle stretching and upper body exercises before the procedure allow patients to be prepared for the postoperative condition and rehabilitation physiotherapy program [10]. Managing patient expectation prior to surgery has been shown to benefit the rehabilitation process and is an important predictor of postoperative outcomes [11,12]. To prepare patients for their TKR surgery and hospital stay, preoperative education may offer advantages for some patients when stratified according to their physical, psychological, and social conditions [13]. Moreover, interventions that help reduce comorbidities and obesity prior to surgery can have postoperative impact, such as improved recovery and reduced chances of adverse events [2].

Most TKR patients experience pain, joint stiffness, insufficient muscle strength, and limited physical activity after surgery [14]. Early mobility following surgery has been shown to improve functional mobility and prevent deep vein thrombosis [2,15]. Studies have shown that postoperative rehabilitation can improve short-term outcomes (3-4 months) with no significant difference between different types of treatment, however the benefits of longer term rehabilitation (4-12 months) are limited [16,17]. Postoperative physiotherapy (6-8 weeks) is common practice in Australia [1], but adherence to physiotherapy programs can be low. Adherence can be low because of pain during exercise and low levels of activity prior to surgery but also because of social and psychological issues such as low self-efficacy, depression, anxiety, and poor social support [18].

Clinicians require information from their patients for diagnosis and monitoring recovery. Many of these indicators are self-reported by the patients, such as completion of physiotherapy, functionality, pain, and sleep quality. Another key measure of progress used by physiotherapists and surgeons is range of motion (ROM), a measure of the flexibility of the knee joint [16].

We are looking at ways to motivate and assist patients to complete rehabilitation programs to realize proven benefits and improve TKR surgery outcomes. We propose a solution in the form of a digital orthopedic rehabilitation platform aimed at supporting patients and their clinicians across phases of TKR, from expectation management when considering TKR surgery right through to patient recovery and rehabilitation.

Our TKR platform comprises a mobile phone app used daily in conjunction with a wrist-worn activity tracker and a clinical Web portal. The aim is to address the challenges of engaging patients with information and physical exercise through self-managed tasks delivered via the app in surgical preparation and recovery and to bridge the communication gap between clinicians and patients via the clinical Web portal. The app is designed to assist patients in achieving meaningful behavior change around uptake, adherence, and completion of rehabilitation programs, along with meaningful education, self-monitoring, and behavior coaching through rich media content.

This paper introduces the TKR platform and details the research protocol of a study to determine the efficacy and associated impact of the platform in assisting patients in their preparation for and recovery from the TKR surgery. An Australian multisite (N=5) randomized controlled trial (RCT) will be conducted for this purpose. The duration of the study is expected to be 24 months, which includes in-hospital setup and staff training, participant recruitment, intervention delivery, and data analysis. The trial will run for 13 months for each patient.

Total Knee Replacement Platform Technology

The design and functionality of the TKR platform have been informed through a user needs analysis. The user needs analysis (paper forthcoming) included interviews and focus groups with patients (n=11), general practitioners (n=8), orthopedic surgeons (n=12), and physiotherapists (n=3). The results of the analysis from the qualitative data clearly identified different stages of the TKR journey, each with different needs and priorities, which has informed the design of our platform technology for TKR. The qualitative data was used to refine features and

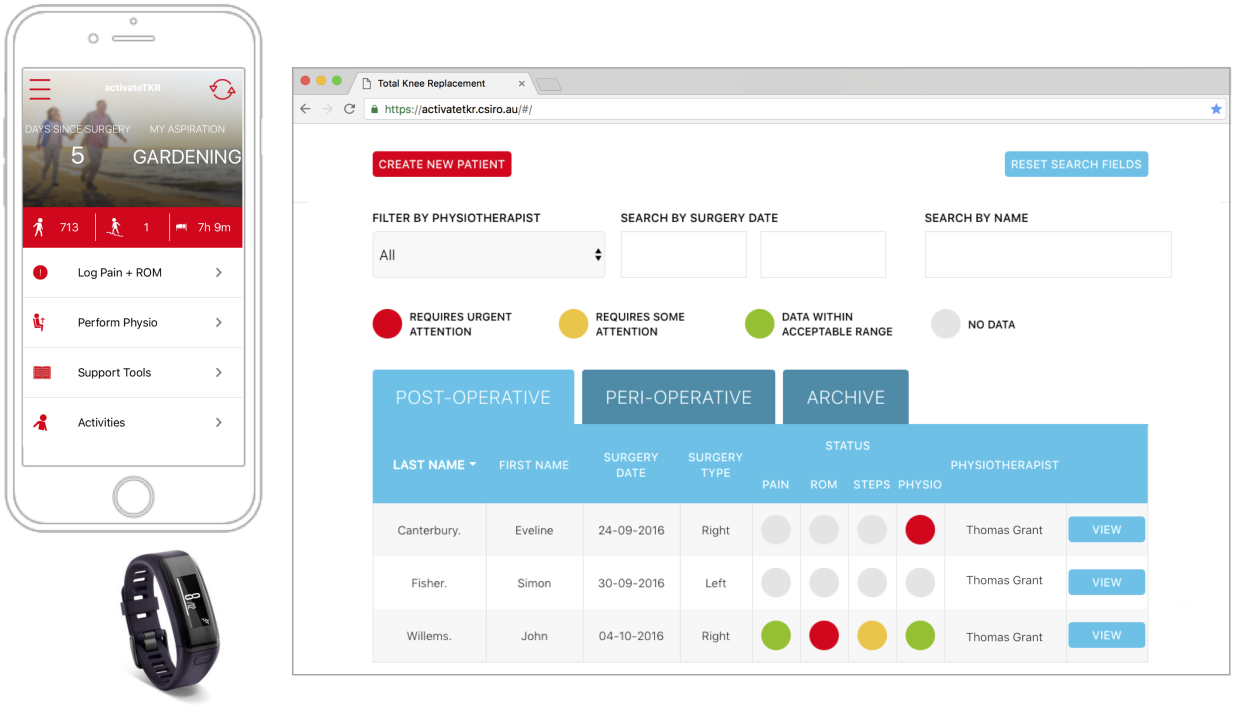
functionalities of the platform, which comprises a patient facing app and activity tracker and a clinical Web portal for use by clinical care teams.

The information delivered via the app been scientifically validated and all exercise videos were created in conjunction with expert physiotherapists working with TKR patients.

In order to foster motivation, the purpose-built app for iOS and Android devices includes weekly psychoeducation sessions and tasks that are delivered by a program guide via text and voice recordings. This content is also reinforced through tasks (eg, goal-setting) that the user can complete outside of the app (eg, on paper). This motivational content was developed using self-determination theory [19] and included techniques designed to foster positive emotions [20]. Tools to assist in behavior change in the app use commonly identified behavior change techniques, such as self-monitoring, goal setting and reviewing, and rewarding/recognizing achievements that appear in various behavioral models which can be broadly encompassed by social cognitive theory [21,22].

The clinical Web portal is designed for clinicians to monitor patient progress and configure physiotherapy programs. Patient data, gathered by the app, is transmitted to the portal for review by members of a patient care team. Physiotherapy programs for each patient are configured from a library of videos typically used for TKR rehabilitation. Once set, programs are available to patients in their app. Figure 1 provides sample screenshots of the TKR platform.

Figure 1. Total knee replacement platform. Left: app used daily in conjunction with a wrist-worn activity tracker. Right: clinical Web portal.



Methods

Overview and Aims

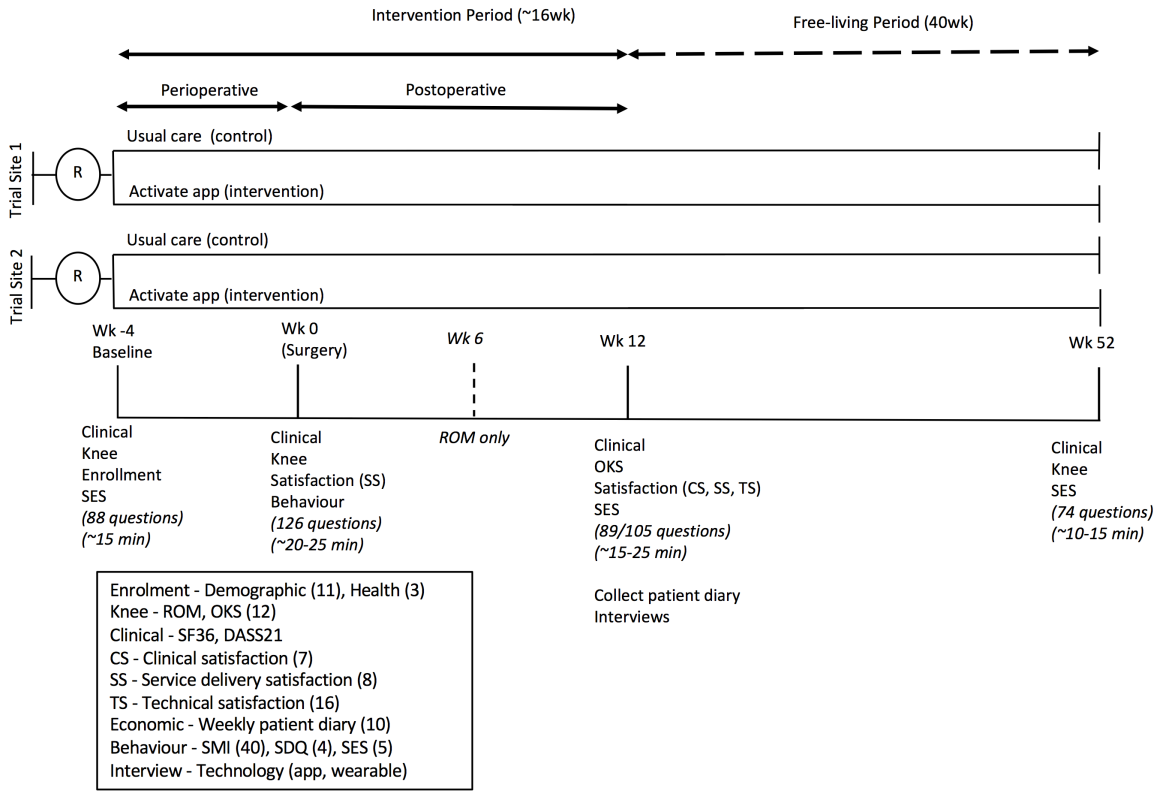
Data will be collected as part of a 13-month (for each participant), multisite unblinded RCT where participants are assigned to 1 of 2 study groups (1:1 allocation ratio). Both groups will undergo TKR surgery and be offered usual care and guidance from their surgeon and nominated health care team. In addition, the intervention group will receive the TKR app and a Garmin Vivosmart HR activity tracker. Patient participants will be scheduled for TKR surgery and managed through a project officer (PO), typically a member of the clinical team. Participants in the intervention group will be provided with instruction from the site PO in regard to using the technology. The aims of the study are as follows:

- To determine the efficacy of the TKR platform in delivering clinical and behavioral outcomes by specifically evaluating group differences
- To understand the impact of the TKR platform components and level of satisfaction with surgery and the care delivery
- To evaluate economic benefits

The study includes an active intervention period commencing when the patient is scheduled for surgery (approximately 4 weeks before surgery) and ending when the patient is 12 weeks postoperative. This is followed by a 40-week free-living period, finishing 1 year after surgery. Paper-based questionnaires will be completed by participants and the PO will be responsible for collecting responses from participants at 4 time points as illustrated in Figure 2.

All access to data will be controlled by authentication and authorization protocols designed to ensure the data is protected and only accessible by authorized persons. All information identifying the participants will be de-identified by a member of research team.

Figure 2. Study design: outcome measures, procedure, and timeline.

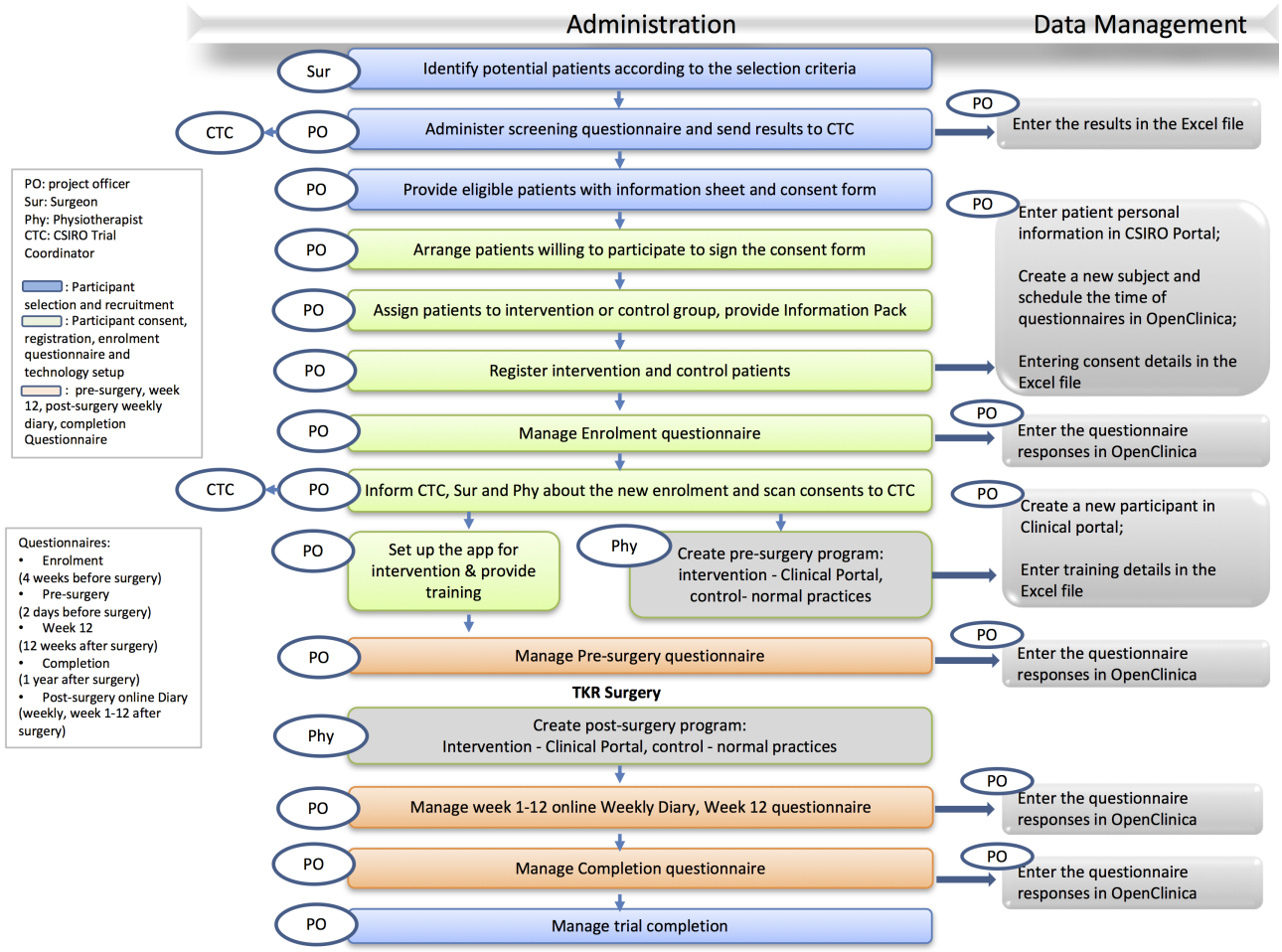


Participants

Recruitment

Patients scheduled for TKR surgery at trial sites will be screened by surgeons for clinical eligibility. Those who meet eligibility requirements will be informed of the study by the site PO and screened for technical eligibility (eg, access to iPhone/iPad, smartphone/tablet, Internet access). Recruitment will be conducted by the PO and coordinated by the Clinical Trial Coordinator (CTC). Figure 3 summarizes the processes involved in the recruitment and enrollment of patients, trial data collection, and data administration.

Figure 3. Process and workflow: patient recruitment, enrollment, trial data collection, and data administration.



Selection Criteria

Patients meeting the criteria as evaluated by the operating surgeon will be approached for recruitment by the PO. Inclusion criteria include:

- patients aged between 50 and 80 years
- suffering osteoarthritis as the principle diagnosis and reason for TKR
- scheduled to undergoing unilateral knee replacement (using commercial partner prosthesis) for the first time on one of the knees
- sufficiently healthy to not be adversely affected by participation in the trial
- deemed suitable candidates for physiotherapy both pre- and postsurgery
- have access to a smartphone/tablet (iOS or a leading Android-based device) with Internet connection via mobile Internet data or Wi-Fi connection
- willing to participate in the study and to have assessments on 4 occasions in line with scheduled appointments with their clinicians
- be sufficiently proficient in the English language to not be affected by participation in the trial

Exclusion criteria include:

- bilateral knee replacement
- previous unicompartmental replacement or tibial osteotomy on the same knee or previous lower extremity joint replacement surgery within the last 6 months
- major neurologic conditions or cognitive impairment that may result in inability to interact with the smartphone app
- uncontrolled diabetes, heart disease, or other medical conditions indicating participation in TKR is nonstandard

Based on the age criteria, surgeons will determine health-related eligibility of patients as well as assessing patient's neurological condition using standard clinical practice.

Randomization

Procedure

Eligible participants at each site will be randomized to 1 of the 2 treatment groups by a member of the research team. A simple randomization allocation technique in blocks of 10 using a randomization table generated by computer software will be used. Each site will have an intervention (ie, TKR platform) and a control group.

Participants will be randomized according to individual trial sites because usual care at each hospital (ie, trial site) will differ. Some hospitals offer presurgery education, others use online resources, and some offer daily outpatient rehabilitation classes or facilities such as hydrotherapy pools and gymnasiums. Other hospitals discharge patients to the community where they can privately engage services.

Intervention: Total Knee Replacement Platform

In stage 1, perioperative (typically 4 weeks before surgery) participants, upon receiving surgery date, will be provided with the TKR mobile app and a Garmin Vivosmart HR activity tracker at no cost. In stage 2, recovery (weeks 1-12 after surgery) participants will continue to use the TKR app and the activity tracker. Participants are expected to use the app daily and wear the activity tracker continuously (including while sleeping) for 16 weeks. Participants will continue to receive any prehabilitation and rehabilitation management as recommended by their surgeon, physiotherapist, or as provided by their hospital.

Control: Usual Care

Participants in the control group will receive the usual inpatient and outpatient prehabilitation and rehabilitation services as recommended by their surgeon, physiotherapist, or as provided by their hospital.

Outcome Measures

Overview

Basic demographic data and a brief history of medical/health conditions will be taken at baseline. PO will be responsible for collecting responses from participants, either face-to-face at the clinic or received by post. OpenClinica (www.openclinica.com) will be used to store digital copies of responses from self-reported questionnaires, which include validated and trial specific questionnaires. The patient diaries and audit questions for health care providers will inform the economic outcomes for this study. Patient diaries will be documented online using SurveyGizmo (www.surveygizmo.com).

Interviews will be conducted with a selected number of patients, their carers, and clinicians in order to capture outcomes related to the TKR platform technology with regard to service delivery satisfaction and usability. Table 1 summarizes the outcome measures, the data collection tools and procedures, and the time points. The remainder of this section details the various outcome measures.

Table 1. Outcome measures, data collection tools and procedures, and timeline.

Outcome		Measurement tool/procedure/ data collection	Time points (weeks)			
			Baseline	*0*	*12*	*52*
Patient self-report						
	Knee	OKS[a]	x	x	x	x
	Quality of life	SF-36[b]	x	x	x	x
	Depression, anxiety, stress	DASS21[c]	x	x	x	x
	Clinical satisfaction	Trial specific questionnaire			x	
	Service delivery satisfaction	Trial specific questionnaire		x	x	
	Technical satisfaction	Trial specific questionnaire			x	
	Self-motivation	SMI[d]		x		
	Self-determination	SDQ[e]		x		
	Self-efficacy	SES[f]	x	x	x	x
	Economic	Patient diary			x	
By clinicians or project officer						
	ROM[g]	Goniometer	x	x	x[h]	x
Structured interviews						
	Service satisfaction (patients, carers, clinicians)				x	
	Technical/usability (patients, carers, clinicians)				x	
Audit						
	Health care provider audit	Trial specific questionnaire			x	

[a]OKS: Oxford Knee Score.

[b]SF-36: Short-Form Health Survey.

[c]DASS21: Depression, Anxiety, and Stress Scale.

[d]SMI: Self-Motivation Inventory.

[e]SDQ: Self-Determination Questionnaire.

[f]SES: Self-Efficacy Scale.

[g]ROM: range of motion.

[h]At 6 weeks.

Primary Outcome

The primary outcome measure is self-reported knee pain and function as measured by the Oxford Knee Score (OKS) [23]. The OKS is 12-item questionnaire with 5 items for assessing pain and 7 for assessing function, each with 5 categories of response. Each item is scored from 1 to 5, from least to most difficulty or severity. A single combined score ranges from 12 (ie, least difficult) to 60 (ie, most difficult), and a lower score indicates a better outcome. The OKS has been developed and validated to specifically assess function and pain after TKR and is widely used by clinicians.

Secondary Outcomes

The secondary outcomes include:

- Quality of life (RAND 36 Item Short-Form Health Survey [SF-36]): SF-36 is a 36-item questionnaire that will be used for constructing summary scores of physical and mental components [24]. The questionnaire assesses 8 domains of wellness through subscales including body pain, physical function, general health, mental health, social functioning, and emotional role. The SF-36 is a popular instrument in the knee domain to measure generic quality of life [25].
- Knee range of motion (ROM): A long-arm goniometer will be used for measuring the knee ROM (flexion and extension) [26]. The goniometer axis will be positioned over the lateral knee joint area and the arms will be aligned with the lateral malleolus using the greater trochanter. The active knee flexion will be measured in the sitting position and the active knee extension will be measured in the long sitting or supine position. ROM as part of week 12 will be

collected during the patients' follow-up clinical visit, typically 6 weeks following surgery.

- The Depression, Anxiety and Stress Scale (DASS21) will be used to measure mental well-being. This is a 21-item questionnaire using a 4-point Likert scale with 7 items per condition (depression, anxiety, stress) [27]. Each item has equal weighting (0 to 3) and a higher score indicates greater symptoms. While SF-36 covers general mental health (psychological distress and psychological well-being), DASS21 is specifically designed to measure negative emotional states and severity of feelings related to depression, anxiety, and stress and has proven to be sensitive to patients' response to treatment.
- Satisfaction with knee surgery and service delivery (prehabilitation, rehabilitation) and the use of technology (eg, app and wearable) will be measured with questionnaires developed by the Commonwealth Scientific and Industrial Research Organization (CSIRO) using a 5-point Likert scale. The questionnaires are designed to capture surgical results, surgical recommendations, interaction with clinicians, empowerment experience, observability, and overall satisfaction with the service delivery. The technical satisfaction questionnaire will capture complexity, compatibility factors, and experience with the app and the wearable.
- Self-motivation will be captured using a validated 40-item scale [28] called the Self-Motivation Inventory (SMI). It has been used previously to assess rehabilitation outcomes for anterior cruciate ligament reconstruction [29]. The scale captures 10 areas of self-motivation and could be a critical predictor of adherence to a rehabilitation program. Therefore, we will be capturing this to control for any confounding effects that this may have on the experimental conditions.
- Self-determination will be captured using a 4-item questionnaire in order to assess whether the intervention group has higher levels of autonomous and/or intrinsic motivation after the presurgery phase (ie, week 0). In line with methods of Sheldon and Kasser [30], participants will be asked to rate 4 reasons for pursuing the goal of successful rehabilitation according to how much each describes their reason for having this goal. These reasons cover the proposed spectrum of possible motivations from external to introjected to autonomous to intrinsic, all derived from self-determination theory. All responses are rated from 1 (not at all because of this reason) to 9 (completely because of this reason).
- Self-efficacy to perform rehabilitation activities is a critical predictor of rehabilitation success. It describes a person's confidence in their ability to perform certain behavior in the face of challenges. In order to capture changes in self-efficacy, we will be using an adapted version of a physical activity Self-Efficacy Scale (SES) [31] designed to ask these questions around rehabilitation physiotherapy exercises rather than general exercise intention. This is a 5-item questionnaire using a 4-point Likert scale.

Technical and Usage Outcomes

Usage logs for the TKR platform (app, activity tracker, and Web portal) will be gathered and analyzed to help understand technology uptake and feature usage by patients and clinicians. Correlations and dependencies between usage and outcomes will be evaluated. Self-reported compliance with physiotherapy programs, content access, activity tracker data, and goal achievements collected from the app will also be analyzed.

Health Economic Outcomes

The economic evaluation will assess the costs and benefits accruing to both patients and service providers. It will also consider broader economic impact such as impact on carers' time, ability to work, and other health system costs (eg, visits to general practitioners).

For service providers, we will estimate the delivery costs of group or one-on-one classes that deliver physiotherapy intended for self-guided physiotherapy including staff time, space, and equipment costs. Each trial site will complete a health care provider audit form for this purpose. Further to this, we will note the time taken to review patient data through the TKR clinical Web portal, time taken on patient phone calls, etc.

For patients and their carers, we focus on the direct and indirect costs, such as impact on work or spare time, various services patients receive from the community, visits they make to see their health care professional, visits related to any nonclinical services, and an estimate of out-of-pocket expense. In most cases patients will not be asked to estimate monetary costs as these are highly variable and often subsidized (eg, by government or health insurers). The research team will assign generic costs to each activity or impact for the analysis. This approach allows the costs and benefits to other stakeholders such as government and health insurers to also be compared across the 2 treatment groups.

Interview Participants

Using a maximum variation sampling [32] technique, intervention group patients (n=20), carers (n=10), and surgeons/physiotherapists (n=10) will be recruited by the site POs with guidance from the CTC for interview. Previous experience suggests that theoretical saturation will be reached with these numbers and a pool of diverse participants will be identified. Patient diversity will focus on gender, age (over 18 years only), TKR experience, education level, and private versus public health care. Carer sampling will target spouses, children, and friends of patients, with a balance of gender and age. All participating clinicians will be invited for interview by a researcher.

Interviews will be semistructured. Interviews will be audiorecorded and transcribed and analyzed using NVivo (QSR International) software. Interviews with patients and carers will focus on technology acceptance, their experience with the app, and what features they liked and disliked. Interviews with surgeons and physiotherapists will focus on features of the clinical Web portal and the usefulness of the portal for monitoring patients postoperatively.

Inclusion criteria for carers include the following: be the person who is nominated as the primary carer after hospital discharge of a patient participating in the TKR study from the intervention group (ie, using the app and activity tracker), be sufficiently healthy to not be adversely affected by the participation in the interview or study, and have the willingness to participate in the study and be interviewed. Clinicians must have provided care to at least 1 patient participant in the TKR study to take part in the interview.

Carers and clinicians participating in an interview will be sent the information sheet and consent form by email or post, separate from the ones used for patients. Paper-based consent will be obtained in face-to-face interviews, and verbal consent will be obtained for telephone interviews.

Estimated times for patient and carer interviews are 30 to 45 minutes, and estimated time for clinicians is 45 to 60 minutes.

Sample Size

The sample size is calculated based on the primary outcome (ie, OKS), by considering 80% power (P=.05) with a 15% difference in the control group and the intervention group. The standard deviation within each group in the TKR trials can vary based on factors such as number of trial sites (eg, single-center vs multicenter) and heath care cover (eg, public patients vs private patients). Furthermore, in a repeated measure scenario or when considering multiple assessments within a trial (eg, baseline, prehabilitation, 12 weeks rehabilitation, 12 months free living), the correlation among repeated measures needs to be considered as well. Based on these factors the sample size is presented in Table 2 for a variety of scenarios. A low subject variation can be expected with participants when considering only 1 trial site or 1 type of health care cover (eg, public), and a high variation can be expected when participants are mixed. A high correlation in repeated measures can be expected for patients with big differences in the outcome measure within the assessment points.

Table 2. Estimated sample size (with 20% loss) based on standard deviation (SD) within groups and correlation among baseline and 3 repeated measures [80% power, P=.05, 15% difference].

SD within group/ correlation repeated measure	Low repeated correlation (SD 0.2)	Mid repeated correlation (SD 0.5)	High repeated correlation (SD 0.8)
Low subject variation (SD 0.2)	31	46	60
Mid subject variation (SD 0.5)	170	262	360
High subject variation (SD 0.8)	432	674	914

We estimate that a total of 262 patient participants would be sufficient for this study; however, we expect a maximum of 320 participants from the 5 trial sites based on their rate of TKR surgeries during the trial timeline. A minimum sample size of 100 is suggested for using OKS as the primary outcome measure [33]. Based on the literature [1,7,34], 80% power (P=.05) with a 15% difference in the control group and the intervention group has been reported for primary outcome measure.

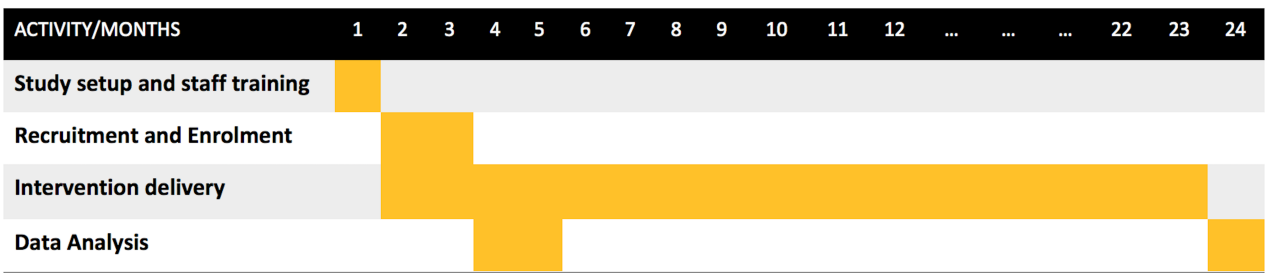
Statistical Analysis

Statistical data analysis will be performed using an intention-to-treat approach. Mixed model analysis will be used for continuous variables (primary and secondary outcomes) measured at week 0, week 12, and week 52 for those receiving the TKR platform compared with usual care by time effects. Fixed effects will be included for the intervention, the time points, and the interaction between the 2 variables. These models will also account for relevant covariates such as baseline (4 weeks before surgery) measures, participant sex, baseline levels of motivation, etc. These covariates will be entered as fixed effects. Due to potential confounding effects between different hospitals, these will be also assessed in the mixed model as random effects. Sensitivity analysis will be used to assess the impact of these covariates before the final model is constructed. Other outcome measures of app usage, self-management (eg, physical activity), and compliance with the program (eg, physiotherapy exercise) will be analyzed using logistic or conditional logistic regression to adjust the comparisons for other variables for categorical or ordinal variables and multiple regression for continuous variables. All statistical analysis will be done using Excel (Microsoft Corp), R (R Foundation), or SPSS (IBM Corp).

Timelines

It is intended that the total study will run for 24 months. This is subject to patient (ie, participants) recruitment. Data capture pertaining to each patient is required for 13 months. Figure 4 presents the expected timeline for this research.

Figure 4. Research timelines.



Results

This research is being conducted by CSIRO and cofunded by commercial partner Johnson & Johnson Medical Australia. The research protocol is approved by the CSIRO and Mater Health Services human research ethics committees.

The development of the TKR platform is complete, and the technology has been deployed for trial. The trial commenced at Gosford Private Hospital in October 2016, and all other sites are expected to come on board early in 2017 once training of relevant trial site staff (ie, POs, surgeons, physiotherapists, fellows) is complete.

Discussion

Variations in the provision of care by health care providers, rising health care costs, and the increased uptake of TKR surgery have recently contributed to the need to ensure that TKR is effective, efficient, and safe as this can have a significant impact on patient satisfaction, medical costs, and access to health care service [35,36]. Rehabilitation programs after TKR surgery are designed to assist in recovery, restoring functional independence through physiotherapy programs and other interventions supporting the process. The programs have been popular in Western countries with both inpatient and outpatient settings.

It is evident that rehabilitation programs are costly and mostly accessed by private health care patients. Patients generally have the option of inpatient or outpatient rehabilitation after TKR. Inpatient rehabilitation clinics are only available in large metropolitan areas and because of the cost only an option for private insured patients [37]. Outpatient rehabilitation usually commences immediately after hospital discharge, which provides supervised (ie, one-on-one or group) exercises to the patients by a physiotherapist and is completed within 6 to 8 weeks after TKR surgery [7,38]. Outpatient rehabilitation has a large component of self-managed exercise at home. Compliance with in-home exercise is a recognized challenge in physiotherapy [39]. Compliance with rehabilitation physiotherapy after TKR is dependent on motivation or self-determination [18].

Our study will test whether a digital orthopedic rehabilitation platform comprising a smartphone-based program with a wearable activity tracking device and a clinical Web portal where clinicians monitor patients can assist TKR patients and their carers in the TKR journey. The proposed platform will provide flexibility, particularly in rural, remote, or busy lifestyles, and has the potential to achieve the same clinical outcomes as normal business as usual care.

Potential barriers to participant adaptation of the intervention may include a lack of technology/eHealth literacy for the targeted age group, contributing to the unwillingness to continue using the app and the wearable activity tracker. The trial is a research project rather than a new health service. It requires clinicians and POs at trial sites to help participants follow the protocol while integrating the intervention into their usual care model.

Acknowledgments

The project is cofunded by Johnson & Johnson Medical Devices Australia and CSIRO. The commercial partner, Johnson & Johnson Medical Devices Australia, has engaged CSIRO to conduct this research on their behalf and has approved the manuscript for publication. We thank Angela Coble, Ben Travers, Julian Ryall, and Nathan Edgington from Johnson & Johnson Medical Devices Australia for their input and contribution.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Questionnaires (i.e. instruments) and interview questions.

[PDF File (Adobe PDF File), 166KB - resprot_v6i3e32_app1.pdf]

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Abbreviations

CSIRO: Commonwealth Scientific and Industrial Research Organization
CTC: clinical trial coordinator
DASS21: Depression, Anxiety, and Stress Scale
OKS: Oxford Knee Score
PO: project officer
RCT: randomized controlled trial
ROM: range of motion
SDQ: Self-Determination Questionnaire
SES: Self-Efficacy Scale
SF-36: Short-Form Health Survey
SMI: Self-Motivation Inventory
TKR: total knee replacement

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Protocol

Innovations in the Management of Musculoskeletal Pain With Alpha-Lipoic Acid (IMPALA Trial): Study protocol for a Double-Blind, Randomized, Placebo-Controlled Crossover Trial of Alpha-Lipoic Acid for the Treatment of Fibromyalgia Pain

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Abstract

Background: Fibromyalgia is a common disorder characterized by chronic widespread pain, sleep disturbance, fatigue, depression, and cognitive dysfunction, resulting in substantial disability. As current analgesics provide incomplete relief and disabling side effects that aggravate fatigue and cognitive dysfunction, there is a need for new pain treatments with better efficacy and tolerability. Alpha-lipoic acid (ALA) is an antioxidant proven effective in painful diabetic neuropathy with minimal side effects.

Objective: We hypothesize that this agent will provide benefits in fibromyalgia because of several similarities with neuropathic pain and also because it does not cause sedation, fatigue, or mental-slowing. To test this, we have designed a clinical trial that will assess pain, side effects, and other outcomes in participants with fibromyalgia.

Methods: Using a crossover design, 24 adults with fibromyalgia will be randomly allocated to 1 of the 2 sequences of ALA and placebo. Participants will take capsules containing ALA or placebo for 4 weeks followed by a 1-week washout followed by a second 4-week treatment and 1-week washout period. ALA (or matching placebo) capsules will be titrated to 1800 mg/day over each 4-week period. The primary outcome will be mean daily pain intensity (0-10) during week 4 of each period. Secondary outcomes, assessed during week 4 of each period, will include global improvement, adverse events, mood, and quality of life.

Results: This trial was registered in the International Standard Randomized Controlled Trial registry March 15, 2016 (Number ISRCTN58259979), and it attained ethics approval on December 3, 2016 (Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board protocol number ANAE-287-15). The recruitment started in February 2017.

Conclusions: This trial will provide evidence for the efficacy of ALA in fibromyalgia.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): 58259979; www.isrctn.com/ISRCTN58259979 (Archived by WebCite at http://www.webcitation.org/6og9JdiyZ)

(JMIR Res Protoc 2017;6(3):e41) doi:10.2196/resprot.7198

KEYWORDS

fibromyalgia; pain; alpha-lipoic acid; antioxidants

Introduction

Fibromyalgia is a multisystem disorder characterized by chronic widespread pain, sleep disturbance, fatigue, irritable bowel syndrome, depressed mood, and cognitive dysfunction, that is reflected in functional disability and impaired quality of life [1,2]. This condition is highly prevalent, with estimates suggesting that 1.6% of men and 4.9% of women are affected [3]; however, the reported prevalence of fibromyalgia is much higher in patients also diagnosed with migraine (22.2%) and low back pain (39%) [4]. Fibromyalgia not only causes suffering, but it is also a substantial financial burden. Canadian estimates put the annual direct health care costs of fibromyalgia at Can $350 million, and annual private insurance costs at Can $200 million [5]. The average 6-month direct and indirect costs of fibromyalgia per person in Canada are Can $2298 and Can $5035, respectively [6]. In the United States, for every dollar spent on fibromyalgia-specific claims, employers spend another US $57-US $143 on additional direct and indirect costs [7]. Thus, in addition to being devastating to the afflicted individual and his or her family, fibromyalgia also exerts a major adverse socioeconomic impact on the society.

Chronic widespread pain is the predominant feature of fibromyalgia [1]. Many drug (eg, nonsteroidal antiinflammatory drugs [NSAIDs], antidepressants, opioids, and anticonvulsants) and nondrug (eg, exercise, acupuncture, cognitive-behavioral therapy) treatments have been evaluated in hundreds of randomized controlled trials (RCTs) [8,9]. In addition to exercise and cognitive behavioral therapy, pharmacotherapy remains an important treatment for fibromyalgia [8]. Evidence-based treatment recommendations from the European League Against Rheumatism, the American Pain Society, and the Association of the Scientific Medical Societies in Germany have included amitriptyline, cyclobenzaprine, tramadol, gabapentin or pregabalin, fluoxetine, and duloxetine [10]. Unfortunately, the current therapies available for treating fibromyalgia do not provide complete relief from all the symptoms. In fibromyalgia (and most other chronic pain conditions), current drugs reduce pain by only 25-40% on average, and meaningful relief occurs in only 40-60% of the patients [9,11]. This is in part due to incomplete efficacy and dose-limiting adverse events associated with these drugs (eg, sedation, cognitive dysfunction, and dizziness). Moreover, some of these side effects (eg, fatigue and cognitive dysfunction) are also common symptoms of the disease, so current drug therapies can actually exacerbate fibromyalgia symptoms. There is some evidence to suggest that combinations of drugs with different mechanisms of action and nonoverlapping side effects may provide superior relief for fibromyalgia patients while minimizing adverse events [12]; however, there are currently very few high-quality trials testing this hypothesis and a related systematic review is currently underway [13].

Careful and extensive clinical observations have identified several similarities between neuropathic pain and fibromyalgia (eg, comorbid depression, disturbed sleep, and similar profiles of sensory symptoms and sensory dysfunction) indicating that considerable similarities and overlap exists between these two conditions, that suggests the possibility of common underlying mechanisms such as central sensitization to nociceptive stimuli [14]. Therefore, it is perhaps not surprising that several treatments effective in neuropathic pain (eg, tricyclic antidepressants, selective norepinephrine reuptake inhibitor [SNRI] antidepressants, gabapentin, and pregabalin) are also effective in fibromyalgia [10]. These converging lines of evidence provide a sound rationale for evaluating new therapies for fibromyalgia that are known to be efficacious in neuropathic pain. One such emerging intervention of interest is antioxidant therapy.

There is growing evidence implicating a role of reactive oxygen species and antioxidants in pain modulation [15-18]. In a mouse pain model, levels of the endogenous antioxidant superoxide dismutase were correlated with the degree of capsaicin-induced hyperalgesia, such that lower antioxidant levels were associated with greater hyperalgesia [19]. These findings suggest that injury-induced pain processing is due in part to accumulation of reactive oxygen species. Furthermore, early preclinical and clinical evidence suggests that various antioxidant compounds have analgesic effects in various pain conditions including vitamin C in complex regional pain syndrome [20], soy protein in neuropathic pain [21], and a combination of different antioxidants in pancreatitis [22]. Alpha-lipoic acid (ALA) has antioxidant activity in its reduced and oxidized forms [23], and is likely the antioxidant that has been studied most extensively for its analgesic efficacy in humans. Over the past several decades, ALA has been studied in the setting of pain in dozens of investigations. Preclinical evidence for analgesic mechanisms of ALA include decreased sensitivity to noxious stimulation through inhibition of T-type calcium (Cav3.2) channels [24]. Clinically, at least sixteen RCTs of ALA involving more than 1320 participants have reported reductions in pain and other diabetic neuropathy symptoms [25-28]. Although symptomatic improvement with ALA has been demonstrated mostly in diabetic neuropathy populations, evidence also suggests the potential for efficacy in other pain conditions such as chemotherapy-induced neuropathy [29,30] and burning mouth syndrome [31].

Current fibromyalgia treatments provide clinically relevant pain relief in only some patients and also frequently exacerbate other disabling features of fibromyalgia. An analgesic agent that does not cause central nervous system depression would be of great benefit to patients suffering from fibromyalgia. Unfortunately, there is no evidence to support the efficacy of acetaminophen or NSAIDs in fibromyalgia, and any potential benefits of NSAIDs are greatly outweighed by their gastrointestinal and other adverse effects such that NSAIDs are recommended against in recent fibromyalgia guidelines [10]. Thus, there is clearly a desperate need for new fibromyalgia treatments with greater analgesic efficacy, but also with a better safety and tolerability profile that is best suited to the constellation of fibromyalgia-related symptoms. ALA has demonstrated safety and efficacy (number-needed-to-treat=~6) in neuropathic pain in 16 RCTs of more than 1320 patients to date [27]. Given the similarities between neuropathic pain conditions and fibromyalgia, we hypothesize that ALA will be effective in reducing pain in fibromyalgia patients. Furthermore, given that ALA is nonsedating with no reported fatigue or cognitive

dysfunction, we expect that ALA will have the added benefit of not exacerbating these fibromyalgia-related symptoms.

Methods

Ethics Approval

This study underwent ethics review and received a compliance notice from the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board. This study protocol will be conducted in accordance with the principles of the Declaration of Helsinki and also consistent with the International Council for Harmonisation Good Clinical Practice: Consolidated guideline.

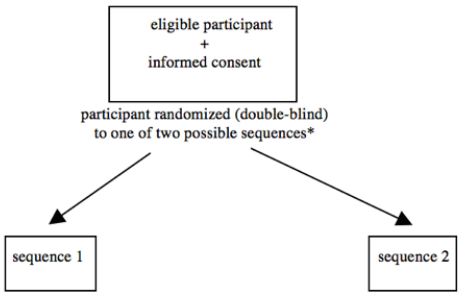
Aims and Hypothesis

The objective of this trial was to evaluate the safety and efficacy of ALA in treating pain in participants with fibromyalgia. Our primary hypothesis is that ALA is safe and superior to placebo in treating pain in fibromyalgia.

Design

This is a double-blind, randomized, 2-period crossover controlled trial comparing ALA to placebo in adults with fibromyalgia (Figure 1). Each of the 2 treatment periods will be 5 weeks in duration, and the entire trial will be 10 weeks long for each participant. Participants will be randomized to one of the two treatment sequences. The randomization sequence will be generated using the Web-based program—randomization.com (Dallal, Tufts University). Participants in sequence 1 will take active inert placebo capsules during the first 4 weeks of the trial (followed by a 1-week washout period) and will subsequently take active ALA capsules for the next 4 weeks of the trial (followed by a 1-week washout period). Participants in sequence 2 will take active ALA capsules during the first 4 weeks of the trial (followed by a 1-week washout period) and will subsequently take inert placebo capsules for the next 4 weeks of the trial (followed by a 1-week washout period). See Figure 1 for a trial design schematic.

Figure 1. Flow of participants through the trial.



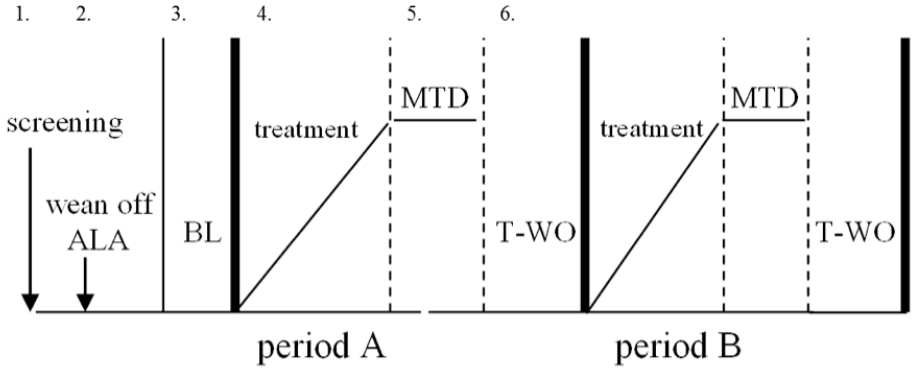
*see below for specific treatment sequences

TREATMENT SEQUENCES

[All participants complete both periods (i.e. A and B) as per the treatment sequence they were randomized to above (i.e. 1 or 2)]

Baseline 7 day washout of prohibited medications (i.e. alpha-lipoic acid)	Sequence	A 5 weeks 3 weeks increasing dose; 1 week steady dose; 1 week stop study medication	B 5 weeks 3 weeks increasing dose; 1 week steady dose; 1 week stop study medication
	1	PLACEBO	Alpha-lipoic acid
	2	Alpha-lipoic acid	PLACEBO

Figure 2. Trial design schematic representation.



1. Screening – Determine participant eligibility using inclusion and exclusion criteria
2. Wean off current alpha-lipoic acid – Participants taking and perceiving benefit from opioids (<200mg/day morphine equivalents), antidepressants, NSAIDs or acetaminophen may continue these at a steady dose during the study. Participants are required to avoid any procedural pain therapies during the study
3. Baseline – 7 day baseline period taking only permitted medications at a steady dose
4. Treatment – Once randomized to 1 of the 2 treatment sequences (1: Period A-ALA, Period B-Placebo, or 2: Period A-Placebo, Period B-ALA), participants will go through a 3 week upward dose titration to a maximum of 1,800mg ALA per day
5. MTD – Participants will be at their maximal tolerated dose of ALA for 1 week, during which the primary outcome measure will be assessed
6. T-WO – Treatment washout of ALA or placebo for 1 week before starting the next treatment period

Setting

Investigators work in a tertiary care health sciences center in Kingston, Ontario, Canada.

Participants

Men and women aged 18 years and older meeting the 2016 American College of Rheumatology revised diagnostic criteria for fibromyalgia will be considered for recruitment following informed consent. The inclusion and exclusion criteria are given in Textboxes 1 and .

Textbox 1. Inclusion criteria for the study.

- Adults aged 18 years and older
- Diagnosed with fibromyalgia using the 2016 American College of Rheumatology revised diagnostic criteria
- Experiencing daily moderate pain (≥4/10 on a Numerical Rating Scale) for at least three months
- Women of childbearing potential must have a negative serum beta-human chorionic gonadotropin (HCG) test and are required to use a highly effective form of contraception while on trial
- Have the necessary abilities, visual acuity, and English language skills to complete questionnaires and pain diaries and to participate in telephone communication with study nurses to permit titration of the study drugs

Textbox 2. Exclusion criteria for the study.

- Presence of a painful condition, including inflammatory rheumatic disease, more than 50% as severe as, but distinct from, fibromyalgia
- Women who are pregnant or lactating
- Women of childbearing potential not using adequate contraceptives
- End-stage kidney or liver disease
- Unstable cardiovascular disease (myocardial infarction within the preceding year, unstable angina, or congestive heart failure) or clinically relevant abnormal 12-lead electrocardiogram
- Any poorly controlled medical condition that, in the opinion of the investigator, would interfere with proper conduct of the trial
- Severe depression, as determined by a Beck Depression Inventory-II score of 29 or more; suicidal ideation, as determined by a Beck Depression Inventory score of 2 or more; any current major psychiatric disorder (eg, schizophrenia, bipolar disorder, and so on) that is not well-controlled
- Hypersensitivity to any of the study medications
- Any current alcohol or drug abuse or dependence (except nicotine and caffeine). Participants with a history of abuse/dependence with more than 1 year of abstinence may be considered for inclusion
- Those taking more than 90 mg morphine equivalents per day

Randomization and Blinding

We will use a balanced Latin Square crossover design in which participants will be allocated to one of the two treatment sequences of ALA and placebo. At the beginning of the trial, an investigational pharmacist will use a computer-generated randomization process to prepare a concealed allocation schedule to randomly assign the treatment sequences, in appropriate block sizes, to a consecutive series of numbers. On enrollment, each participant will be assigned to the next consecutive number, and the corresponding series of study medications will be dispensed (eg, ALA followed by placebo or placebo followed by ALA). Study medications will be formulated in an identical fashion across treatment periods. Treatment codes for each study participant will be generated by an investigational pharmacist and will not be disclosed to study personnel or participants until completion of all participants in the trial. Study outcome measures will be evaluated and recorded by the research study nurse who will be blinded (as will the rest of the research team) to treatment group assignments until trial completion. As an assessment of blinding to treatment group, each participant and the study nurse will complete a blinding questionnaire at the end of each treatment period.

Cointerventions and Rescue Medication

Any enrolled participants already taking ALA will be weaned off during a pretrial washout of at least seven days. Participants taking and perceiving benefit from opioids (<90 mg morphine equivalents), antidepressants (tricyclic, selective serotonin reuptake inhibitor, or SNRI), NSAIDS, or acetaminophen may continue these medications at a steady daily dose for the duration of the study. Any ongoing cognitive-behavioral therapy and exercise programs perceived as beneficial will be allowed to continue only if it is certain that these will be evenly used throughout the trial. Participants will not be allowed to start new medications, cognitive-behavioral therapy, or exercise programs at any point during the study. Participants will be required to avoid any procedural pain therapies (eg, neurosurgical interventions, nerve blocks, or acupuncture) during the study. Participants will be permitted to take acetaminophen (≤8 tablets, 325 mg/tablet daily) for inadequate pain relief only during the taper and washout phases of each treatment period. Acetaminophen consumption will be recorded as a secondary outcome measure.

Study Treatment Dosing Schedule

ALA active study medication and matching placebo is being supplied by SiSU Incorporated (Burnaby BC, Canada) and encapsulated by Central Medical Pharmacy Inc (Toronto, ON, Canada). During each period of this trial, participants will receive 1 set of capsules (ALA capsules) containing ALA 300 mg or placebo (lactose capsules) to be taken 30 min before meals. Each period will last 5 weeks, with a 4-week treatment period and a 1-week washout period. During week 1 of each treatment period, participants will take 2 capsules before bedtime. During week 2, participants will take 2 capsules at dinnertime and 2 capsules before bedtime. During weeks 3 and 4, participants will take 2 capsules in the morning, 2 capsules at dinnertime, and 2 capsules before bedtime. On the basis of previous studies, we expect virtually all trial participants to tolerate and reach the ceiling dose of ALA 1800 mg/day. However, during this flexible dose titration, the final dose arrived at during the maximal tolerated dose week (week 4 of the treatment period) could be lower than the ceiling dose of 1800 mg, if side effects encountered during the dose titration (eg, nausea) are suspected to be due to ALA. Thus, this trial will not use a forced titration to the ceiling dose of 1800 mg/day. Week 5 would be a complete washout, and participants will take no study medication.

Outcome Measures

During the trial, the study nurse will contact participants by telephone at least once a week to evaluate adverse effects, assess pain intensity, and encourage compliance. Furthermore, participants will be evaluated in the clinic on 1 of the 5 weekdays of week 4 of each treatment period for vital signs and assessment of secondary outcomes. Finally, participants will be followed up by telephone 2 weeks and 3 months following the completion of the study to document any subsequent problems or adverse events. See Table 1 for the schedule of study assessments.

Table 1. Schedule of assessments.

Assessment	Screen	Baseline	Treatment periods			3-Month Posttrial completion
			Weeks 1-3	Week 4	Week 5 (Washout)	
Days per treatment period	−14	−7	1-21	22-28	29-35	
Present pain intensity, 0-10 numerical rating scale (average and worst)	*[b]					
Concurrent medications[a]	*	*	*	*	*	*
Demographics and medical history	*					
Vital signs and weight	*			*		
Clinical biochemistry	*					
Adverse events[a]	*	*	*	*	*	*
Other adverse effects[a]			*	*	*	
Drug dispensing		*		*		
Drug compliance and accountability				*		
Daily pain diaries		*	*	*	*	
Maximal tolerated dose levels			*	*	*	
Medical Outcomes Study-Sleep Scale		*		*		
Patient global impression of change			*	*	*	
Brief Pain Inventory		*		*		
Beck Depression Inventory-II	*	*		*		
Medical Outcomes Study 36-item short-form health survey		*		*		
Rescue acetaminophen[a]			*	*	*	
Fibromyalgia Impact Questionnaire		*		*		
Short-form McGill Pain Questionnaire		*		*		
Blinding questionnaire				*		

[a]Evaluated during weekly participant telephone contacts with research nurse.

[b]* indicates timing of each trial assessment.

The primary outcome is the mean daily "average" pain intensity experienced while on the maximal tolerated dose of ALA or placebo during week 4 (days 22-28). This will be determined from participants' ratings of their "average pain over the last 24 hours" completed in patient diaries every morning using a numerical rating scale from 0 to 10. Secondary outcomes include: frequency or severity of treatment-emergent adverse effects, Fibromyalgia Impact Questionnaire, Medical Outcomes Study Sleep Scale, Patient Global Impression of Change, Brief Pain Inventory, Beck Depression Inventory-II, Beck Anxiety Inventory, the short form McGill Pain Questionnaire, the SF-36 survey, blinding questionnaires, and acetaminophen consumption. All these outcomes will be assessed at the baseline and during week 4 of each treatment period, except for adverse effects and acetaminophen consumption, which will be assessed weekly during each treatment period. In addition, plasma RNA samples will be collected to search for transcription and protein markers of treatment response.

Sample Size

Statistical considerations underlying this sample size calculation are based on the null hypothesis that there is no difference in pain intensity between the study treatments and the alternative hypothesis that ALA is different from placebo. Systematic reviews of placebo-controlled chronic pain trials consistently reveal that statistically significant treatment-placebo group differences vary between 0.5 and 1.5 points depending on the magnitude of placebo response in any given trial [32]. Thus, on the basis of previous estimates of within-participant variation in fibromyalgia [33], we project that a sample size of 21 participants would provide an 80% chance of detecting (at an alpha level of .05) a mean treatment group difference of 1.5 points on a 0-10 numerical rating scale. In order to have a sample size divisible by 4, we have adjusted the sample size to 24 participants. Accounting for trial dropout rates from our previous trials and for a 2-period crossover design, we expect that the recruitment of 30 enrollees for each trial will yield the above number of completers.

Recruitment

One-month lead time will be allowed to begin recruiting study participants. A maximum of 15 participants will be on each treatment period at any given time. On the basis of these factors, our projected trial completion time is 24 months. As we have been doing for our previous and ongoing chronic pain trials [34-37], a concurrent series of participant recruitment methods will be used [38].

Statistical Analysis

Participants who complete both treatment periods will be included in trial efficacy analyses. When data from only one period are available, sensitivity analysis including all participants will also be performed, by assuming some reasonable but extreme values for the remaining periods. Those receiving at least one dose of study drug will be included in the safety analyses.

The primary outcome will be calculated as an average of pain scores as recorded in the participant pain diaries within the last 7 days (at maximal tolerated dose in week 4 of the treatment), if more than 50% of the information (at least four days) is not missing [39]. Otherwise, mean daily pain will be treated as missing data. Sensitivity analyses on the basis of the average of all available pain scores will also be performed to confirm the results of the primary analysis. A linear mixed model with sequence, period, treatment, and the first order carryover as fixed effects and participant as a random effect [39] will be used to test whether there is any treatment difference among groups and to estimate the least square mean of the mean daily pain intensity for each treatment group, adjusting the carryover and period effects. The pairwise comparison between ALA and placebo will be performed on the basis of the least square means and standard deviations from the linear mixed model. Sensitivity analyses will be performed using a pattern-mixture model [40] on the basis of patterns of missing data so as to check the robustness of results in the case that data may not be missing at random. A Fisher's Least Significant Difference [41] procedure will be used to adjust the *P* values for ALA versus placebo comparisons.

Secondary outcomes will be analyzed similarly except that (1) only 1 measurement will be analyzed in the last week for the singular measures (ie, final week questionnaires), and (2) the scoring algorithms developed for the Brief Pain Inventory, the Beck Depression Inventory-II, the Beck Anxiety Inventory, and the SF-36 will be first used to derive the subscales or domains within these instruments and the scores on these subscales or domains will be used as response variables in the linear mixed model analysis.

Results

This trial has been funded by the Physicians' Services Incorporated Foundation. It was registered in the International Standard Randomized Controlled Trial registry March 15, 2016 (Number ISRCTN58259979), and it attained ethics approval on December 3, 2016 (Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board protocol number ANAE-287-15). The recruitment started in February 2017.

Discussion

Trial implications

Fibromyalgia remains a challenging condition to treat, with current recommended pharmacological therapies providing only partial relief from pain, and sometimes exacerbating other symptoms. To the best of our knowledge, this proposed trial is the first to investigate the safety and efficacy of the antioxidant, ALA, for the treatment of fibromyalgia pain. As ALA has shown promise in patients with neuropathic pain, which has similar features to fibromyalgia, we expect this antioxidant to provide pain relief with minimal side effects in patients suffering from fibromyalgia.

As with all clinical trials, possible threats to our proposed study include problems with patient recruitment, noncompliance, protocol violations, and early dropouts. However, we are confident that our study design and our experience in leading chronic pain RCTs in this region will mitigate these threats. Furthermore, as in our previous trials, noncompliance, protocol violations, and early dropouts will be minimized by our proposed crossover design, thorough study participant teaching, and close weekly follow up of participants.

Given the current lack of, and desperate need for, new improved fibromyalgia treatments, this research is expected to provide rigorous evidence for a safer and more effective treatment strategy for fibromyalgia. The development of this proof-of-concept RCT of ALA in fibromyalgia will facilitate future confirmatory RCTs and the implementation of ALA into clinical practice such that its benefits may be realized by patients globally.

Consent for Publication

We will obtain informed consent from all trial participants.

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Authors' Contributions

All authors read and approved the manuscript. IG led the writing of this manuscript and the development of this protocol. DT led the development of the statistical analysis plan and contributed to writing of this manuscript and the development of the protocol.

RRH participated in the writing of this manuscript and the initial protocol development, including selection of mood and quality-of-life measures. TT, DZ, LW, RM, and CPG participated in the writing of this manuscript and the initial protocol development. All the Authors will be involved in data analysis and interpretation and in manuscript preparation.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer Review Document.

[PDF File (Adobe PDF File), 140KB - resprot_v6i3e41_app1.pdf]

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Abbreviations

ALA: alpha-lipoic acid
NSAID: nonsteroidal antiinflammatory drug
SNRI: selective norepinephrine reuptake inhibitor

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Protocol

Patterns and Predictors of Adherence to Statin Therapy Among Older Patients: Protocol for a Systematic Review

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Abstract

Background: The benefits of statin therapy are significantly compromised by noncompliance. Although elderly patients may have particular challenges with medication adherence and persistence, previous reviews on statin adherence have not focused on this population. Additionally, comparisons of adherence and persistence specific to statin indication (primary or secondary prevention) have not been thoroughly explored.

Objective: We aim to assess the extent of, and factors associated with, adherence and persistence to statin therapy among older populations (aged ≥65 years).

Methods: A systematic review will be undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations. Searches will be performed using multiple electronic databases (Ovid MEDLINE, EMBASE, PsycINFO, CINAHL, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, and the National Health Service Economic Evaluation Database) to identify relevant randomized trials and observational studies that evaluated statin adherence and/or persistence as an outcome. Eligible studies will include those involving community-living or outpatient elderly individuals. The methodological quality of randomized controlled trials (RCTs) will be assessed via the Joanna Briggs Institute's critical appraisal checklist for RCTs, and the quality assessment of observational studies will be undertaken using a set of questions formulated with resort to the National Institute of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. When possible, meta-analyses will be conducted using random-effect modeling and generic inverse variance analyses for adjusted-effect estimates. Heterogeneity across studies will be quantified using the I^2 statistic. The presence of publication bias will be assessed using funnel plots and Egger's regression tests. A leave-one-out sensitivity analysis will also be conducted to assess the impact of individual study results on pooled estimates. To explore possible sources of heterogeneity across studies, subgroup analyses will be performed based on covariates such as study design, statin indication, country of study, and length of patient follow-up.

Results: The electronic database searches were completed in December 2016. Retrieved articles are currently being screened and the entire study is expected to be completed by June 2017.

Conclusions: This systematic review will provide further understanding of the patterns of, and barriers to, statin adherence and persistence among older patients. The findings will inform clinical practice and the design of appropriate interventions.

Trial Registration: PROSPERO CRD42016053191

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KEYWORDS

statin therapy; adherence; compliance; persistence; elderly patients; geriatrics

Introduction

Beginning with their discovery in the 1970s, and becoming available for clinical use in the 1980s [1], 3-*hydroxymethyl*-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are one of the most frequently prescribed medications, with global users estimated to be more than 1 billion in 2014 [2]. Several clinical trials and reviews have reported statins to be highly efficacious for the prevention of cardiovascular events [3,4]. The biological role of statins in the reduction of cholesterol levels has also led to suggestions of possible use of statins as preventive agents for other conditions, such as dementia [5] and cancer prevention [6,7].

Statins are generally well tolerated by most patients [8], but nonadherence has been reported across observational studies and from analyses of large population-based registries [9]. A meta-analysis estimated that only approximately half (49%) of all patients in observational studies were adherent to statin therapy at 1 year of follow-up [10], although much higher adherence (90.3%) has been observed in randomized trials [10], in which participants were often motivated, and rigorous follow-up was usually in place.

Furthermore, studies have demonstrated increased risk of adverse outcomes following poor statin adherence [11-13]. In some cases, outcomes among nonadherers and those who discontinued statin therapy were found to be even worse than for those who had not initiated treatment [13].

Several systematic reviews have been published on adherence among statin users [9,14,15]. However, no reviews have focused on elderly patients who may face unique challenges with adherence and persistence, especially since this group experiences greater comorbidity and polypharmacy, which are two key contributing factors to these phenomona [16-18]. Additionally, the balance of the risks and benefits associated with statin therapy (particularly for primary prevention) remains unclear and highly debated for the elderly [19,20]. These factors may further impact on patients' willingness to adhere to treatment.

Ongoing demographic changes, characterized by an increasing number of elderly individuals [21], suggests that this population will constitute a significant proportion of current and future statin users. In light of this reality, a systematic review that seeks to explore issues of adherence and persistence specific to the older population is necessary to: (1) identify relevant barriers, (2) compare the level of adherence and persistence relative to statin indication (primary or secondary prevention), and (3) inform the design of appropriate interventions.

Methods

This systematic review will be carried out in line with recommendations specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22]. The protocol has also been prepared in accordance with PRISMA Protocols guidelines (Supplemental File 1) [23].

Review Objectives

This study will assess the extent of, and factors associated with, adherence and persistence to statin therapy among older populations. More specifically, the review objectives are:

- To quantify the proportion of older statin users who are adherent, and compare rates reported in randomized trials to those reported in observational studies, as well as by statin indication (primary vs secondary prevention).
- To assess the level of persistence to statin therapy among older patients, and compare rates between primary and secondary prevention patients.
- To assess, summarize, and provide estimates of risk indicators associated with nonadherence and nonpersistence to statin therapy in the elderly.

The key components of the review will follow the standard *population, intervention, comparison, outcome, and study design* (PICOS) approach (Textbox 1) [24].

Textbox 1. Key components of the systematic review following the standard PICOS approach.

- Population: older patients (aged ≥65 years) undergoing primary or secondary prevention treatment
- Intervention: all statins (HMG-CoA reductase inhibitors)
- Comparison: none
- Outcomes: proportion of patients who were adherent, proportion of patients who were persistent at predefined periods, risk factors associated with nonadherence, risk factors associated with nonpersistence
- Study design: randomized controlled trials and observational studies (prospective and retrospective)

Intervention

The study will focus on all statins and will consider their use for primary and secondary prevention among elderly populations. The outcome(s) evaluated will not be compared across the different statins, and comparisons related to dosing regimen (eg, once or twice daily dosing) will not be carried out.

Outcomes

The use or nonuse of prescribed medicines by patients is often described using a variety of terms such as *adherence*, *compliance*, *persistence*, or *concordance*, which can cause confusion [25-27]. Nonetheless, *adherence*, *compliance*, and *concordance* are often used in relation to instances involving medication doses that are missed [28], and *persistence* is often used in relation to the time from initiation to termination of treatment [29]. Medication concordance, conversely, is usually used to emphasize that the doctor and patient have achieved some level of agreement regarding the therapeutic goal(s) [30]. For this review, *adherence* and *compliance* will represent the same thing, and be used interchangeably. When reference is made to *persistence*, this will relate to the duration of statin use. The benefits of statin therapy are likely to accrue over time [31], making persistence an important measure that is closely related to adherence. Adherence and persistence are detailed below.

Adherence

Adherence refers to, "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [29]. At the individual level, adherence may be estimated via the proportion of doses taken (PDT), which is calculated as: (number of pills taken in time Y)/ (number of pill prescribed for time Y)*100 [32]. Adherence may also be expressed as the proportion of days covered (PDC) which is calculated as: (total days drugs available)/(days in follow-up period)*100 [33]. Furthermore, adherence may be quantified in terms of the medicines possession ratio (MPR) which is calculated as: (number of days of medication supplied within refill interval)/(number of days in refill interval)*100] [33]. In this review, we will define adequate adherence to represent instances in which the MPR, PDC, and PDT are each ≥80%[10,14]. As such, for studies adopting the MPR, PDC, PDT, and similar methodologies, we will only include those that report sample-level adherence rates based on the application of the ≥80% threshold to individual patients. Studies that measure adherence as a continuous (rather than dichotomous) variable using MPR, PDC, PDT, and similar methodologies will be excluded. Studies that utilize other tools, including self-reported scales (eg, Morisky Medication Adherence Scale [34]), and classify patients as *adherent* will use the tool's established recommendations. Of note, adherence rates in this review will not include *primary nonadherence*, which indicates instances that patients failed to fill their first statin prescription [35].

Persistence

Persistence refers to the continuous use of medication by patients for the required duration. Although various methods exist for estimating medication persistence, including the use of medication possession at a fixed point in time, the most commonly adopted approach involves quantifying the gaps between prescription refills [36]. Patients are often considered to have discontinued (been nonpersistent) if they have exceeded a permissible gap (number of days allowed between refills). No standardized permissible gap typically exists, as this will often be dictated by the length of previous prescriptions. However, a range of 1.5-3 times the days' supply of preceding prescription has often been used [37]. We will consider all studies that report sample-level persistence rates, whether based on a defined permissible gap or where there is evidence of discontinuation, such as patient self-reports.

This study will also assess factors that are reported to influence adherence and persistence to statin therapy among elderly patients. These factors will be grouped under five themes, in line with the World Health Organization's classification of predictive factors of nonadherence [38,39]: (1) patient-related factors (eg, gender), (2) socioeconomic factors (eg, educational status, family support), (3) therapy-related factors (eg, concurrent drug therapy, adverse effects), (4) health system-related factors (eg, proximity to pharmacy), and (5) disease-related factors (eg, presence of comorbidities).

Study Inclusion and Exclusion Criteria

For the current review, both observational (prospective and retrospective) studies and randomized controlled trials (RCTs) that evaluated statin adherence and/or persistence as an outcome will be included. In line with similar reviews [28], we will focus on noninstitutionalized persons and will exclude studies conducted solely on participants within nursing or care homes and inpatient settings. Studies in which medications were administered by a carer or healthcare personnel will be excluded [28]. For studies to be eligible, adherence and/or persistence should also have been assessed over a defined period using an objective measure (eg, pill count, medication refill data) or via a validated self-reported instrument. Studies that mixed older (≥65 years years) and younger individuals (<65 years) will be excluded unless specific results have been presented for the elderly population, or where efforts to retrieve such data from authors have been successful. Studies that do not report adherence and/or persistence solely on statins (eg, where statins are mixed with other medications including other lipid-lowering drugs) will be excluded. Studies with sample sizes <50 will be excluded [40]. No country restrictions will be imposed.

Search Strategy

To identify appropriate studies for the review, searches were performed using Ovid MEDLINE, EMBASE, CINAHL, PsycINFO, Database of Abstracts of Reviews of Effects, National Health Service Economic Evaluation Database, and the Cochrane Central Register of Controlled Trials. The main keywords that were used included, "statins *or* HMG-CoA reductase inhibitors *or* individual generic and propriety names" and, "medication compliance *or* adherence *or* persistence *or* treatment refusal *or* drop out *or* discontinuation". Table 1 presents the search strategy for Ovid MEDLINE developed in consultation with an information management specialist (librarian) [41]. This search strategy was replicated for the remaining databases, and modifications were made in-line with individual database requirements if necessary. All electronic searches were completed on December 12, 2016 and only studies published before this date will be considered for inclusion in this review. The reference list of all selected articles will be screened for additional studies. In view of limited time and resources, only studies published in English will be considered for the review.

Table 1. Search strategy developed for Ovid MEDLINE.

Block 1: Statins	
	1. exp hydroxymethylglutaryl-coA reductase inhibitors/
	2. statin*.mp.
	3. ([hmg-coa reductase or hydroxymethylglutaryl coa or hydroxymethylglutaryl-coenzyme a] adj2 inhibit*).mp.
	4. (atorvastatin or lipitor).mp.
	5. (simvastatin or zocor).mp.
	6. (cerivastatin or lipobay or baychol).mp.
	7. (lovastatin or mevacor or altoprev).mp.
	8. (fluvastatin or lescol).mp.
	9. mevastatin.mp.
	10. (rosuvastatin or crestor).mp.
	11. (pitavastatin or livalo).mp.
	12. (pravastatin or pravachol).mp.
	13. ([lipid or cholesterol] adj3 lower*).mp.
	14. (antilipid* or anti-lipid*).mp.
	15. or/1-14
Block 2: Adherence/compliance/persistence	
	16. exp patient compliance/
	17. exp medication adherence/
	18. (complian* or noncomplian* or discontinu* or adher* or persist* or concordance or non-adher* or nonpersist* or dropout* or drop-out*).mp.
	19. (patient* adj3 [attitude* or acceptance* or satisf*]).mp.
	20. (treatment* adj3 [stop* or abandon* or refus*]).mp.
	21. or/16-20
Block 3: Study designs	
	22. ([observation* or prospective* or retrospective*] adj2 [study or studies]).mp.
	23. randomized controlled trial.pt.
	24. controlled clinical trial.pt.
	25. randomized.ab.
	26. placebo.ab.
	27. drug therapy.fs.
	28. trial.ab
	29. groups.ab.
	30. or/22-29
Search hits	
	31. 15 and 21 and 30
Limits	
	32. exp animals/not humans.sh.
	33. 31 not 32
	34. limit 33 to English language

Study Selection

Results of individual database searches will be exported to Endnote referencing software and duplicates will be removed. Titles and abstracts of studies will initially be screened, and those that are likely to be of interest and relevance will be shortlisted for full-text examination. The full-text assessment will be undertaken with consideration of the study inclusion/exclusion criteria. We will link studies with multiple publications. The study-screening process will be conducted by RO and validated by another member of the team. Disagreements will involve consultation with a third team member and any issues will be addressed using a consensus-based approach. The entire screening and selection process will be summarized using a PRISMA flow chart and reasons for exclusion of studies will be documented.

Study Quality Appraisal

The methodological quality of RCTs will be assessed using the Joanna Briggs Institute's critical appraisal checklist for RCTs (Supplemental File 2) [42]. This tool includes 13 questions that relate to randomization, allocation concealment, blinding, and data analysis. For observational studies, quality assessments will be undertaken using a set of questions formulated with resort to the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (Supplemental File 3) [43]. The NIH tool includes 14 questions that relate to reporting, sample size estimation, loss-to-follow-up, outcome measurement, validity, and generalizability. The quality of each study will be rated as either *good*, *fair*, or *poor*.

Data Extraction

A data extraction tool that incorporates relevant items (recommended by the Cochrane handbook for systematic reviews of interventions [44]) will be used to extract and record data from the studies. The descriptive characteristics of each study, including citation, author details, year, country, study design, sample size, participant composition (eg, percentage of females), and statin indication (primary or secondary prevention) will be summarized. Additionally, we will collect information on adherence and persistence definitions and measurement technique(s), as well as adherence and persistence rates and reported predictive factors. If adherence is measured using more than one technique, the average adherence will be calculated and the results of various techniques will be extracted for a sensitivity analysis. Studies evaluating the impact of an intervention will only have baseline (or comparative control group) results selected. We anticipate variations in the duration of patients' follow-up, and we will report adherence and persistence rates for both short-term (eg, 3 months, 6 months, 12 months) and long-term (24 months or more, up to 5 years) follow-ups, to the extent that available data allows. Individual study data will be extracted separately by two members of the team (RO and another team member) and compared to ascertain consistency and reliability. Any discrepancies will be resolved through consensus-based discussions among the reviewers. Corresponding authors will be contacted via email for assistance if missing or unclear data cannot be reliably extracted. Authors that have not responded within a set period of time will be declared *unreachable*.

Analyses

Adherence and persistence represent different aspects of medication usage [28,29], so separate analyses of these outcomes will be conducted. Adherence and persistence rates reported from individual studies will be logit transformed using the formula: $x=\text{logit}(p)=\text{In}(p/1-p)$, where p is the proportion of patients who were considered to be adherent or persistent. Meta-analyses will be performed using a random-effect model weighted by the inverse variance. Results will be back-transformed into proportion (using the formula $p=\text{logit}^{-1}[x]=e^x/e^x+1$) to ensure comprehensive interpretation of results [45]. Cases in which adherence or persistence are reported only by distinct groups (ie, gender, age groupings) will have subgroups included as separate terms in the meta-analyses. For factors reported to be associated with adherence or persistence, the odds ratios (ORs) along with 95% CIs will be used for quantitative pooling. If the measures of association are reported as other parameters (eg, relative risk and standard mean difference), these will be converted to ORs. Instances in which a study reports an insignificant association without data will have an OR of 1 assigned. Log ORs and standard errors will be combined using the generic inverse-variance method. For each predictive factor, results will be quantitatively pooled, if reported by a minimum of two studies. Results of meta-analyses will be presented as forest plots. The level of heterogeneity resulting from variations of effects from individual studies will be assessed based on I^2statistics. I^2values of 30-60% may denote moderate heterogeneity, 50-90% substantial heterogeneity, and 75-100% considerable heterogeneity [46]. We will evaluate the presence of publication bias by assessing the asymmetry of effect sizes in funnel plots using the trim-and-fill method [47], and Egger's regression tests will be used to quantify small study effects [48]. Additionally, a leave-one-out sensitivity analysis will be conducted by iteratively removing one study at a time to assess the impact of each study on the overall pooled adherence and persistence estimates [49]. Subgroup analyses will be performed based on covariates such as study design, country of origin, method used to estimate adherence, length of patient follow-up, and statin indication. Meta-analyses will be conducted using Comprehensive Meta-Analysis software (version 3.0, Biostat, New Jersey).

Ethics and Dissemination

This study is based on published aggregate data. No identifiable individual data will be utilized, making a formal ethical approval unnecessary. This study has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) with reference number CRD42016053191. If any aspect of the review is modified, this protocol will be updated in the registry. This systematic review will form a chapter of RO's PhD thesis. The results of the study will also be disseminated through publications in peer-reviewed journals and presentations at relevant conferences and seminars.

Results

The electronic database searches for relevant articles were completed in December 2016. The searches resulted in retrieval of over 10,000 articles. Removal of duplicates resulted in approximately 8000 articles that are currently being screened. The screening processes and analysis are expected to be completed by June 2017.

Discussion

This systematic review, along with the potential to conduct meta-analyses, will provide important information regarding issues of adherence and persistence to statin therapy among older patients. The population of the world is aging [21], and most countries are expected to witness an expansion in the size of elderly populations. The elderly often face the greatest morbidity and mortality burden, making curative and preventive therapies intended to improve survival, minimize morbidity, and enhance quality of life extremely essential [50,51]. Enhancing adherence is one of the key ways of improving medication effectiveness. The findings of this study are therefore expected to inform the design of appropriate interventions that will improve adherence to statin therapy among elderly patients, so that optimal benefits can be accrued from such interventions.

Strengths and Limitations of Study

The strengths and limitations of this study are summarized in Textbox 2.

Textbox 2. Study's strengths and limitations.

- Appropriate search strategy has been designed in consultation with an information management specialist who is experienced in conducting systematic reviews
- This study will be the first to evaluate statin adherence and persistence issues specific to older patients, and to compare variability across statin indications
- Our study does not impose any restriction on time period or geographic location
- Non-English articles will be excluded from the review, which may introduce some bias
- Study assessments will involve reviewer judgements, which may introduce bias

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Authors' Contributions

RO designed the initial protocol, which was subsequently reviewed by all authors. All authors read and approved final protocol before submission.

Conflicts of Interest

SZ reports past participation in advisory boards and/or receiving honoraria from: Amgen Australia; AstraZeneca/Bristol-Myers Squibb Australia; Janssen-Cilag; Merck, Sharp, and Dohme (Australia); Novartis Australia; Novo Nordisk; Sanofi; Servier Laboratories; Takeda Australia; and Monash University (undertaking contract work for AstraZeneca Pty Limited/Bristol-Myers Squibb Australia Pty Limited).

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Abbreviations

HMG-CoA: 3-hydroxymethyl-3-methylglutaryl coenzyme A
MPR: medicines possession ratio
NIH: National Institutes of Health
OR: odds ratio
PDC: proportion of days covered
PDT: proportion of doses taken
PICOS: population, intervention, comparison, outcome, and study design

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial

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Original Paper

A Personal Electronic Health Record: Study Protocol of a Feasibility Study on Implementation in a Real-World Health Care Setting

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Abstract

Background: A significant potential for patient empowerment is seen in concepts aiming to give patients access to their personal health information (PHI) and to share this PHI across different care settings and health systems. Personal health records (PHRs) and the availability of information through health information exchanges are considered to be key components of effective and efficient health care. With tethered PHRs, as often used in the United States, patients' opportunities to manage their PHI are strongly restricted. Therefore, within the INFOPAT (information technology for patient oriented care) project (2012-2016) in Germany, funded by the Federal Ministry of Education and Research (BMBF), the development of a patient-controlled "personal electronic health record" (PEPA) was based on user requirements right from the beginning.

Objective: The overall objective of the study is to implement and evaluate a PEPA prototype for patients with colorectal cancer who are treated at the National Center for Tumor Diseases in Heidelberg. To achieve this aim, this study has 2 parts: a pre-implementation study (phase 1) and an implementation study (phase 2). The pre-implementation study will include a usability evaluation of the PEPA approach and the consideration of organizational preconditions for the implementation. With the implementation study, we will evaluate the process of implementation (eg, barriers or facilitators), the need for organizational change (eg, processes of communication), and the impact on outcomes (eg, self-efficacy, involvement in care).

Methods: The pre-implementation study is based on a mixed methods approach and comprises qualitative and quantitative element according to our research aim. We will use a think-aloud method for the usability analysis. Additionally, participants will be asked to evaluate their overall satisfaction based on a standardized questionnaire, the System Usability Scale. For the analysis of preconditions, we will conduct semistructured personal interviews with, for example, patients, medical assistants, and physicians. Within the implementation study the outcome evaluation is planned as a prospective, 3-month, open-label "before and after" trial. Additionally, for the analysis of processes and the need for organizational change, we will conduct interviews with the participants (eg, patients, general practitioners, physicians) of the before and after trial.

Results: This project is part of the INFOPAT project, which is funded (2012-2016) by the Federal Ministry of Education and Research (BMBF). The enrolment was completed in July 2016. Data analysis is currently under way and the first results are expected to be submitted for publication at end of 2017.

Conclusions: Existing approaches of PHRs aim to give patients access to their treatment data. With the PEPA approach and this study, we go a step further: patients have access to their PHI and they can give other persons (eg, their general practitioner) access. With this approach, new possibilities for professional collaboration and the engagement of patients can arise.

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KEYWORDS

self-efficacy; personal electronic health record; colorectal cancer; chronic care; interprofessional collaboration; telemedicine; feasibility studies

Introduction

If patients are being treated across various health care settings or health systems, having access to their complete personal health information (PHI) can be problematic. This can lead to inefficiencies and may hinder coordination and continuity of care [1,2]. However, the health information exchange between different care settings and health systems is a key issue for a multidisciplinary approach in chronic care [3]. Additionally, a significant potential for patient empowerment is seen in concepts aiming to give patients access to their own health- and treatment-related data [4-6]. In particular, personal health records (PHRs) and the availability of information through health information exchange are considered to be key components of effective and efficient health care [7-9].

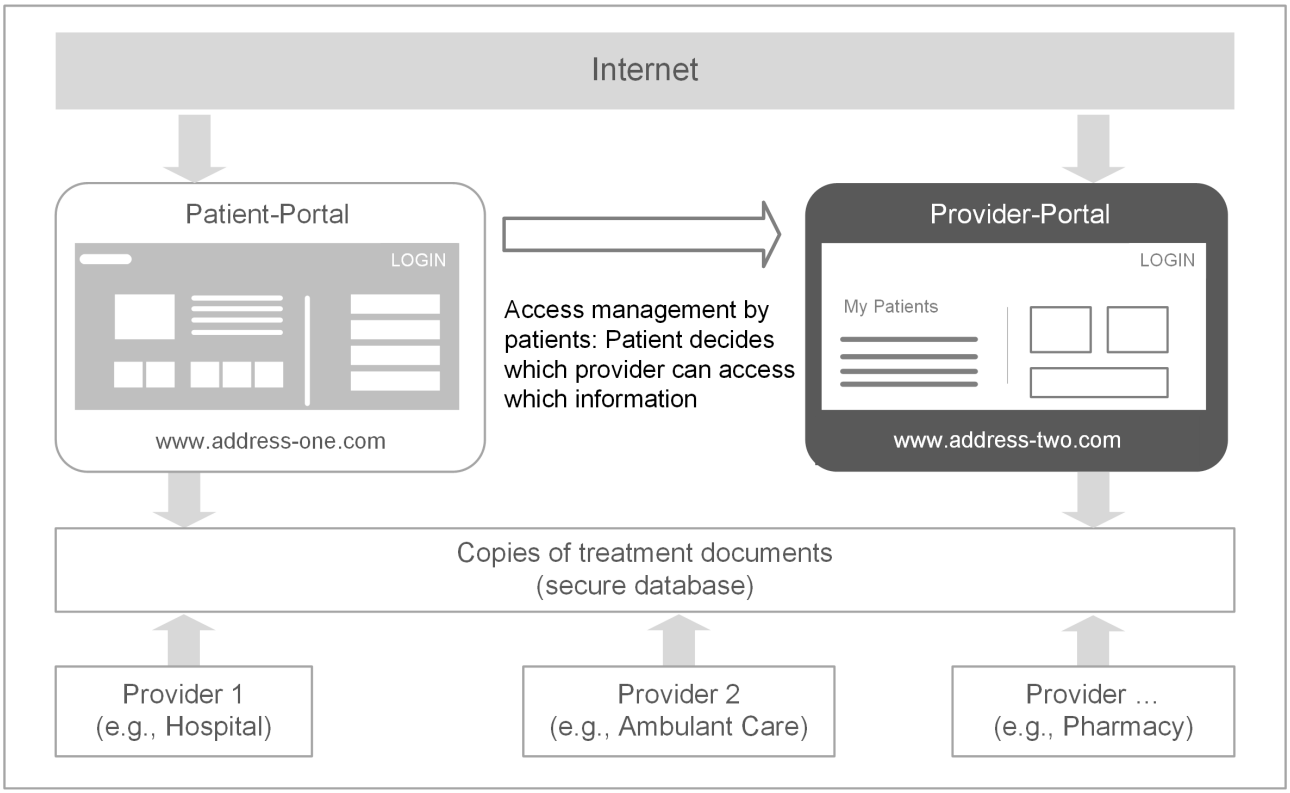
PHR systems, as often used in the United States, allow patients to access primary data from a provider-managed electronic health record through a patient portal (tethered PHRs). With these PHRs, patients' opportunities to manage and to share their health information in cross-sectoral care are nevertheless restricted. In order to promote a more active patient role, it is important to empower patients to take more responsibility and participate actively in their health care. This may include controversial aspects such as allowing patients to decide which physician or other health care professional (HCP) gets access to their PHI during the course of treatment [10,11].

However, design and implementation of PHRs have not proven to be easy. Experiences from a nationwide implementation of PHRs (HealthSpace, England) have shown that they can fail because of a lack of alignment with users' expectations and self-management practices [12]. According to adoption and use, the participation of patients and users (eg, physicians, other HCPs) in the development, implementation, and evaluation of innovative PHR approaches is central [8,12].

Within the INFOPAT project (2012-2016) in Germany, funded by the Federal Ministry of Education and Research (BMBF), the development of a patient-controlled "personal electronic health record" (PEPA) was based on user requirements right from the beginning (first study phase) [13]. The technical PEPA development is based on established health information technology standards and, in particular, "Integrating the Healthcare Enterprise." As a subset of PHR, the Web-based PEPA would enable patients to access, maintain, and manage (including access management) a secure copy of their PHI from various primary systems of service providers (eg, electronic medical record in hospital, electronic health record in general practice).

The PEPA concept comprises 2 Web-based portals, one for patients ("patient portal") and one for HCPs ("professional portal"). Patients can log in to the patient portal and gain insight about their PHI. For managing the access to PEPA, the patient can decide in detail which HCP is able to access which PHI via the professional portal (Figure 1, adapted from [10]).

Figure 1. The PEPA (personal electronic health record) approach.



Methods

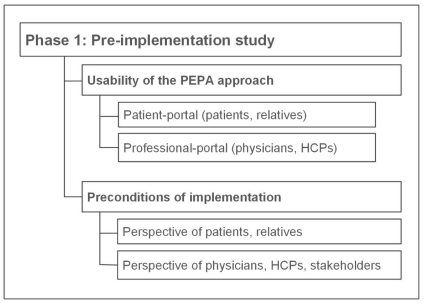
Since the development of the PEPA proceeded [8-10], as a next step of the INFOPAT project the current version of the prototype will be brought into use for the first time. In order to do this, our feasibility study (ISRCTN: 85224823) for the implementation in a real-world health care setting is divided into 2 parts: pre-implementation (phase 1) and implementation (phase 2). Both phases will be described in detail in the following sections.

Phase 1: Pre-implementation Study

When bringing new technologies into daily practice, it is inevitable that challenges will arise from system immanent conditions. If an implementation strategy does not focus on problems that patients and HCPs experience in their everyday life, it is doomed to fail. For that reason, it is envisaged to perform a pre-implementation study focusing on those factors that are crucial for implementation success or failure before determining the underlying implementation procedure.

With the findings of the pre-implementation study it will be possible to improve the prototype and to create a catalog of requirements that addresses patients' and professionals' needs for PEPA usage as well as the surrounding conditions of the care setting. The catalog will serve as a precondition for the planned implementation of the PEPA. The pre-implementation study comprises 2 parts: the usability evaluation of the PEPA approach and the analysis of preconditions for implementation (Figure 2).

Figure 2. Parts of the pre-implementation study. PEPA: personal electronic health record; HCP: health care professional.



Objectives

Usability of the PEPA Approach

As described below (see Figure 1), the PEPA approach comprises 2 separate portals: patient portal (prototype) and professional portal (existing product). The usability evaluation of the patient portal aims to identify factors that may have an influence on the transfer of the prototype to the real-world health care setting. Those factors could be, for example, either issues of usability or other patient-perceived implementation barriers. Therefore, the usability evaluation of the patient portal places emphasis especially on unique features that have been identified as crucial for patients' benefit of using a PHR [11,13]. The focus is on functionalities such as patient-controlled access to the PEPA, patient-controlled information exchange between HCPs, and patient-controlled data storage within the PEPA.

In contrast to the patient portal, the professional portal is not a prototype but an existing product that has already been used before in another health care environment. The usability

evaluation will help to understand whether the professional portal can be integrated adequately into the PEPA context. In this context, relevant features are (1) the easy log-in and log-out, (2) the automatic data transmission, (3) interprofessional cooperation and communication, and (4) the manual upload of documents.

Overall, the research question for the usability evaluation of the PEPA approach is as follows: Do the patient portal and the professional portal meet the demands of their users regarding design, functionality, and usage? Answering this question includes the following objectives: to (1) point out specific challenges that arise during the testing of the PEPA approach and (2) to map demands for a training program and further development.

Preconditions of Implementation

The evaluation of preconditions aims to analyze potential barriers within the organizational or personal conditions of all user groups (patients, relatives, physicians, HCPs, stakeholders) and necessary requirements concerning transfer of the PEPA approach to a real-world health care setting. The analysis of preconditions will be helpful to derive more specific indications on how to design the training concept and support options or instructions for patients and family members working with the PEPA (eg, email support, hotline, manuals). With the analysis of the professional perspective, relevant organizational aspect and processes will be taken into account. The research question for this analysis is as follows: What are the potential barriers and necessary requirements for implementation of the PEPA approach in a real-world health care setting? Answering this question includes the following objectives: to (1) point out relevant organizational preconditions for the PEPA implementation and (2) to obtain further results about the necessities for basic support and training courses.

Study Design and Methods

The pre-implementation study is based on a mixed methods approach and comprises qualitative and quantitative elements – according to our research aim. We will use a think-aloud method (asking participants to verbalize their thoughts while completing the tasks) for the usability analysis [14]. Additionally, participants will be asked to evaluate their overall satisfaction based on a standardized questionnaire, the System Usability Scale (SUS) [15,16]. For the analysis of preconditions, we will conduct semistructured personal interviews with patients, relatives, HCPs, physicians, and stakeholders.

Sample Size

The usability evaluation and the analysis of preconditions are based on 10-15 patients, 10-15 relatives, and 10-15 HCPs as well as physicians. Additionally, we will conduct interviews with up to 20 stakeholders (preconditions of implementation).

Recruitment Strategy

Eligible patients will be asked by their responsible physicians in the outpatient clinic of the National Center for Tumor Diseases (NCT) Heidelberg to participate in the study. For recruiting patients' relatives, all patients participating in the pre-implementation study will also be asked about family members or friends who are supporting them in dealing with the disease. If patients name a certain person, they will be asked to deliver to this person background information about the study.

For recruiting physicians and HCPs at the NCT, we will contact the management of the different professional groups (eg, physicians, nursing staff, social worker, stoma-therapists, nutritionists) and ask for assistance in the recruitment of the participating staff. For recruiting general practitioners and their medical assistants, the Department of General Practice and Health Services Research (GP-HSR; University Hospital Heidelberg) will contact cooperating primary care practices. In addition, representatives of relevant organizations (stakeholder) will be contacted by GP-HSR and asked to participate.

All potential participants will get a written invitation to participate in the study, including background information as well as a declaration of participation and agreement. The written approval for study participation is included in the informed consent document. The signed declaration of participation and agreement must be sent by mail to GP-HSR. There, researchers will contact the participants to arrange an appointment for the usability test and the interview.

Inclusion and Exclusion Criteria

To be eligible for participation in the pre-implementation study, patients must have a diagnosis of colorectal cancer (*International Classification of Diseases, Tenth Revision*, ICD-10: C18, C19, C20). The participants must be 18 years of age or older and their disease status has to be classified as Union for International Cancer Control (UICC) stage III-IV. Patients' relatives do not have to be "related by blood" and could, for example, also be close friends of patients. To be eligible for participation, HCPs have to belong to one of the following groups: clinicians at the NCT, other HCPs such as nursing staff, social worker, stoma-therapists, and nutritionists who are connected to the NCT, as well as general practitioners, according to German regulations, and their medical assistants.

Participating stakeholders should be from organizations such as health insurance funds, large medical centers, medical associations, or political institutions (eg, German Federal Ministry of Health). The sampling of participating stakeholders is based on (1) their thematic interest (2) the position or reputation of the specific stakeholder and (3) the potential impact to foster political decisions for a broader PEPA implementation.

All participants who do not meet the inclusion criteria will be excluded. Additional exclusion criteria for patients are severe acute psychiatric disorders (eg, schizophrenia, schizotypal and delusional disorders); dementia; mental and behavioral disorders due to psychoactive substance use; insurmountable language and communication problems; and emergent cases.

Data Collection

The usability evaluation of both portals—patient and professional—aims to simulate activities that should be covered if the PEPA approach is used in real-world health care contexts. Therefore, a test scenario that consists of realistic activities will be developed for the evaluation of the usability. In this test scenario, users will process a multi-item task concerning the

functionalities of the patient portal or the professional portal. A think-aloud protocol will be incorporated into the usability test by asking participants to verbalize their thoughts while completing the tasks. After each task, participants will be asked questions about performance and suggestions for improving the system. At the end of the test, participants will be asked to evaluate their overall satisfaction based on the SUS. The SUS allows for calculating a single number representing a composite measure of the overall usability of the PEPA prototype [15]. A German version of the SUS will be used [17]. The whole usability evaluation will be recorded on videotape and should not exceed 60 minutes.

The second part of the pre-implementation study aims to analyze the preconditions of implementation. Therefore, all participants of the usability test are also invited to join a personal interview about potential barriers, ideas for further development, and requirements for transferring the PEPA approach to the care setting. Because external stakeholders will not be participating in the usability test, they will be contacted for these interviews separately. The basis for all interviews will be a semistructured and pilot-tested interview guide. Themes and questions of this interview guide are based on theoretical considerations and findings from a literature review. The interviews will be audiotaped and transcribed verbatim.

Data Analysis

Researchers will review and organize qualitative data of the usability test (think-aloud protocols, notes) and the analysis of preconditions (interview transcripts). The qualitative content analysis will include the inductive development of categories and a deductive application of categories. In a first step, transcripts will be reviewed independently by the researchers and key issues will be identified. After summarizing and labeling key issues as codes, these codes will be sorted into main categories and subcategories. The codes will be clearly defined and linked with representative examples from the original texts. After discussing and further modifying all categories within the research team, a consensus on the final category system should be achieved.

To calculate the SUS score, we will first score contributions from each item. In a last step, we will multiply the sum of the scores by 2.5 to obtain the overall value of the SUS [15]. All of these steps (qualitative and quantitative) will be applied in accordance with the particular part of the pre-implementation study and its specific objectives (usability, preconditions).

Phase 2: Implementation Study

On the basis of the results of the pre-implementation study, the PEPA prototype will be implemented (only for this study) in a regional care setting. The PEPA implementation aims to give patients access to their treatment documents and to improve processes of care (Figure 3). During the whole study, patients will receive technical and social support.

Within this study, patients have access to their PHI and can also give others (eg, their general practitioner) access to selected or all treatment-related data. In this project, we will use these functionalities to change the process of preparation for chemotherapy. Within the current process, the general practitioner informs the NCT about the latest blood test results via fax 1 day before the patient's appointment for chemotherapy.

The new PEPA-based process targets the electronic sharing of those blood test results. General practitioners taking part in the study will be able to upload the test results to the PEPA so that the clinicians at the NCT can access the information before the patient arrives for chemotherapy. In addition, the general practitioner will be able to access diagnostic findings and documentation uploaded to the PEPA by the patient or the clinicians at the NCT (Figure 3).

All functionalities for general practitioners or clinicians are only possible with permission of the patient. Overall, this feasibility study will consider how patient outcomes can be improved and processes can be changed through the implementation of the PEPA approach. This study comprises 2 parts: outcome evaluation as well as process evaluation and organizational change (Figure 4).

Figure 3. Implementation in a regional care setting. PEPA: personal electronic health record; NCT: National Center for Tumor Diseases.

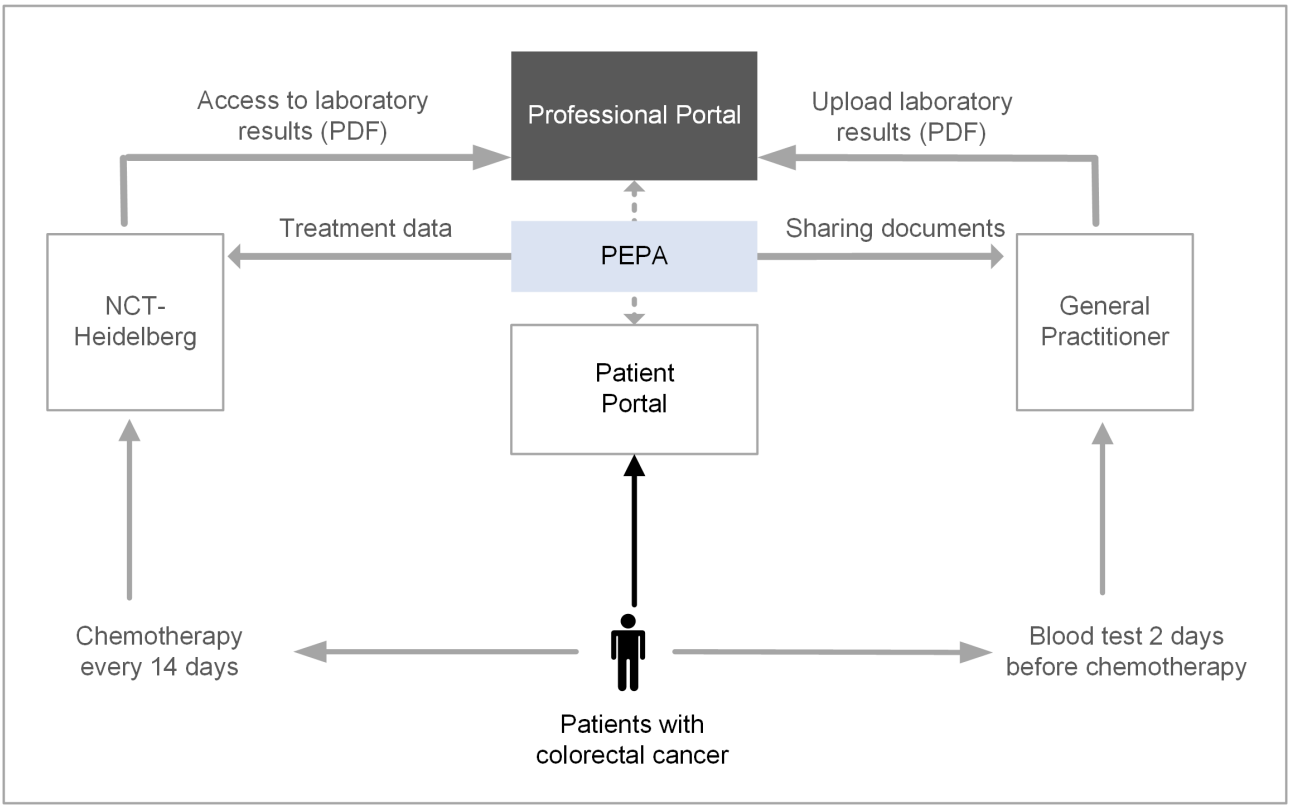
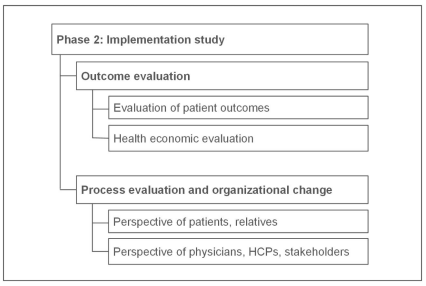


Figure 4. Parts of the implementation study. HCP: health care professional.



Objectives

Outcome Evaluation

The primary objective of this study is to assess patients' self-efficacy, among all participants, using the German version of the Cancer Behavior Inventory–Brief Version (CBI-B-G). CBI-B-G has high internal consistency (Cronbach alpha=.85) and correlates substantially with generalized self-efficacy (r=.57, P<.001) and emotional functioning (r=.53, P<.001) [18].

CBI-B-G scores are assessed at baseline (T0) and after 12 weeks of PEPA usage (T1). We will determine whether there is a difference in CBI-B-G scores after using the PEPA prototype for 3 months (T1) compared with baseline (T0). Furthermore, a number of secondary outcomes will be measured (see Table 1).

Table 1. Overview of outcome parameters and measurement instruments in this study.

Outcome parameters	Measurement instruments	Items
Patient self-efficacy (primary outcome)	German version of the Cancer Behavior Inventory–Brief Version (CBI-B-G) [18]	14
Control preferences	Control Preferences Scale [19]	5
Psychosocial distress	Distress Thermometer [20]	1
Utilization of medical services	[Mannheimer Module Resource Consumption][a]	30
Involvement in care	Perceived Involvement in Care Scale [21]	13
Usability of PEPA[b] prototype	System Usability Scale [15]	10

[a]Not published.

[b]PEPA: personal electronic health record.

In terms of health economic evaluation, it has been hypothesized that PHRs increase the virtual access to care and reduce health care costs [22,23]. The objective of this health economic work package is to collect data likely to support or reject these assumptions. This includes the following:

- to collect data on service utilization and unit cost of treatments or service contacts in order to assess direct medical costs of study subjects 3 months before the intervention and during the PEPA-intervention phase
- to collect data on work absentees and productivity loss 3 months before the intervention and during the PEPA-intervention phase to estimate indirect costs of study subjects
- to identify potential factors and PEPA-related effects likely to influence health care costs from the health system and societal perspective

Process Evaluation and Organizational Change

The aim for this analysis is to understand which factors promote or hinder the implementation of the PEPA approach in the defined care setting (see Figure 3). With the process evaluation, we will focus on the identification of facilitators and barriers within the implementation process. Relevant in this context is how the PEPA implementation may affect health care organizations and lead to the need for organizational change. Additionally, we will specify relevant change management standards for a successful implementation of the PEPA approach in health care organizations.

Research questions for this analysis are as follows: Is it feasible to implement and use the PEPA approach under real-world health care conditions? What are the relevant change management strategies that are able to support successful implementation process in health care organizations? Answering these questions includes the following objectives: to (1) track relevant barriers and facilitators of the implementation and (2) create relevant change management standards for health care organizations.

Study Design and Methods

The outcome evaluation is planned as a prospective, 3-month, open-label “before and after” trial. Additionally, for the analysis of processes and organizational change, we will conduct interviews with general practitioners, HCPs, physicians, and patients who are participating in the before and after trial.

Sample Size

For the planned before and after trial, the sample size of up to 30 patients is solely based on matters of feasibility (due to the exploratory nature of the trial). With this number of patients, a standardized treatment effect of 0.53 can be demonstrated with a power of $1-\beta=0.8$ at a (descriptive) two-sided significance level of alpha=.05 by applying a paired-sample *t* test. Additionally, we will conduct interviews with all participating patients and professionals.

Recruitment Strategy

Physicians and HCPs will be contacted directly. Potential participants will get a written invitation to participate in the study, including background information for physicians and other HCPs as well as a declaration of participation and agreement. The written approval for participation in the study is included in the informed consent document. The potential participants will send their declaration and participation agreement by mail to GP-HSR. All clinicians at the NCT using the PEPA will receive training demonstrating how to deal with this new instrument.

All patients matching the inclusion criteria will be contacted by their responsible physician at the NCT and asked to participate in the study. The responsible physician will inform them about aims, content, privacy issues, and risks related to the study. After patients give their consent to participate in the study, they will receive a pseudonym. Subsequently, patients will be invited to come to the GP-HSR and receive comprehensive training for handling the PEPA. This training includes a complete introduction to the functionalities of and consequences of working with the PEPA (eg, data security issues, allocating access authorizations). Then the PEPA will be set up individually for every patient, including the transfer of existing PHI (eg, former findings) to the PEPA (via PDF upload).

On the basis of the care setting of the intervention, the general practitioners (and their medical assistants) will be recruited depending on the selected patients. The corresponding general practitioners of the selected patients will be contacted and asked to participate in the study by GP-HSR. With an existing interest, the potential participants will get a written invitation to participate in the study, including background information for physicians and other HCPs as well as a declaration of participation and agreement. Causes for nonparticipation will be documented by GP-HSR. The informed consent document contains the request to give their written approval for participation in the study. The potential participants will send their declaration and participation agreement by mail back to GP-HSR. All participating general practitioners and their medical assistants will receive PEPA training.

Inclusion and Exclusion Criteria

Patients must have a diagnosis of colorectal cancer to be eligible for participation (ICD-10: C18, C19, C20). Furthermore, they should be receiving either chemotherapy with curative approach at the NCT after their primary surgery (at least for the next 2 months) or chemotherapy after relapse with symptom-relieving approach at the NCT. The participants must be 18 years of age or older and their disease status has to be classified as UICC stage III-IV.

To be eligible for participation in the study, the clinicians and other HCPs of the NCT as well as general practitioners and their medical assistants have to cooperate closely with the included patients during their treatment at the NCT. Prerequisite for inclusion of patients and professionals in analysis of processes and organizational change is participation within the before and after trial.

All participants who do not meet the inclusion criteria will be excluded. Additional exclusion criteria for patients are severe acute psychiatric disorders (eg, schizophrenia, schizotypal and delusional disorders); dementia; mental and behavioral disorders

due to psychoactive substance use; insurmountable language and communication problems; and emergent cases.

Data Collection

Data will be collected from patient survey responses and shall be obtained for all patients. Additionally, a sociodemographic questionnaire will help to gain information on age, sex, diagnoses, and educational level. Patients will receive a paper-based outcomes survey questionnaire right before the intervention starts (baseline) and at the end of the 3-month test period. The completion of each questionnaire will take about 45 minutes. All data will be pseudonymized. The collected data will be entered into a database and stored on a secured server.

The basis for conducting interviews will be a semistructured and pilot-tested interview guide. Each interview will be conducted until no newer aspects will be addressed. The interviews will be performed by a trained researcher (the moderator). All interviews will be audio- and videotaped and transcribed verbatim. Videotapes will be used to assist with the transcription of group data. Additionally, sociodemographic data will be collected anonymously using a study-specific questionnaire.

The health economic evaluation focuses on patients and their health services utilization. All consumed goods and services will be assessed from the societal perspective. This perspective assures that all relevant cost categories are included. Service utilization and intervention-related costs are measured by an adopted version of the "Mannheimer Module Resource Consumption" questionnaire. The consumed resources are weighted by standardized unit costs to derive direct and indirect costs.

Data Analysis

Because of the exploratory nature of the trial, the primary outcome "self-efficacy"—captured by the CBI-B-G [18]—will be evaluated descriptively at time points T0 and T1, by tabulating the respective means, SDs, medians, first and third quartiles, and minimum and maximum. Furthermore, descriptive *t* tests for paired samples will be applied to investigate potential differences between time points T0 and T1 and descriptive *P* values and 95% confidence intervals will be given. Missing values for the primary outcome at T1 will be replaced by multiple imputation [24] taking the baseline value (T0) into account. Best- and worst-case imputation will be conducted as sensitivity analyses. As in the case of the primary outcome, all secondary outcomes (see Table 1) will be analyzed descriptively by tabulating the measures of the empirical distributions. For continuous outcomes, means, SDs, medians, first and third quartiles, and minimum and maximum will be provided. For categorical outcomes, absolute and relative frequencies will be reported.

For health economic evaluation, descriptive analysis of the excess costs related to the participating patients will be scrutinized. Standard measures of central tendencies and dispersions are selected. This type of cost-of-illness study yields empirical insights into costs and cost components of the PEPA under real-world conditions.

In terms of process evaluation and organizational change, the transcribed texts of all interviews will be the basis for performing the qualitative content analysis. Data will be taken from the transcribed texts, edited, and analyzed [25]. This will be done by using a preliminary category system (search grid), which is based on themes and questions of the interview guide. In addition, the category system will be continuously adapted during the analysis process. For data analysis, in a first step, 2 out of all transcriptions will be analyzed independently by 3 members of the research team to identify relevant key issues. Following that, the key findings will be discussed within the research team and the preliminary category system will be adapted. Afterward, all key issues will be labeled as codes and these codes will be organized into main categories and subcategories. Each code will be clearly defined and linked with samples from the transcriptions. Labeling categories will be performed by using ATLAS.ti version 7.0.80 (Scientific Software Development GmbH).

Development of a Training Program

On the basis of the investigations that will be made in the other study parts, a training program will be developed. It is a planned by-product that characterizes one essential element for a successful future implementation of the PEPA in a real-world health care setting. The aspired function of the training concept is to cover the demands of the patients, family members, and HCPs for support required for using the PEPA in their daily routine. All patients and staff members using the PEPA prototype will receive training demonstrating how to deal with this new instrument.

Ethical Consideration

The pre-implementation study as well as the implementation study will be conducted in accordance with medical professional codex and the Declaration of Helsinki (2013). The study is also in accordance with German Federal Data Protection Act (BDSG). All professionals participating in the study are obliged to adhere to the abovementioned declarations and laws. Participation for patients and HCPs is voluntary. Consent can be withdrawn at any time without any consequences for patients' (usual) care. If a patient withdraws his or her consent, data that have already been collected can either be destroyed upon request of the respective patient (if the data have not been included in an already published work) or will be analyzed if he or she agrees. All patients will be informed about aims, content, duration, and process of the trial, particularly as far as risks and unintended consequences are concerned, through written information brochures and through face-to-face communication with staff of the study central office and with the responsible physician at the NCT. All collected data (eg, questionnaires, audio- and videotapes) will be saved according to applicable laws and regulations and afterward irretrievably deleted.

This study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg (S-462/2015).

Results

This project is part of the INFOPAT project, which is funded (2012-2016) by the Federal Ministry of Education and Research (BMBF). The enrolment was completed in July 2016. Data analysis is currently under way and the first results are expected to be submitted for publication at end of 2017.

Discussion

Summary

If health care is provided in more than one care setting or health system, the availability of treatment-related data within the process of care and the option for patients to manage their own PHI are limited. This may have consequences for the efficacy of treatment and options for the engagement of patients within their treatment (self-management). The development of the PEPA approach aims to address these problems. However, with this study and for the first time we will implement the PEPA approach in a real-world health care setting. Existing approaches of PHRs aim to give patients access to their treatment data. With this study, we go a step further: patients have access and they can also give other persons (eg, their general practitioner) access to their treatment data. With this approach, new possibilities of collaboration between different providers and for the engagement of patients may arise. However, study design and sample size are based on pragmatic considerations and closely related to challenges of the PEPA implementation in a real-world health care setting. In this way, the transferability of our study results may be limited.

Strength and Limitations

One major strength of this feasibility study is that we do not focus only on outcomes. Instead, we are taking the whole process of implementation into account. This means that we will start with a usability evaluation and the consideration of organizational preconditions for the implementation of the PEPA approach (pre-implementation study). Additionally, we will evaluate the process of implementation (eg, barriers or facilitators), the need for organizational change (eg, processes of communication), and the impact on outcomes (eg, self-efficacy) within the implementation study.

However, this study has a number of limitations. The implementation of the PEPA approach in this study is focused on patients with colorectal cancer. Conclusions for other chronic diseases may not be conceivable. Additionally, the evaluation of outcomes is based on a before and after trial, with a small number of participants and only 3 months of exploration. Causal correlations cannot be explained with this approach as the evaluation of outcomes is only explorative.

In terms of risks and (unintended) effects, for the participation in focus group discussions or guided interviews no severe or unexpected adverse events are mentioned within the literature. Nevertheless, it has to be kept in mind that the participants could feel uncomfortable within the discussion or interview setting. Furthermore, the participation could strengthen already established misgivings concerning the use of innovative health information technology. Additionally, it is possible that patients using the PEPA and the included complex information get a much deeper look into their PHI, which could lead to arising uncertainty or feelings of being overloaded.

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Authors' Contributions

All authors have participated in designing the study. AK, SP, HH, JK, LU, CJ, EW, and JS will conduct the study. MQ is responsible for data management. AK and SP drafted the study protocol. DO drafted this manuscript. All authors have critically read and modified this manuscript, previous drafts of the manuscript, and have approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

BMBF: Federal Ministry of Education and Research
CBI-B-G: Cancer Behavior Inventory–Brief Version (German version)
GP-HSR: Department of General Practice and Health Services Research
HCP: health care professional
ICD-10: International Classification of Diseases, Tenth Revision
INFOPAT: information technology for patient oriented care
NCT: National Center for Tumor Diseases

PEPA: personal electronic health record
PHI: personal health information
PHR: personal health record
SUS: System Usability Scale
UICC: Union for International Cancer Control

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Protocol

Enhancing mHealth Technology in the Patient-Centered Medical Home Environment to Activate Patients With Type 2 Diabetes: A Multisite Feasibility Study Protocol

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Abstract

Background: The potential of mHealth technologies in the care of patients with diabetes and other chronic conditions has captured the attention of clinicians and researchers. Efforts to date have incorporated a variety of tools and techniques, including Web-based portals, short message service (SMS) text messaging, remote collection of biometric data, electronic coaching, electronic-based health education, secure email communication between visits, and electronic collection of lifestyle and quality-of-life surveys. Each of these tools, used alone or in combination, have demonstrated varying degrees of effectiveness. Some of the more promising results have been demonstrated using regular collection of biometric devices, SMS text messaging, secure email communication with clinical teams, and regular reporting of quality-of-life variables. In this study, we seek to incorporate several of the most promising mHealth capabilities in a patient-centered medical home (PCMH) workflow.

Objective: We aim to address underlying technology needs and gaps related to the use of mHealth technology and the activation of patients living with type 2 diabetes. Stated differently, we enable supporting technologies while seeking to influence patient activation and self-care activities.

Methods: This is a multisite phased study, conducted within the US Military Health System, that includes a user-centered design phase and a PCMH-based feasibility trial. In phase 1, we will assess both patient and provider preferences regarding the enhancement of the enabling technology capabilities for type 2 diabetes chronic care management. Phase 2 research will be a single-blinded 12-month feasibility study that incorporates randomization principles. Phase 2 research will seek to improve patient activation and self-care activities through the use of the Mobile Health Care Environment with tailored behavioral messaging. The primary outcome measure is the Patient Activation Measure scores. Secondary outcome measures are Summary of Diabetes Self-care Activities Measure scores, clinical measures, comorbid conditions, health services resource consumption, and technology system usage statistics.

Results: We have completed phase 1 data collection. Formal analysis of phase 1 data has not been completed. We have obtained institutional review board approval and began phase 1 research in late fall 2016.

Conclusions: The study hypotheses suggest that patients can, and will, improve their activation in chronic care management. Improved activation should translate into improved diabetes self-care. Expected benefits of this research to the scientific community and health care services include improved understanding of how to leverage mHealth technology to activate patients living with type 2 diabetes in self-management behaviors. The research will shed light on implementation strategies in integrating mHealth into the clinical workflow of the PCMH setting.

Trial Registration: ClinicalTrials.gov NCT02949037. https://clinicaltrials.gov/ct2/show/NCT02949037. (Archived by WebCite at http://www.webcitation.org/6oRyDzqei)

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KEYWORDS

mHealth; diabetes mellitus; patient activation; patient-centered medical home; patient centered care; eHealth; health information

Introduction

Diabetes mellitus is a chronic disease with high rates of disability, impaired quality of life, and premature death [1-4]. The prevalence of type 2 diabetes is increasing at an alarming rate in the United States; in 2013, the estimated number of patients was between 20 million and 27 million, or about 7% to 10% of the adult population [2,3]. Research suggests that, if current trends continue, diabetes will be diagnosed in 1 in 3 adults in the United States by 2050 [4,5]. Diabetes is the leading cause of blindness, nontraumatic amputations, and adult renal failure, and reduces life expectancy by 5-10 years [2]. The individual symptom burden (eg, chronic pain, neuropathy, depression, and physical disability) is substantial and significantly increases in the older adult population [1]. In the United States, an average individual with diabetes incurs medical expenditures of about US $13,700 a year, of which about US $7900 is attributable to diabetes [4]. This represents an expenditure about 2.3 times greater than that for a diabetes-free individual [4].

Numerous primary care-based efforts have been aimed at reducing both the disease burden on individuals and the cost of diabetes care. A contemporary strategy is the management of patients with diabetes within the context of the patient-centered medical home (PCMH) setting. A key PCMH principle is the appropriate use of information technology to support optimal patient care, performance measurement, patient education, and enhanced communication [6]. Several case studies from various US health systems show the benefit of the PCMH model to improved diabetes care [7]. There is published evidence on the positive impact of PCMH-based care in psychosocial outcomes of patients with diabetes [8].

The potential of mHealth technologies in the care of patients with diabetes and other chronic conditions has captured the attention of clinicians and researchers. Efforts to date have incorporated a variety of tools and techniques, including Web-based portals [9-11], short message service (SMS) text messaging [9,12-14], remote collection of biometric data [12,15], electronic coaching [14], electronic-based health education [13], secure email communication between visits [16-18], electronic collection of lifestyle and quality-of-life surveys, and personal health records (PHRs). Each of these tools, used alone or in combination, has demonstrated varying degrees of effectiveness. Some of the more promising results have been demonstrated using regular collection of biometric devices (eg, glucometers, activity monitors) [12], SMS text messaging [12-14], secure email communication with clinicians and clinical teams [9,16,17], and regular reporting of quality-of-life variables aligned with decision support. In this study, we seek to incorporate many of the most promising mHealth capabilities in a PCMH workflow led by a clinical advisory team. We aim to address underlying technology needs and gaps related to the use of mHealth technologies and the activation of patients with type 2 diabetes.

The Concept of Patient Activation

Self-management for patients with type 2 diabetes and other chronic conditions includes following complex treatment regimens, monitoring chronic conditions, and making lifestyle changes [19-22]. The chronic care model suggests that activated patients are better able to function in the role of self-manager [21,23]. An activated patient has the motivation, confidence, and skills necessary to enact behavioral changes and make health-related decisions [24-27]. These patients ask questions and collaborate with their health care provider [19,26-28]. Research shows that activated patients have more positive clinical outcomes, are more likely to receive preventive care, and have lower health care-related costs [24,26,29].

A recommended strategy in patient activation is the concept of “preactivating” patients prior to clinical encounters [20,30]. The concept incorporates active targeted communication and follow-up from the health care team [30]. Interventions to include educational programs [31], care coaching [32], and motivational interviewing [33] have been attempted to improve patient activation with varied success [34]. However, these efforts have infrequently been tailored to potential intrinsic differences in how the patients approach their disease. Theoretically, research suggests that patient activation can be increased [19,35-37]. Conceptualizing activation as a dynamic variable allows researchers to target this motivating factor that can potentially influence health behaviors [21,24,38,39].

Previous Research on Patient Portals, Personal Health Records, Patient Activation, and Improved Outcomes

Federal legislation and movement toward patient centeredness in the United States has fueled interest in providing patients with access to their health information, enhanced communication with clinical environments, and greater emphasis on self-care [40-43]. Early research on portal and PHR use and patient activation provided mixed results. Several studies reported a positive significant relationship between use of portals and

PHRs and activation of patients [41,43-45], while other studies did not realize a significant finding [40,46,47]. The design of these published studies prevented any in-depth inquiry into why (or not) portal and PHR use influenced patient activation. Their authors posited a variety of possible factors, including the target patient population [44], time since severe diagnosis or symptoms and episodes [46,47], and patient age (activation being higher in adults than in children) [45]. One study suggested that tailoring a portal or PHR intervention to the patient activation level may optimize intervention efficiency [43].

Early research on increased activation and improved clinical outcomes using patient portal and PHR-based interventions has also provided mixed results. Several studies demonstrated a relationship between increased patient activation and improved intermediate clinical outcomes (eg, hypertension, smoking, body mass index, and glycated hemoglobin [HbA_{1c}]) [48], while a major study did not record a significant finding regarding the same outcomes [42]. It is noteworthy that these early studies did not provide substantial detail on design issues related to the portal or PHR, or whether the intervention included behavioral reinforcement.

User-Centered Design

Design science will inform our development and testing [49,50]. User-centered design will guide development, following participatory design methods to understand more specifically how patients experience diabetes on a daily basis, what clinicians need to know from patients, and how to create a shared communication system for better decision making [51]. Consistent with the guidelines set forth by the Science Panel on Interactive Communication and Health [52], our evaluation design will incorporate the 3 elements of formative, process, and outcome evaluation. Methods include (1) clinician focus groups and in-depth patient interviews to define key knowledge variables that are personally and clinically relevant, (2) iterative usability testing with patients, and (3) iterative observations of the system in clinical settings [53].

Military Health System: An Overview

The US Military Health System (MHS) is a large integrated health system that cares for about 9.39 million beneficiaries through its TRICARE insurance product and its substantial direct care system consisting of tertiary facilities, community hospitals, and clinics globally. Nearly 35% of its beneficiary pool are active duty members and their dependents, with a larger population (about 56%) being retirees and their beneficiaries [54]. The MHS direct care system is robust. Facilities are accredited by the Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations), and the MHS operates a dedicated educational infrastructure to support medical and nursing education programs [54]. The MHS has a connecting health information technology infrastructure to support clinical care and clinical operations.

Hypotheses

Hypothesis 1: User-centered design will allow developers to create a patient-centered interactive and tailored mobile technology for use in the PCMH setting.

Hypothesis 2: The use of interactive and tailored mobile technology, the Mobile Health Care Environment (MHCE), employed in the PCMH setting will increase the activation of patients with chronic type 2 diabetes.

Hypothesis 3: The use of interactive and tailored mobile technology in a PCMH setting will increase diabetes self-care activities.

Hypothesis 4: Patients who engage at a higher rate with the interactive and tailored mobile technology in a PCMH setting will realize greater improvement in clinical measures.

The primary goal of the research is to enhance patient activation levels and improve self-management of type 2 diabetes through the use of the MHCE in the PCMH setting. While there are published studies aimed at improving the activation and care of patients with diabetes in the United States, to our knowledge, no study has sought to enhance care of patients with diabetes using a fully comprehensive and adaptable MHCE-like system. We seek to demonstrate improvement in patient activation measured by the Patient Activation Measure (PAM) instrument [21,55]. We believe that, in improving their activation, patients will also realize an improvement in diabetes self-care activities measured by their Summary of Diabetes Self-Care Activities (SDSCA) [56] scores.

Methods

Trial Design

This is a multisite, phased study conducted within the MHS that includes a user-centered design phase and a PCMH-based feasibility trial. In phase 1, we will assess both patient and provider preferences regarding the enhancement of the MHCE technology capabilities for type 2 diabetes chronic care management. The phase 2 research will be a single-blinded (patients only) 12-month feasibility study that will incorporate randomization principles. We will employ a 1:1 allocation ratio between intervention and control.

Inclusion and Exclusion Criteria

Inclusion criteria for patient participation in phase 1 or 2 research are the following: (1) men and women aged 18 years or older, (2) able to understand and read English, (3) enrolled for primary care to one of the target PCMH sites, and (4) having a diagnosis of type 2 diabetes. Additionally, with respect to phase 2 patients, we will seek to recruit a maximum of 120 (per site), with a distribution of patients with PAM levels 1-4, a sample representative of the patients enrolled in the PCMH. We did not derive the 120 per site recruitment numbers from power calculations, but deemed them to be sufficient. Finally, participants for phase 2 must be available for a 12-month study.

Inclusion criteria for clinician participation in phase 1 or 2 research are the following: (1) being a physician, physician assistant, nurse practitioner, or nurse employed at the target site, and (2) providing care for patients with type 2 diabetes.

Exclusion criteria for patient participation in phase 1 or 2 research are the following: (1) pregnant women, (2) non-English-speaking patients, (3) receiving hospice care, (4) having active cancer and receiving treatment with chemotherapy

or radiation therapy, (5) taking warfarin, (6) recipient of gastric bypass or similar procedure, (7) having a diagnosis of uncontrolled hypothyroidism, (8) having known Cushing syndrome, (9) being treated with oral steroids, (10) having known liver disease, (11) having a current diagnosis of cognitive impairments that would interfere with use of technology, (12) having congestive heart failure, in New York Heart Association functional class 3 or 4, and (13) unable to use a mobile device due to cognitive or physical impairments during initial screening. We exclude pregnant women because they require careful monitoring due to potential medical complications for the woman and unborn child. While some mHealth studies seek to include additional exclusions based on age, educational level, or technical literacy, our research team rejected adding any additional exclusion criteria beyond the 13 listed above. We purposely seek the "average" patient with type 2 diabetes in the target population. Feedback from our clinician investigators and research staff at our clinical sites is encouraging that these patients will be capable of using the intervention technology.

Exclusion criteria for clinician participation in phase 1 or 2 research are the following: (1) not affiliated with the target site, and (2) not providing care for patients with type 2 diabetes.

Participant Enrollment

We will recruit patients via review of the PCMH clinic schedule, referrals from providers, distributed posters and fliers, and population health databases. Potential participants will be prescreened through verification of the inclusion and exclusion criteria based on a medical record review. Interested participants will be scheduled for a screening visit with study staff to provide informed consent and be administered the PAM instrument. Patients' PAM scores will place them in a stratified group, where they will be randomly allocated.

Clinicians practicing in the respective PCMH sites will be invited to participate by word of mouth from the site's principal investigator; this is a convenience sample. The clinician participants who would like to participate in the study will meet with the senior research associate to review the minimal-risk information sheet to be included in the study. For phase 2, clinicians will sign an informed consent form. The clinician participants will not be blinded in the study, nor allocated to intervention or control groups.

Setting and Site Selection

We seek to purposefully assess the MHCE implementation for diabetes care in 2 distinctly different PCMH environments and geographic locations. The risks of attracting very different populations are mitigated by rather comprehensive inclusion and exclusion criteria, which will ensure similarity regarding patient acuity. The patient base includes those on active duty, retirees, and dependents who have typically spent years in the military and have been stationed at various locations. Both of the selected facilities are federal facilities and operated by the MHS.

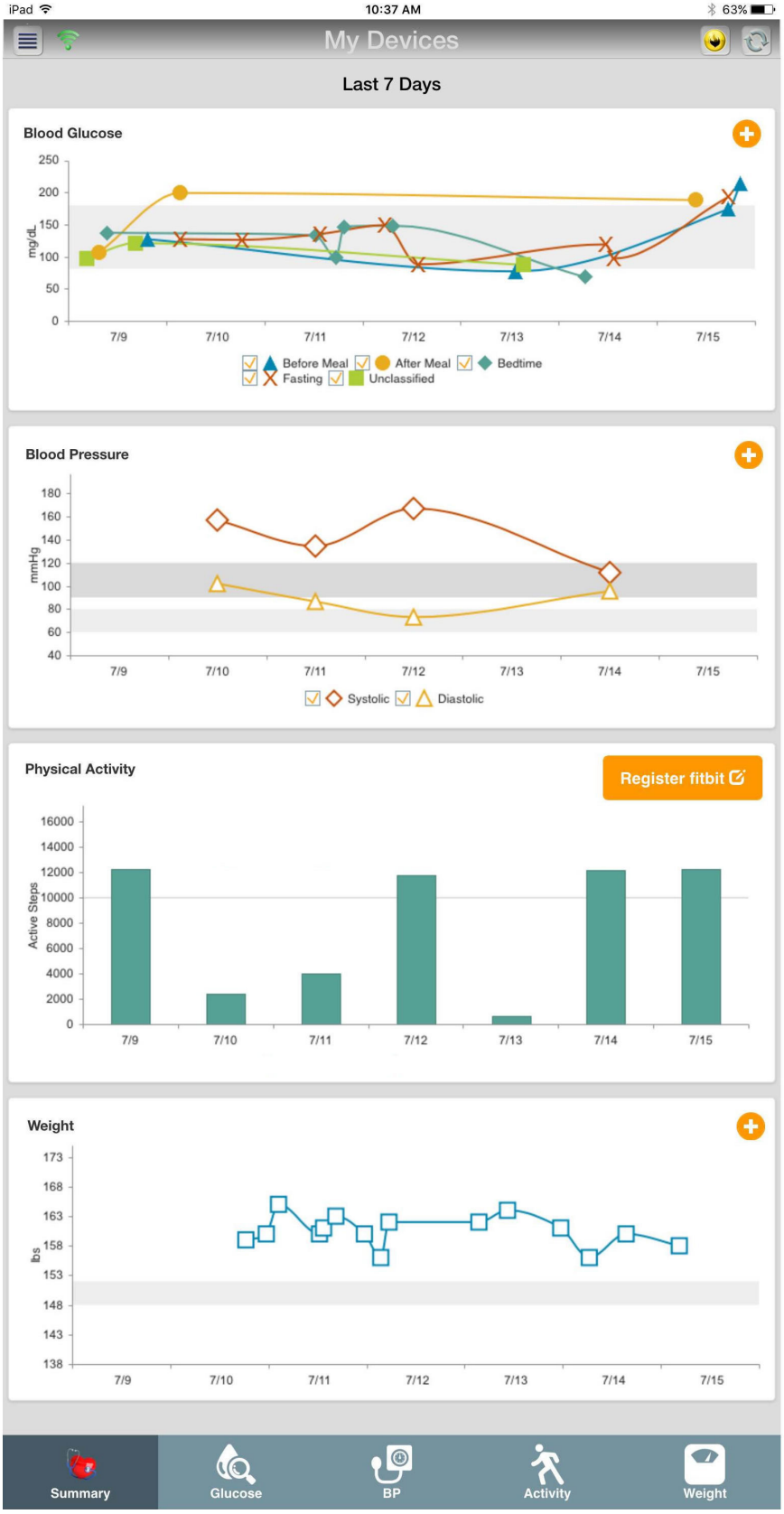
Madigan Army Medical Center, the US Army's second largest military treatment facility located in Tacoma, Washington, is a tertiary facility with a level II trauma center and robust graduate medical education programs. They serve a patient base of approximately 118,000 patients; about 7500 (or >6%) are living with type 2 diabetes. Of the diabetes population, about 15% are active duty members or their dependents, and about 85% are retirees and their dependents. Over half of the patients with diabetes are 57-76 years of age. The study location within the medical center is a PCMH managed by the Department of Internal Medicine. There are approximately 14,300 patients enrolled in this PCMH supported by a staff of 77 (12 staff physicians; 8 residents) responsible for their care.

Mike O'Callaghan Federal Medical Center is a federal facility in the greater Las Vegas, Nevada area, that serves approximately 47,000 patients; about 4500 (or >9%) are living with type 2 diabetes. Of the diabetes population, about 4% are active duty members or their dependents, and about 96% are retirees and their dependents. Over 72% of the patients with diabetes are in their 60s or older. The study location within the medical center is a PCMH managed by the Department of Family Medicine. There are approximately 7500 patients enrolled in this PCMH supported by a staff of 62 (9 staff physicians; 26 residents) responsible for their care.

Description of the Mobile Health Care Environment

The US Department of Defense (DoD) MHCE system is a secure health information system designed to support health services delivery and mHealth. The MHCE meets all physical and information security mandates, as prescribed by federal law and DoD regulation, for the protection of personal health information and personally identifiable information. The MHCE was developed by the DoD Telemedicine and Advanced Technology Research Center as a platform to support mHealth. Its first major application was to support patient engagement for wounded warriors rehabilitating in their communities. In the study, soldiers on average responded to ≥60% of weekly questionnaires related to behavioral health challenges, posttraumatic stress, or traumatic brain injury [57]. Our study is Telemedicine and Advanced Technology Research Center's second major application. The MHCE is designed to remotely support patients by sending automated reminders, announcements, wellness tips, alerts, and status questionnaires. Figure 1 is a visual example of the graphical user interface that patients will see when accessing the MHCE. In this study, we enhance MHCE capabilities in several ways.

Figure 1. Mobile Health Care Environment home screen (patient view). BP: blood pressure.



Intervention Overview

Our intervention is based on an enhanced MHCE in several ways. First, we add the capability to include collection and visualization of data from Bluetooth-enabled medical devices. This includes mapping data from device output into the MHCE, developing data visualization appropriate for mHealth and clinical care (eg, graphing outcomes, temporal trend patterns), migrating data in an analysis cell, and developing decision-support algorithms that signal safety alerts and need

for behavioral reinforcement. Devices used in this study include a scale, glucometer, blood pressure reader, and activity monitor. Second, we expand the capacity of the MHCE analysis cell to manage large amounts of data and to conduct both routine reports and research applications. Third, we add patient activation and associated measurement instruments for capturing baseline and ongoing changes to patient activation. Fourth, we expand the MHCE messaging platform that research associates, and later clinical support staff, can use to send tailored behavioral messaging to patients in an effort to influence greater activation and reinforce positive behavior.

The MHCE can be accessed by mobile phones or tablets that use either an IOS or Android platform. The MHCE requires Internet access for patients to sync data from devices (addressed above) to the MHCE backend portal, to receive tailored behavioral messages, or to use other functions. During the study, patients will additionally receive SMS messages with hyperlinks to a separate secure information system platform used for administration and analysis of PAM and SDSCA instruments. MHCE activity, or lack thereof, will be monitored by senior research associates, who can prompt patients via tailored behavioral messages or direct contact.

Tailored Behavioral Messaging

A primary component of the MHCE system is tailored behavioral messaging. Tailored behavioral messages are more likely than generic messages to facilitate health behavior change when they are aligned with individuals' beliefs, lifestyle, demographics, social norms, or interests [58-60].

In this study, the research team has developed behavioral messages tailored for each of the 4 PAM score levels; in total we have developed 360 messages. The messages fall within 9 functional areas common to diabetes care: nutrition, home monitoring, physical activity, blood pressure, foot care, medications, smoking, glucose control, and general behavioral reinforcement. The messages are consistent with general concepts and goals of self-management behaviors consistent with the DoD-Veterans Affairs clinical practice guideline for type 2 diabetes and the SDSCA survey instrument.

Since different PAM levels require different strategies, we addressed varying needs through a combination of applied constructs. Specifically, level 1 messages must address the emotional state of feeling overwhelmed and passive with an emphasis on the importance of taking action. To address the needs of PAM level 1 patients, we use constructs from social networks and social support theory [61], specifically that of emotional support that emphasizes expressions of empathy and caring. We encourage a sense of hope by expressing the belief and expectation that the message recipient can change his or her situation and overcome difficulties. Constructs from the transtheoretical model [62] such as visioning, dramatic relief, self-reevaluation, and environmental reevaluation also guided level 1 message development.

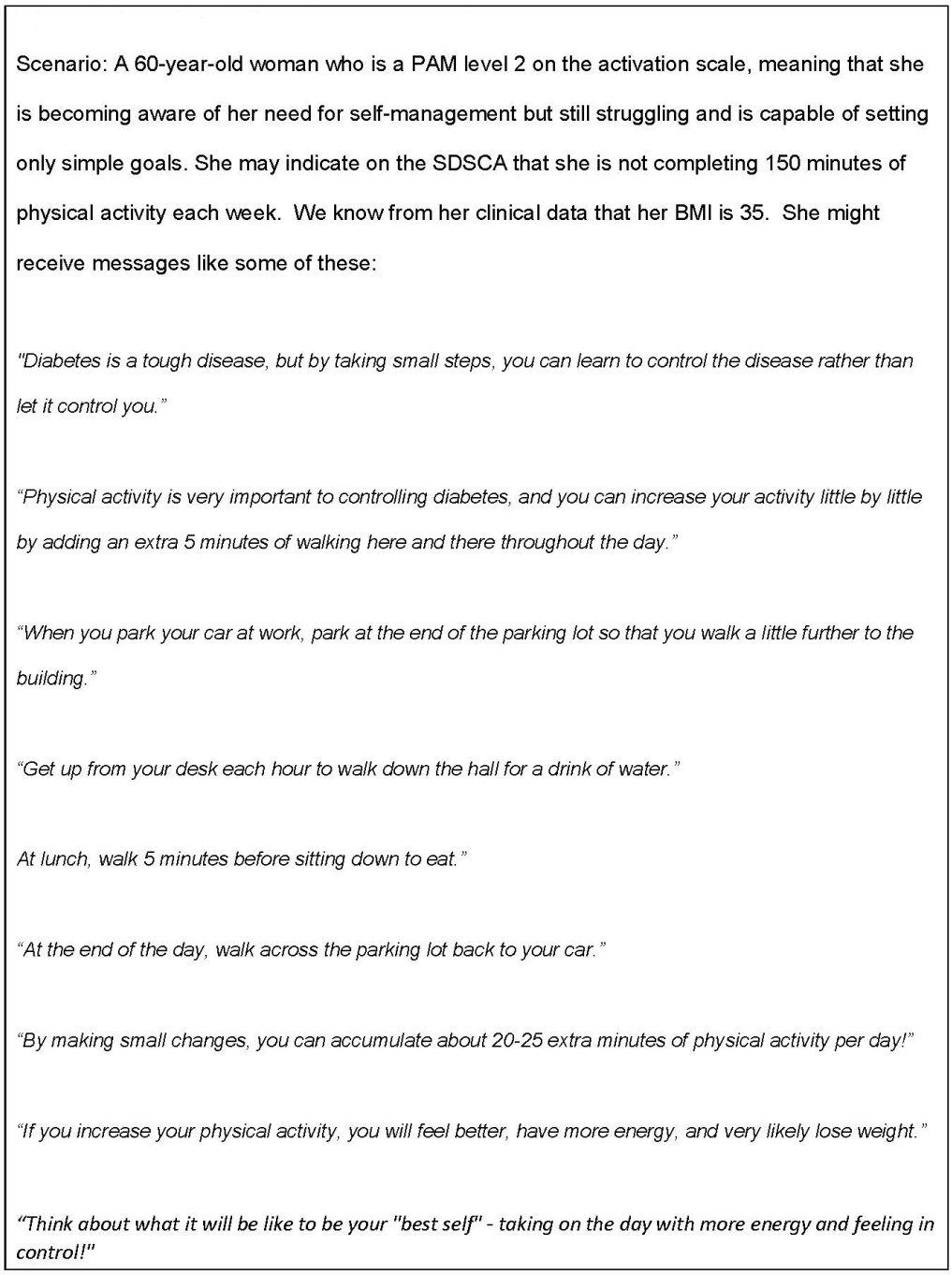
PAM level 2 messages build knowledge and self-efficacy to engage in a behavior and focus on ways to take small steps that don't require much in-depth knowledge. Self-efficacy and the confidence a person feels about performing a particular activity was a primary construct used to develop these messages with a focus on one of the main strategies to build self-efficacy, that of taking small steps that are likely to result in performance accomplishment. Outcome expectations, or the anticipatory outcomes of a behavior, stated in ways that would likely appeal to the expectancies or values a person places on the outcome, was also an important construct [63].

PAM level 3 messages assume some knowledge and focus more on building self-management skills such as goal setting and self-monitoring. For messages in this level, we used transtheoretical model [62] constructs relevant to the preparation and action stages of behavior change.

PAM level 4 messages about staying the course and avoiding relapse when stressed were grounded in the transtheoretical model constructs guiding processes used in the maintenance stage of change. Also used in level 4 message development were strategies developed in a relapse prevention model [64] such as identifying high-risk situations for relapse and the development of specific coping strategies for those situations.

In phase 2 of our study, tailored behavioral messages will be sent to each intervention group participant, via the MHCE accessed through their mobile device, based on both senior research associate-initiated and algorithm-automated schedules and thresholds developed according to PAM level, SDSCA responses, and agreed-upon general rotation. Figure 2 offers examples. The senior research associates will use the MHCE backend portal control panel for manual rotational scheduling of messages to be delivered 3 days per week (typically Monday, Wednesday, and Friday) within the MHCE system. Participant responses to the SDSCA may trigger additional messaging if their clinical readings from biomedical devices exceed established safety thresholds.

Figure 2. Example of tailored health messaging.



Phase 1 User-Centered Design Study Flow

In phase 1 we will evaluate and gain feedback from patients with diabetes regarding MHCE app navigation, use of external devices, ease of use, and satisfaction. We will collect baseline research participant data to include basic demographic data and clinical measures following verification of informed consent. One researcher-facilitator will lead individual participants through usability testing and the additional researcher-observer will document observations. During a facilitator-provided demonstration of the MHCE, the facilitator will ask each participant to concurrently navigate to each component of the MHCE system via a mini tablet device under their control. For each task, we will ask 3 open-ended questions to evaluate task-specific user satisfaction regarding the look and layout of the app, how the app functions, and any specific issues that are confusing. Next, the facilitator will give a brief demonstration of the external devices that will be used in the study: a blood pressure monitor, a glucometer, a digital precision weight scale, and a Fitbit Charge wireless activity and sleep wristband. For each device, we will ask participants to (1) manually upload data, (2) sync each device with the app, and (3) interpret graphs. While it would be preferable to observe the MHCE in the context of where the patient would actually use the system, financial limitations prohibit such expanded usability observation research.

Research staff will evaluate usability by applying definitions and usability evaluation metrics guided by the International Organization for Standardization's 9241-11 usability framework

and mHealth usability research [65]. Specific metrics to evaluate usability are effectiveness, efficiency, and satisfaction. We will evaluate effectiveness via task completion and error coding. We will assess timed task completion as a task being completed with ease, being completed with minor mistakes, or not completed. Errors will be coded using a codebook developed by the phase 1 team. The observer will also note when users commit errors they cannot solve or commit errors that prevent further progress. We will use the Single Ease Question to evaluate informant satisfaction immediately after performing each task [66]. The System Usability Scale (SUS) will evaluate overall informant satisfaction with the MHCE [67].

We will also assess provider preferences in phase 1 using focus groups of clinicians and nurses recruited from the 2 study sites. Two trained qualitative researchers will facilitate the focus groups. We will take field notes during the focus groups and audio record each session to ensure accuracy of the field notes. The facilitators will use a semistructured interview guide to elicit clinician and nurse feedback about the MHCE. After briefly demonstrating the app, facilitators will ask 6 broad questions (with probes), developed by the phase 1 team in conjunction with study coinvestigators. These questions are designed to elicit feedback from participants regarding app design, alerts (general), wording of alerts, perceived usefulness to patients for promoting self-management, clinical usefulness and workflow, and backend portal data summaries. We will probe specific issues related to clinical usefulness of the MHCE in the context of the clinical workflow of the PCMH environment.

A 4-member team will complete a thematically organized data analysis of the clinician and nurse feedback using an inductive narrative approach [68-70]. We will begin with an analysis of field notes from 1 randomly selected provider and 1 nurse to create an initial codebook. We will expand the codebook as we continue to code field notes. The analysis team will divide the coding duties so that each transcript is coded by 2 independent coders [71]. The team will meet during the coding process to address consensus, update the coding structure, and revisit any previously coded field notes that need to be reviewed again based on these updates. Codes will be applied to the transcripts using Atlas.ti software version 7.5.10. Codes drawn from the interview guide will serve as the organizing framework for analysis. As new themes emerge, we will expand the narrative.

Phase 2 Controlled Study: Patient Enrollment and Study Flow

For phase 2 we will recruit 240 patients (120 per site), with half assigned as a control group. Eligible patients will be first assigned to 4 strata according to their PAM score. After all patients are identified and assigned into the strata, simple randomizations will be performed within each stratum to assign patients to either the MHCE or usual care groups. Patients will be randomly allocated to either the control or the intervention group based on their PAM scores.

We will modify the MHCE system between phase 1 and phase 2 research, incorporating phase 1 observations and optimizing system usability at the patient level. We will collect baseline research participant data, including basic demographic data and clinical measures, following verification of informed consent.

MHCE Intervention Versus Usual Care

Patients in both the intervention and usual care (control) groups will receive a device package as outlined in Textbox 1. These devices will collect and record biometric data. All patients will be trained in using biomedical devices and peripheral equipment.

Textbox 1. Patient device package (intervention and control groups).

- Activity monitor (Bluetooth and cloud enabled)
- Scale (Bluetooth enabled)
- Blood pressure cuff (Bluetooth enabled)
- Glucometer (Bluetooth enabled)

For the patient groups allocated to the intervention, their devices will be mapped to the MHCE system accessible from the patients' mobile phone or an iPad mini tablet device. Data from their biomedical devices will be visually presented in the MHCE with trend and scalable options (Figure 3).

Safety algorithms will be mapped to these clinical data to alert the patient and, depending on the measure, the clinical team when readings exceed established thresholds. The intervention groups will also have full access to and will receive the tailored behavioral messaging outlined above. At time of study enrollment, we will provide a tablet device to patients who are fully eligible to participate, are allocated to the intervention group, but do not have a mobile phone (with iOS or Android operating system).

In both the intervention and control groups, the patients' clinician and PCMH support team will be notified of the patients' enrollment in the study. The intervention patients will be encouraged to regularly use the MHCE system as a tool to improve their diabetes self-care.

Figure 3. Example of visualization of patient data. BP: blood pressure.

Initial Outcome Measures for Patient Component

Primary outcome measures are PAM scores. Secondary outcome measures in the study are (1) SDSCA responses, (2) clinical measures (Textbox 2), (3) comorbid conditions (eg, uncontrolled plasma glucose, hypertension, hyperlipidemia, stoke, eye disease, coronary heart disease), (4) SUS survey scores, (5) MHCE usage statistics, and (6) health services utilization measures.

Textbox 2. Clinical measures in phase 2.

- Glycated hemoglobin (HbA_{1c})
- Low-density lipoprotein
- High-density lipoprotein
- Height and weight
- Abdominal circumference
- Systolic blood pressure
- Diastolic blood pressure

Patient Activation Measure Instrument

The self-reported PAM survey is associated with self-management behaviors, medication adherence, patient satisfaction, and quality of life [55,72]. Within a diabetes-specific population, PAM is not related to knowledge regarding HbA_{1c} (the standard measure of average blood glucose level [73]), but is associated with better glycemic control [74]. Interventions, including educational programs [31], care coaching [32], and motivational interviewing [33], have been attempted to improve this activation with varied success. Specifically, patient activation can be increased with targeted, patient-centered, repeated messaging [19]. The PAM is a valid, reliable, unidimensional, probabilistic Guttman-like scale that was validated over a decade ago [21] and is a standard tool to measure patient activation. We will administer the PAM at screening visits in phases 1 and 2, and electronically every 3 months during phase 2 for both the intervention and control groups. Figure 4 outlies the 4 PAM levels.

Figure 4. The 4 levels within the Patient Activation Measure (PAM) survey.

Summary of Diabetes Self-Care Activities Instrument

The SDSCA instrument is a brief self-report instrument for measuring levels of self-management across different components of the diabetes regimen [56]. The SDSCA includes 11 core items associated with diabetes self-care. The SDSCA has been successfully used in numerous diabetes studies both within and outside the United States [56,75-78]. The SDSCA has been validated and is considered a standard instrument in diabetes care for measuring self-care activities, with its validation and reliability published nearly two decades ago [56]. We will administer the SDSCA at the intake visit for phase 2, and electronically every 2 weeks during phase 2 for both the intervention and control groups.

Clinical Measures

We will collect clinical measures (Textbox 2) from patients at intake during phase 1 research. We will collect and compare changes in patient clinical measures for both groups in phase 2 at 3 points: intake, midpoint (month 6), and conclusion (month 12). For patients assigned to the MHCE intervention group, the MHCE system will also record weight, systolic blood pressure, diastolic blood pressure, and blood glucose values to the MHCE module on a regular basis via Wi-Fi or Bluetooth-enabled peripheral equipment.

Clinician Support for Patient Activation Measure

The Clinician Support for Patient Activation Measure (CS-PAM) instrument measures clinician beliefs about patient self-management behavior. The CS-PAM has been a valid and reliable instrument in use since 2010 [25]. The CS-PAM score indicates an individual clinician's overall level of endorsement or belief about the importance of patient self-management, as well as beliefs about the importance of specific patient competency categories [25].

In phase 2, we will measure clinician support for patient self-management by the CS-PAM. PCMH clinicians (ie, physicians, nurse practitioners, and physician assistants) in this study will take the CS-PAM at 3 points in the study: beginning, midpoint (month 6), and conclusion (month 12).

System Usability Scale Survey

The SUS survey is a 10-item Likert-like scaled survey used to convey a subjective assessment of system usability. The instrument was developed over 15 years ago and is used to measure the usability of websites. The SUS was validated on several occasions, with perhaps the largest validation study (including 10 years' worth of data) conducted in 2008 [79]. In this study we will substitute the term "MHCE system" for the term "website" in the instrument. We will conduct the SUS survey at the conclusion of the encounter for phase 1 patients, and at midpoint (months 5-6) and study conclusion (months 11-12) for phase 2 patients in the intervention group.

MHCE Usage Statistics

Our technology enablement partners will embed counters (invisible to patients) that track usage of MHCE components. These counters will export usage data to our research analysis database. Summary statistics and trends will be analyzed with comparison.

Comorbid Conditions

We will assess and document comorbid conditions (eg, hypertension, hyperlipidemia) among both the control and intervention groups during prescreening of eligibility, at intake, at study midpoint, and at study conclusion. While not primary outcome measures, any change over time and whether the number and type of comorbid conditions influence patient use of MHCE will be assessed.

Data Analysis Strategy

We will conduct the primary analyses for phase 2 using an intent-to-treat approach. Study participants will be retained in their original assignment groups after the random allocation in the analysis. Achievement of randomization will be evaluated through the comparison of baseline key variables between the MHCE intervention group and the control group. We will also compare baseline key characteristics between eligible patients who participate in the study and those who do not participate to examine the potential for bias.

To test hypotheses 2 and 3, that patients who participate in MHCE will have higher PAM, SDSCA, and SUS scores and improved selected clinical outcomes and comorbid conditions than their counterparts in usual care, we will use multivariate regression models (logistic regression if the outcome is a binary variable and linear regression if the outcome is a continuous variable) with the intervention assignment as the primary independent variable. Stratified analyses will be conducted (eg, sex, race, and initial PAM score).

The primary comparison will be outcomes at 12 months. Additional analyses will use longitudinal analysis models using a generalized estimating equation, which will include outcomes at both 6 and 12 months.

To test hypothesis 4, that patients who engage at a higher rate with the interactive and tailored mobile technology in MHCE will realize greater improvement in clinical measures (eg, HbA_{1c} values; Textbox 2), we will use multivariate linear regression models. Clinical outcomes will be the dependent variables and will be tested separately. The main independent variable will be MHCE usage. We will examine the association between the dependent variable and MHCE usage by using the generalized estimate equation with adjustment of potential confounders (eg, age, sex, race, duration of disease, use or nonuse of insulin).

Trial Status

At the time of publication, we have completed phase 1 data collection. Formal analysis of phase 1 data has not been completed. Institutional review board approval (study and site implementation) has been obtained and phase 1 research commenced in late fall 2016.

Results

The hypotheses of the study suggest that patients can, and will, improve their activation in chronic care self-management. Improved activation should translate into improved diabetes self-care. While not powered in this study, improved self-management activities should lead to fewer emergency situations (and trips to the emergency department), weight loss (in many cases), improved blood pressure, and improved clinical measures. Cumulatively, the gains should translate into improved quality of life if our hypotheses are supported.

This study has been approved by the institutional review boards of Clemson University (protocol #IRB2015-234) and the Madigan Army Medical Center (representing both DoD sites; reference #216073). Study personnel will follow protocol with all informed consent mandates directed by the institutional review boards; informed consent in this study includes both patients and clinicians or key clinical staff. This trial was registered with ClinicalTrials.gov (NCT02949037) on October 31, 2016.

Discussion

Expected benefits of this research and development effort to the scientific community and health care services include improved understanding of how to advance 3 joint PCMH principles (ie, better coordination of care, improved quality and safety, and enhanced access to care) through the use of mobile technology and improved understanding of how to include mHealth technology in the clinical workflow of the PCMH health services model, as well as improved understanding of how to use mHealth technology to activate patients with a diagnosis of type 2 diabetes in disease self-management behaviors. We also expect to improve understanding of how patient complexity and degree of “sickness” may influence patient use or nonuse of mHealth technologies in self-management of their disease, and to explore how to map patient-entered biomedical data onto clinical documentation and a decision-support platform useful in chronic care management.

Our study design is not immune from potential threats to validity. Patients allocated to the control arm will be issued the same peripheral devices as the intervention group and, while they may not achieve the same degree of activation, they may realize improvement if they use the equipment being issued to them. Though this behavioral mechanism could benefit patients in the control group, a strong activation change in the control arm could conceal the behavioral benefit of our intervention when we compare patient behavior from the 2 arms.

We are aware that we did not conduct a power calculation for sample size, since this project was funded as a feasibility study, not a randomized controlled trial. Thus, sample size estimates are neither required nor appropriate. We additionally recognize that a formal randomized controlled trial would be preferred to our current design. A follow-on randomized controlled trial is our goal once we have collected sufficient data and have a better understanding of how patients will use this chronic care health

information technology system. At that point we will legitimately be able to predict the intervention effect and properly power the study.

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Authors' Contributions

RG initially conceptualized the study, and both RG and LS wrote the initial draft of the manuscript. PC, EAS, RG, WWS, KWE, MH, and JBM assisted in the setting narrative, enrollment strategies, and institutional review board-related issues. The technical aspects of the intervention and MHCE description were authored by JRL and RG. The biostatistics and data analysis strategy were developed by LC and KT. The patient activation and behavioral messaging component, including examples, was developed by CJD, JEW, SFG, and KOJ. The user-centered design component was researched and authored by JEW and SFG. The outcome measures component was conceptualized and authored by PC, EAS, KT, LS, CJD, JEW, LC, JBM, MH, WWS, and KWE. The clinical components, including inclusion and exclusion criteria, were developed by PC, EAS, CD, WWS, JBM, MH, KWE, and RG. The MHS review and component were authored by JBM, MH, KWE, and RG. All authors read, contributed to, critically reviewed, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CS-PAM: Clinician Support Patient Activation Measure
DoD: Department of Defense
HbA1c: glycated hemoglobin
MHCE: Mobile Health Care Environment
MHS: Military Health System
PAM: Patient Activation Measure
PCMH: patient-centered medical home
PHR: personal health record
SDSCA: Summary of Diabetes Self-Care Activities
SMS: short message service
SUS: System Usability Scale

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Protocol

Biometrics and Policing: A Protocol for Multichannel Sensor Data Collection and Exploratory Analysis of Contextualized Psychophysiological Response During Law Enforcement Operations

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Abstract

Background: Stress experienced by law enforcement officers is often extreme and is in many ways unique among professions. Although past research on officer stress is informative, it is limited, and most studies measure stress using self-report questionnaires or observational studies that have limited generalizability. We know of no research studies that have attempted to track direct physiological stress responses in high fidelity, especially within an operational police setting. The outcome of this project will have an impact on both practitioners and policing researchers. To do so, we will establish a capacity to obtain complex, multisensor data; process complex datasets; and establish the methods needed to conduct idiopathic clinical trials on behavioral interventions in similar contexts.

Objective: The objective of this pilot study is to demonstrate the practicality and utility of wrist-worn biometric sensor-based research in a law enforcement agency.

Methods: We will use nonprobability convenience-based sampling to recruit 2-3 participants from the police department in Durham, North Carolina, USA.

Results: Data collection was conducted in 2016. We will analyze data in early 2017 and disseminate our results via peer reviewed publications in late 2017.

Conclusions: We developed the Biometrics & Policing Demonstration project to provide a proof of concept on collecting biometric data in a law enforcement setting. This effort will enable us to (1) address the regulatory approvals needed to collect data, including human participant considerations, (2) demonstrate the ability to use biometric tracking technology in a policing setting, (3) link biometric data to law enforcement data, and (4) explore project results for law enforcement policy and training.

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KEYWORDS

psychophysiology; law enforcement; sensor, wearable; clinical trial; digital health

Introduction

Stress experienced by law enforcement officers is often extreme and is in many ways unique among professions. Unlike in most jobs, police officers are regularly exposed to violence, human suffering, and death, and they routinely have to deal with unpredictable and uncontrollable events [1,2]. In addition, many officers are required to work nonstandard work schedules (i.e., rotating or irregular, evening, night, or split shifts), for which the negative effects on individuals and families are well documented [3-6]. Research has found that unpleasant interactions with the public and exposure to disturbing situations (e.g., responding to incidents involving child victims) are important sources of stress among police officers [1]. In turn, high levels of work-related stress can lead to negative health outcomes for officers, including fatigue, insomnia, depression and anxiety, and a range of psychosomatic issues such as lower back pain, headaches, and digestive problems [7-9]. Stress also affects health through its relationship to harmful behaviors, such as increased alcohol use, smoking, and lack of physical leisure activities [9], as well as eating a higher-fat diet [10]. In the longer term, chronic work stress can increase the risk of heart disease and diabetes [11].

Work stress affects not only officers' health, but also their job performance, which can influence their interactions with community members and ultimately the safety of the communities they serve. Some laboratory-based studies have found a curvilinear relationship between stress and performance; however, in the field, especially when complex tasks are at hand, moderate to high levels of stress have been found to be detrimental to performance [12]. For instance, job-related stress is positively associated with the likelihood of being injured on the job [13], absenteeism [14], and turnover intentions and behaviors [15]. Work-related stressors can also correspond with negative emotions, such as aggression and hostility, increasing the likelihood of interpersonal problems with coworkers [16]. Stress can also affect interactions with the community; for instance, officers who report more burnout—the result of prolonged exposure to work stress—report more favorable attitudes toward the use of violence [17].

Critical for our study, a significant body of research indicates that exposure to stress can directly or indirectly affect decision-making capabilities. When exposed to a threatening or stressful event, the sympathetic nervous system is activated, while the parasympathetic nervous system (responsible for calming the body) is deactivated [18]. Greater perceptions of threat correspond to higher levels of sympathetic nervous system arousal (also known as fight-or-flight responses) and the release of stimulant hormones (e.g., cortisol, adrenaline) that can impair fine motor skills, reduce focus, and negatively affect decision making [19,20]. Specifically, the release of adrenal stress hormones constricts blood vessels and decreases oxygen levels in the prefrontal cortex, which limits the individual's ability to access stored memories and experiences [21].

Moreover, heightened physiological arousal may drive individuals into a state of hypervigilance, in which they rely more on their reactive limbic system than on their frontal lobe, which is used for reasoning and analytical thinking [22]. Baradell and Klein [23] argued that stressful events encourage "resource depletion," in which cognitive resources are dedicated to managing the anxiety that is generated from exposure to a stressful event. Resource depletion interferes with the capacity to consider options or alternatives or to scan the environment for additional information when interpreting a situation. Fight-or-flight responses have also been linked to perceptual distortions (e.g., tunnel vision, narrowing of auditory information) [24,25], which can slow reaction time and impede the ability to identify and understand potentially life-threatening cues. Evidence also suggests that stress negatively affects sleep quality [26], which in turn degrades individuals' abilities to perform well on complex decision-related tasks [27].

Recent high-profile events involving law enforcement's deadly use of force have intensified scrutiny on American policing and initiated national conversations about the need for systematic police reform. Larger discourse related to the "crossroads in American policing" has criticized law enforcement for what is perceived to be poor decision making among officers during several highly publicized events, including the deaths of Eric Garner and Michael Brown [28]. These perceptions have led some practitioners and social commentators to campaign for improved decision-based training or other efforts to enhance decision-making skills among officers [29]. As we have described, stress is a key component of poor decision making. Fortunately, there is an extensive knowledge base pertaining to ways that organizations can ameliorate the effects of stress on employees, and work is being done to translate this literature into a police organizational setting.

Organizational Responses to Stress

Robson and Manacapilli [30] described several ways in which employees within an organization become competent in stress management skills: (1) prehire screening designed to select individuals more likely to succeed in stressful environments, (2) deliberate removal of those who are not operating well under stress, (3) allowing employees who are unable to cope with stressors to select themselves out of the job, and (4) using training to minimize the impacts of stress.

Law enforcement agencies engage in a battery of prehire tests, some of which are relevant to screening out individuals who do not possess the disposition necessary to cope with the stresses of policing. Options 2 and 3 can be more challenging. These options can be expensive (e.g., employee turnover), difficult to implement (e.g., removing an officer with civil service protection), or outside of the agency's control (e.g., officer volunteering to leave). From a pragmatic perspective, developing behavioral and cognitive skills to minimize the damages of stress is the most efficient method of dealing with officer stress. This takes advantage of the human capital contained within well-trained officers, leverages the training capabilities of modern law enforcement agencies, and makes use of a growing body of evidence-based trainings.

In other settings, workplace-based stress management programs have been found to improve a variety of employee outcomes, including reduced stress and enhanced emotional and physical health (e.g., reduced blood pressure) [31]. There are multiple

types of workplace health trainings, and each has been associated with different outcomes. For example, cognitive behavioral training is effective in improving perceived quality of work life, and psychological resources and responses [32]. Trainings designed to teach employees effective coping strategies, appropriate for different kinds of workplace stressors, reduce the effect of potential stressors on health and well-being.

Organizations can also undertake more substantial organizational changes to address known stressors. For example, shift work is a recognized contributor to employee stress and negative health outcomes [33]. Research on police shift work identified certain kinds of work schedules that minimize, to the extent possible, the negative effects of shift work and rotating schedules [34]. The extent to which these organizational changes are effective, however, is largely unknown. This demonstration project seeks to develop a methodology that could be used to evaluate interventions of these types.

Study Objective

Recent advances in smartphone and wristband sensor technology allow for the study of affect from several important perspectives that will enable understanding of the interplay between affect and physical health in our everyday lives. First, advances in wearable sensor technology allow for the collection of precise and reliable data on psychophysiological indicators (e.g., electrodermal activity [EDA] and galvanic skin response, heart rate, heart rate variability, physical activity) that have been linked to affect in previous research [35-37]. These devices provide a continuous stream of biometric data and can be worn throughout the day with no interruption to daily routines. The study of affect in the naturalistic setting, outside of the laboratory, is particularly important, as little is known about the day-to-day physiology of affect, largely due to the low levels of precision and high levels of noise in data collected to date in environments where people are ambulatory.

This demonstration project is based on 2 established research findings: (1) stress has negative implications for both individuals and the organization they work in, and (2) stress management training has shown positive results for managing stress and ameliorating the negative impact of stress. Broadly, our research objective for this study is to demonstrate the practicality and utility of biometric sensor-based research in a law enforcement agency. Although past research on officer stress is informative, it is limited. Most studies have measured stress using self-report questionnaires or were observational studies with limited generalizability. Objective physiological assessment of individuals in occupational settings other than law enforcement has demonstrated the utility of heart rate variability analysis to identify effort at work [38], psychological distress [39], and self-reported burnout [40]. We know of only 2 other research studies that have attempted to track direct physiological stress responses within an operational police setting [41,42].

Moreover, previous studies on law enforcement stress management were hampered by poor design and evaluations with low statistical power. The outcome of this project will have an impact on both practitioners and policing researchers. To do so, we will establish a capacity to conduct this type of research by obtaining complex, multisensor data; processing complex datasets; and establishing the methods needed to conduct idiopathic clinical trials on behavioral interventions in similar contexts. Our research objectives are to (1) explore the viability of using commercially available biometric tracking technology in a law enforcement setting, (2) determine whether biometric data can be linked to law enforcement data stored in a records management systems, (3) explore the results in the context of policy and training implications for law enforcement agencies, and (4) document the viability of using biometric-related data in an evaluation framework in a law enforcement agency.

The study will use an innovative and methodologically sophisticated research design to address a critical issue in contemporary law enforcement: officer stress. Previous research has shown that police officers are vulnerable to a variety of stressors that are a result of organizational issues, operational experiences, or individual-level characteristics. Likewise, an extensive body of research has demonstrated linkages between stress and several deleterious officer health-related outcomes such as fatigue, insomnia, and anxiety. Importantly, stress can also manifest itself as impaired decision making. Given the current national scrutiny on American policing and the perceived need for enhanced decision-based training, it is imperative that researchers strengthen the knowledge base about both officer stress and stress management techniques appropriate for police agencies.

Methods

Study Design

This pilot study is intended to explore the feasibility of using wrist-worn biometric sensors in law enforcement. We will use nonprobability convenience-based sampling to recruit 2-3 participants from the police department in Durham, North Carolina, USA.

Recruitment

We will rely on agency executive staff to distribute recruitment material to all sworn patrol officers and to assist in identifying those who may be interested in participating. The recruitment email will include the study goals, expectations, and compensation. If the individual is interested, we will schedule an in-person or telephone meeting to discuss their participation further. To prevent any coercive effects, we will reach out directly to potential participants. During the meeting we will discuss the following: the study's goals; that this is not a medical study; the potential risks to participants; expectations for wearing the device; compensation and compensation structure; the number of contacts needed during the study; other data we will collect from the agency; and our inability to provide true confidentiality. At this meeting, we will also demonstrate use of the device to the participant.

Inclusion and Exclusion Criteria

Recruitment will be limited to sworn officers, employed by, and in good standing with, the Durham Police Department in Durham, North Carolina. Among sworn officers, we will limit recruitment to those officers who operate in a standard patrol capacity.

Ethics and Confidentiality

This study has been reviewed and approved by the RTI International institutional review board. Device handling and data management protocols were reviewed by RTI's Cloud Computing Security Team.

Data Collection

We will collect three major types of data (biometric, operational, and spatial) from a variety of sources for each officer over 4 weeks. We describe each data type and source in more detail below.

Biometric Data

The use of biometric data will provide a highly nuanced look at physiological stress response. The Empatica E4 (Empatica Inc, Boston, MA, USA) is a wrist-worn wireless device capable of monitoring physiological signals through multiple sensors. EDA is used to determine the occurrence of stress or excitement by monitoring involuntary changes in skin conductivity mediated by the wearer's sympathetic nervous system. Heart rate and other cardiovascular measures are derived from the blood volume pulse signal, measured through a *photoplethysmographic* sensor. A 3-axis accelerometer records the user's physical activity, and an infrared thermophile captures the user's skin temperature. All recordings have a time stamp, which we will use as the merge key for the agency data described below. Earlier versions of the E4 have been used in prior research studies to measure stress, skin conductance, and heart rate [43,44].

When a person is exposed to a stressor, the autonomic nervous system is triggered, resulting in the secretion of hormones into the bloodstream. These hormones lead to increased blood pressure, increased muscle tension, and changes in heart rate and heart rate variability [38]. This process is commonly known as the fight-or-flight reaction. When the stressor is no longer present, a negative feedback system stops this response and reestablishes the typical physiological balance for the individual.

During the last few decades, researchers have used subtle changes in heart rate to measure mental stress. Heart rate variability is calculated based on variation of time, in milliseconds, between 2 heartbeats. This parameter provides an observation of the heart's ability to respond to normal regulatory impulses and can reflect changes in stress while other physiological parameters remain in normal or accepted ranges.

EDA, or galvanic skin response, describes involuntary changes in the electrical properties of the skin. Increased EDA indicates sympathetic activation or arousal and is widely used as a sensitive index of emotional processing. EDA is considered the most useful index of changes in sympathetic arousal that are traceable to emotional and cognitive states and is the only autonomic psychophysiological variable that is not contaminated by parasympathetic activity.

In the study, we will give participating officers a copy of the E4 device manual and training to operate the device. Officers will be instructed to wear the device and initiate a recording session at the beginning of each 12-hour shift.

Operational Data

Like most modern police departments, the Durham Police Department uses computer-aided dispatch (CAD) to facilitate the management and safety of patrol officers. CAD data capture a wide array of information on calls received from the public, calls initiated by officers, and the status of agency resources. For the purposes of this study we will extract 4 pieces of information. First, we will obtain officer identifiers to limit data processing to only the study participants. Second, we will extract relevant call details such as the type of event and the priority with which it is dispatched. We hypothesize that calls with higher priority or calls that involve violence or a higher degree of situational uncertainly will be associated with greater physiological reaction. Third, we will capture information on participant status. CAD data allow us to know what each participant is doing at any given time. Officers can be assigned to a call (dispatched), en route to a call, at the scene of a call, transporting an arrestee, or cleared from a scene. We will broadly classify these as allocated (assigned to a call) or unallocated (unassigned to any specific activity). We will further refine this classification and investigate the relationship between calls that are self-dispatched (e.g., a traffic stop) or citizen initiated (e.g., a call of a fight in progress). Fourth, we will extract various time components such as when the call is received, when the participant is dispatched, and when the participant has returned to service. We will use this time to link biometric data with participant activity data.

Spatial Data

Related to the CAD system, automated vehicle-locating technology is also used by the Durham Police Department to aid in police operations, especially with regard to dispatch decision making. Global positioning system (GPS) devices located in the patrol vehicle routinely report on the vehicle's location, direction, speed, and heading. These data are stored by the Durham Police Department for a period of 30 days. The Durham Police Department will export these data for us regularly during the study period so that we will have full coverage of all participants during the biometric monitoring phase. The automated vehicle-locating data extract comes as a comma-separated values (CSV) file, where each row represents one location ping. Ping frequency depends on the speed of the vehicle; location is updated more frequently when the vehicle is moving and less frequently when the vehicle has been stationary. We will extract 4 pieces of information from this dataset: (1) vehicle *xy*-coordinates for location awareness, (2) time of ping occurrence to allow syncing with biometric data, (3) status and call identifier to understand what participants were doing, and (4) officer identifier to extract data on participants.

Table 1. Multichannel data sources that will be assimilated in the Biometrics & Policing Demonstration pilot.

Data	Source	File type	Resolution	Use
Blood volume pulse	Biometric sensor	CSV[a]	64 Hz	Cardiovascular function
Interbeat interval	Biometric sensor	CSV	N/A[b]	Heart rate variability
Physical activity and posture	Biometric sensor	CSV	32 Hz	Physical measure
Electrodermal activity	Biometric sensor	CSV	4 Hz	Stress metric
Skin temperature	Biometric sensor	CSV	4 Hz	Stress metric
Automatic vehicle locators	Agency	Spatial point	Approximately every 3-30 seconds	Correlation of location and stress
Calls-for-service	Agency	Spatial point	Event level	Workload, time on-call, time off-call, call ordering
Incident data	Agency	Spatial point	Event level	Area crime patterns and stress

[a]CSV: comma-separated values.

[b]N/A: not applicable.

Study Outcomes and Data Analysis

Data Management and Analysis Plan

The proposed project will require the assimilation of the data sources shown in Table 1. This assimilation presents several data management challenges. We will use data from the Empatica E4 to capture and quantify the autonomic stress response an officer experiences during work activity. Data from the agency's CAD system will determine the types and durations of the activities an officer performed during a shift. We will derive the approximate locations of participants using the automated vehicle-locating logs. This integration will allow us to characterize stress responses with relevant situational and locational context. Multimedia Appendix 1 shows the Biometrics & Policing Demonstration pilot project data model, detailing the concurrent acquisition of biometric, operational, and spatial data, and the processing pathways for each data type. Multimedia Appendix 2 shows how the processed data are fused for analysis and statistical modeling.

Signal Processing

The E4 provides EDA, skin temperature, and 3 axes of accelerometer data. We will use these raw data streams to compute parameters on a common time scale to facilitate statistical analysis. Nonoverlapping 20-second windows will be chosen. The skin temperature data will be mean averaged over this window. The 3 axes of accelerometer data will be condensed to a single activity parameter reflecting overall level of motion at the wrist. The EDA data cannot be condensed to a single average value, because the time-varying component of the EDA signal contains significant information. We will compute 12 different parameters from the raw EDA data stream. The raw EDA signal will be decomposed into 2 frequency bands: 0-0.04 Hz to capture the baseline value or general trend, and a 0.04-0.4 Hz band to capture the fluctuations in EDA around this baseline value. From the baseline signal, we will compute an average EDA baseline value over the 20-second time window, but this value is influenced by many confounding factors, such as the quality of the electrode contact to the wrist and skin moisture level. Therefore, this average baseline value may be normalized using both a difference and a *z* score based on the previous 20-minute time segment. The slope of the baseline EDA will also be computed on 2 different time windows to capture change in baseline EDA. The magnitude of the time-varying component of the EDA signal will be captured using the root mean square (RMS) value of the 0.04-0.4 Hz signal. This RMS EDA value will also be normalized using a difference and *z* score from the previous 20 minutes. Counting the number of peaks in the 20-second window exceeding specified thresholds captures the level of EDA fluctuation. We will report all of the computed metrics along with the corresponding time window. Events noted in the police log will be obtained on the same 20-second time scale.

Detailed Description of Metrics

We will compute 19 metrics on 20-second nonoverlapping windows: *time* (3): time stamp, elapsed time, and elapsed time from midnight; *event* (1): event code; *bad data* (1): bad data value; *activity* (1): average activity count; *skin temperature* (1): average temperature; *EDA* (12): average EDA level, average EDA level difference, average EDA level *z* score, 20-second EDA level slope, 120-second EDA level slope, RMS EDA, RMS EDA difference, RMS EDA *z* score, number of peaks (high threshold), average peak height (high threshold), number of peaks (low threshold), and average peak height (low threshold).

Time

The start time of the Empatica data file will be taken as the start time of the derived metrics file. A *time stamp* will be computed every 20 seconds from that start time. Additionally, we will report both *elapsed time* and *elapsed time from midnight*.

Event

The *event code* for a 20-second window will be computed as the mode of the event assignment values (sampling rate=1 Hz). The event assignment values are as follows:

- 0.5: call was ultimately canceled
- 1.0: dispatch to arrive 1
- 2.0: arrive 1 to arrive 2, transport, *or* cleared (depends on what next event is)
- 2.5: arrive 2 to transport (if arrive 2 occurs before transport)

- 3.0: transport to cleared.

Bad Data

This data stream will be computed using an algorithm provided by Empatica that returns –1 if the data are bad and 1 if the data are good on 5-second intervals. The *bad data value* reported for a 20-second window will be the sum of the 4 values in the bad data stream spanned by this window:

- 4: all of the data are good (100% good)
- 2: one bad data point (75% good)
- 0: two bad data points (50% good)
- –2: three bad data points (25% good)
- –4: all of the data are bad (0% good)

Activity

The activity signal will be computed from the 3-axis accelerometer signal (sampling rate=32 Hz), where *activity* = $\sqrt{x^2 - y^2 + z^2}$. The activity signal will be filtered to the 0.1-7 Hz band using a zero phase fifth-order Butterworth filter. Then, the activity count will be computed over 1-second nonoverlapping epochs as follows: *activity count* = $\sum|$ *activity* $|$.

The *average activity count* will be the average activity count (sampling rate=1 Hz) over the 20-second window.

Skin Temperature

The *average temperature* will be the average temperature (sampling rate=4 Hz) over the 20-second window.

Electrodermal Activity

The EDA signal (sampling rate=4 Hz) will be filtered into 2 bands:

- *Baseline:* 100-point third-order polynomial filter (cutoff frequency=0.04 Hz); effectively, this signal will be the EDA signal that has been filtered to the 0-0.0 4 Hz band (i.e., the EDA level).
- *Bandpass:* baseline will be removed from the EDA signal, and the resulting signal will be further filtered using a 10-point third-order polynomial filter (cutoff frequency=0.4 Hz); effectively, this signal will be the EDA signal that has been filtered to the 0.04-0.4 Hz band.

The *average EDA level* will be the average of the baseline signal over the 20-second window. We will apply 2 forms of normalization to this metric to account for slow drift in baseline EDA value.

The *average EDA level difference* will be the current window minus the average of the windows from 20:20 to 0:20 previous.

The *average EDA level* z *score* will be the *z* score using the current window, where the population is considered to be the windows from 20:20 to 0:20 previous.

The *20-second EDA level slope* will be computed by fitting a line to the baseline signal over the 20-second window.

The *120-second EDA level slope* will be computed by fitting a line to the baseline signal over a window spanning 60 seconds before and after the current point.

The *RMS EDA* will be the RMS of the bandpass signal over the 20-second window. This reflects the amount of fluctuation in EDA.

The *RMS EDA difference* will be the current window minus the RMS of windows from 20:20 to 0:20 previous.

The *RMS EDA* z *score* will be the *z* score using the current window, where the population is considered to be windows from 20:20 to 0:20 previous.

The *number of peaks (high threshold)* will be the number of peaks in the 20-second window of the bandpass signal, separated by at least 1 second, that have a height ≥0.15 microsiemens. The *average peak height (high threshold)* will be the average of these peaks.

The *number of peaks (low threshold)* will be the number of peaks in the 20-second window of the bandpass signal, separated by at least 1 second, that have a height ≥0.02 microsiemens The *average peak height (low threshold)* will be the average of these peaks.

Multimedia Appendix 3 is a CSV file sample of the treated dataset. Variables have been cleaned, filtered, and conflated; this structure will be used as the basis for statistical analysis.

Heart Rate and Heart Rate Variability Analysis

Before we can analyze heart rate variability, we will assess the quality of the *photoplethysmographic* sensor output, blood volume pulse, and interbeat interval. Session data for each participant will be visually inspected to provide a qualitative assessment of signal fidelity. We will then quantify 3 parameters of signal quality for the interbeat interval data: (1) the longest segment of valid data, (2) the mean and standard deviation of the gaps in the signal, and (3) the signal quality for each 20-second segment of interbeat interval data for consistency with the rating of the EDA signal. These qualitative and quantitative findings will inform the extent to which heart rate variability will be assessed and integrated with other measures.

Data Fusion

Before within-participants analysis can be conducted, a variety of data sources must be combined. We will synchronize datasets to a common UNIX time stamp, align the sample rates, and produce a single, comprehensive artifact of filtered and preprocessed data for each officer's shift suitable for statistical analysis.

Mixed-Model Trajectory Analysis

Statistical analyses will be conducted separately per data stream as the outcome (e.g., average EDA level separately from activity). Mixed-model trajectory analysis (MMTA), derived from hierarchical linear modeling, will quantify each individual officer's time series data at level 1, while aggregates of officer data across individuals are analyzed at level 2 [45-48]. Hence, observations are clustered within individuals. Maximum likelihood estimation and fit statistics test which model components provide (or do not provide) improved fit to the observed data. Compared with traditional hierarchical linear modeling, several adjustments are needed to counter the potential for biased estimates in small sample sizes [45-48].

First, during the model fitting process, the Kenward-Roger correction is used to reduce the probability of a type 1 error [49-51]. Then, after the best-fitting model is determined, restricted maximum likelihood estimation is used to derive parameter estimates, because the full maximum likelihood underestimates parameter variance due to how degrees of freedom are allocated and is especially problematic in small samples [52-54]. This modeling will facilitate understanding how factors such as (1) efficacy of intervention, (2) demographics (e.g., age), (3) officer activity (e.g., managing a domestic dispute vs patrolling a high-crime neighborhood), and (4) and error covariance structures (e.g., autoregressive integrated moving average vs Toeplitz) affect the officer's physiological stress response. We will conduct analyses using SAS 9.3 (SAS Institute Inc).

Considerable evidence in using MMTA to quantify individual time series and outcomes is available from health and nonhealth fields (e.g., animal husbandry and genetics) in the context of best linear unbiased predictors [51,55,56]. Within-person MMTA can be represented by the single regression equation $Y_{it} = \beta_0 + u_{0i} + \beta_1(\text{time}) + u_{1i}(\text{time}) + \beta_2\ \text{Intx}_{it} + \beta_3(\text{Intx*time})_{it} + e_{it}$, where Y_{it} is an outcome for individual i at time t; the intercept for individual i is a function of the average sample intercept (β_0) plus individual i 's deviation from this average (u_{0i}, which is assumed to have a normal distribution and each time point is uncorrelated with all others, using an error covariance structure to parse out autocorrelation); change in the outcome over time is a function of the sample average trend (β_1) plus individual i 's deviation from that trend (u_{1i}, assumed to be normally distributed); differences between baseline and intervention phases are modeled as differences between phase intercepts ($\beta_2\ \text{Intx}_{it}$) and trends ($\beta_3(\text{Intx*time})_{it}$); and e_{it} denotes random error (an aggregate term that can be parsed into multiple sources of error). Important for analysis of biosensor data, "time" often fits the data best as a fixed effect per shift (i.e., time is coded as zero at the start of each shift) because of factors such as the accumulation of sweat at the sensors during a shift.

The term "mixed model" refers to categorization of model variables into fixed and random effects. Fixed effects involve variables assumed to have no measurement error, are constant across individuals, and have values that are equivalent across studies (e.g., most demographics, passage of time, study arm assignment). Random effects involve variables that represent random values from a larger population or involve generalizing inferences from the effect beyond the observed values (e.g., Gaussian psychological characteristics, an effect of time that varies across persons). While not discussed here due to space limits, this distinction is fundamental in terms of both analytic techniques and interpretation of results [57]. The planned analyses include statistical control variables (time; potential sources of stress that occur with every call to a scene, such as the initial communication and travel to the scene), while we will test highly stressful calls (e.g., a crime scene characterized by violence or high unpredictability) for the sources of stress and as fixed effects.

Sample Size and Power

The stream of biosensor data will provide large statistical power to detect associations between physical stress response and specific experiences of police officers. The amount of biosensor data proposed to be collected will come from 12-hour shifts of 2-3 officers over 1 month (estimated to result in more than 500 hours of monitoring data). To illustrate this, we analyzed two brief splices of EDA data collected during the Biometrics & Policing Demonstration project.

Multimedia Appendix 4 shows the changes in the officer's EDA throughout (A) a full shift (with 5 calls demarcated) and (B) a domestic dispute call versus (C) stolen vehicle recovery. MMTA results suggest a statistical model of the difference in EDA between a domestic dispute (B) and a less-stressful call (C). The respective mean EDA levels were 0.77 (SD 0.362) vs 0.11 (SD 0.095), reaching a $P<.0001$ level of statistical significance.

Results

Data collection was conducted in 2016. We will analyze data in early 2017 and disseminate our results via peer reviewed publications in late 2017.

Discussion

The Biometrics & Policing Demonstration project was developed to provide a proof of concept on collecting biometric data in a law enforcement setting. As part of this effort, we will recruit 3 officers from a large police department to participate in biometric data collection during their duty shifts over a 4-week period. This effort will enable us to (1) address the regulatory approvals needed to collect data, including human participant considerations, (2) demonstrate the ability to use biometric tracking technology in a policing setting, (3) link biometric data to law enforcement data, and (4) explore project results for law enforcement policy and training.

If this project is successful, future directions for expanding data collection will include obtaining regular self-report on affect and valence using ecological momentary assessment instruments; collecting biological specimens for assessment of concurrent biomarker variation alongside biometric response; applying instrumentation to individual participants with a GPS sensor to track the location of officers during time spent away from their patrol vehicle; incorporating nonworkday data collection to establish a nonoccupational baseline; and integrating biometric readings with body-worn or dash camera media.

Recommendations from the US President's Task Force on 21st Century Policing [58] call for an enhanced focus on improving officer health and wellness. The proposed demonstration pilot will serve as a major step forward in understanding how to use an innovative but not field-tested data collection methodology using advanced biometric sensors. These efforts will establish a framework for other related lines of research. Programs designed to improve overall officer health, for example, can be better assessed using the nuanced information provided by biometric sensors. Officer-worn biometric sensors also have the long-term potential to directly enhance officer safety. At

least one wearable biometrics company has explored the use of the devices for real-time monitoring of officer safety. The proposed study is a critical step in advancing our state of knowledge with regard to the utility of wearable biometrics in law enforcement and may lead to officer safety improvements.

Another relevant policy consideration is the potential for unmanaged stress to have negative implications on the operations of law enforcement agencies. High levels of stress can be associated with increased absenteeism, use of sick leave, and employee turnover. These employee actions can create management difficulties for agencies, which suggest that agencies have a vested interest in keeping employees healthy. Poor stress management for officers can also lead to acute problems, such as diminished decision-making capacity in highly charged situations, like use-of-force incidents.

Stress-compromised decision making can lead to negative police-community interactions. The relationship between high-stress situations and use of force is obvious. Officers may be more likely to use force inappropriately when operating under long-term stress. Nevertheless, use of force is relatively rare. A more frequent concern may be how stress affects the more routine interactions between officers and citizens. Officer stress may lead to police-community interactions with greater levels of tension and disrespect. These routine interactions have a profound effect on police-community relations. Efforts to better manage officer stress may ultimately improve police-community relationships.

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Authors' Contributions

RDF contributed to the initial conception and design of the study, contributed to the data analysis considerations, and wrote the first draft of the manuscript.
TT Contributed to the initial conception and design of the study, revised the first draft, and provided critical review of the manuscript.
AMO, MHC, KHG, and TAR contributed to the initial conception and design of the study, contributed to the data analysis considerations, and provided critical review of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Biometrics & Policing data model.

[PDF File (Adobe PDF File), 235KB - resprot_v6i3e44_app1.pdf]

Multimedia Appendix 2

Combined variables inventory.

[PDF File (Adobe PDF File), 123KB - resprot_v6i3e44_app2.pdf]

Multimedia Appendix 3

Sample of the treated data set.

[CSV File, 1KB - resprot_v6i3e44_app3.csv]

Multimedia Appendix 4

Image showing electrodermal activity data from one officer's shift.

[PDF File (Adobe PDF File), 460KB - resprot_v6i3e44_app4.pdf]

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Abbreviations

CAD: computer-aided dispatch
CSV: comma-separated values
EDA: electrodermal activity
GPS: global positioning system
MMTA: mixed-model trajectory analysis
RMS: root mean square

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Original Paper

Get+Connected: Development and Pilot Testing of an Intervention to Improve Computer and Internet Attitudes and Internet Use Among Women Living With HIV

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Abstract

Background: For persons living with chronic medical conditions, the Internet can be a powerful tool for health promotion, and allow for immediate access to medical information and social support. However, women living with human immunodeficiency virus (HIV) in the United States face numerous barriers to computer and Internet use. Health behavior change models suggest that the first step towards adopting a new health behavior is to improve attitudes towards that behavior.

Objective: To develop and pilot test Get+Connected, an intervention to improve computer and Internet attitudes and Internet use among women living with HIV.

Methods: To develop Get+Connected, we reviewed the extant literature, adapted an existing curriculum, and conducted a focus group with HIV-positive women (n=20) at a community-based organization in the Bronx, New York. Get+Connected was comprised of five weekly sessions covering the following topics: basic computer knowledge and skills, identifying reliable health-related websites, setting up and using email and Facebook accounts, and a final review session. We recruited 12 women to participate in pilot testing. At baseline, we collected data about participants' sociodemographic information, clinical characteristics, and technology device ownership and use. At baseline, intervention completion, and three months postintervention, we collected data regarding attitudes towards computers and the Internet (Attitudes Towards Computers and the Internet Questionnaire [ATCIQ]; possible scores range from 5-50) as well as frequency of Internet use (composite measure). To examine changes in ATCIQ scores and Internet use over time, we used generalized estimating equations. We also collected qualitative data during intervention delivery.

Results: Among women in our sample, the median age was 56 years (interquartile range=52-63). All participants were black/African American and/or Latina. Seven participants (7/12, 58%) had a high school diploma (or equivalent) or higher degree. Ten participants (10/12, 83%) reported owning a mobile phone, while only one (1/12, 8%) reported owning a computer or tablet. Only one participant (1/12, 8%) reported having ever used the Internet or email. Internet nonusers cited lack of computer/Internet knowledge (6/11, 54%) and lack of access to a computer or similar device (4/11, 36%) as the main barriers to use. Over time, we observed an improvement in attitudes towards computers and the Internet (ATCIQ scores: 33.5 at baseline, 35 at intervention completion, and 36 at three months postintervention; P=.008). No significant increase in Internet use was observed (P=.61). Qualitative findings indicated excitement and enthusiasm for the intervention.

Conclusions: In our sample of urban, technology-inexperienced HIV-positive women, participation in Get+Connected was associated with an improvement in attitudes towards computers and the Internet, but not Internet use. Changing attitudes is the first step in many health behavior change models, indicating that with improved access to computer and Internet resources,

frequency of Internet use may also have increased. Future studies should consider addressing issues of access to technology in conjunction with Get+Connected.

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KEYWORDS

women and HIV; Internet literacy; technology intervention; digital divide; information seeking behavior; access to health information

Introduction

The Internet is a powerful tool for health promotion and disease management, and allows for immediate access to medical information and social support. According to a 2014 Pew Research Survey, 87% of Americans use the Internet [1]. Seventy-two percent of Internet users reported looking online for health-related information [2], with over 60% searching for information on specific disease conditions and roughly half searching for medical treatments [3,4]. Among those diagnosed with a chronic medical condition, nearly half used the Internet for advice or information on their illness [5]. Persons with chronic medical conditions are more likely than those without a chronic medical condition to track their health profile and health indicators online [6]. The Internet also provides access to social support by facilitating linkages among persons with chronic medical conditions via peer networks, online forums, and chat rooms [7].

Despite the Internet's seeming ubiquity and the increasing popularity of leveraging the Internet for health promotion, significant disparities exist with respect to use [8]. For example, recent studies suggest that leveraging the Internet for health information and social support can improve health-seeking behaviors and outcomes in persons living with human immunodeficiency virus (HIV) [9-12]. More specifically, health-related Internet use among persons living with HIV is associated with greater medication adherence and use of active coping strategies, higher self-efficacy and CD4 white blood cell count, and an increased sense of social connectedness [13-15]. However, these studies were conducted with samples that were primarily male and white, and therefore may not be generalizable to other sociodemographic groups. Those who are economically disadvantaged, socially marginalized, and less educated are less likely to use the Internet for health-related purposes [16-18]. Among Internet users, including those living with HIV, there is a clear *digital divide*, with more affluent whites using the Internet more frequently than their African American and Latino counterparts, even after controlling for socioeconomic status [18-20]. The consequences of such disparities are profound and limit the potential resources that certain demographic groups living with HIV can leverage to improve their health.

Women living with HIV are largely socioeconomically disadvantaged, and therefore may be unlikely to reap the benefits of available electronic health information due to limited Internet access and/or use [21-25]. Among an urban, community-based sample of women living with HIV, Blackstock et al [26] found that the overall proportion of women using the Internet was lower than that of the general population (61% vs 84%). This study also found that reported barriers to Internet use among non-Internet-using HIV-positive women included a lack of interest, knowledge, and experience in navigating computers and the Internet [26]. However, among Internet-using women in the study, most (86%) were actively engaged in using the Internet for obtaining health-related and general information (75%), showing the potential benefits that could be reached once barriers to use are addressed [26].

According to the Theory of Planned Behavior, improving attitudes towards a behavior can enhance uptake of that behavior [27,28]. Therefore, among HIV-positive women, we sought to improve computer and Internet attitudes, and ultimately Internet use, by designing and pilot testing the *Get+Connected* intervention. This paper describes the development of *Get+Connected* as well as results from pilot testing of the intervention.

Methods

Get+Connected Intervention Development

The development of *Get+Connected* was based on a review of the literature on Internet use and health-related outcomes among HIV-positive women, adaptation of an existing online health information curriculum from the National Institutes of Health (NIH), and focus group findings [29,30]. The focus group was conducted at a community-based organization (CBO), which serves as a skilled nursing facility that provides onsite housing and supportive services to persons living with HIV in the Bronx, New York. Individuals were eligible to participate in the focus group if they self-identified as cis-gender women, were proficient in English, and expressed interest in participating in the focus group. Participants were actively recruited to participate by a CBO staff member who described the study in person to potential participants. Written informed consent was obtained from all participants. Traditionally, focus groups are conducted with a smaller number of participants; however, due to scheduling challenges, we conducted one focus group with 20 participants. Due to this known limitation, the focus group facilitators used strategies to help ensure that all participants were given equal time to respond to questions and accompanying probes; these included directly asking underrepresented participants their opinions, presenting multiple perspectives, reminding participants that there is no *correct answer*, and providing ample time for participants to organize and vocalize their thoughts. Participants were asked about their prior experiences with computers and the Internet, as well as what online skills they were most interested in learning (eg, *search for health-related information*, *use email*). Participants received US $10 and a round-trip Metrocard (value US $5) for their time.

The study received Institutional Review Board (IRB) approval from Albert Einstein College of Medicine.

To identify prominent themes related to computer and Internet interest and use, we conducted a content analysis of the focus group transcript using a qualitative descriptive approach [31]. The focus group transcript was sorted into several content areas related to computers and the Internet, including experience, interest, and desired skills or related activities (eg, how to email, how to use social media). The transcripts were read several times by the study team. Text corresponding to these content areas were extracted and coded, and codes were consolidated into themes.

Our findings indicated that most women had minimal to no experience using a computer or the Internet. However, participants were interested in learning the following skills or activities: typing fluency and speed, how to set up an email account, and how to conduct an Internet search for general health-related purposes (eg, information on HIV, mental illness, managing chronic diseases and pain, general women's health, and medication interactions). Participants expressed interest in: learning how to use social media sites, including Facebook, to reconnect with friends and family; joining support groups for persons living with HIV; and accessing online forums to ask questions and exchange information related to chronic disease management. The most commonly cited reasons for wanting to use the Internet were reconnecting with family and old friends, learning more about their health, and keeping abreast of technological trends (eg, many women expressed a desire to show their children and grandchildren that they could use email and Facebook). Similar to the findings of a previous study [26], lack of computer and/or Internet knowledge and access to technology were cited as additional barriers to Internet use.

Intervention Description

Get+Connected consisted of five weekly 45-minute sessions held at the CBO. Each session was led by a member of the study team with one or two other members present to assist as needed. The curriculum (see Multimedia Appendices 1-4) was delivered using Microsoft PowerPoint presentations projected onto a screen at the front of the room. For each session, participants were provided with a laptop (Google Chromebook) to follow along with the lesson. If requested, a specialized ergonomically correct mouse was provided to participants with limited hand mobility. Focus group participants reported a lack of computer and/or Internet access, so all participants were given library cards and shown how to access the nearest public library (six blocks away from the CBO) as part of the intervention [32]. The library provides free computer and Internet use during business hours, in addition to other educational resources.

Session 1

The first session, which was delivered by a librarian from the local branch of the city library system who specializes in computer literacy for low-income individuals, introduced participants to the fundamentals of computer and Internet use. The lesson began with how to operate the laptop, including how to *wake up* the computer, how to use a mouse to navigate on the computer screen, and how to open an Internet browser. Participants received contextual information, including what a browser is and how browsers can be used to access information. Participants were asked to search for something basic online (eg, "cats") and shown how to view online content, images, videos, and maps. Throughout this search, participants were shown how to scroll up and down on a web page, how to navigate forwards and backwards, how to copy and paste text, and how to save an image to the desktop. Participants also learned how to search for their local public library branch to access free computers and Internet service using Google Maps. Participants were reminded about the free computer access that was available, and were encouraged to visit the library whenever possible.

Session 2

The second session was intended to help participants identify reliable health websites based on defined criteria and was adapted from an NIH computer literacy training curriculum for seniors [30]. Modifications in language, format, and delivery were made to optimize the curriculum for the study's target population. This lesson taught participants how to identify specific website components that gauge the reliability of a given site. These components include: identifying a website's sponsor; identifying the purpose of the website; finding the site's author, date of publication, or date of last update; and checking for plausibility of website content. Two websites were used as examples of trustworthy and credible sites for participants to identify the above components [33,34].

Session 3

This session sought to guide participants through setting up an email account, and taught them how to use email as a mode of communication. Participants created a new account using Gmail, were given basic tips on how to create a username and secure password, and were shown how to update their profiles. Instructions on how to compose a new email were provided, including: how to input an email address, subject heading, and text body; how to open incoming messages; and how to reply to messages. Participants with prior computer or Internet experience were taught to attach saved files and insert articles into their emails. Participants then practiced these skills by sending short emails to each other and to their friends and family.

Session 4

In session four, participants learned how to sign up for a Facebook account, but were first coached on safety and security issues. Following registration, participants were guided through Facebook's features, including how to search for friends, how to send a friend request, how to accept or deny a friend request, how to comment on others' Facebook pages, and how to browse through photos. Participants were also encouraged to *follow* relevant health websites, including *The Well Project*, a nonprofit organization dedicated to serving women and girls with HIV [35]. The instructor explained that such health websites periodically post relevant information, and guided participants on how to open posts of interest. Participants spent the remainder of the session independently navigating through their Facebook and email accounts.

Session 5

Session five was a review session incorporating all of the material learned in sessions 1 through 4. This session was intended to serve as a refresher course, and consisted primarily of the instructor asking individual participants to verbally and physically perform certain computer and Internet navigation functions. Participants were asked if they could: open a browser; conduct a Google search to find web content, images, and videos; and to find directions to their local library using Google Maps. Participants were then asked to reiterate the specific components of identifying a trustworthy website, open their email accounts to compose and reply to an email, and to navigate through their Facebook accounts to find health information of interest. The session concluded with participants receiving a certificate of completion for their efforts.

Settings and Participants

Get+Connected pilot testing took place at the same CBO in which the focus group was conducted. Of the 20 women who participated in the focus group, 12 participated in the intervention. We conducted three waves of pilot testing with each cohort consisting of four participants. Written informed consent was obtained from all participants. The study received IRB approval from Albert Einstein College of Medicine.

Data Collection

Quantitative data was collected from participants at baseline (immediately prior to session 1), intervention completion (immediately after session 5), and three months after completion of the intervention. Baseline self-report surveys were obtained using Audio Computer-Assisted Self-Interview (ACASI) technology on (1) sociodemographic and clinical characteristics, (2) technology device ownership and use, and (3) attitudes towards computers and the Internet along with frequency of Internet use. Follow-up surveys at intervention completion and at three months only collected data regarding attitudes towards computers and the Internet, and frequency of Internet use. During the study visits, two members of the study staff were available nearby to provide assistance with use of ACASI as needed. During the intervention sessions, we collected participants' verbal feedback about *Get+Connected.*

Measures

Sociodemographic and Clinical Characteristics

Sociodemographic characteristics included age, race (black/African American, white, Asian, Native Hawaiian or Pacific Islander, Native American or Alaskan Native, more than one race, or other), ethnicity (Hispanic or Latina), primary language (English, Spanish, French, Haitian Creole, Other, or don't know), and highest grade completed in school. Clinical characteristics included self-perceived health status (excellent/very good/good vs fair/poor), comorbid medical conditions, and time since HIV diagnosis.

Intervention Retention

We calculated the average number of women in attendance at each session.

Technology Device Ownership and Use

We asked participants to report whether they owned the following devices: desktop, laptop or notebook, mobile phone, electronic book, or tablet. For those who owned a mobile phone, we asked whether they had used their mobile phones to do the following: send or receive texts, send or receive email, access the Internet, use apps to track health, or to look up health or medication information.

Attitudes Towards Computers and the Internet

At baseline, intervention completion, and three months after completion of the intervention, we used the Attitudes Towards Computers and the Internet Questionnaire (ATCIQ) to assess participants' attitudes about computers and the Internet, which was adapted from the Attitudes Towards Computers Questionnaire [36] to include the Internet in addition to computers. The ATCIQ is comprised of 10 items, which include a 5-item computer/Internet interest subscale and a 5-item computer/Internet efficacy subscale. Responses for each item are ranked on a 5-point Likert scale ranging from *strongly disagree* (1) to *strongly agree* (5). Examples of questions include, "I know that if I worked hard to learn about computers/Internet, I could do well", "Computers/Internet are *not* too complicated for me to understand" and, "I think I am the kind of person who would learn to use a computer/Internet well." Potential total scores for the questionnaire range from 10 to 50, with a higher score indicating greater computer/Internet interest and/or efficacy. This tool has been recommended for use in socioeconomically disadvantaged demographics [18].

Internet Use

An *Internet user* was defined as an individual that had ever used the Internet or email (yes/no). At baseline, if the participant was an Internet user, they were asked about their Internet use over the past three months, including how many times they had used the Internet in general and for the following reasons: to email, to find general information, to search for health-related information, to search specifically for HIV-related information, to take part in chat rooms and online discussions with other people, to use social media networking sites, and to use Instagram. Participants' responses to these items could include any number. At intervention completion and three months postintervention, participants were asked the same questions about their Internet use for the previous month. For each time point, we created a composite Internet use measure that included the sum of all individual Internet measures for each participant.

Statistical Analyses

We examined descriptive statistics for all variables at baseline. For attitudes towards computers and the Internet, we calculated median composite ATCIQ scores for the study sample at baseline, at completion of the intervention, and at three months postintervention. To examine whether there was a trend in composite ATCIQ scores over time, as well as the two ATCIQ subscales, we conducted analyses using generalized estimating equations (GEEs). Similarly, for the composite Internet use score, we calculated the median number of times the Internet or related technology was used at baseline and follow-up time points. To examine whether there was a trend of use in the

composite measure of Internet use over time, we conducted analyses using GEEs. Due to our study's limited sample size, adjustment for covariates was not preformed. All analyses were conducted using SAS statistical software (SAS 9.4, SAS Institute, Inc., Cary, North Carolina).

Results

Characteristics of Participants

We enrolled 12 participants in the pilot study. Median age was 56 years (interquartile range [IQR]=52-63). All but one participant self-identified as black or African American (11/12, 91%) and two self-identified as Latina ethnicity (2/12, 17%). English was the primary language for all participants. Seven participants had completed high school or higher degree (7/12, 58%), and nine rated their health as good, very good, or excellent (9/12, 75%). Half of the participants (6/12, 50%) reported having hypertension and 42% (5/12) reported a chronic lung disease. Median time since HIV diagnosis for our sample was 25.5 years (IQR=15-33).

Retention in the Intervention

The average proportion of the study sample in attendance at each weekly session was 95% (range=75-100).

Technology Device Ownership and Use

At baseline, no participants reported owning a desktop computer or e-book (Table 1). One participant reported owning a laptop computer or notebook and another reported owning a tablet. In contrast, 83% (10/12) of participants owned a mobile phone and approximately half of these individuals used it for texting. Use of mobile phones for other activities was minimal.

Table 1. Technology device ownership and use (n=12).

Measure	n (%)
Own a desktop computer	0/12 (0%)
Own a laptop computer or notebook	1/12 (8%)
Own a mobile phone	10/12 (83%)
Use mobile phone to send or receive texts	5/10 (50%)
Use mobile phone to send or receive email	1/10 (10%)
Use mobile phone to access the Internet	1/10 (10%)
Use mobile phone for apps to track your health	1/10 (10%)
Use mobile phone to look up health or medical information	1/10 (10%)
Own an electronic book or e-book reader	0/12 (0%)
Own a tablet computer	1/12 (8%)

Attitudes Towards Computers and the Internet

There was a significant increase in composite ATCIQ scores over time. The median composite ATCIQ scores were 33.5 (IQR=30-34) at baseline, 35 (IQR=33-35) at intervention completion, and 36 (IQR=35-38) at three months postintervention (P=.008). For the ATCIQ computer/Internet interest subscale, there was also a significant increase over time (20, IQR=16.5-20.5 at baseline; 20, IQR=19-21 at intervention completion; and 23, IQR=20-25 at three months postintervention; P=.02). However, for the ATCIQ computer/Internet efficacy subscale, there was no significant change over time (13, IQR=11.5-14 at baseline; 14, IQR=13-15 at intervention completion; and 13, IQR=13-14 at three months postintervention; P=.40).

Internet Use

At baseline, only one participant reported having ever used the Internet or email (1/12, 8%). Among the 11 participants who had never used email or the Internet (11/12, 92%), the main reasons for not using these technologies were not knowing how to email or use the Internet (6/11, 55%) and not having access to a computer or similar device (4/11, 36%). All participants reported that in order to start using email or the Internet they would need someone to help them. Only three participants had asked a friend or family member to look something up or complete a task on the Internet for them (3/11, 27%). We did not find a significant trend in our composite Internet use measure over time. Our median composite Internet use measure at baseline was 0 (IQR=0-0), 1 (IQR=0-20) at intervention completion, and 0 (IQR=0-11.5) at three months postintervention (P=.61).

Participants' Impressions of Get+Connected

Qualitative data showed that participants expressed excitement and approval for the intervention. Participants expressed enthusiasm for being able to connect with family members using social media and email (eg, *"Now I can talk with my grandkids more often!"; "My son was so happy when he saw my [first] email!"*). Participants shared their eagerness to find old friends on social media (eg, *"I want to learn to use Facebook so I can find old friends."*), and also expressed interest in being able to keep up with technological trends (eg, *"I want to be able to keep up with the times"; "I told my son I'm going to learn how to use Google Maps!"*). These findings allude to the acceptability of *Get+Connected* among our study sample.

Discussion

Principal Results

We developed and pilot tested *Get+Connected*, an intervention to improve computer and Internet attitudes and Internet use among women living with HIV. *Get+Connected* provided instructions on how to use a computer, navigate the Internet, conduct basic general and health-related Internet searches, and connect with others on a social media website. We also provided library cards for participants to access computers at their local library. We found that most women in our study owned mobile phones, but not other electronic devices. Mobile phones were used primarily for texting rather than Internet use. At baseline, only one participant reported ever using the Internet. The main reasons cited for lack of Internet use included lack of digital literacy and computer/Internet access. We found that participating in *Get+Connected* was associated with an improvement in women's attitudes towards computers and the Internet over time. Specifically, interest in computers and the Internet increased over time; however, there was no significant change in computer and Internet efficacy. Additionally, Internet use did not increase over time.

There are several possible explanations for our findings regarding computer and Internet attitudes and Internet use. With regards to attitudes towards computers and the Internet, it is likely that exposure to computers and the Internet, and the instructions provided as part of *Get+Connected*, enabled participants to feel more comfortable and familiar with these technologies, thereby increasing computer and Internet interest. More computer and Internet use beyond that provided by the intervention may have been needed for participants to build greater confidence (ie, self-efficacy) in their ability to navigate computers and the Internet on their own. It is also conceivable that, due to living arrangements and limited physical mobility, providing information on how to use the Internet without increasing access to computers is insufficient to increase self-efficacy and actual Internet use. For example, many women had difficulty walking and the local library may not have been easily accessible to them. Additionally, the residential facility had only one working computer, and participants reported long wait times and restrictions on social media sites (including Facebook) which likely discouraged use. It is also possible that our small sample size may have precluded our ability to find a significant difference over time in our computer/Internet efficacy subscale and composite Internet use measure.

This pilot study of *Get+Connected* adds valuable information to the literature regarding computer and Internet use among individuals living with HIV. Previous research shows that the Internet can be a useful tool to improve the health of persons living with HIV. A study by Kalichman et al [12] demonstrated that an Internet skills training intervention for persons living with HIV improved Internet use for health, information, coping, and social support (compared to a control group). Another study found that increasing Internet health literacy for individuals living with HIV who have low literacy increases consumption of health information resources [24]. Unlike prior studies [37-40], our study focused specifically on HIV-positive women, a largely socioeconomically disadvantaged demographic group that faces unique health concerns and significant barriers to computer and Internet use. Therefore, this population may require specific interventions tailored to those needs. To our knowledge *Get+Connected* is the first intervention for persons living with HIV to include instructions in the use of social media that allows for peer-to-peer communication (ie, Web 2.0 technology). Social media, which can be leveraged to improve social support, has been shown to influence health outcomes among women with HIV [41,42].

Areas for Future Research

Due to the ubiquity of mobile phones, future research should consider this platform for computer and Internet training interventions for HIV-positive women. Study participants had difficulty accessing a computer as well as the Internet, indicating that they were likely limited in their ability to practice what they had learned. Using mobile phones for Internet training may help to facilitate greater participation and practice outside of the classroom. Additionally, specific attention should be given to the types of mobile phone plans that participants have, in order to assess the feasibility of this approach. However, Internet access remains a significant barrier to use for women living with HIV. As such, future research will need to explore innovative approaches to providing Internet access to individuals with limited socioeconomic resources. Future interventions of this type should consider providing a list of locations with free WiFi access (eg, libraries, other CBOs). However, it is likely that more widespread policies will be needed to enhance Internet access, such as providing free WiFi in public spaces, funding Internet access at CBOs, and equipping low-incoming housing with free computers and WiFi. Unlike previous Internet skills training interventions for persons with HIV [24,37-39], our intervention provided instructions in the use of a social networking site (Facebook), a potentially important platform for harnessing social support and providing useful health information for women living with HIV. Future studies should consider how best to use social networking sites to connect people living with HIV with one another, and with informational resources.

Limitations

There are important limitations to be considered in our study. First, our sample size was small and may have been underpowered to find an effect of the intervention on Internet use. However, it is important to note that this is a pilot study with the primary purpose of assessing the intervention's feasibility and preliminary efficacy. Second, due to the nature of the study and limited resources, increasing Internet access was not addressed. Further studies should consider developing ways to increase Internet access, which remains a prominent barrier to Internet use in this demographic group. Third, while we found a significant difference in participants' change in attitudes towards computers and the Internet over the follow-up period (as measured by the ATCIQ scale), there is no existing data on what would be considered a clinically meaningfully change in ATCIQ score; as such, we may need to be cautious in our interpretation of the intervention's potential effect. Fourth, participants lived onsite at the CBO where the intervention took

place and received weekly reminders to attend the *Get+Connected* sessions. Therefore, the high participation rate observed may not reflect the true acceptability of the intervention if participants had lived offsite from the intervention. Due to this limitation, our findings may not be generalizable to women with HIV who live in other settings. Lastly, our study did not include the evaluation of HIV-positive transgender women, which is a population that is also marginalized and lacks access to computer and Internet access. Future studies should consider the unique needs of this sociodemographic group and use the extant literature to develop interventions accordingly.

Conclusions

Studies show that the Internet can be a powerful tool for health promotion, yet there is a clear divide in Internet use along socioeconomic lines. Among women living with HIV, *Get+Connected* sought to address this gap by improving attitudes towards and, ultimately, use of the Internet with this specialized training curriculum. Results showed that compared with baseline, participation in the intervention was associated with an improvement in women's attitudes towards computers and the Internet over time. However, we did not find a change in participants' Internet use over time. Further research focused on enhancing Internet access and use among women living with HIV should address issues of computer and Internet accessibility, and test other potential platforms (eg, mobile phones) for delivering similar interventions.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

[PPT File (Microsoft PowerPoint Presentation), 1MB - resprot_v6i3e_app1.ppt]

Multimedia Appendix 2

[PPT File (Microsoft PowerPoint Presentation), 856KB - resprot_v6i3e_app2.ppt]

Multimedia Appendix 3

[PPT File (Microsoft PowerPoint Presentation), 642KB - resprot_v6i3e_app3.ppt]

Multimedia Appendix 4

[PPT File (Microsoft PowerPoint Presentation), 686KB - resprot_v6i3e_app4.ppt]

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Abbreviations

ACASI: Audio Computer-Assisted Self-Interview
ATCIQ: Attitudes Towards Computers and the Internet Questionnaire
CBO: community-based organization
GEE: generalized estimating equation
HIV: human immunodeficiency virus
IQR: interquartile range
IRB: Institutional Review Board
NIH: National Institutes of Health

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Protocol

Workability and Muscle Strength in Patients With Seropositive Rheumatoid Arthritis: Survey Study Protocol

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Abstract

Background: Rheumatoid arthritis (RA) and other rheumatic conditions not only fundamentally affect patients' quality of life and physiological needs but are also negatively associated with work ability. The costs of poor work ability, which, in sum, are more than treatment costs, pose an economic burden to society and patients. Work ability in RA appears to be multifactorial; symptoms such as pain, swelling, and stiffness play a major role, as these directly affect functional disability. Also, RA patients typically suffer from reduced muscle strength. Lower extremity function and grip strengths especially impair their quality of life. However, the role of muscle strength and disease activity as determinants of work ability have not yet been studied.

Objective: The primary objective of this study is to compare work ability in working-age participants with seropositive RA and with high and low disease activity; the secondary objective is to evaluate the association of muscle strength, functional ability, and frailty with work ability.

Methods: This monocentric cross-sectional study will be conducted at a rheumatologic outpatient clinic and day hospital with approximately 100 seropositive RA patients aged <65 years. A clinical disease activity index as a measure for rheumatoid disease activity will be assessed during the patients' routine visits at the clinic. Work ability, frailty, and functional disability will be evaluated with (self-reported) questionnaires as well as with physical tests (Work Ability Index/Score; Health Assessment Questionnaire Disability Index; Survey of Health, Ageing, and Retirement in Europe Frailty Instrument; Short Physical Performance Battery). Muscle strength will be determined with dynamometer measurements of isometric hand grip strength and quadriceps femoris muscle contraction strength. Sleep quality (Medical Outcomes Study Sleep Scale) and sexual functioning as physiological needs will additionally be determined with self-reported questionnaires.

Results: For this study funding has already been awarded and enrollment has been completed. Data are currently being evaluated.

Conclusions: This study will evaluate the association of work ability with modifiable parameters such as muscle strength and functional ability. It will provide further insights into work ability in RA and its associated risk factors. Any evidence of association will motivate further research, and the findings might encourage interventions focused specifically on improving muscle strength and lower extremity function to positively affect work ability.

Trial Registration: ClinicalTrials.gov (NCT02581852); https://clinicaltrials.gov/ct2/show/NCT02581852 (Archived by WebCite at http://www.webcitation.org/6oNcelHtQ)

(JMIR Res Protoc 2017;6(3):e36) doi:10.2196/resprot.6449

KEYWORDS

rheumatoid arthritis; work ability; frailty; muscle strength; functional disability; lower extremity function; sexual functioning

Introduction

Background

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that is most prevalent in individuals aged 40 years and above. RA affects about 1% of the world population, and the risk of developing RA is markedly higher in women. This disease is the most common form of chronic joint inflammation and causes joint pain, swelling, reduced muscle strength, and, as a consequence, impaired physical function [1]. In our experience, due to physical limitations, RA patients often suffer from impairment in their social life and their work life. Working is an important predictor of physical health–related quality of life in arthritis patients [2], and reduced muscle strength can cause physical limitations and a more frail condition, which in turn might have an impact on work ability. Beside obvious symptoms that directly cause physical limitations, physicians less often pay attention to physiological needs such as sleep and sexual functioning, which are also negatively associated with RA and in turn might unfavorably impact work ability.

Rheumatoid Arthritis and Work Ability

Chronic diseases such as RA are negatively associated with work ability. Work ability, as described by Ilmarinen from the Finnish Institute of Occupational Health, is the interaction of individual determinants (health, competence, and attitudes) and the work environment [3]. It is determined by an individual's perception of the demands at work and the ability to cope with them [4]. Although RA-induced work disability rates seem to decrease because of new therapeutic concepts, RA is still a fundamental burden for many patients [5]. The costs of work disability in rheumatic conditions are high, generally higher than the treatment costs [6]. Furthermore, from the patients' perspective, work disability significantly affects their basic income [7].

Work disability in RA appears to be multifactorial; symptoms such as pain, swelling, and stiffness play a major role, as they directly affect functional disability [8]. RA is associated with loss of muscle mass and diminished strength. In healthy individuals, only a weak association between muscle strength and workability could be found [9]. The influence of strength on the work ability of RA patients has yet to be determined.

Rheumatoid Arthritis and Muscle Strength

Body composition, particularly the amount of lean mass in the arms and legs, is associated with disability in RA patients. A large number of RA patients suffer from an increased loss of muscle mass with a significant impact on these patients' quality of life [10]. This condition is commonly known as rheumatoid cachexia and has been reported in two-thirds of all RA patients, including patients with stable RA [11,12]. In geriatric patients, cachexia is associated with higher-than-normal concentrations of tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6; a reduction in these proinflammatory cytokines is associated with weight gain [12,13]. The loss of body cell mass in RA patients is associated with proinflammatory cytokine–induced altered energy metabolism and intake despite a theoretically adequate diet [14,15].

In an x-ray computed tomography–based study, RA patients had a significantly higher body mass index and fat area but lower muscle area, muscle density, and muscle strength than healthy individuals. Furthermore, a higher degree of joint destruction and disease activity were shown to be associated with higher muscle deficits and impaired muscle strength [16]. Stucki et al [17] found that in patients with RA quadriceps muscle strength explained 12% of the variance in the self-reported activities of daily life, and women with RA were reported to have 20% lower quadriceps strength than the controls [18]. Isotonic and isometric hand exercise in RA patients can decrease pain and disease activity and increase muscle strength and function as well as quality of life [19]. Hand grip strength was shown to discriminate between various disease states of RA and seems to return to near-normative level when the disease is in remission [20].

Rheumatoid Arthritis and Sleep

Most patients with RA experience insomnia, general fatigue, and mental fatigue, which negatively affect their physical and cognitive functioning and health. Arthritis pain can lead to sleep deprivation and a lack of sleep, which, in turn, contribute to increased pain and fatigue [21-24]. Poor sleep has also been shown to negatively influence work ability in otherwise healthy individuals [23].

Rheumatoid Arthritis and Sexual Functioning

All aspects of life may be affected by RA. Pain, stiffness, and fatigue may impair not only functional disability but also sexual functioning in RA patients. As summarized by a recent review, aside from functional problems, depression, anxiety, a negative body image, reduced libido, and the application of certain drugs can negatively influence sexual activities [25].

Rheumatoid Arthritis and Frailty

Frailty, as defined by Fried et al, refers to a state of increased vulnerability to external and internal stressors caused by a reduction in physiological reserves. It has been described as a clinical phenotype of unintentional weight loss, low energy, slow walking speed, low physical activity, and low grip strength (weakness). The presence of 3 out of 5 of these criteria indicates frailty, and the presence of 1 or 2 indicates a prefrailty state [26-28]. Frailty has been associated with a higher risk of adverse health outcomes, mortality, hospitalization, and functional impairment [26,29,30]. Several studies have shown a heightened inflammatory state in frail adults [31], and similar to other markers of frailty, gait speed has been shown to be associated with elevated levels of inflammation markers such as C-reactive protein (CRP), IL-6, and TNF-α [32].

The population of elderly and frail individuals with RA is increasing [24]. However, although older people are more likely to develop long-term illnesses, muscle loss, and reduced

strength, age is not the sole predictor of frailty, and it may occur in younger patients [33]. Generally, RA patients appear to be more prone to frailty because loss of muscle mass and an increase in proinflammatory cytokines are clinical characteristics that are also present in young RA patients. The association of the frailty of young RA patients and work ability has yet to be examined.

Aims and Objectives

The primary objective is to assess work ability in patients with seropositive RA in the working age and the association of work ability with disease activity (high, medium, low, or remission). The secondary objectives are to assess the association of muscle strength, lower extremity function, functional ability, and frailty with work ability in RA and determine the association of disease activity with selected physiological needs (sleep quality, sexual functioning) in RA.

Methods

Study Design

This study will be conducted as a monocentric cross-sectional study in seropositive RA patients at the rheumatology outpatient clinic and ambulatory day clinic of the Second Medical Division of the Sozialmedizinisches Zentrum (SMZ)-Süd, Vienna, Austria. Eligible patients will be consecutively included during an expected period of 1 year. Ethical review committee approval was obtained from Gemeinde-Wien (EK 15-173-0915). The study is registered at ClinicalTrials.gov [NCT02581852].

Study Population

The study will involve 100 patients of working age between 18 and 65 years with seropositive RA according to 2010 European League Against Rheumatism classification. Eligible patients will be identified by staff members, and eligibility will be confirmed by the physician in charge at the outpatient or day clinic. Written informed consent will be obtained from each patient before enrollment. Patients who do not wish to sign the informed consent, are unable to follow advice for physical measurements and understand interview questions, and those with severe comorbidities will be excluded from the study. Questionnaires will be provided in German, English, Turkish, and Serbo-Croatian. Translations will be provided by Frauengesundheitszentren-Integration and Health Center (SMZ-Süd).

Sample Size

The sample size was calculated to determine the difference in work ability between patients with high versus low disease activity. We estimate the percentage of patients with good work ability to be 40% in patients with high disease activity and 80% in patients with low disease activity. Furthermore, we estimate that 70% of the included participants will have a low disease activity. With an alpha risk of .05 and a beta risk of .2 accepted in a 2-sided test, 71 patients need to be included (results were obtained with nQuery Advisor 7.0, Statcon). With a 30% rate of loss assumed (because of noncompliance during physical tests, lack of understanding, or refusal to participate), a total of 100 included patients will be required.

Data Collection and Procedures

Demographic, clinical data, and disease activity will be assessed through clinical examination and administration of an interview questionnaire. The demographic characteristics include gender, age, marital status (married/common law, single/widowed/divorced), highest level of education (compulsory schooling, secondary school graduation, higher education), and type of occupation.

Disease-specific clinical characteristics include disease duration (months) and current medication use for each of the following categories: analgesics/nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, biologic agents (biologicals), and drugs for other medical conditions.

Pain will be assessed via a visual analog scale (VAS), a unidimensional measure of pain intensity that has been widely used in diverse adult populations, including those with rheumatic diseases. The VAS consists of a 10 cm line anchored by verbal descriptors (1=no pain at all, 10=maximum pain) [34]. The patient will be asked to place a line perpendicular to the VAS line to indicate his or her current pain intensity.

Overall disease activity will be measured with the Clinical Disease Activity Index (CDAI). The CDAI is validated and widely used [35], with the scoring done as per the following formula: CDAI = SJC-28 + TJC-28 + PGA + EGA, where SJC-28 is the Swollen 28-Joint Count (shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints including thumb interphalangeal joint, knees), TJC-28 is the Tender 28-Joint Count, PGA is the Patient Global Assessment (patient's self-assessment of the overall RA disease activity on a scale of 1 to 10, where 10 is the maximal activity), and EGA is the Evaluator's Global Assessment (evaluator's assessment of the overall RA disease activity). As proposed by the American College of Rheumatology 2008, the CDAI score will be interpreted as follows: remission = CDAI ≤ 2.8, low disease activity = CDAI > 2.8 and ≤ 10, moderate disease activity = CDAI > 10 and ≤ 22, and high disease activity = CDAI > 22.

Laboratory assessments include CRP (mg/dL), IL-6 (pg/mL), and TNF-α (ng/mL). For the detection of IL-6 and TNF-α, high-sensitivity enzyme-linked immunosorbent assay will be used, assayed in duplicates. The CRP will be measured with the patients' routine laboratory assessments. Blood samples will be analyzed at the Institute for Laboratory Medicine of the SMZ-Süd, Vienna, Austria.

Primary Outcome

The primary outcome is self-reported work ability measured by the Work Ability Index (WAI), the most commonly used instrument to assess work ability, with an adequate test-retest reliability [36]. The WAI is a questionnaire consisting of 7 subscales: (1) current work ability compared with the lifetime best, (2) work ability in relation to the demands of the job, (3) number of current diseases diagnosed by a physician, (4) estimated work impairment because of disease, (5) sick leave during the past 12 months, (6) own prognosis of work ability 2 years from now, and (7) mental resources. The cumulative index of WAI ranges from 7 to 49 points, divided into the following

4 categories: poor (7-27 points), moderate (28-36 points), good (37-43 points), and excellent work ability (44-49 points) [37-39].

The methodological problem with using the WAI in unemployed patients is that most points of the self-evaluation reference to the current work setting. Thus, for unemployed and early retired patients, only 1 dimension of WAI, the Work Ability Score (WAS), will be assessed. The WAS comprises only the first WAI question: work ability compared with the lifetime best.

Justification on the use of WAS as 1 single question is based on previous studies that showed a high correlation between WAI and WAS [40,41]. As proposed by Gould et al [42], the classification of WAS will be conducted according to WAI as follows: poor (0-5 points), moderate (6-7 points), good (8-9 points), and excellent work ability (10 points).

Secondary Outcomes

Muscular Strength Measurement

Muscle strength measurement will be performed by a trained sport scientist at the Institute of Physical Medicine situated adjacent to the rheumatologic clinic.

Musculus Quadriceps Femoris Maximum Voluntary Contraction Strength

Quadriceps muscle strength will be measured with an isokinetic dynamometer. The patients will sit straight with 90° flexion in the hips and with fixed hip and thigh support and arms crossed. The ankles will be fixed in a flexed position to the dynamometer, and a measuring box (Chatillon, Ametek Inc) is connected to the ankle via a length-adjustable rope. The patient will be instructed to perform 1 maximal voluntary contraction of the quadriceps muscle. Strength will be assessed 3 times for both legs with a 2-minute break between measurements. The mean value of both legs will be used in the statistical analysis.

Maximal Voluntary Isometric Hand Grip Strength

The maximum grip strength will be measured with a portable Jamar hydraulic hand dynamometer (Patterson Medical). The patients will be examined in a standard position, in which they sit upright with their upper arm adducted and the elbow flexed at 90°. The dynamometer will be used according to the instructions in the operating manual. The dynamometer will be placed in a patient's hand, and after the instruction is given, 3 maximum voluntary grip strength contractions will be performed with each hand. Measurements will be done in an alternating order with a 2-minute break between measurements. The mean value of each hand will be recorded for analysis.

Functional Disability

The Health Assessment Questionnaire Disability Index (HAQ-DI) will be used to assess the extent of patients´ self-reported functional disability. The HAQ-DI has been used to measure functional status in RA in multiple settings and languages since 1980, and it has shown good reliability and validity [43]. It examines patients' usual abilities in using their regular equipment during the past week. The scoring of the HAQ-DI is patterned after the functional classes of the American Rheumatism Association/American College of Rheumatology. A total of 20 questions are included in the following 8 categories of functioning: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities.

Self-reported difficulties to perform these activities are scored on a scale from 0 to 3, representing normal (no difficulty) (0), some difficulty (1), much difficulty (2), and unable to do (3). For any component question, the highest score determines the score for that respective domain. The overall disability index is a value between 0 (no functional disability) and 3 (severe functional disability), representing the average score across the domains [44].

Survey of Health, Ageing, and Retirement in Europe Frailty Instrument

Frailty will be assessed with the Survey of Health, Ageing, and Retirement in Europe Frailty Instrument (SHARE-FI). This instrument was developed on the basis of the results of the Survey of Health, Ageing and Retirement in Europe and serves as a rapid measurement tool with good predictive validity. The assessment comprises 5 variables: grip strength measurement and 4 questions related to weakness, exhaustion, slowness, and activity level. With the use of the 5 variables, DFactor scores will be calculated with the gender-specific SHARE-FI formula. For each participant, the frailty score will be computed, and the participants will then be categorized as nonfrail, prefrail, or frail [45].

Short Physical Performance Battery

Lower extremity function will be measured with the Short Physical Performance Battery (SPPB). The SPPB is a group of measures including gait speed, chair stand, and balance tests. For each test, a 5-level categorical score will be assessed, with 0 representing inability to complete the test and 4 representing the highest level of performance. The summary score ranges from 0 (worst performance) to 12 (best performance). The SPPB has been shown to have good predictive validity, has been used in the RA population before, and can be used as a predictive tool for possible disability and mortality in older people [46-49].

Medical Outcomes Study Sleep Scale

The patients' quality of sleep will be assessed with the Medical Outcomes Study Sleep Scale (MOS-SS) questionnaire, which was created as a part of the Medical Outcomes Study, a large public health initiative that also developed practical tools for the routine monitoring of patient outcomes [50].

The MOS-SS is a 12-item self-report questionnaire involving a retrospective assessment over the past 4 weeks. The MOS-SS measures 6 sleep dimensions: (1) initiation (time to fall asleep in minutes), (2) quantity (hours of sleep each night), (3) maintenance, (4) respiratory problems, (5) perceived adequacy, and (6) somnolence. The last 4 items will be assessed via a 6-item scale ranging from "all the time" to "none of the time" [51].

The questionnaire yields 2 sleep problem indexes and 6 scores, of which sleep problem indexes I and II and the sleep disturbance scale were shown to have acceptable validity in RA patients [52]. Furthermore, the MOS-SS has been applied in several arthritis studies, and its good reliability and validity have been established [53]. Additional questions will assess the

significance of pain in sleeping difficulties and the frequency of pain and sleep medication use.

Sexual Functioning

Sexual functioning will be measured via a self-assessment questionnaire individually designed for this study. Standardized questionnaires on sexual functioning such as the questionnaire for screening sexual dysfunctions or gender-focused questionnaires such as the Female Sexual Function Index are extensive and very detailed. For questions related to sexuality, people tend to react apprehensively, so data collection (completion of the questionnaires) will be conducted in the rheumatology outpatient department (not as an online or mail survey). A short screening tool that focuses on the main problems that RA patients face with regard to sexual function was created.

Based on a recent review [25] and a multicenter study [54] on the impact of RA on sexual function, the questionnaire was designed consisting of 2 sections addressing sexual disability (difficulties in performing sexual intercourse), represented by question 1, and sexual drive (reflected in sexual desire and satisfaction), represented by questions 2 to 5. Scoring ranges from 1 to 10, and anchor points are set according to the question. The overall sexual functioning score ranges from 5 points (poor sexual functioning) to a maximum of 50 points.

Statistical Analysis

All statistical computations will be performed with SPSS version 22.0.2 (IBM Corp). The primary hypothesis of the study, "A difference in work ability and muscle strength exists in patients with high versus low disease activity," will be tested with a Pearson chi-square test. For the descriptive statistics, mean values will be calculated for continuous variables, and categorical variables will be presented in percentages. Continuous parameters will be checked for normal distribution (Kolmogorov-Smirnov test, Levene test, histogram, and Q-Q plot check), and an unpaired Student *t* test will be performed, as appropriate. Otherwise, the Mann-Whitney U test will be used to identify differences between patients with high versus low disease activity. For categorical parameters, a Pearson chi-square test or Fisher exact test will be used if the cell count is <5. Binary logistic regression will be used to evaluate the impact of frailty, functional ability, and muscle strength on work ability. For metric data, Pearson correlation or Spearman rank correlation (given outliers or nonlinear but monotone associations) will be used to evaluate associations of interest. A *P* value of <.05 will be considered statistically significant for all tests.

Results

For this study, funding has already been awarded and enrollment has been completed. Data are currently being evaluated.

Discussion

Summary

This cross-sectional study was designed to evaluate work ability in a population of seropositive RA patients and its association with RA disease activity, muscle strength functional disability, lower extremity function, and frailty. This study will also assess the quality of sleep and sexual functioning in RA and the respective association of these factors with disease activity.

Implications for Research and Clinical Practice

On the basis of the large number of people affected, RA not only lowers patients' quality of life but also poses an economic burden to both patients and society in general [55]. The direct health care–related costs of RA are dominated by in-patient care, but the total costs are found to be mainly related to work disability and temporary or permanent loss of work [55,56].

This study will allow the estimation of the rates of RA patients at risk for incapacity for work and will evaluate the association of work disability with modifiable parameters such as muscle strength and functional ability, which has not been investigated in RA before. It will provide further insights into work ability in RA and its associated risk factors. Any evidence of association may motivate further research, and the findings might encourage interventions focused specifically on improving muscle strength and lower extremity function to positively affect work ability. The outcomes of this study may also motivate clinicians to screen for work ability and modifiable parameters in the RA population.

Aside from work ability, quality of sleep and good sexual functioning beneficially affect one's quality of life [57]. This study will provide insights into the rates of RA patients with impaired sleep and sexual dysfunction and the association of these functions with RA disease activity. The findings may encourage future research and interventions for the improvement of RA-associated problems, which tend to be poorly addressed in routine care. A screening tool for sexual functioning in RA patients was used in this study, and the applicability of the tool will be evaluated.

Strengths and Limitations

The study is limited by its cross-sectional design, which allows us to draw a conclusion about association but not causality. However, as we intend to analyze multiple outcomes and potential risk factors, we considered this approach to be ideal for generating hypotheses for further interventional approaches or longitudinal studies. Another potential limitation might be the pain-related noncompliance of patients during physical measurements. High disease activity and pain may possibly lead to some degree of bias in the results.

An advantage of this study is the availability of patients from various settings. Through recruitment at an outpatient clinic and a day clinic, the whole spectrum of different disease activities can be investigated. All study-related measures can be performed in short time periods without the necessity of a second appointment, thereby assuring high patient compliance and a marginally low drop-out rate.

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Conflicts of Interest

None declared.

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Abbreviations

CDAI: Clinical Disease Activity Index
CRP: C-reactive protein
EGA: Evaluator's Global Assessment
HAQ-DI: Health Assessment Questionnaire Disability Index
IL: interleukin
MOS-SS: Medical Outcomes Study Sleep Scale
PGA: Patient Global Assessment
RA: rheumatoid arthritis
SHARE-FI: Survey of Health, Ageing and Retirement in Europe–Frailty Instrument
SJC-28: Swollen 28-Joint Count
SMZ: Sozialmedizinisches Zentrum
SPPB: Short Physical Performance Battery
TJC-28: Tender 28-Joint Count
TNF-α: tumor necrosis factor-α
VAS: visual analog scale
WAI: Work Ability Index
WAS: Work Ability Score

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Protocol

Gender-Specific Combination HIV Prevention for Youth in High-Burden Settings: The MP3 Youth Observational Pilot Study Protocol

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Abstract

Background: Nearly three decades into the epidemic, sub-Saharan Africa (SSA) remains the region most heavily affected by human immunodeficiency virus (HIV), with nearly 70% of the 34 million people living with HIV globally residing in the region. In SSA, female and male youth (15 to 24 years) are at a disproportionately high risk of HIV infection compared to adults. As such, there is a need to target HIV prevention strategies to youth and to tailor them to a gender-specific context. This protocol describes the process for the multi-staged approach in the design of the MP3 Youth pilot study, a gender-specific, combination, HIV prevention intervention for youth in Kenya.

Objective: The objective of this multi-method protocol is to outline a rigorous and replicable methodology for a gender-specific combination HIV prevention pilot study for youth in high-burden settings, illustrating the triangulated methods undertaken to ensure that age, sex, and context are integral in the design of the intervention.

Methods: The mixed-methods, cross-sectional, longitudinal cohort pilot study protocol was developed by first conducting a systematic review of the literature, which shaped focus group discussions around prevention package and delivery options, and that also informed age- and sex- stratified mathematical modeling. The review, qualitative data, and mathematical modeling created a triangulated evidence base of interventions to be included in the pilot study protocol. To design the pilot study protocol, we convened an expert panel to select HIV prevention interventions effective for youth in SSA, which will be offered in a mobile health setting. The goal of the pilot study implementation and evaluation is to apply lessons learned to more effective HIV prevention evidence and programming.

Results: The combination HIV prevention package in this protocol includes (1) offering HIV testing and counseling for all youth; (2) voluntary medical circumcision and condoms for males; (3) pre-exposure prophylaxis (PrEP), conditional cash transfer (CCT), and contraceptives for females; and (4) referrals for HIV care among those identified as HIV-positive. The combination package platform selected is mobile health teams in an integrated services delivery model. A cross-sectional analysis will be conducted to determine the uptake of the interventions. To determine long-term impact, the protocol outlines enrolling selected participants in mutually exclusive longitudinal cohorts (HIV-positive, PrEP, CCT, and HIV-negative) followed by using mobile phone text messages (short message service, SMS) and in-person surveys to prospectively assess prevention method uptake, adherence, and risk compensation behaviors. Cross-sectional and sub-cohort analyses will be conducted to determine intervention packages uptake.

Conclusions: The literature review, focus groups, and modeling indicate that offering age- and gender- specific combination HIV prevention interventions that include biomedical, behavioral, and structural interventions can have an impact on HIV risk reduction. Implementing this protocol will show the feasibility of delivering these services at scale. The MP3 Youth study is one of the few combination HIV prevention intervention protocols incorporating youth- and gender-specific interventions in one delivery setting. Lessons learned from the design of the protocol can be incorporated into the national guidance for combination HIV prevention for youth in Kenya and other high-burden SSA settings.

Trial Registration: ClinicalTrials.gov NCT01571128; http://clinicaltrials.gov/ct2/show/NCT01571128?term=MP3+youth&rank=1 (Archived by WebCite at http://www.webcitation.org/6nmioPd54)

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KEYWORDS

HIV; combination prevention; Kenya; youth; PrEP; VMMC; mobile health; family planning; cash transfer; biometrics

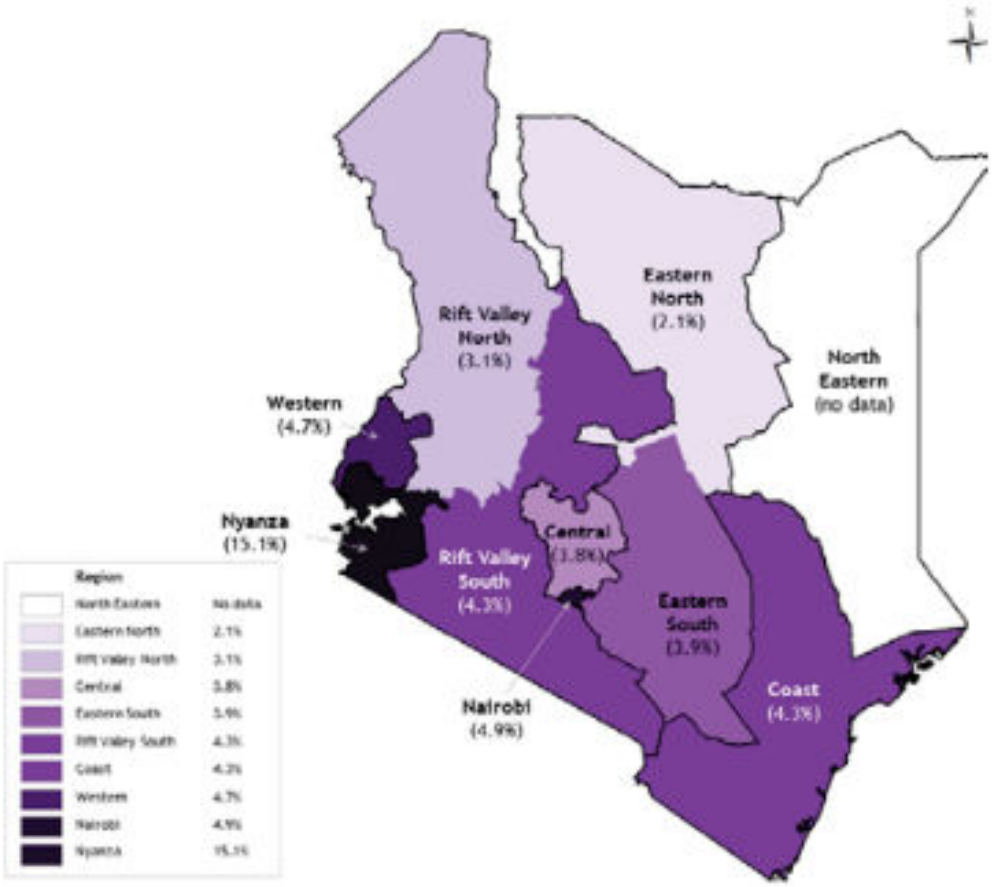
Introduction

Nearly three decades into the epidemic, sub-Saharan Africa (SSA) remains the region most heavily affected by human immunodeficiency virus (HIV), with nearly 70% of the 34 million people living with HIV globally residing in the region [1-4]. Youth aged 15 to 24 years bear the highest burden of new infections, and in SSA, account for 80% of the 1.9 million new infections each year [5,6]. Young females are twice as likely as their male counterparts to be infected [4,6], making females 15 to 24 years in SSA the most at-risk group for HIV infection. The incidence and prevalence of HIV among youth in SSA remains high [4] and literature shows that programs for youth are often vertical, uncoordinated, and not evidence-based [7,8]. The delivery of proven interventions needs to account for the complexity of the interconnected drivers of HIV, especially among youth, necessitating combination prevention packages relevant to the target population(s). We set out to develop a protocol for a cross-sectional and longitudinal pilot study of a sex- and gender-specific combination HIV prevention approach in western Kenya for youth called "MP3 Youth." The focus of this paper is to outline the development details of the protocol, which includes a multi-method approach for designing a pilot study of combination HIV prevention.

HIV in Kenyan Youth

The study setting for this protocol is Kenya, where national HIV prevalence is 5.6% among individuals aged 15 to 49 years [9,10]. With the exception of the Nyanza Province where the study will take place, HIV prevalence in Kenya has declined [9-11]. The prevalence of HIV varies markedly by region, and ranges between 2% to 15% (Figure 1) [11,12]. Children and youth aged 0 to 24 years represent 55.6% of Kenya's population [12] and surveillance data indicates that most new HIV infections occur among youth 15 to 24 years of age [11,12]. Females between the ages of 20 to 24 have a risk of HIV infection, four times higher than males of the same age [10-12]. The 2012 Kenya AIDS indicator Survey (KAIS) shows that nationally the prevalence of HIV among females aged 15 to 19 is 1.1%, a reduction from the 3.5% reported in 2007. The HIV prevalence for females aged 20 to 24 years is 4.6% (previously 7.5%) [12]. The prevalence of HIV among males is much lower than females of the same age group. HIV prevalence among males aged 15 to 19 and 20 to 24 years old is 0.9% and 1.3%, respectively [10,11].

Figure 1. Map of HIV prevalence in Kenya (KAIS, 2014).



Theoretical Basis for Combination HIV Prevention Package

The evidence-based methodology for the MP3 Youth combination intervention protocol is guided by a multi-theoretical approach grounded in social ecological theory (Figure 2) [13,14]. The combination prevention approach needs to address behavioral, biomedical, and structural levels, and tailor interventions to address each level according to age and sex. MP3 Youth focuses on the context in which an individual finds him or herself socially and physiologically. The prevention framework includes reducing health risks associated with age, gender, and biological susceptibility. HIV prevention requires not only equipping youth with knowledge, skills, risk perception, condoms, and positive social norms, but also instituting systems change [15]. Systems change includes policies that prioritize youth sexual and reproductive health across sectors. MP3 Youth builds upon these psychosocial determinants of HIV prevention and consolidates the prominent themes into the MP3 Youth framework. The social ecological theory guides MP3 Youth to address the gender-specific risks across this broad spectrum of factors from individual to structural (including economic factors) [13,14]. The final package of interventions to be selected for inclusion in the protocol meets all aspects of the social ecological framework.

The interventions will be offered in a mobile health setting. Mobile health events involve determining an appropriate place in the community and setting up a temporary health center using vans, tents, or other temporary structures. Mobile events are effective for reaching rural and other hard-to-reach populations. The mobile health setting will take into account the socio-political and community context of the participants. This context will drive the location, time, and manner in which the interventions are offered.

The four aims of the MP3 Youth study are shown in Textbox 1. Each of the aims has specific analytic objectives and outcomes. This paper will focus on the development of the objectives and outcomes for Aim 3 (the pilot study). We hypothesize that by strategically designing and piloting a gender- and youth-specific combination HIV prevention intervention, we can learn important lessons about scaling up combination prevention to curb the HIV epidemic among young people.

Textbox 1. Aims of the MP3 Youth study.

Aim

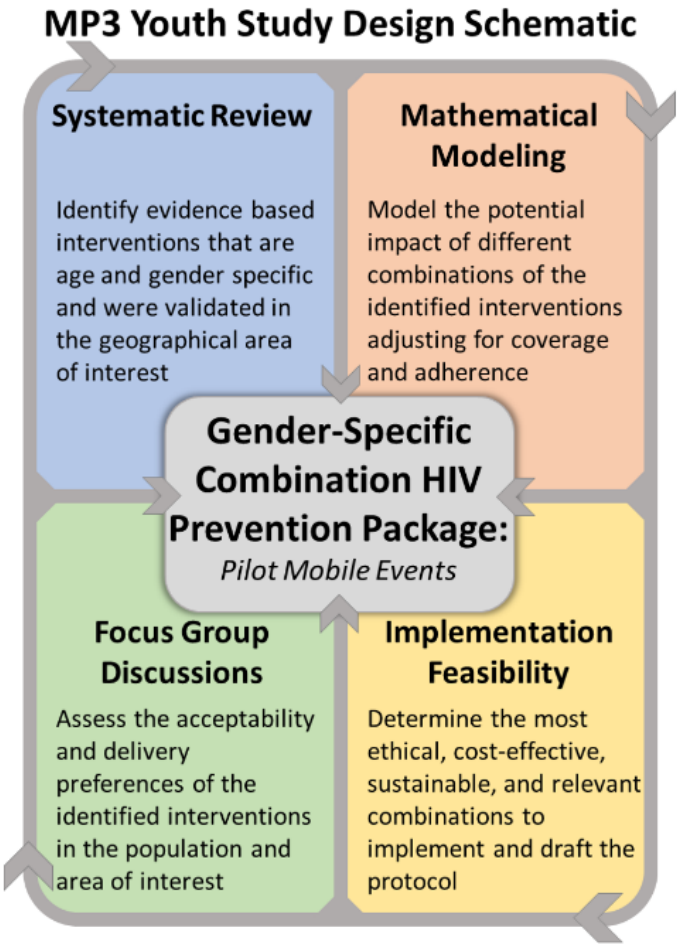
- Aim 1: Select a package of interventions by identifying epidemiologic targets for HIV prevention among youth in sub-Saharan Africa through a systematic review, meta-analysis, and qualitative data collection.
- Aim 2: Perform mathematical modeling for selection of interventions with the highest population impact.
- Aim 3: Develop a protocol and implement a pilot study of a gender-specific combination HIV prevention package for youth (aged 15 to 24) in western Kenya.
- Aim 4: Derive lessons from the pilot for future combination HIV prevention evaluations.

Figure 2. Social ecological framework (Centers for Disease Control and Prevention, 2013).

Methods

MP3 youth is a mixed-methods study incorporating quantitative, qualitative, and modeling approaches, and capturing cross sectional and longitudinal data elements. A multi-method process was undertaken to design the MP3 Youth combination HIV prevention pilot study protocol (Aim 3) (Figure 3). To determine the most effective evidence-based interventions for youth HIV prevention in SSA, we first conducted a systematic review of the literature. In addition to the evidence, the study collects formative data through focus groups to determine the knowledge, attitudes, and preferences of youth about which interventions are most acceptable, as well as by whom and where they would like them to be delivered. Mathematical modeling will be used to determine the impact of the interventions, considering coverage and adherence levels, as well as to determine the most cost-effective combination of interventions (Figure 3). All of these methods are useful for determining the best "package" of gender-specific interventions during the intervention design phase. The steps for developing the multi-method protocol for the field pilot study (Aim 3) are outlined below.

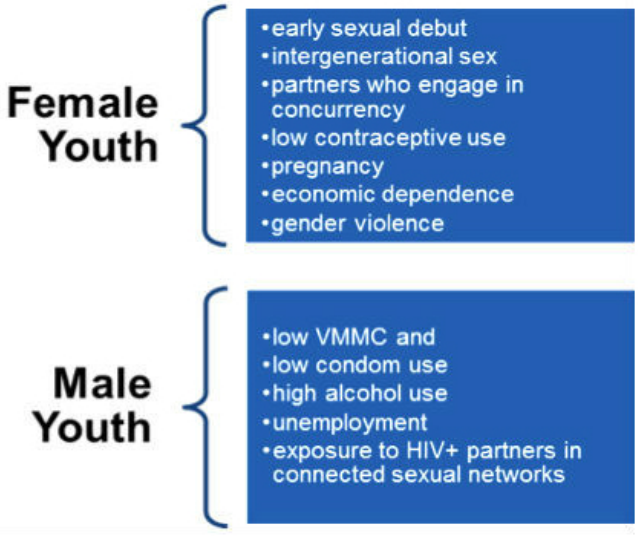
Figure 3. MP3 Youth Study Design Schematic.



Aim 1: Review and Selection of Package Components Procedures

To develop the protocol, our team compiled a priori knowledge of what drivers may be most important to target for HIV prevention among SSA youth (Figure 4). These include early initiation of sex, lack of circumcision, alcohol abuse, power structure (intergenerational sex, gender violence), lack of HIV serostatus knowledge, low contraceptive use, and high rates of unintended pregnancy. Our approach was to understand not just modifiable drivers of HIV transmission among youth, but also to lay out a replicable strategy for assessing whether there were sufficient evidence-based interventions to address each driver. We constructed a framework with "strength of evidence" thresholds to determine whether to include specific interventions in the combination package for the protocol.

Figure 4. Key drivers of youth HIV risk in sub-Saharan Africa.



Systematic Review

The development of the combination package included a systematic review and meta-analysis where we conducted a systematic review using standardized procedures [16]. The review question (gender-specific modifiable drivers of the epidemic and evidence-based interventions among youth) yielded a critical base of evidence that fed into the development of the focus group discussions, the mathematical modeling, and the overall protocol design. While a detailed account of the methods and results of the systematic review will be reported in a separate publication, they were mentioned here to show the groundwork for the pilot study protocol elements.

Focus Group Discussions

The development of this protocol includes an appreciation of the sociocultural and community context in which youth experience. Community context is critical to a comprehensive protocol that will lead to successful pilot study implementation. To assess the acceptability of the components in the pilot study protocol, we collected qualitative data using focus groups with youth and community leaders to assess HIV risk and protective factors and the best location and format for the delivery of the combination prevention interventions. Topic guides for these groups were informed by the systematic review and key stakeholders. The detailed methods and results of the focus group discussion will be outlined in a separate publication. The description of this aim here is intended to illustrate the foundation upon which the pilot study protocol was built.

Aim 2: Mathematical Modeling for Component Selection

Components from the systematic review and focus group discussions were fed into the development of a mathematical model that was used to triangulate the appropriateness and potential effectiveness of the interventions to be included in the pilot study protocol. Results of the systematic review and epidemiologic analyses were used to provide the modeling parameters. Mathematical modeling was used to assist in selecting components of intervention packages most likely to have complementary or synergistic effects. The modeling provided estimated impact and costs of strategies that focus interventions on different sub-populations according to sex, age, risk behavior, and other factors. An appropriate model structure was agreed upon following detailed consultations with the study team and reviews of the modeling literature. The model incorporated sex- and age- specific coverage to long-term interventions and risk compensation that could undermine intervention package efficacy over time. The model was designed, constructed, solved, and analyzed using modern computational software (MathWorks, MATLAB) using techniques developed by Hallett et al [17]. A user-friendly toolkit was built using MATLAB and several stakeholders were trained on how to use the modeling tool for intervention selection and program planning.

The model will be continuously updated with information generated during the implementation of the pilot study to produce more refined and robust projections of both impact and cost-effectiveness. Model projections were fed into study design considerations in Aim 3 (pilot study) and Aim 4 (the effectiveness trial). The full details of the methods and results of the modeling will be reported in another paper. The inclusion of the modeling here is intended to show the process for finalizing the component selection of a combination HIV prevention package described in depth in this protocol.

Aim 3: Pilot Study

The previous aims were completed to inform Aim 3 of this protocol. This section provides an overview of setting, participants, and details of how interventions can be implemented and how data should be collected. Our preliminary research confirmed that there were numerous examples of individual HIV prevention interventions aimed at addressing the drivers of the HIV epidemic among youth [18-30]. Many of the vertically-focused single interventions were efficacious, but there remained a need for combination approaches [8]. The studies reviewed as part of the systematic review informed our decision about the most effective and feasible components to include in the protocol for the combination package. These components are HIV testing and counseling (HTC) [31,32], condoms [33,34], family planning (contraception) [35,36], voluntary medical male circumcision [37-39], conditional cash transfers (CCTs) [40-44], pre-exposure prophylaxis (PrEP) [40,45,46], and HIV care and treatment [47,48]. All interventions included in the protocol to be offered as part of MP3 Youth were chosen because they were efficacious, youth-friendly, possible to implement in a mobile health setting, and potentially sustainable following the MP3 Youth study.

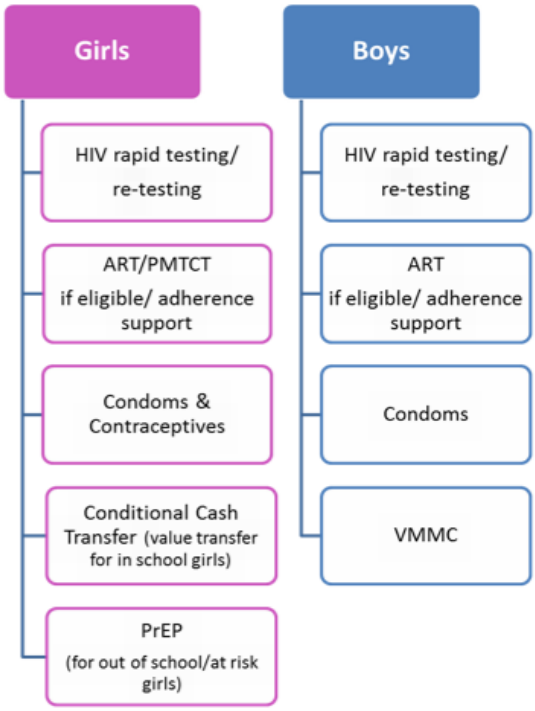
MP3 Youth Package

Based on results of the first two aims, the gender-specific MP3 Youth package was developed (Figure 5). The tailoring of interventions to specific individuals is referred to as the “MP3 Youth package of services.” For all participating youth, the package will include HIV counseling and testing. For all HIV-positive participants, the package will include point of care cluster of differentiation 4 (CD4) and viral load testing, and facilitated linkage to care (n is approximately 100), including prevention of mother-to-child transmission for pregnant females. For all participating males, the package will also include condoms and voluntary medical male circumcision, whereas for all participating females the package will also include contraception (both male and female condoms) and family planning. PrEP will be included for HIV-negative, out-of-school females while CCT will be included for HIV-negative, in-school females. The protocol aims for approximately 1000 youth to be enrolled in the pilot study and from these, sub-cohorts of youth (approximately 300) will be followed up prospectively for 12 months to document behaviors and adherence related to selected interventions. In addition, follow-up by phone to approximately 100 youth who are HIV negative at baseline will assess whether or not they were HIV retested over the last 12 months or if they are willing to be retested at the 12-month follow-up period.

The combination MP3 Youth package menu options will be delivered through community-based mobile health teams and all interventions will be offered on-site. PrEP and CCT cohort enrollment will also be initiated on site and followed-up

prospectively off-site. Mobile health teams will be able to select the most appropriate location within a community to set up tents to deliver the MP3 Youth packages. Mobile health events increase accessibility to the interventions and reduces stigma by offering it in the context of a health event where other youth-friendly services are also being provided [32,49].

Figure 5. MP3 Youth packages.



Study Objectives

The objectives of the pilot study were developed based on the formative stages of the protocol development by an expert panel that recognized the gaps that this study could fill. The primary objective is to determine the feasibility and acceptability of a pilot combination HIV prevention package specific for female and male youth (MP3 Youth) in Homa Bay County, Nyanza Province, Kenya. This will be determined by examining uptake and coverage of the intervention package among youth. The secondary objectives are (1) to examine adherence to HIV care including antiretroviral therapy (ART) among HIV-positive males and females 15 to 24 years of age; (2) to evaluate the feasibility of offering PrEP to high HIV risk out-of-school females 18 to 24 years of age and to contribute data to the current question of how best to initiate and support ongoing adherence for females using PrEP; (3) to assess the feasibility of delivering CCT to keep girls in school over the 12 months; and (4) to evaluate school attendance over 12 months of CCT cohort participants. For the logic model, see Multimedia Appendix 1.

Setting

The mobile health events for intervention delivery are proposed to be held in Homa Bay County, Nyanza Province, Kenya using the infrastructure of our community partner Impact Research and Development Organization (IRDO).

Participants and Sample Size

In the cross-sectional portion of the study, we plan to enroll approximately 1000 youth (ages 15 to 24) over the course of 10 mobile events, held for 7 to 10 days each. We plan on enrolling a sub-section of the enrolled participants into longitudinal cohorts (approximately 300 youth).

The pilot study is not meant to provide a definitive test of the combination package efficacy. Nevertheless, power calculations can provide an idea of the magnitude of temporal effects on ART adherence or school attendance that could be reliably detected using conventional tests of significance. Assuming at least an 80% retention rate at the 12-month follow-up, a minimum of 40 CCT cohort participants, 40 PrEP cohort participants, and 80 HIV-positive cohort participants will contribute data for all planned assessments. A paired-samples *t* test with 80 pairs can detect a difference in means of one-third of a standard deviation (d=.33) with 83% power. A paired-sample *t* test with 40 pairs can detect a difference in means of d=.45, 80% power.

Unique Interventions

Many of the interventions selected to be offered as a part of the MP3 Youth protocol have been well documented in the literature and outlined in other papers [7,50,51]. This paper does not describe the rationale or process for HIV testing, linkage to care, family planning (condoms and contraception), or male circumcision—these processes are well known and documented—but discusses PrEP and CCT, two of the unique intervention components included in the MP3 Youth pilot study combination package. We outline our specific procedures for implementing these interventions as part of the innovation of the MP3 Youth protocol.

Pre Exposure Prophylaxis

For PrEP, Truvada or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) will be offered to out-of-school females aged 18 to 24 years as part of a demonstration project within this pilot study. Given that HIV prevalence for women in Kenya peaks earlier than men [11], we believe it is reasonable to provide PrEP only to eligible females aged 18 to 24 years. Our MP3 Youth mathematical modeling confirmed the additive role of PrEP as a prevention intervention component for women when offered during the highest window of HIV risk (from ages 18 to 24). The National AIDS and STI Control Program (NASCOP) in Kenya will offer PrEP as part of their prevention services as PrEP was officially approved for use in Kenya [52]. The US President's Emergency Plan for AIDS Relief (PEPFAR) program in Kenya has also included PrEP as an intervention for the HIV prevention initiative called DREAMS [53]. This protocol will assess potential feasibility and implementation issues of offering PrEP to adolescent females in Kenya.

We will measure adherence to TDF/FTC for PrEP by employing pharmacological and non-pharmacological measures of adherence. Measures include self-report, electronic medication vials (eCAPs), and analysis of tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) drug levels as assayed from dried blood spots (DBS). eCAPs record the time and date when each pill bottle is opened. This technology was successfully used in other studies [54,55]. DBS will provide biomarker data for participant adherence to TDF/FTC for PrEP. DBS is relatively easy to collect, store (within time constraints), and transport [56-58], making it an appropriate method for mobile health events.

Conditional Cash Transfers

CCTs will be offered to girls enrolled in school (aged 15 to 24 years) and their families as part of the MP3 Youth package. The girls will be required to attend school at least 80% of the time in order for her and her family to receive the CCT. This will be measured by visiting the schools to check attendance. Much of the CCT evidence base has come from government sponsored programs, like the Mexico Opportunidades program designed as an anti-poverty program with positive impacts on social, economic, and health indicators [59]. CCT programs have demonstrated multiple impacts, such as keeping girls in school and measurable health benefits. The National Government of Kenya, in collaboration with the United Nations Children's Fund (UNICEF) and the World Bank, initiated a program in 2002 called the "Kenya *Cash Transfer Program* for Orphans and *Vulnerable Children.*" The program transferred USD $14 to $28 per month (depending on the number of vulnerable children in the household) to vulnerable youth in Kenya [60]. A recent study by Handa and colleagues (2014) evaluated the Kenya cash transfer program and found a 31% reduction in sexual debut [61]. The MP3 Youth pilot study protocol will offer critical information on the feasibility of keeping girls in school using CCT as an intervention.

Cohort Follow-Up Schedules

Participants who attend the mobile MP3 Youth events will be enrolled into 4 cohorts which will be followed up for a period of 12 months via unstructured supplementary service data (USSD) and SMS text message (short message service, SMS) surveys and/or in-person computer-assisted personal interview (CAPI) surveys. The PrEP cohort will be followed up monthly for the first 6 months and every 3 months for the remaining 6 months in a mixture of in-person clinical visits and SMS and USSD surveys to facilitate adherence and conduct laboratory assessments (for HIV and pregnancy). The CCT cohort will be followed up every 3 months (0, 3, 6,9,12 months) for 12 months using an in-person CAPI and school registers checked for attendance. The HIV-positive cohort will also be followed up at intervals of 3 months via SMS and USSD surveys. A random subset of the HIV-negative youth who agree to be called in one year will receive a phone call to assess their HIV retesting behaviors and intentions. The HIV-positive cohort will undergo a clinical assessment at baseline and at month 12 (CD4 and viral load). The CCT cohort will undergo a clinical assessment at baseline and at month 12 (HIV testing and counseling and pregnancy testing). We will administer SMS and/or USSD and CAPI surveys to the cohorts to assess longitudinal self-reported behaviors. During all clinical/laboratory assessments, adverse events will be assessed.

Biomarkers and Adherence

Although efficacy of the individual components of the intervention package was already demonstrated in well-conducted randomized trials, we are electing to re-do CD4 and viral load levels (biomarker proxy for adherence) at 12 months in the HIV-positive cohort and collect biomarker data from the PrEP cohort to monitor adverse events and, in case of seroconversion, resistance. eCAPs and DBS will be used to monitor adherence to TDF/FTC. This combination of self-report and biomarker data will be sufficient to determine the feasibility of implementing the package of interventions and tracking youth sexual behaviors prospectively.

Study Population

The eligibility criteria for MP3 Youth are shown in Textbox 2.

Textbox 2. General eligibility requirements for the pilot study.

Criteria

- Inclusion criteria
  - Any male or female between the ages of 15 to 24 years.
  - Able to understand spoken English, Kiswahili, or Dholuo.
  - Willing to give informed consent (including emancipated minors), or, if younger than 18 years of age, has a parent or guardian willing to provide consent in addition to the minor's assent.
  - Willing to be tested for HIV.
  - Willing to get a participant identification (ID) based on biometric finger scanning.
- Exclusion criteria
  - Any male or female younger than 15 years or older than 24 years of age.
  - Unable to understand spoken English, Kiswahili, or Dholuo.
  - If under 18 years of age, not an emancipated minor, and unable to get parental consent.

Target Sample Size

As stated previously, the MP3 Youth package will be offered to approximately 1000 youth who attend the mobile events. These participants will be part of the cross-sectional analyses. In addition, a subset of youth will be enrolled in longitudinal cohorts. The cohorts and their corresponding sample sizes are shown in Textbox 3.

Textbox 3. Cohorts and sample sizes.

Cohorts

- HIV-positive cohort:
  - All participants who test HIV positive (including participants who report being positive at baseline and are retested) during all mobile events will be invited to enroll in the longitudinal cohort using SMS/USSD surveys to collect data.
  - Participants will be given mobile phones.
  - The target HIV-positive sample size is approximately 100.
- Conditional cash transfer (CCT) cohort:
  - In-school girls between 15 to 24 years of age who test HIV negative will be screened for eligibility at each of the mobile events.
  - The target CCT sample size is approximately 50.
- Pre-exposure prophylaxis (PrEP) cohort:
  - Out-of-school girls who test HIV negative and are between 18 and 24 years of age will be screened for eligibility at each of the mobile events.
  - Participants will be given mobile phones.
  - The target PrEP sample size is approximately 50.
- HIV-negative cohort:
  - A random selection of participants who test HIV negative at the mobile events will be asked to complete one follow-up phone call at 12 months to assess willingness and intention to undergo HIV retesting (no study phone will be provided).
  - The target sample size is approximately 100.

Study Outcomes

Study outcomes were developed by an expert panel during the formative phases of protocol development to evaluate the objectives of the study and the aforementioned methods employed to deliver the interventions (see Multimedia Appendix 1). The primary and secondary outcomes of MP3 Youth are shown in Textbox 4.

Textbox 4. Primary and secondary outcomes of the MP3 Youth protocol.

Outcomes

- Primary study outcomes (cross-sectional and cohort)
  - Intervention uptake (acceptability) and coverage (feasibility)
  - Coverage
    - The proportion of youth in the community who attend each mobile event (estimated from youth population denominator)
  - Enrollment
    - The number of participants who consent to being enrolled in the study during each mobile event.
  - Uptake
    - The proportion of eligible participants who choose one or more components of their tailored combination package (including combinations of interventions components)
  - Intervention acceptability
    - Satisfaction with mobile event services (computer-assisted personal interview at exit from mobile event)
- Secondary study outcomes
  - Adherence to medication (HIV-positive and pre-exposure prophylaxis cohort participants only)
    - Adherence to once daily Truvada (pre-exposure prophylaxis, PrEP) among HIV-uninfected eligible females and patterns of adherence and sexual HIV acquisition risk exposure (PrEP cohort participants only).
    - Measured by self-report, electronic medication vial, and clinical assessments: monthly for the first 6 months and every 3 months thereafter and dried blood spot for analysis of tenofovir disoproxil fumarate/emtricitabine and tenofovir diphosphate and emtricitabine triphosphate at month 2 and 9.
  - Adherence to antiretroviral therapy (ART) (HIV-positive cohort participants only)
    - Measured by quarter annual text messages/unstructured supplementary service data self-report at 0, 3, 6, 9, and 12 months.
    - Point of care cluster of differentiation 4 (CD4) and baseline viral load by dried blood spot or plasma will be measured at mobile event baseline and repeated at 12 months.
  - Feasibility of administering conditional cash transfer to keep girls in school over 12 months.
    - Measured by school attendance (self-report and random checks for school attendance verification).

Data Collection

This section of the protocol outlines the components that need to be included in order to collect and evaluate the cross-sectional and longitudinal data required to measure the pilot study outcomes. All MP3 Youth mobile event participants who are eligible, consent, and register for MP3 Youth will be required to complete a baseline behavioral CAPI survey and an exit acceptability interview. Participants who are eligible and enrolled in a sub-cohort will be required to complete SMS/USSD mobile phone surveys every month (PrEP cohort) or every 3 months (CCT and HIV-positive cohort). Participants in the PrEP cohort will be required to complete monthly clinical/laboratory visits for the first 6 months and every 3 months thereafter. The following sections describe the specific types of data that will be collected and the suggested data platforms to be implemented.

Behavioral Baseline Interview

The behavioral survey will be a staff-administered CAPI at the mobile events. For sensitive questions (which will be identified in the survey), youth will be instructed that they can tap on the answer with the tablet facing away from the interviewer and the answer will not be visible after entry; this incorporates elements of “ballot box response” or *audio computer-assisted self-interview* (ACASI) approaches while reducing issues around lack of literacy and unfamiliarity with tablet computers [62].

The CAPI will collect the following types of information, including but not limited to the types of services the participant is most interested in accessing: (1) basic demographic information, (2) sexual risk behaviors, (3) HIV risk behaviors, (4) attitudes and/or knowledge about HIV transmission and prevalence, (5) knowledge and acceptability of specific HIV prevention interventions, (6) knowledge and acceptability of family planning methods, and (7) attitudes towards the delivery of services (collected at the exit interview).

The CAPI will provide data that will lead to a better understanding of the combination HIV prevention interventions and prevention behaviors of youth. The responses will help determine the package of services for which the participant is eligible.

Follow-Up Text Message and Unstructured Supplementary Service Data Survey

Using the EchoMobile platform, study staff will make SMS/USSD text contact using an agreed-upon code, to ensure the phone user is the study participant. Staff will then wirelessly transfer airtime, so the cohort participant can send surveys using SMS/USSD [63]. The SMS/USSD survey will be a brief 10-question survey tailored to the cohort population. The surveys will be short to reduce barriers to completion. The responses will be analyzed to assess change in behavior over time as a part of the longitudinal cohort.

The SMS survey will collect information that includes but is not limited to (1) sexual risk behaviors; (2) school attendance (for CCT cohort); (3) adherence barriers and facilitators (PrEP and HIV-positive cohort); and (4) status disclosure (HIV-positive cohort).

Biometric Data Collection

Biometrics will be used to correctly identify participants, track repeat visits, and protect subject privacy and information. There will be a tablet connected via *Universal Serial Bus* (USB) to a biometric (fingerprint) scanner at the mobile events and during follow-up visits. This technology will be used to track uptake of services and to exclude individuals who try to enroll multiple times. The fingerprint software will translate a fingerprint into a code containing numbers and letters; no image of the fingerprint will be stored. In testing this procedure, we will take several measurements of correctly positioned clean fingers to ensure accurate measurement and re-measurement. The code will not be a personal identifier and it will not be possible to use it to recreate a fingerprint. These codes will be stored separately from other data. This technology has been used successfully in other projects in Kenya [64].

Biomedical Data Collection

Urine specimen will be collected for pregnancy testing for women with reproductive capacity and for dipstick analysis of protein and glucose levels (PrEP cohort only). In the PrEP cohort only, blood specimens will be collected for (1) HIV rapid testing, with confirmatory testing if one or both tests are reactive; (2) complete blood count (CBC); (3) serum creatinine (for estimated creatinine clearance); (4) serum phosphate; (5) aspartate transaminase (AST)/alanine transaminase (AST) ratios; (6) hepatitis B surface antigen (HepBsAg) (ineligible for PrEP if positive); (7) hepatitis B surface antibody (HepBsAb) and hepatitis B Core antibody (HepBCore Ab) testing (if HepBsAg is negative); and (8) DBS for study drug levels as a measure of adherence. Blood specimens will also be collected to determine the CD4 cell count in any participant with confirmed HIV infection and viral load testing.

Implication of Pilot Study Results

Data from Aim 3 (the pilot study), the mathematical modeling sensitivity analyses, and the population impact projections will help establish the acceptability, feasibility, potential synergies or antagonisms, safety, and potential efficacy of the package before moving to a larger-scale evaluation phase IV study design (Aim 4).

Aim 4: Combination Prevention Effectiveness Study Design

Using lessons from Aims 1 to 3 of the protocol, we present a preliminary outline for the design of a future effectiveness trial of the MP3 Youth package. The objective of the effectiveness trial will be similar to the pilot, but the trial will focus on effectiveness and not on feasibility.

Arguably, insufficient attention has been given to moving phase III efficacy trial interventions to phase IV effectiveness designs applied in heterogeneous real-world settings [65]. Several study designs can be considered to evaluate actual population-level impact of gender-specific combination prevention intervention packages for youth (Table 1), including cluster randomized controlled trials (cRCTs) using parallel or stepped wedge (ie, staggered) assignment. The advantage of cRCTs over individually randomized controlled trials (iRCTs) is that the former allows evaluation of the total effect of a combination package, especially if the sum of the intervention package components is greater than its parts [66]. They would also allow assessment of targeted interventions to subpopulations (eg, in the case of MP3 Youth males vs females or pregnant vs non-pregnant females) while the impact would be measured on the whole community. The feasibility of tracking an HIV incidence outcome for either an iRCT or cRCT would depend on development of improved cross-sectional HIV incidence assays. It would also depend on the expected HIV incidence in the control arm and likely HIV-incidence reduction effect size in the combination arm.

Table 1. Potential designs for a testable combination HIV prevention intervention study protocol.

Study design	Advantages	Disadvantages	Considerations
iRCT[a]	Rigorous control of confounders	Can't evaluate population HIV impact	Need high incidence; control condition can weaken intervention detection
cRCT[b]	Rigorous, can assess impact beyond individual	Cost, complexity	Unit of randomization, and number of clusters and individuals within clusters
cRCT stepped wedge randomization	Easier to add interventions, once shown effective	Implementation delays can reduce effectiveness and power	Appropriate when logistically difficult to roll-out prevention service all at once
Program demonstration	Could be done in large scale in existing programs	Less rigorous, results can be inconclusive	Selection/matching of intervention and control communities; incidence measures

[a]iRCT: individually randomized controlled trial.

[b]cRCT: cluster randomized controlled trial.

We can use findings from Aims 1 to 3 to inform choice of (1) study design (including standard of care elements); (2) high HIV incidence setting (in Kenya or elsewhere) with sufficient HIV events expected; and (3) HIV incidence measurement for a full-scale evaluation of a gender-specific youth combination prevention package. Other key considerations that can be reviewed include what the trial unit of randomization should be, standard of care and/or comparator, timeframe expected for seeing an intervention effect, length of follow-up period needed to observe sufficient number of new HIV infections, sample size, participant inclusion/exclusion criteria, and how best to engage active and ongoing community involvement in large-scale trial design and conduct. Safety considerations and adverse event tracking must be delineated. We must also consider broader issues of the logistics of program coverage, cost-effectiveness, and sustainability beyond the study period. After compiling the possible options, we will collaborate with our research team to review our recommended study elements and make final trial design recommendations.

Human Participants

The MP3 Youth study has institutional review board (IRB) approval from Kenyatta National Hospital/University of Nairobi-Ethics and Research Committee (KNH-ERC) and from New York University's governing IRB, University Committee on Activities Involving Human Subject (UCAIHS).

Results

Quantitative data analysis will be conducted using Stata software [67] and R statistical software [68]. Initial analyses will involve inspecting frequency distributions to identify outlying values and skewed variables requiring transformation. Descriptive analyses will provide means, medians, or prevalence of risk factors with associated confidence intervals. Analytic comparisons of pilot cohort drop-outs versus retained subjects will be done using multivariate analysis of variance (MANOVA) for normally distributed continuous variables with log10 (X+1) transformations on skewed behavioral variables, and chi-square tests for categorical variables and Wilcoxon tests for ranked data, with significance levels adjusted for multiple testing.

For the PrEP, CCT, and HIV-positive cohorts, changes over time in risk behaviors will be estimated focusing on initial change (baseline vs 6 months) and delayed change or persistence of initial effects (6 months vs 12 months). We anticipate minimal missing data due to use of CAPI and SMS/USSD data. The primary goal of the longitudinal cohorts is to provide data needed to describe the feasibility of PrEP, ART, and CCT, including medication adherence and school attendance over time. Levels of and changes in adherence and school attendance will be presented graphically, for example, with box plots at each assessment point and trajectory plots. For a detailed analysis plan, see Multimedia Appendix 2.

Discussion

Principal Findings

The MP3 Youth study designed and created a protocol to pilot and evaluate a gender- and youth-specific combination HIV prevention study in Kenya. We propose that offering youth a combination of HIV prevention interventions in a mobile health setting will be convenient and effective based on our preliminary research. Our formative research indicated that youth are interested in receiving multiple services in one place. We anticipate that the results of the exit interview we will conduct at the mobile events will yield positive feedback on the delivery of the interventions as the events will be conveniently located and youth friendly. Cross-sectional analyses of the mobile health data will provide insights into the uptake of interventions and feasibility of offering them in a one-stop-shop integrated services delivery modality. The results of the longitudinal cohort data will provide innovative information on the potential impact of the interventions and the behavioral changes among the cohort participants over time. The pilot study will give new insights into how components do or do not fit together in a real-world combination prevention package. The results of the pilot will then be used to refine the design of an effectiveness trial or a large-scale program evaluation.

MP3 Youth is one of the few combination HIV prevention interventions incorporating elements of behavioral, biomedical, and structural interventions in one delivery setting and developed for youth. Despite the fact that youth are both at highest risk for HIV and the largest proportion of the global population, only recently have they been targeted for comprehensive HIV prevention interventions.

The mobile health event strategy outlined in this protocol to identify youth is unique. We were able to use the information gleaned from focus groups to target the location and delivery of services and to use the literature and lessons learned from previous studies to design a protocol to deliver evidence-based interventions that are youth-friendly and gender-sensitive. The logistics of implementing mobile health events for 10 days at a time will involve setting up and breaking down a clinic that is completely equipped to handle HIV testing, CD4 and viral load analysis, family planning, a surgical theatre for male circumcision, and a pharmacy. This strategy will be effective for reaching youth who are at risk and in need of a variety of services. We will enroll participants using biometrics. This strategy will allow us to track participant flow and uptake of services during the mobile events. Biometrics will also allow us to successfully identify participants during follow-up visits [69].

Limitations

This is a pilot feasibility study using mixed-methods (mathematical modeling, qualitative data, cross-sectional, and longitudinal cohort elements). As this pilot study does not employ a controlled trial design or comparator, population-level effectiveness of the combination HIV prevention approach cannot be determined. The logistics required to implement a combination HIV prevention study may be expensive and may require a lot of up front staff and referral partner capacity building that may delay implementation.

Conclusion

The MP3 Youth lessons learned will provide real-world contributions to implementation science regarding uptake of

combination prevention. Some of the preliminary lessons learned in developing the protocol were considered as part of the Kenya national health strategy; one of the 8 countries participating in the PEPFAR DREAMS initiative. The analyses conducted for MP3 Youth will be key in highlighting evidence for a scaled-up youth prioritized HIV/AIDS strategy in Kenya and other high HIV burden settings.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Logic Model.

[JPG File, 276KB - resprot_v6i3e22_app1.jpg]

Multimedia Appendix 2

Evaluation plan.

[JPG File, 172KB - resprot_v6i3e22_app2.jpg]

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Abbreviations

ART: antiretroviral therapy
CAPI: computer-assisted personal interview
CCT: conditional cash transfer
CD4: cluster of differentiation 4
cRCT: clustered randomized controlled trial
DBS: dried blood spots
eCAP: electronic medication vial
HepBsAg: hepatitis B surface antigen
HIV: human immunodeficiency virus
IRB: institutional review board
iRCT: individually randomized controlled trials
PrEP: pre-exposure prophylaxis
SSA: sub-Saharan Africa
TDF/FTC: tenofovir disoproxil fumarate/emtricitabine
USSD: unstructured supplementary service data

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Original Paper

Implementation of a Home Monitoring System for Heart Failure Patients: A Feasibility Study

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Abstract

Background: Improving the management of patients with complex chronic disease is a substantial undertaking with the simultaneous goals of improving patient outcomes and controlling costs. Reducing avoidable hospitalization for such patients is a step toward both objectives. Some of the deterioration experienced in chronic disease patients occurs outside the view of their clinicians, and before the patient becomes overtly symptomatic. Home monitoring has been used for more than 20 years to detect deterioration earlier so that the patients could be treated before they became ill enough to require hospitalization. Patient participation is an important requirement for successful home monitoring. There has been some concern that patients would be unwilling or unable to engage in a program that collected multiple measurements. The Cedars-Sinai Cardiology Center provides a high-touch, intense management program for patients with congestive heart failure (CHF). A group of their patients were chosen to join a complex, multidevice home monitoring system to see whether such patients would find value in the additional effort.

Objective: The objective of our study was to determine whether patients already actively engaged in a high-touch intensive management program for CHF would take on the additional burden of a complex home monitoring effort.

Methods: A total of 20 patients from the Cedars-Sinai group were enrolled in a monitoring program utilizing 5 different devices. Anonymous surveys were collected from the patients to assess their satisfaction with the program.

Results: In total, 90% (18/20) completed the program, and 61% (11/20) submitted the survey. Among the 18 patients, overall compliance with the requested measurements was 70%. It was found that 73% (8/11) felt better about their health as a result of the program, whereas another 73% (8/11) believed that the care team now had a better picture of their health.

Conclusions: Substantial patient compliance and satisfaction can be achieved in a sophisticated home monitoring program.

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KEYWORDS

heart failure; home monitoring; predictive analytics; patient engagement

Introduction

The management of chronic disease is a substantial burden, both for the patients and the provider organizations supporting them. In total, 71% of health care expenditures in the United States result from patients with multiple chronic diseases such as congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and diabetes [1]. A substantial fraction of the cost is generated by repeated hospitalization and emergency department (ED) visits [1]. The incidence of chronic disease continues to grow, in part because of an aging population and improved management of chronic diseases. Better acute

coronary care, with a 38% decrease in the death rate from coronary artery disease in the last decade [2], results in more patients surviving and living with CHF. Further, changes in the social environment have resulted in more seniors living independently, often at a distance from children who might be monitoring their well-being. One of the strategies for controlling the cost of health care, while simultaneously improving outcomes and quality of life for patients, is to reduce avoidable hospitalization for patients with chronic diseases. CHF, COPD, and diabetes are included in the list of ambulatory care sensitive diseases, as defined by the Agency for Healthcare Research and Quality (AHRQ), meaning improved outpatient care can reduce the need for hospitalization [3].

Identifying patients early in the course of decompensation provides the opportunity for a modest intervention to reduce the likelihood of hospitalization. Since patients spend most of their lives without direct communication with their clinical care team, early deterioration can be missed. There have been attempts to close that communication gap with "high-touch" programs involving frequent phone contact or home visits to improve outpatient follow-up and evaluation. Many of these programs have been effective in reducing the number of hospitalizations, but have been hampered by their labor-intensive, high-cost structure, which has made it difficult to scale the programs beyond a small number of patients [4-7].

Over the last 20-30 years, home monitoring devices have been used to make outpatient evaluation more effective. Some such efforts resulted in a reduction in hospitalizations, but were plagued with false alarms and missed opportunities [4,5], whereas others reported no benefit [6,7].

Patient participation has been a challenge. Many of the earlier devices either required patients to actively take measurements, such as blood pressure or weight, and record it in a log or submit the result by phone [8]. Reports on patient compliance in monitoring programs are mixed. Patient adherence to the monitoring protocol was often good when only a small number of measurements with a small number of devices were required [9-11]. However, others reported poor compliance [12,13]. The inefficiency of the process, and demands on the patient, were disincentives to participation. Devices that automatically recorded and transmitted the readings became available, but were expensive and still required substantial effort on the part of the patient. One group reported high compliance in telephone mediated reporting of multiple measures, after specifically excluding patients for "poor compliance with HT systems" [8]. Another report, also working with exclusion criteria, reported a sharp decrease in compliance over 6 months of the study [6]. It may be appropriate to treat remote monitoring as you would any other intervention, namely, selecting patients who are more likely to benefit. Financial incentives provided little long-term improvement in participation, with modest compliance in the incentivized groups and poor compliance in the unincentivized group [14].

Fortunately, device technology has evolved rapidly, making it easier to safely and securely collect and transmit data [15]. This allows us to work with multiple data streams, rather than just one or two. New measures previously not readily available, such as oxygen concentration or intrathoracic fluid assessment increase opportunity to incorporate novel data streams. However, just collecting data has relatively little value. The expanded interest in and availability of patient generated health data (PGHD), including patient-reported outcomes, means we need to better understand patient willingness to participate in more complex monitoring programs [16]. The data has to be analyzed to provide actionable insights used by decision makers, be they the patient, the patient's family or the clinicians, to help make better decisions. Improvement in analytic techniques allows us to find data patterns with strong predictive power, well beyond that obtained by having someone "eyeball" the collected data. Humans rely on experience and intuition, which cannot effectively deal with the volume and complexity of big data [17].

For most patients with diseases such as CHF and COPD, the processes that lead to severe symptomatic acute illness develop over time, sometimes weeks before the patient presentation or clinical discovery. Even though the patient may not overtly recognize that illness is progressing, seeking patterns in physiologic data such as heart rate, heart rate variability, oxygen concentration, and blood pressure could allow the early detection of those processes. With earlier detection, there may be opportunities for prevention of progression to symptoms and clinical decompensation in advance of severe acute illness that might require hospitalization or other major intervention.

Target outcomes of modern monitoring technology with predictive analytics are reduced hospitalizations, ED visits, or unscheduled office visits, compared with a baseline of such events in the absence of monitoring. Concomitants for obtaining benefit from the early warning provided by the predictive analytics are a system that promotes patient participation and a care management program that can respond effectively to the notifications and track the events. Given the reports of limited patient participation in systems using a small number of devices [9-11], we want to determine if patients already engaged in a high-touch, effective treatment program will participate in a complex home monitoring effort using multiple devices.

This report describes the WEAR-HeFT (Wearable Device Monitoring Heart Failure) trial, which is a pilot program designed to address all the requirements of an effective home monitoring program for patients with late stage CHF. The Cedars Sinai Medical Group in Los Angeles, CA has implemented the Heart Failure Drug Therapy Management Program to improve outcomes and reduce hospitalization. It targeted patients with high levels of hospitalization and utilization of acute care services. The program was effective in that it reduced both CHF and all cause admissions by 50% compared with a 36% reduction in a control group [18].

Sentrian Remote Patient Intelligence is a commercial predictive analytic, machine-learning platform created to provide the data management and predictive analytics necessary to process home monitoring data. The goal is to identify patterns in the data that suggest early deterioration and generate the notification that a patient will become acutely ill some days hence. The Sentrian platform is device and data stream agnostic. It can, for example, utilize data from home monitoring devices such as oxygen

saturation, blood pressure, or temperature. It can also work with laboratory results such as natriuretic peptide, activity, sleep quality, and patient reports of matters (eg, pain and anxiety). The Sentrian system allows the clinicians to create rules to analyze the data streams over both short and long-term trends to generate notifications when specified conditions are met. The rules are designed to be appropriate for the individual patient. The accuracy of predictions about deterioration is one of the sources of feedback to support machine learning to improve predictive power. Health care organizations are charged a monthly fee for each monitored patient.

The pilot WEAR-HeFT trial is designed to demonstrate whether patients who are already engaged in an intensive outpatient program for CHF will participate in a complex home monitoring program. Successful patient engagement is a predicate for further study to assess the predictive power of the analytic platform. This report specifically addresses lessons learned about the implementation process to enroll patients in a monitoring program, teach them the use of the devices, and overcome obstacles, both anticipated and unanticipated.

Methods

Inclusion and Exclusion Criteria

Patients for the program were chosen by the staff at Cedars-Sinai Medical Center from the group that was enrolled in the Heart Failure Drug Therapy Management Program. Specific inclusion and exclusion criteria are listed in Textboxes 1 and 2. The project was reviewed and approved by the Cedars-Sinai Institutional Review Board.

Textbox 1. Inclusion criteria for the study.

Inclusion criteria

- Patient with New York Heart Association (NYHA) Class 2-4
- Brain natriuretic peptide (BNP) greater than 150pg/mL
- History of heart failure admission at least one time in the previous 12 months or requiring frequent outpatient follow-up (repeat visits on a monthly or weekly basis)
- Competent to give informed consent
- Deemed to be good candidates for the study by investigators

Textbox 2. Exclusion criteria for the study.

Exclusion criteria

- Unable to give informed consent or understand research protocol
- Immobile
- Physically unable to wear devices
- History of missing clinic appointments
- Unwilling to complete follow up evaluation
- Unstable psychiatric illness
- End stage renal disease (CrCl <15mL/min)
- Recent history of pneumonia

Safety Parameters

A set of devices was chosen for each patient to provide the desired measurements. The devices approved by Food and Drug Administration (FDA) were the ForaCare W310B Weight scale, ForaCare D40D Blood Pressure Monitor, ChoiceMed MD300C318T2 Pulse Oximeter, and the CoVa from ToSense for intrathoracic fluid. Additionally, the Fitbit Flex (Fitbit, San Francisco, CA) was used for tracking numbers of steps. Qualcomm's 2Net Hub was used to link the devices to the cloud in a Health Insurance Portability and Accountability Act (HIPAA) compliant environment. Potential participants in the program met with the cardiology staff and had the details of the program explained to them, including potential benefit and risks. The Fitbit Flex was worn continuously, whereas the other measurements (weight, blood pressure, pulse oximeter, CoVa) were performed once a day first thing in the morning. Pulse rate was detected from the oximeter. Patients were asked if they had wireless Internet access since such access was required for data transmission and acquisition. Those that agreed to participate were given instruction in the use of the devices and provided a phone number to call for any additional instruction or troubleshooting. All participants signed an approved informed consent document. Patients were enrolled on a gradual basis and duration of participation ranged from 40 to 117 days.

The ultimate purpose of Sentrian's analytics is to predict deterioration in advance and not as an alarm for critical conditions. However, the Cedars team established criteria as a fail-safe for which a cardiologist would be notified immediately,

shown in Textbox 3. The Cedars investigators were kept blinded with respect to the data. An independent cardiologist was notified when the safety parameters were exceeded.

Textbox 3. Safety parameters.

- Systolic blood pressure (SBP) >180mmHg
- Diastolic blood pressure (DBP) <50mmHg
- Heart rate (HR) >150bpm
- HR <50bpm
- Pulse oximetry <90%
- Weight gain 5 lb in 24 h
- Weight loss 5 lb in 24 h

Several issues arose during the early stages of the project. First, despite what were thought to be careful explanations there was a misunderstanding of wireless and Internet connections among the patients. Several patients claimed they had wireless access when they did not and thus had to be provided with an Internet hot spot (Mifi) to participate. Most of the patients had difficulty with the finger dexterity necessary to close the clasp on the Fitbit. An alcohol-based hand sanitizer was used as a short-acting lubricant to facilitate clasp closure.

All patients were asked to evaluate the program through an anonymous survey at the conclusion of the program. Each question was answered by marking the desired response: strongly agree, agree, neutral, disagree, and strongly disagree. The survey was completed on paper with the patients circling one of the responses to each question. Textbox 4 provides the items included in the survey.

Textbox 4. Items included in the survey.

- I feel better connected to my Care Team.
- The time spent taking measurements is worthwhile.
- I feel better about my health.
- The Technical Assistance has been very helpful.
- It is easy to contact Technical Support, if needed.
- The program provides a more complete picture of my health to my provider.
- My Care Team has been responsive and helpful.
- I have been compliant taking my measurements.
- I take my measurements at the same time each day.
- If I forget to take my measurements, a reminder would be helpful.

We also tracked compliance with the measurement regimen as the fraction of expected measurement received.

Results

Patient Compliance

A total of 20 patients were enrolled in this pilot clinical trial; of which, 2 patients, numbers 4 and 13, dropped out and 18 completed the study, which ended on February 10, 2015. At that time, all data were collected for analysis and reporting. Patient compliance with the measurement schedule is shown in Table 1. The rate of compliance with measurements (fraction of expected measurements received) in the 18 patients who completed the study was 70%. There is a clear demarcation between patients that were actively engaged and those that were not. Five of the patients, including the 2 that dropped, were compliant less than 36% of the time. The minimum compliance in the more active group was 55%. Compliance in the active group was 78%. Patients that dropped out or stopped collecting data gave several explanations, including a too complex regimen, frustration with the devices, inability to complete the measurement protocol (too sick or too busy), or physical limitations on completing measurements (inability to balance on weight scale). The compliance experience emphasizes the importance of predicting which patients are more likely to actively engage in the program, as noncompliant patients get no value for the cost of the program. The desired clinical value and economic efficiency are most readily achieved if we learn enough about patients who will not participate to focus on those who will. We also need to learn more about the personalized support that may be needed to keep patients actively engaged.

Table 1. Patient compliance.

Patient number[a]	Rate of compliance (%)
1	95
2	36
3	83
4	23
5	96
6	89
7	82
8	46
9	71
10	77
11	68
12	57
13	0
14	55
15	35
16	95
17	89
18	76
19	58
20	76

[a]Patients 4 and 13 dropped out.

Survey for Patient Satisfaction

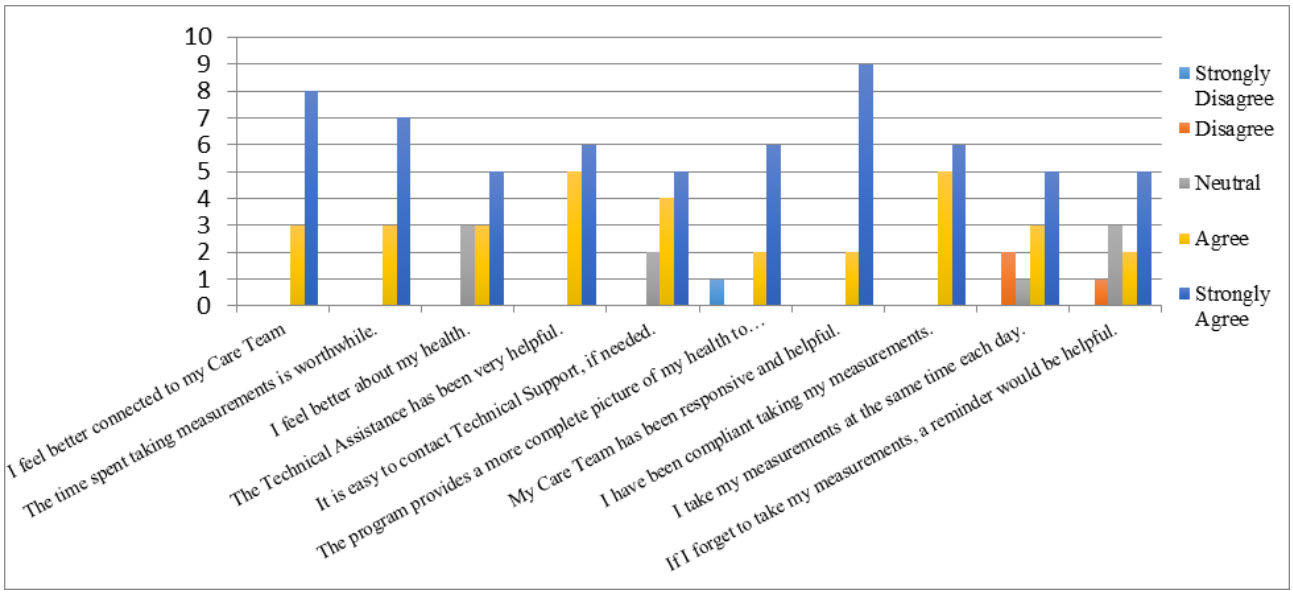
The results of the patient satisfaction survey are shown in Table 2 and displayed graphically in Figure 1. Eleven patients (61%) completed the satisfaction survey. Since the survey was anonymous, we could not determine why the others did not respond. Two patients did not answer all the questions. All patients either agreed or strongly agreed that they felt better connected to their care teams and that taking the measurements was worthwhile. It was found that 8 of the 11 patients (73%) felt better about their health as a result of the program, whereas another 8 of 11 (73%) believed that the care team now had a better picture of their health.

Table 2. Patient satisfaction survey.

Item	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Did not answer
I feel better connected to my Care Team.	0	0	0	3	8	0
The time spent taking measurements is worthwhile.	0	0	0	3	7	1
I feel better about my health.	0	0	3	3	5	0
The Technical Assistance has been very helpful.	0	0	0	5	6	0
It is easy to contact Technical Support, if needed.	0	0	2	4	5	0
The program provides a more complete picture of my health to my provider.	1	0	0	2	6	2
My Care Team has been responsive and helpful.	0	0	0	2	9	0
I have been compliant taking my measurements.	0	0	0	5	6	0
I take my measurements at the same time each day.	0	2	1	3	5	0
If I forget to take my measurements, a reminder would be helpful.	0	1	3	2	5	0

A chi-square contingency table analysis was performed on the response data in Table 2, using Microsoft Excel 2016, version 16.0.6965.2115. It did not quite reach statistical signification, with a *P* value of .12, in part due to lack of independence among the responses. A positive response to one question was likely associated with a positive response to another question.

Figure 1. Patient satisfaction survey.



Discussion

Principal Findings

Several issues arose during the early stages of the project. First, despite what were thought to be careful explanations there was a misunderstanding of wireless and Internet connections among the patients. Several patients claimed they had wireless access when they did not and thus had to be provided with an Internet hot spot (Mifi) to participate. Many of the patients had difficulty with the finger dexterity necessary to close the clasp on the Fitbit. An alcohol-based hand sanitizer was used as a short-acting lubricant to facilitate clasp closure.

A few of the patients relied on a wheeled walker for ambulation. Weight measurements for those patients were unreliable as they were affected by the variations in level of support that each patient needed from the walker. Although we intentionally limited the number of devices requiring active participation by the patients, a few patients initially felt that the measurement process was too complex. The problem seemed to diminish as the patients became more accustomed to the process. Some of the patients had substantially healthier spouses or significant others that provided support and helped the patients with the measurement process. On one hand, there was an advantage to the help provided. However, sometimes the spouse answered questions for the patients or dominated the discussion so that it was difficult to ascertain the patient's level of understanding. It became clear that special care was necessary to ensure that both the patient and the care-giver had the same understanding.

Some of the participants had already been using home monitoring devices such as blood pressure cuffs and weight scales. Some patients were concerned by the different readings from the new devices provided for the study. The team explained that such differences were minor and expected and were not alarming and that data trends were more important. Although each patient was given personal instruction in the use of devices, most benefited from phone support when setting up the monitors. There were several cases of idiosyncratic behaviors, with some patients calling technical support or not wanting to use a particular device, requiring additional support.

Many previous reports on compliance in home monitoring involved the use of one or two devices. We added a regimen with multiple devices to an existing intense, management program that already placed heavy demands upon the patients. We have shown that home monitoring produces additional value in such a comprehensive environment. Compliance in our group was at least comparable with compliance reported in other studies, confirming that a complex home monitoring regimen is feasible [10,11,14,15].

There was a high level of satisfaction among the patients, with strong feelings that the program improved their comfort with their health and left them more connected with their health care team. The sharp demarcation between patients that were either poorly compliant with the measurement schedule or dropped out of the program emphasized the need for a personalized approach to home monitoring. Despite a robust implementation and training program, some patients stopped taking the measurements. Distinguishing between patients who will participate if given extra support from those who will not engage is an important part of implementing a clinically and economically valuable program.

Limitations

This was a small study with a group of patients chosen who already had a close relationship with their care providers. The patients were chosen by the staff cardiologists to include patients that had been heavy utilizers of acute health services. However, we cannot exclude bias in that selection process, which might affect the results. It may not be generalizable to a broader group

of patients with less tight ties. Also, 7 of the 18 patients did not respond to the survey. It is possible that all of those patients found little value in the program. If so, it would still leave a majority of the patients finding value. Despite the preexisting strong association with the cardiology team, many patients felt that the monitoring program added to the relationship. Since this was a feasibility study with no control group, no comparative statistical analysis was possible. Since the survey was anonymous, it was not possible to relate the responses to individual patient characteristics, such as time in the program, which could have biased the result.

Conclusions

A carefully designed, home monitoring pilot implementation program using commercially available wearable devices in an insured elderly CHF cohort demonstrates feasibility in using a multimodality home monitoring strategy for selected patients. The study validated that patients can work with multiple devices, providing an array of data streams, as well as insights into unexpected challenges. Most obstacles to patient engagement can be overcome with appropriate support and encouragement. Cooperation between the clinical and technical teams is the key, as is identifying patients more likely to benefit from the program, those that need extra support, and those who will find no value in it.

Future directions would include expanding to larger numbers of patients with multiple chronic conditions, identifying which combinations of devices and data streams are most helpful for particular patients and refining impactibility, which patients are likely to benefit from home monitoring.

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Conflicts of Interest

All Sentrian authors are employees, and stockholders, in Sentrian. All Cedars-Sinai authors are employees of Cedars-Sinai Medical Center.

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Abbreviations

AHRQ: Agency for Healthcare Research and Quality
BNP: Brain natriuretic peptide
CHF: congestive heart failure
COPD: chronic obstructive pulmonary disease
DBP: diastolic blood pressure (DBP)
ED: emergency department
FDA: Food and Drug Administration
HIPAA: Health Insurance Portability and Accountability Act
HR: heart rate
NYHA: New York Heart Association
PGHD: patient generated health data
SBP: systolic blood pressure (SBP)
WEAR-HeFT: Wearable Device Monitoring Heart Failure

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Original Paper

Use of the Total Cancer Care System to Enrich Screening for CD30-Positive Solid Tumors for Patient Enrollment Into a Brentuximab Vedotin Clinical Trial: A Pilot Study to Evaluate Feasibility

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Abstract

Background: One approach to identify patients who meet specific eligibility criteria for target-based clinical trials is to use patient and tumor registries to prescreen patient populations.

Objective: Here we demonstrate that the Total Cancer Care (TCC) Protocol, an ongoing, observational study, may provide a solution for rapidly identifying patients with CD30-positive tumors eligible for CD30-targeted therapies such as brentuximab vedotin.

Methods: The TCC patient gene expression profiling database was retrospectively screened for CD30 gene expression determined using HuRSTA-2a520709 Affymetrix arrays (GPL15048). Banked tumor tissue samples were used to determine CD30 protein expression by semiquantitative immunohistochemistry. Statistical comparisons of Z- and H-scores were performed using R statistical software (The R Foundation), and the predictive value, accuracy, sensitivity, and specificity of CD30 gene expression versus protein expression was estimated.

Results: As of March 2015, 120,887 patients have consented to the institutional review board–approved TCC Protocol. A total of 39,157 fresh frozen tumor specimens have been collected, from which over 14,000 samples have gene expression data available. CD30 RNA was expressed in a number of solid tumors; the highest median CD30 RNA expression was observed in primary tumors from lymph node, soft tissue (many sarcomas), lung, skin, and esophagus (median Z-scores 1.011, 0.399, 0.202, 0.152, and 1.011, respectively). High level CD30 gene expression significantly enriches for CD30-positive protein expression in breast, lung, skin, and ovarian cancer; accuracy ranged from 72% to 79%, sensitivity from 75% to 100%, specificity from 70% to 76%, positive predictive value from 20% to 40%, and negative predictive value from 95% to 100%.

Conclusions: The TCC gene expression profiling database guided tissue selection that enriched for CD30 protein expression in a number of solid tumor types. Such an approach may improve screening efficiency for enrolling patients into biomarker-based clinical trials.

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KEYWORDS

antitumor agents; CD30 antigen; clinical trial; database management systems; medical oncology

Introduction

Background

With the genomic age providing a greater understanding of the complexity of cancer origin and progression, the environment for cancer drug development holds great opportunity but also significant challenge [1,2]. The biopharmaceutical industry has responded by developing a treatment armamentarium that capitalizes on tumor-specific features and improves outcomes for select patient populations. These targeted therapies include small molecule inhibitors, monoclonal antibodies, antibody-drug conjugates (ADCs), and more recently, cell-based immunotherapies [2]. Despite this progress, significant challenges have emerged in the translation of genomic discoveries into clinical practice, resulting in high costs and long development times [1,3,4].

Poor clinical trial accrual rates are a leading barrier to clinical research and can impede trial efficiency [5]. Clearly, the advent of target-based therapies shows promise for identifying and selecting patients most likely to benefit from treatment; however, identifying a subset of patients who meet specific, comprehensive eligibility criteria that includes the presence of specific molecular aberrations is a significant challenge [4,6]. It is not uncommon to screen hundreds of patients over extended periods of time in order to identify a few who are phenotypically/genotypically eligible. In addition, there is often a limited window of opportunity to identify a patient that meets a trial's eligibility criteria before their clinical status deteriorates rendering them ineligible [7]. This risk is most severe in patients with rapidly progressing diseases (metastatic disease, pancreatic or late-stage lung cancers) where treatment and survival timelines are generally very compressed. Unfortunately, these patients are often in greatest need of novel therapies. One approach to address these challenges is to use patient and tumor registries to prescreen patient populations to identify those who are phenotypically/genotypically eligible for target-based clinical trials [7]. This may allow for the identification of the most appropriate patients for treatment in an efficient manner and enhance the understanding of biomarkers found in specific tumors/patient subsets.

CD30 and Brentuximab Vedotin

CD30, a transmembrane glycoprotein receptor, is a member of the tumor necrosis factor receptor superfamily [8-10]. While the function of CD30 has not been clearly defined, it has been implicated in both cell death and proliferation [11]. It has limited expression in healthy tissue or on resting lymphocytes; normal CD30 expression is restricted to the surface of activated T- and B-cells [12]. In contrast, CD30 is uniformly expressed on the malignant Reed-Sternberg cells of Hodgkin lymphoma (HL) and in systemic anaplastic large cell lymphoma (sALCL) [11,13]. It is also variably expressed in other types of non-HL including cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma, diffuse large B-cell lymphoma (DLBCL) [14,15], and some follicular lymphomas [16,17]. This expression profile makes CD30 an attractive therapeutic target for antibody-directed therapies. CD30 is also expressed in nonlymphomatous malignancies; however, the level of expression in these tumor types is variable and the prevalence of CD30 expression in these patient populations is low. CD30 expression has been reported in testicular embryonal carcinoma [18,19], multiple myeloma [20], thyroid cancer [21], lung adenocarcinoma and mesothelioma [22], mesenchymal tumors including osteosarcoma and rhabdomyosarcoma [23], undifferentiated nasopharyngeal carcinoma [24], granulocytic sarcoma [25], and acute myelogenous and mast cell leukemia [26,27]. Few data are available on CD30 protein expression across other solid tumor types.

Brentuximab vedotin (Adcetris, Seattle Genetics Inc), an anti-CD30 ADC, represents a therapeutic application that combines the target specificity of a monoclonal antibody with the cell-killing activity of a cytotoxic small-molecule drug [28]. It consists of 3 components: the anti-CD30 chimeric immunoglobulin (Ig) G1 antibody cAC10 [11,13], the microtubule-disrupting agent monomethyl auristatin E (MMAE) [13,29], and a protease-cleavable linker that covalently attaches MMAE to cAC10 [13,29,30]. Upon binding to CD30 on the surface of malignant cells, the ADC-receptor complex is internalized and traffics to the lysosome where MMAE is released by proteolytic cleavage [31]. Binding of MMAE to tubulin disrupts the microtubule network, inducing apoptotic death of the tumor cell [13]. Brentuximab vedotin is being investigated for the treatment of a variety of CD30-positive malignancies. It received accelerated approval from the US Food and Drug Administration for the treatment of HL patients who have relapsed after autologous stem cell transplant (ASCT) or after ≥2 prior multiagent chemotherapy regimens in patients ineligible for ASCT, as consolidation for HL patients at high risk of relapse or progression post-ASCT, and for the treatment of sALCL patients after failure of ≥1 prior multiagent chemotherapy regimens [32]. Brentuximab vedotin received conditional approval from the European Medicines Agency for the treatment of adult patients with relapsed/refractory (R/R) CD30-positive HL following ASCT or ≥2 prior multiagent chemotherapy regimens when ASCT or multiagent chemotherapy is not a treatment option, as consolidation for CD30-positive HL patients at increased risk of relapse or progression following ASCT, and for the treatment of R/R sALCL [33]. Approval was based on the efficacy and safety results from 2 pivotal phase 2 studies in R/R HL [34,35] and sALCL [36,37]. Brentuximab vedotin activity in solid tumors is an active area of investigation; however, due to the variable expression and low prevalence of CD30 expression in these tumors, a mechanism is required to select for CD30-positive patients that may benefit from CD30-targeted treatment.

Objective

The Total Cancer Care (TCC) Protocol, developed at the Moffitt Cancer Center in 2006 and operationalized by M2Gen, is a personalized cancer care initiative designed to identify and address patients' needs throughout their lifetime, including matching patients to target-based trials [38]. Here we demonstrate that the TCC Protocol may provide a solution for rapidly identifying patients with CD30-positive tumors eligible for CD30-targeted therapies such as brentuximab vedotin.

Methods

Total Cancer Care Protocol and Multidimensional Total Cancer Care Data Warehouse

The TCC Protocol is an ongoing, prospective, observational study used by a consortium network of 18 US hospitals that aims to recruit millions of cancer patients to deliver personalized cancer care. It requests the patient's permission to access their entire medical history, access their tumor for research involving molecular/genomic analysis, and be recontacted in the future if a new finding is discovered that could influence their care such as eligibility for a trial. This lifetime prospective follow-up allows for the discovery and validation of biomarkers, epidemiological studies, and the development of evidence-based practice guidelines [39-41].

The consortium network sites enrolled patients into the TCC Protocol and collected tumor, blood, and urine samples. Tissue samples were snap-frozen within 15 minutes of surgical removal, shipped to M2Gen, macrodissected to ≥85% tumor purity, and quantified for the percent of malignancy, cellularity, stroma, normalcy, and necrosis. An oversight committee ensured proper access and use of tissue and that all Health Insurance Portability and Accountability Act and Human Subject Research requirements were met. The consortium network sites provided longitudinal clinical data from consented patients for integration into the multidimensional TCC Data Warehouse, a multifaceted database established to collect, relate, and interpret clinical and molecular data from all patients seen at the H Lee Moffitt Cancer Center and Research Institute and the Moffitt Cancer Center Screening and Prevention Center since 1998. Both the TCC Protocol and the TCC Data Warehouse have been previously described in detail [38].

The TCC Data Warehouse includes, but is not limited to, cancer registry data, electronic medical record data, tissue data, consent data, molecular data, imaging data, and patient self-reported data. Important to the task of matching patients to target-based clinical trials is the ability to directly query phenotypic/genotypic data residing in the Data Warehouse to perform cohort identification. A front-end tool allows investigators with a specific trial in mind to identify groups of patients based on a set of parameters, including patient inclusion/exclusion criteria and molecular signatures that define the initial patient population to be screened. Once the population has been identified and refined, physicians are notified regarding the availability of a trial and patients are evaluated for their overall suitability to participate. Investigators can also assess whether a certain trial is feasible by determining the number of patients with specific phenotypic/genotypic characteristics available to perform the trial.

Data Extraction

The TCC Protocol was approved on January 16, 2006, by the University of South Florida Institutional Review Board and has been approved by 20 different institutional review boards across 11 states for the community hospital consortium participating in the TCC Protocol. Clinicopathological data, expression profiling, and archival tissue were extracted using deidentified linkages.

Measurement of CD30 Gene Expression Levels

Gene expression data were generated from tumors collected from TCC-consented subjects. The TCC patient gene expression profiling database was retrospectively screened for CD30 expression. The data source was the HuRSTA-2a520709 Affymetrix arrays (GEO GPL15048). Briefly, RNA was extracted from fresh frozen tissue, amplified, and hybridized on Affymetrix GeneChips. The Affymetrix expression arrays were normalized using the Micro Array Suite 5.0 algorithm, scaled to a trimmed mean of 500 and log2 transformed. CD30 expression was extracted using the merck-NM_001243_at probeset (GPL15048). One key question to answer in the current work is what tumor types may have a clinically meaningful subset of high CD30 gene expression samples, and for this purpose the entire data set (all tissue types, primary and metastatic disease) was used to generate a global Z-score. Tumors were categorized into 3 groups: low (Z-score ≤–1), medium (–1> Z-score <1), and high (Z-score ≥1) CD30 gene expression. The distribution plot was generated in MATLAB (R2014B, The MathWorks Inc).

Measurement of CD30 Protein Expression Levels

Banked formalin-fixed paraffin-embedded (FFPE) tumor tissue samples were provided for CD30 protein expression analysis by semiquantitative immunohistochemistry (IHC) at Quest Diagnostics (Teterboro, NJ). Briefly, tissue slides were deparaffinized using a Dako PT LINK system, washed with a Dako wash buffer, and loaded on the LINK 48 autostainer. The staining run consisted of a peroxidase block, then incubation with either a primary antibody to CD30 (clone Ber-H2 Dako) or a negative mouse IgG1 control (BD Biosciences). Visualization of the staining was performed with Dako Flex polymer-based secondary antibody and chromogen 3,3'-diaminobenzidine.

Stained slides were evaluated by board-certified pathologists at Quest Diagnostics. Based on the eligibility criteria of the phase 3 trial (NCT01578499) of brentuximab vedotin versus physician's choice (methotrexate or bexarotene) in patients with CD30-positive CTCL [42], CD30 positivity was defined as membranous, cytoplasmic, or Golgi CD30 expression by ≥10% of either total lymphocytes or neoplastic cells at any intensity >0 on a scale of 0 to 3+. Additionally, CD30 expression was semiquantitatively determined using a composite H-score, calculated by summing the product of the percentage of cells stained (0%-100%) at each given staining intensity (0-3+). Samples were assigned to the CD30-positive protein expression

group if their H-score was ≥10 or the CD30-negative protein expression group if their H-score was <10.

Enrichment for CD30 Immunohistochemistry Staining Positivity

Statistical comparisons of Z- and H-scores were performed using R statistical software (The R Foundation), and the caret R-package was used to estimate the predictive value, accuracy, sensitivity, and specificity of CD30 gene expression.

Results

Patient Population

As of March 2015, the Data Warehouse had a total patient population of 426,284 patients, 120,887 of whom had consented to the TCC Protocol. In total 39,157 fresh frozen tumor specimens were collected, from which over 14,000 samples have been analyzed for gene expression (Table 1).

Table 1. Total number of patients enrolled in the Total Cancer Care Protocol and the type and number of molecular assays performed on tumor specimens as of March 2015.

Patients enrolled/assays performed		Number
TCC[a]Protocol as of March 2015		
	Consented patients	120,887
	Tumors/tissues collected	39,157
	Gene expression profiles	14,218
Data generated from specimens		
	CEL files[b](gene expression data)	14,218
	Targeted exome sequencing samples	4016
	Whole exome sequencing samples	933
	Whole genome sequencing (melanoma)	13
	SNP[c]/CNV[d](lung, breast, colon) samples with normal pairs	559
	RNA sequencing samples	696

[a]TCC: Total Cancer Care.

[b]CEL files: data files created by Affymetrix DNA microarray image analysis software.

[c]SNP: single-nucleotide polymorphism.

[d]CNV: copy-number variation.

The following steps were taken to identify patients with a solid tumor indication and high CD30 gene expression (defined as CD30 global Z-score ≥1) from the TCC Data Warehouse. Of the 120,887 patients who had consented to the TCC Protocol, 99,241 patients had an active TCC consent (not withdrawn from the TCC Protocol and site open to accrual), 49,562 patients were alive, 12,802 of whom had a tumor specimen collected as part of TCC, and gene expression profiles were available for 8307 of these patients. These gene expression profiles indicated that across solid tumor indications, 1138 patients had a CD30 Z-score ≥1 (Table 2).

Table 2. Identification and refinement of patient populations with a solid tumor indication with a CD30 Z-score ≥1 (n=1138) using the Total Cancer Care Data Warehouse.

TCC[a] patients meeting the criteria	Number
Patients consented to the TCC Protocol	120,887
Patients with an active TCC consent	99,241
Patients with a vital status of “Alive”	49,562
Patients with clinical FFPE[b] available	12,802
Patients with a CEL file[c] to evaluate CD30 mRNA expression	8307
Patients who express CD30 with a Z-score ≥1	1138

[a]TCC: Total Cancer Care.

[b]FFPA: formalin-fixed paraffin-embedded.

[c]CEL files: data files created by Affymetrix DNA microarray image analysis software.

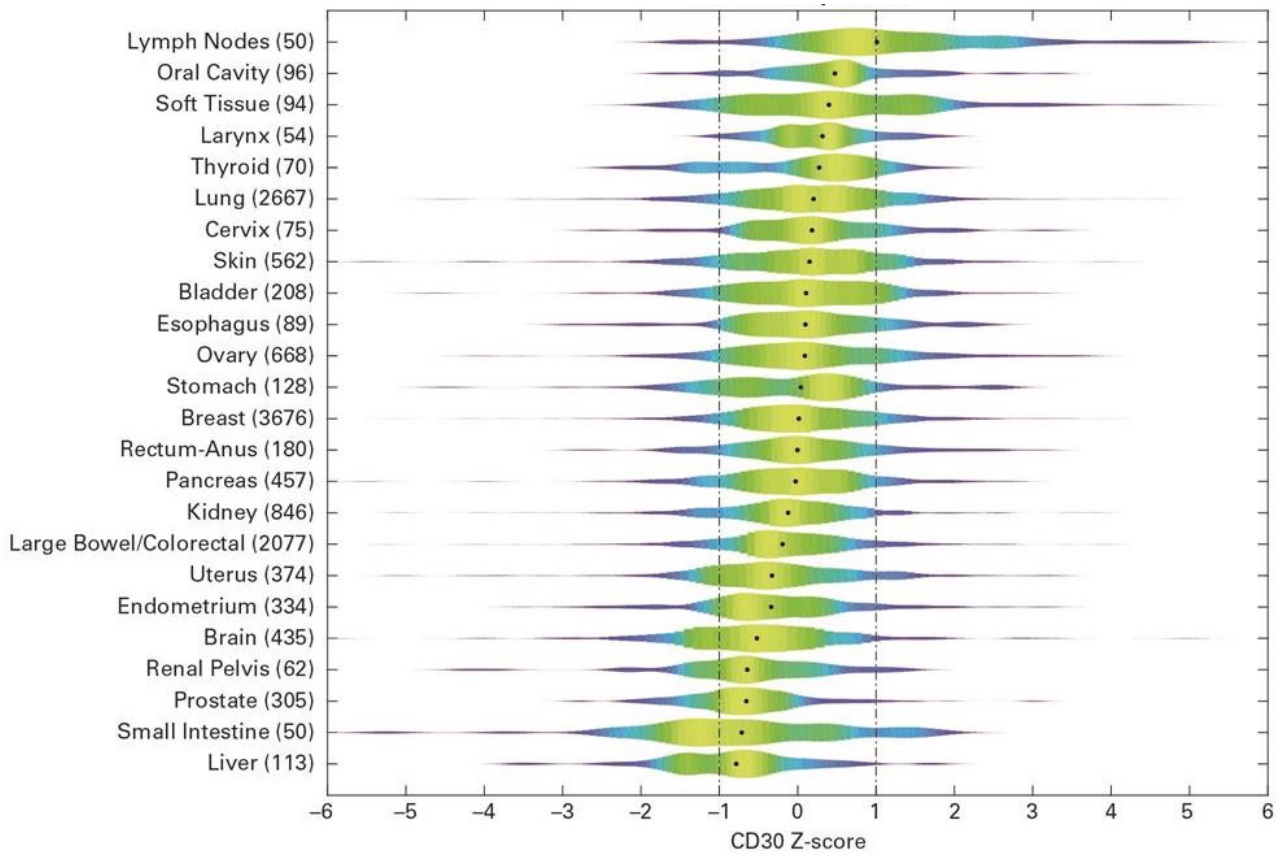
CD30 Gene Expression Levels in Total Cancer Care Data Warehouse

CD30 expression across all solid tumors (n=14,218) is shown grouped by primary site in Figure 1. Aside from lymph nodes, oral cavity tumors and soft tissue (many sarcomas) show the highest median CD30 RNA expression, followed by tumors of the larynx, thyroid, lung, cervix, and skin (mostly melanoma). Table 3 lists the number of samples available, percentage of samples that tested positive (Z-score ≥1) in each group, and summarizes over or under expression of CD30. Soft tissue, skin, lung, and ovary were significantly overrepresented (P<.05).

Table 3. The enrichment of tumor site of origin for overall Z-Scores ≥1 (threshold for high-CD30 gene expression group).

Tissue type	Samples n	Samples with Z-score ≥1 n (%)	Fisher exact	Mean	Median	Standard deviation
Lymph nodes	50	25 (50)	8.12E–10	1.271	1.011	1.382
Soft tissue	94	30 (32)	5.03E–06	0.512	0.399	1.237
Ovary	668	141 (21)	6.23E–08	0.182	0.092	1.104
Oral cavity	96	20 (21)	0.051	0.444	0.475	0.887
Lung	2667	503 (19)	2.71E–17	0.178	0.202	0.986
Esophagus	89	16 (18)	0.217	0.092	0.099	0.988
Skin	562	101 (18)	0.003	0.062	0.152	1.132
Cervix	75	13 (17)	0.315	0.204	0.183	0.939
Bladder	208	35 (17)	0.185	0.087	0.107	0.996
Breast	3676	529 (14)	0.122	0.065	0.015	0.913
Rectum-anus	180	26 (14)	0.743	0.084	–0.003	0.961
Larynx	54	7 (13)	1.000	0.285	0.317	0.648
Small intestine	50	6 (12)	1.000	–0.721	–0.713	1.356
Stomach	128	15 (12)	0.606	–0.061	0.040	1.125
Uterus	374	43 (11)	0.252	–0.251	–0.329	1.036
Pancreas	457	49 (11)	0.071	–0.046	–0.026	0.940
Thyroid	70	7 (10)	0.485	0.024	0.274	0.946
Endometrium	334	30 (9)	0.012	–0.293	–0.339	0.986
Large bowel /colorectal	2077	178 (9)	1.76E–14	–0.152	–0.193	0.871
Kidney	846	53 (6)	2.72E–12	–0.154	–0.123	0.866
Brain	435	24 (6)	3.51E–08	–0.500	–0.520	1.059
Renal pelvis	62	3 (5)	0.041	–0.612	–0.643	1.022
Prostate	305	9 (3)	1.92E–10	–0.636	–0.655	0.802
Liver	113	2 (2)	2.22E–05	–0.826	–0.784	0.915

Figure 1. Density plot of CD30 expression Z-score across Total Cancer Care primary tumor types with ≥50 samples. The dots indicate the median value for each tissue type and the dotted lines show the Z-score cut-off.



CD30 Protein Expression Levels in Archived Tumor Samples and Enrichment for CD30 Immunohistochemistry Staining Positivity

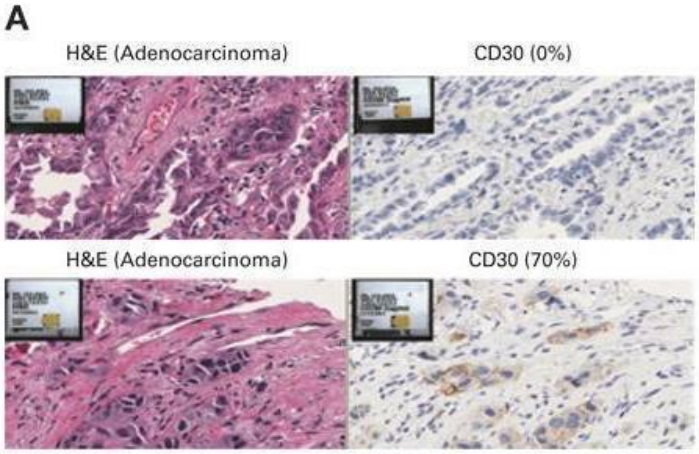
High-level CD30 gene expression was strongly associated with IHC staining positivity. Due to the large number of tumor samples available in the TCC tissue bank for breast, large bowel, lung, skin, and ovary tumors, these tissue types were selected for confirmation of CD30 RNA expression at the protein level using IHC staining. Figure 2 A shows representative images of IHC CD30 staining for 2 lung adenocarcinoma FFPE selected based on TCC Data Warehouse CD30 gene expression. Figure 2 B shows the distribution of gene expression Z-values and IHC H-scores among all analyzed samples. For lung, skin, breast, and ovary samples, in the CD30 RNA-low group 0 out of 39 samples tested IHC-positive, in the RNA-medium group 1 out of 39 samples tested positive, and in the RNA-high group 12 out of 39 samples tested positive (Table 4). There are several reasons that may explain why only a portion of RNA-high samples (12 out of 39) tested IHC-positive. Direct estimation of CD30 expression has its limitations and this is especially true for cell-surface proteins. IHC may underreport true protein expression levels since cell surface proteins such as CD30 are continuously internalized, degraded, and reexpressed over time. It is possible that RNA could be a more sensitive measure for determining CD30 expression. A tumor sample expressing CD30 RNA but having no discernible protein expression during a discrete snapshot in time may still be able to respond to brentuximab vedotin therapy as the protein is reexpressed at the cell surface. For example, brentuximab vedotin has demonstrated significant activity in R/R DLBCL patients with variable or even apparently absent CD30 expression levels, with objective responses in 44% (17/39) and 27% (6/22) of patients, respectively [43,44]. Further studies in this area are underway. Table 4 shows that 9 or 10 random samples were chosen from RNA-low, RNA-middle, or RNA-high groups. This is an arbitrary number and is not proportional to number of samples in each group, since the goal of this work was to evaluate whether RNA expression can be used as a patient selection/enrichment strategy. All large bowel tissue samples stained negative for CD30 expression (data not shown).

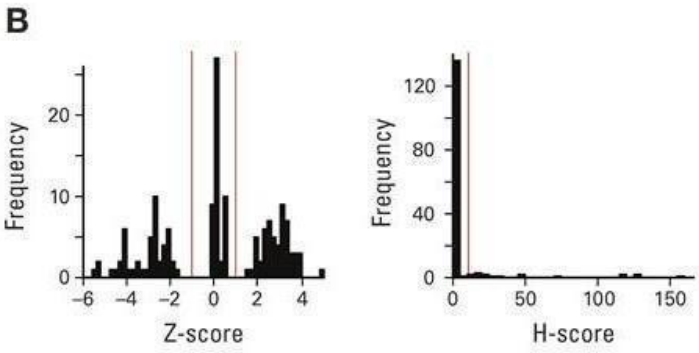
Considering samples from all 4 CD30 positive tumor types, there was a significantly higher proportion of CD30 IHC-positive samples in the RNA-high group relative to low and median groups (P=.00018 and .0015, respectively). Across these same tumor types (lung, skin, breast, and ovary), accuracy ranged from 72% to 79%, sensitivity from 75% to 100%, specificity from 70% to 76%, positive predictive value from 20% to 40%, and negative predictive value from 95% to 100% (Figure 2 C).

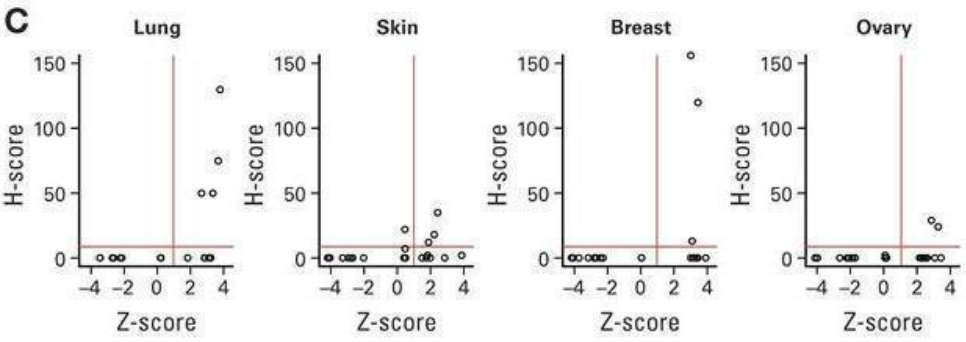
Table 4. Enrichment of immunohistochemistry-positive samples from the CD30 RNA-high, -median and -low groups for breast, lung, skin, and ovarian cancer for the immunohistochemistry staining.

Diagnosis	Samples with RNA screened n (RNA-high)	RNA-low samples		RNA-middle samples		RNA-high samples	
		Screened n	CD30-positive n (%)	Screened n	CD30-positive n (%)	Screened n	CD30-positive n (%)
Breast	3676 (529)	10	0 (0)	10	0 (0)	10	3 (30)
Lung	2667 (503)	9	0 (0)	10	0 (0)	10	4 (40)
Ovary	668 (141)	10	0 (0)	9	0 (0)	10	2 (20)
Skin	562 (101)	10	0 (0)	10	1 (10)	9	3 (33)

Figure 2. (A) Representative images of immunohistochemistry CD30 staining for 2 lung adenocarcinoma formalin-fixed paraffin-embedded slides selected based on Total Cancer Care Data Warehouse CD30 gene expression. Top: Low (0%) CD30 protein expression (H-score = 0) from medium (Z-score = 0.173) CD30 gene expression sample (ML-03-054). Bottom: High (70%) CD30 protein expression (H-score = 130) from high (Z-score = 3.784) CD30 gene expression sample (ML-03-065). (B) Distribution of gene expression Z-scores and immunohistochemistry H-scores among samples selected from the Total Cancer Care Data Warehouse. (C) Evaluation of CD30 gene expression-based enrichment of high CD30 protein expression samples.







	Lung (%)	Skin (%)	Breast (%)	Ovary (%)
Accuracy	79	76	77	72
Sensitivity	100	75	100	100
Specificity	76	76	74	70
Positive predictive value	40	33	30	20
Negative predictive value	100	95	100	100

FPE, formalin-fixed paraffin-embedded; TCC, Total Cancer Care; H&E, hematoxylin and eosin; IHC, immunohistochemistry;

Discussion

Principal Findings

This study reports on the utility of the TCC Protocol and demonstrates how the TCC Protocol may provide a solution for rapidly identifying patients with CD30-positive tumors eligible for treatment with the targeted therapy brentuximab vedotin. Gene expression screening was shown to enrich for protein-level CD30 expression in a number of solid tumor types, thereby demonstrating an important first filter for targeted treatment trials.

Targeted therapy is usually effective in a subset of patients with particular molecular characteristics; however, as a consequence of conducting clinical trials only in these strictly selected populations, the eligible patient pool can be low and accrual becomes more difficult [4,6]. In addition, prescreening a population of patients can be a lengthy process. Not all centers have the facilities to identify a full range of potential biomarkers, and sending tumor tissue to a central laboratory for molecular analysis to identify eligible patients can substantially extend the time between molecular analysis and treatment initiation [7]. Here we demonstrate that the TCC Protocol could help expedite clinical trials of therapies that target rare cancer populations.

In the clinical setting, patient enrollment to trials is frequently determined via protein-based IHC assay. Our results showed that CD30 expression at the RNA level significantly enriched for high CD30 protein expression and that the RNA expression level can be used as a cutoff to reliably enrich for high protein expression. Using the TCC Data Warehouse, its large volume of samples, and pregenerated large-scale expression data, we were able to identify and rank solid tumors that express CD30. CD30 is uniformly expressed in HL and sALCL [11,13]; however, few data are available on CD30 protein expression in solid tumors. Therefore a mechanism is required to select for patients with CD30-positive solid tumors that may benefit from CD30-targeted treatment. The current study indicates CD30 RNA is expressed in a number of solid tumors, and expression is highly variable, being expressed in only a subset of patients' tumors with varying intensities. Aside from lymph nodes, oral cavity tumors and soft tissue (many sarcomas) show the highest median CD30 RNA expression, followed by tumors of the larynx, thyroid, lung, cervix, and skin (mostly melanoma). Patients with these solid tumors could serve as a baseline cohort for any subsequent subject selection for a trial where CD30 expression is used as part of the selection criteria. We acknowledge that the global Z-score cutoff used in the study may not fit well with cancer types that have very high (eg, lymph nodes) or very low (eg, liver) CD30 gene expression levels, indicating the potential future need to adjust the Z-score cutoff in individual cancer type focused clinical trials.

Tissue arrays can screen through tens to perhaps as many as several hundred samples [45]; however, the variability in technical factors and the resulting quality of tissue specimens means that the integrity of tissue samples are in many instances compromised. The TCC Protocol uses well-established, standardized processes for collecting and storing biological samples. Thousands of tumor samples can be simultaneously screened at the RNA level, providing sufficient power to identify low-prevalence markers, including CD30. Matched tumor samples collected during the same protocol period enables direct comparison between gene and protein levels within the same tumor biopsy.

IHC analysis confirmed CD30 expression at the protein level and indicates that CD30 is expressed on tumor cells and not on infiltrating lymphocytes. CD30 gene expression can therefore be considered a reliable indication of CD30 protein expression in a number of solid tumors that may benefit from treatment with a targeted CD30 therapy such as brentuximab vedotin, including breast, melanoma, ovarian, and non–small cell lung cancer. Conversely, no colorectal cancer samples (n=28) had IHC-positive CD30 protein expression (data not shown).

The TCC Protocol is unique in its approach, coordinating patient records and standardizing data collection and sample handling protocols between a wide consortium network of 18 hospitals, resulting in an extremely large reference dataset. Individual clinical studies are heavily selected for a particular study population, exclusively examining small, specialized groups, making population-level variability much harder to identify. By contrast, the TCC Protocol and the Data Warehouse captures a much larger, real-world representation of disease prevalence and may be more likely to detect gene/signature prevalence without the bias of a particular trial population.

Conclusions

High-level CD30 gene expression can be used to significantly enrich patient populations for CD30 protein expression and could be used to guide future protein screening. The TCC Data Warehouse is not anonymized; patients are consented and enrolled into the TCC study with the full knowledge that future screening of the Data Warehouse may identify them as potential candidates for novel treatments and allows for patients to be recontacted. A uniform, large reference data warehouse like TCC may substantially increase the screening efficiency for enrolling patients into biomarker-based trials and as a consequence overcome difficulties associated with recruitment and accelerate the clinical development process. Such an approach could help to expedite clinical trials of therapies that target rare cancer populations.

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Conflicts of Interest

Bin Li, Hadi Danaee, and William L Trepicchio have been employed by Takeda Pharmaceuticals International Co. Steven A Eschrich has been employed by, compensated in a leadership role for, and held ownership in Cuergenx, Inc; received research funding from M2Gen; and has a patent or intellectual property interest in Moffitt Cancer Center. Melissa Mitchell has been employed by M2Gen. David Fenstermacher has been compensated in a consulting or advisory role by M2Gen. Hongyue Dai has been employed by, compensated in a leadership role for, owns stock in, and has a patent or intellectual property interest in M2Gen and has been employed by and owns stock in Merck. William S Dalton has been employed by, compensated in a leadership role for, and owns stock in M2Gen; received honoraria from Genentech; and received research funding from Millennium Pharmaceuticals Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. Anders Berglund and Daniel Sullivan have no conflicts of interest to disclose.

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Abbreviations

ADC: antibody-drug conjugate
ASCT: autologous stem cell transplant
CNV: copy-number variation
CTCL: cutaneous T-cell lymphoma
DLBCL: diffuse large B-cell lymphoma
FFPE: formalin-fixed paraffin-embedded
H&E: hematoxylin and eosin
HL: Hodgkin lymphoma
Ig: immunoglobulin
IHC: immunohistochemistry
MMAE: microtubule-disrupting agent monomethyl auristatin E
R/R: relapsed/refractory
sALCL: systemic anaplastic large cell lymphoma
SNP: single-nucleotide polymorphism
TCC: Total Cancer Care

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Original Paper

Internet-based Self-Management Support for Patients With Well-Controlled Type 2 Diabetes: A Real-Life Study

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Abstract

Background: Little attention has been paid to self-management support of patients with well-controlled type 2 diabetes mellitus (T2DM). Most studies evaluated the addition of self-management support to regular diabetes care, but self-management as an alternative for part of regular diabetes care has hardly been studied. In this study, we offered patients with well-controlled T2DM the opportunity to perform the 3 quarterly monitoring sessions at home using an Internet-based self-management program, resulting in online personalized advice.

Objective: The aim of our study was to assess the reach and feasibility of an Internet-based diabetes self-management support program for patients with well-controlled T2DM, addressing both primary care providers' (PCPs) opinions and patients' willingness to participate in such a support program.

Methods: PCPs assessed patients' eligibility for Internet-based self-management, and patients were offered the opportunity to participate. Characteristics of eligible and ineligible patients were compared, as well as those of participants and nonparticipants, also with regard to quality of life, treatment satisfaction, and illness perceptions. Multivariate logistic regression models were performed and odds ratios (ORs) calculated with 95% CIs.

Results: Almost half (128/282, 45.4%) of the patients with well-controlled T2DM were considered ineligible by their PCPs mainly because of cognitive impairment and language barriers (8.2% and 8.9%). Older patients (OR for each year 1.06, 95% CI 1.03-1.09, $P<.001$), non–Western European patients (OR 3.64, 95% CI 1.67-7.92, $P=.001$), and patients with a longer diabetes duration (OR for each year 1.56, 95% CI 1.04-2.34, $P=.03$) were more often regarded as ineligible. Of the 154 patients considered eligible, 57 (37.0%) consented to participate and 30 (10.6%) started the program. Of 57 participants, 45 returned the 3 questionnaires; 21 of 97 nonparticipants returned the questionnaires. Nonparticipants less often thought that their disease would last their entire life (median 8.0 vs 10.0, $P=.03$) and they were more satisfied with their current treatment than participants (DTSQ total score 44.0 vs 40.0, $P=.05$). There was no significant difference in quality of life between the 2 groups.

Conclusions: PCPs considered half of their patients with well-controlled T2DM incapable of Internet-based self-management mainly because of cognitive impairment and language barriers; of the selected patients, about 1 out of 3 was willing to participate. Older patients, non–Western European patients, and patients with a higher BMI were less likely to participate. Predominantly, practical issues (such as Internet problems) hindered implementation of the Internet-based self-management program.

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KEYWORDS

type 2 diabetes mellitus; self-care; telemedicine; mild cognitive impairment

Introduction

In response to the expanding impact of type 2 diabetes mellitus (T2DM) on health care systems, research has focused on the effectiveness of strategies to improve diabetes self-management. Diabetes self-management support is not restricted to the patient-provider encounter; it needs to be an ongoing process [1]. The type of support can be behavioral, educational, psychosocial, or clinical. Over the last few years, the approach has changed from a didactic one, providing information, to a more empowering type of support, focusing on helping those with diabetes make informed self-management decisions [2,3]. Ideally, empowered patients develop personal goals together with their health care provider and make daily decisions in tuning the management of their disease to circumstances [3]. With diabetes self-management education (DSME), the skills and abilities necessary for diabetes self-care are facilitated in an ongoing fashion [2,4]. We speak of diabetes self-management education and *support* (DSME/S) to underline the importance of ongoing support for individuals with diabetes, particularly to encourage behavioral change, the maintenance of healthy diabetes-related behaviors, and to address psychosocial concerns. Strategies supporting DSME/S are diverse, for example, using telephone follow-up calls or Web-based technologies [1].

Self-management support research mainly focuses on improving self-management of patients with poorly controlled T2DM; less attention has been paid to the support and skills of individuals with well-controlled T2DM. Moreover, research mostly evaluates the *addition* of self-management education or support to regular diabetes care but hardly evaluates the promotion of self-management support as an *alternative* for part of regular diabetes care [5-8]. Patients with well-controlled T2DM, with assumed good self-management skills and behaviors, might benefit from an individualized treatment approach that requires less frequent monitoring by their health care provider. Indeed, glucose levels, blood pressure, and lipid levels in patients with well-controlled T2DM who received 2 checkups per year did not differ from patients who received 4 checkups per year. These results suggest sufficient self-management competence of patients with well-controlled T2DM to maintain adequate cardiometabolic control [9]. However, offering patients the choice of different number of practice visits (2, 3, or 4 times per year) is not yet usual care. Whether just 1 annual checkup at the health care center in combination with adequate self-management support might be sufficient is not known.

Internet-based self-management programs offer new opportunities for patients to practice diabetes self-management at home at a convenient time; they might be less time-consuming for both the patient and the primary care provider (PCP) [5,10]. Nurses estimate the self-care capacities of their patients lower than patients themselves [11]. Practicing self-management is not only related to cardiometabolic control, but also to other aspects of diabetes as a chronic condition, such as health-related quality of life, treatment satisfaction, and illness perceptions [12]. Because ethnic differences, sex, and comorbidities can influence quality of life and illness perceptions, they might also determine patients' diabetes self-management [13]. Health care providers should therefore consider those aspects when providing self-management support [14].

We aimed to determine the reach and feasibility of an Internet-based diabetes self-management support program for patients with well-controlled T2DM, addressing both PCPs' opinions and patients' willingness to participate in Internet-based self-management and investigating the role of treatment satisfaction, health-related quality of life, and illness perceptions in this respect.

Methods

Study Design and Participants

The study was conducted among 36 PCPs (26 general practitioners and 10 practice nurses) in 4 primary care centers of the Leidsche Rijn Julius Health Centers in Utrecht, the Netherlands, delivering care to 890 T2DM patients. In a previous study, patients with well-controlled T2DM were selected on the basis of their individualized treatment targets for hemoglobin A_{1c} (HbA_{1c}), systolic blood pressure (SBP), and low-density lipoprotein (LDL) cholesterol as defined in the Dutch guidelines for T2DM and cardiovascular risk management [15]. According to the Dutch individualized approach for HbA_{1c}, individuals aged <70 years and those aged ≥70 years with lifestyle advice only or receiving metformin monotherapy should achieve an HbA_{1c} target of ≤53 mmol/mol (≤7%). Those aged ≥70 years who are using more blood glucose–lowering agents than metformin and with a diabetes duration of less than 10 years should achieve an HbA_{1c} level of ≤58 mmol/mol (≤7.5%); those with diabetes duration more than 10 years should achieve an HbA_{1c} level of ≤64 mmol/mol (≤8%) [16]. The individualized target level for SBP depends on age; patients aged <80 years should achieve an SBP of ≤140 mm Hg, and those aged ≥80 years should achieve an SBP of ≤160 mm Hg [16,17]. Only in patients with an indication for primary or secondary prevention of cardiovascular disease, the target level for LDL cholesterol is ≤2.5 mmol/L. To determine whether primary prevention is needed, the Dutch guideline uses the Systematic Coronary Risk Evaluation (SCORE) risk function, based on age, sex, smoking status, SBP, and total cholesterol/high-density lipoprotein cholesterol ratio, to determine the 10-year fatal and nonfatal cardiovascular disease risk [17]. Because of the increased risk of cardiovascular disease among patients with T2DM, 15 years is added to the calendar age of patients with T2DM to determine their 10-year cardiovascular disease risk from the SCORE risk function. Patients with a 10-year risk greater than 20% have an indication for primary prevention and thus a target LDL level of ≤2.5 mmol/L. The same holds for patients with 10%-20% risk and with one or more additional risk factors, that is, poor metabolic control, microalbuminuria, overweight, decreased estimated glomerular filtration rate (eGFR), reduced physical activity, or a positive family history of cardiovascular disease. Secondary prevention is indicated in all patients with macrovascular disease [17]. According to these Dutch guidelines, 282 patients (31.7%) had good cardiometabolic control and were eligible to be included in this study [15].

First, the general practitioners, in collaboration with the practice nurses, were asked to judge the eligibility of their patients with well-controlled T2DM and to motivate them to participate in an Internet-based self-management program (see below) to replace 3 out of the 4 regular diabetes monitoring visits.

Second, the patients eligible for Internet-based self-management were offered the opportunity to participate in the Internet-based self-management support program. They could mark their preference and motivation to participate in the Internet-based self-management support program or to continue their care as usual on a return form. If patients decided to participate, they gave informed consent during the next regular practice visit and were enrolled in the study. They performed their first Internet-based self-monitoring session 3 months after their enrollment.

Third, all eligible patients received 3 validated questionnaires regarding quality of life, treatment satisfaction, and illness perceptions before they started the Internet-based self-management (see below).

All available data of participants were collected and the database was locked 1 year after the enrollment of the first patient.

The study was approved by the Medical Research Ethical Committee of the University Medical Center Utrecht.

Internet-based Self-Management Program

Individualized treatment goals were set for the patients with well-controlled T2DM in collaboration with their PCP, during the last practice visit before the enrollment into the Internet-based self-management program. The Internet-based self-management support system was explained to the patients as an alternative for 3 out of 4 regular diabetes checkup visits at the primary care center. Every 3 months, patients received an Internet-based reminder to perform the Internet-based quarterly monitoring. If the patient did not perform the monitoring, he or she received a second reminder. The monitoring consisted of two parts. First, patients were asked about their physically and mentally perceived health in the preceding 3 months and more specifically about their body weight, the presence of diabetic ulcers, their feet, and about cardiovascular problems. Also, medication adherence and medication side-effects were registered. Second, the current weight, fasting blood glucose level, and blood pressure were self-measured and filled in, for which purpose patients had to possess or buy blood glucose and blood pressure measuring devices (cost: €20 in total). On the basis of the entered data, patients received advice, for example, “contact your PCP directly/next working day.” Advice was based on predefined cutoff values for blood glucose, blood pressure, and answers on the questions about physically and mentally perceived health and medication adherence and/or medication side-effects.

Patient Characteristics

Characteristics of all patients with well-controlled T2DM were retrieved from electronic patient records in August 2014 and included age, sex, ethnicity (“Western European” or “non–Western European” based on country of origin of their parents), educational level, duration of diabetes, body mass index (BMI), the presence of microvascular complications and cardiovascular disease, and type of treatment (lifestyle advice only, oral blood glucose–lowering agents, insulin). Educational level was classified as low, middle, or high, according to the Dutch National Public Health Compass [18]. Registered microvascular complications were diabetic nephropathy (eGFR<30 mL/min/1.73m^2 or presence of macroalbuminuria), retinopathy, or neuropathy (SIMMS classification ≥1). Macrovascular diseases including angina pectoris, myocardial infarction, chronic ischemic heart disease, transient ischemic attack, cerebral infarction, intermittent claudication, or aortic aneurysm were recorded.

Questionnaires

Quality of Life

The EQ-5D consists of 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression, each with 3 options of choice ranging from 1 (no problems) to 3 (severe problems). The EQ-5D health state utility scores range from −0.33 to +1.00 and were computed using the Dutch tariff as described by Lamers et al [19,20]. A score of 0 is equal to death, whereas 1 indicates full health. Negative values represent a health state worse than death, meaning an extreme low quality of life. The EQ visual analogue scale (EQ VAS) is a scale ranging from 0 to 100, where respondents can rate their overall health state. A value of 0 indicates the worst imaginable health state, whereas 100 indicates the best imaginable health state [21].

Diabetes Treatment Satisfaction

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) includes 8 items: overall treatment satisfaction, frequency of hyperglycemia and hypoglycemia, treatment convenience and flexibility, satisfaction with understanding of diabetes, and willingness to continue the present treatment and to recommend it to others. All items can be scored ranging from 0 (eg, very dissatisfied) to 6 (eg, very satisfied), with a total score that ranges from 0 to 48. To calculate this total score, the Likert scales used for measuring the frequency of hypoglycemia and hyperglycemia were reversed [22].

Illness Perceptions

The Brief Illness Perception Questionnaire (BIPQ) consists of 9 questions. The first 8 items are scored on an 11-point Likert scale, ranging from 0 to 10, with a different meaning for each question: consequences (the impact of the disease on daily life), timeline (duration of the disease), personal control, treatment control, identity (symptoms experienced), concern, understanding, and emotional response. The ninth question is open-ended and consists of mentioning the 3 most important causes of the disease according to the patient [23,24].

Statistical Analysis

To determine differences between eligible and ineligible patients and between participants and nonparticipants, descriptive statistics were performed. Categorical variables are reported as counts and percentages, continuous variables as means with SD or medians with interquartile range (IQR) for nonnormally distributed variables. The chi-square test was used to assess

differences between groups for categorical variables, the unpaired *t* test for normally distributed continuous variables (age, EQ VAS), and the Mann-Whitney *U* test for nonnormally distributed continuous variables. To analyze the BIPQ items, Mood's median test and the Mann-Whitney *U* test were used. To determine which variables were independently associated with eligibility for Internet-based self-management according to the PCPs, multivariate regression analyses were used with eligibility as the dependent variable, adjusted for clustering at practice level. Included determinants were age, sex, diabetes duration (square root transformed), microvascular complications, cardiovascular disease, using insulin, "lifestyle advice as only treatment," and BMI. Because data on ethnicity were missing for 12% of the patients, ethnicity was included in a second model to analyze its association with eligibility of patients for Internet-based self-management.

To determine which variables were independently associated with participation in the Internet-based self-management support program, multivariate regression analysis was performed, with participation as the dependent variable, adjusted for clustering. On the basis of the results of the first logistic regression analysis and clinical relevance, the following determinants were selected: age, diabetes duration, ethnicity (no missing data), microvascular disease, cardiovascular disease, and BMI.

Results of the logistic regression models are presented as odds ratios (ORs) with 95% CIs and *P* values. A *P* value of <.05 was considered statistically significant. IBM SPSS Statistics version 22 (IBM Corporation) was used.

Results

Health Care Providers

All PCPs, 26 general practitioners and 10 practice nurses, participated. Their mean age was 44.0 (SD 8.2) years, 32 PCPs were female (87%), and the years of experience in primary care ranged from 10 to 15 years. General practitioners and practice nurses assessed eligibility in collaboration.

Study Population

A total of 282 patients with T2DM had reached their treatment targets for HbA_{1c}, SBP, and LDL cholesterol at the time of selection. They had a mean age of 63.0 (SD 13.5) years, with a median diabetes duration of 6.6 years (IQR 7.0); 160 patients were male (56.7%) and 184 patients were of Western European origin (184/247, 74.5%; Table 1).

Ineligible patients were older and more often female than eligible patients, they had a higher HbA_{1c} level, a longer diabetes duration, more microvascular and macrovascular complications, and they used insulin more often (Table 1).

Table 1. Characteristics of all (N=282), eligible (n=154), and ineligible (n=128) patients for Internet-based self-management.

Characteristics	Patients with well-controlled T2DM[a], N (%)	Eligible patients, n (%)	Ineligible patients, n (%)	*P* value (eligible vs ineligible)
Total number of patients	282 (100)	154 (54.6)	128 (45.4)	
Age in years, mean (SD)	63.0 (13.5)	59.3 (12.1)	67.6 (13.8)	<.001
Sex, female	122 (43.3)	58 (37.7)	64 (50)	.04
Ethnicity, Western European[b]	184 (74.5)	121 (78.6)	63 (67.7)	.06
Educational level, low[c]	53 (58.2)	39 (52.7)	25 (65.8)	.15
Diabetes duration, years, median (IQR[d])	6.6 (7.0)	5.5 (5.2)	7.7 (7.5)	.002
HbA_{1c}[e] (mmol/mol), median (IQR[d])	48.0 (6)	48.0 (7)	49.0 (7)	.01
HbA_{1c} (%),median (IQR[d])	6.5 (0.6)	6.5 (0.6)	6.6 (0.6)	.01
LDL[f] cholesterol (mmol/L), median (IQR[d])	1.90 (0.6)	2.00 (0.7)	1.90 (0.7)	.15
Systolic blood pressure (mm Hg), median (IQR[d])	128 (15)	128 (18)	129 (17)	.06
BMI[g] (kg/m^2), median (IQR[d])	28.0 (6.1)	27.6 (5.8)	28.7 (6.8)	.33
Microvascular complications	77 (28.6)	33 (22.9)	44 (35.2)	.03
Cardiovascular disease	66 (23.4)	29 (18.8)	37 (28.9)	.05
Lifestyle advice only	49 (17.4)	31 (20.1)	18 (14.1)	.18
Insulin use	29 (10.3)	10 (6.5)	19 (14.8)	.02

[a]T2DM: type 2 diabetes mellitus.

[b]Ethnicity N=247; n=154 in eligible patients and n=93 in ineligible patients.

[c]Education N=112; n=74 in eligible patients and n=38 in ineligible patients.

[d]IQR: interquartile range.

[e]HbA_{1c}: hemoglobin A_{1c}.

[f]LDL: low-density lipoprotein.

[g]BMI: body mass index.

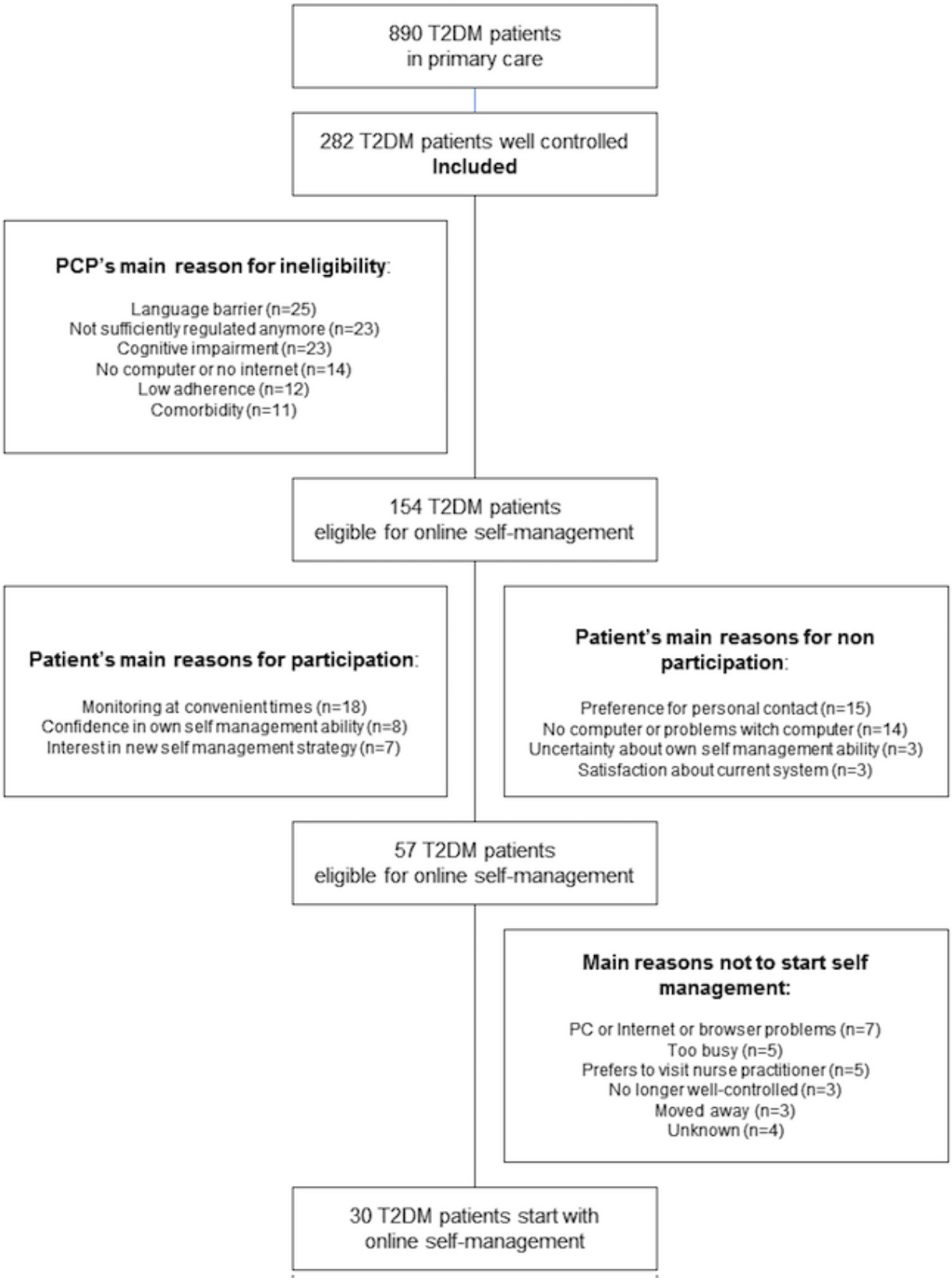
Slightly more than half of the patients with well-controlled T2DM (154/282, 54.6%) were considered eligible for Internet-based self-management (Figure 1). The remaining patients were considered incapable of using the Internet-based self-management program mainly because of “language barrier” (n=25), “not sufficiently controlled diabetes anymore” (n=23), or “cognitive impairment” (n=23; Figure 1).

Older patients were more likely to be considered ineligible for Internet-based self-management by their PCPs compared with younger patients (OR for each year 1.05, 95% CI 1.03-1.08, *P*<.01). After adding ethnicity, patients with non–Western European ethnicity (OR 3.64, 95% CI 1.67-7.92, *P*<.01) and those with a longer diabetes duration (OR for each year 1.56, 95% CI 1.04-2.34, *P*=.03) were also more likely to be considered ineligible by their PCP (Table 2).

Table 2. Ineligibility of patients with well-controlled type 2 diabetes for Internet-based self-management; models are adjusted for health center.

Characteristics	Model 1		Model 2 (including ethnicity)	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age in years	1.05 (1.03-1.08)	<.01	1.06 (1.03-1.09)	<.001
Sex, female	1.55 (0.90-2.67)	.11	1.27 (0.68-2.38)	.45
Diabetes duration in years	1.07 (0.78-1.47)	.69	1.56 (1.04-2.34)	.03
Microvascular complications (present)	1.14 (0.62-2.11)	.68	0.94 (0.46-1.94)	.87
Cardiovascular disease (present)	1.19 (0.61-2.31)	.61	1.41 (0.67-3.00)	.37
Insulin use (present)	1.65 (0.63-4.30)	.31	1.63 (0.66-4.79)	.37
Lifestyle advice only (present)	0.61 (0.29-1.28)	.19	0.56 (0.23-1.36)	.20
Body mass index (index scores)	1.04 (0.98-1.11)	.16	1.05 (0.98-1.12)	.15
Ethnicity (non–Western European)	-	-	3.64 (1.67-7.92)	.001

Figure 1. Flow chart of the study.



Willingness to Participate: Preferences of the Patients Themselves

The 154 eligible patients were invited to participate. Their mean age was 59.3 (SD 12.1) years, their median diabetes duration was 5.5 years (IQR 5.2), 62.3% (96/154) of the patients were male, and 78.6% (121/154) were Western European (Table 3). Of the 154 patients, 57 (37%) were willing to participate (Figure 1). Nonparticipants were older, had more often a low educational level, and had a longer diabetes duration than participants (Table 3).

Table 3. Characteristics of patients invited for Internet-based self-management.

Characteristics	Total population, N (%)	Participating patients, n (%)	Nonparticipating patients, n (%)	*P* value
Total number of patients	154 (100)	57 (37)	97 (63)	
Age in years, mean (SD)	59.3 (12.1)	55.2 (10)	61.7 (13)	.001
Sex, male	96 (62.3)	40 (70)	56 (58)	.12
Ethnicity (Western European)	121 (78.6)	47 (83)	74 (76)	.37
Educational level, low (n=74)	39 (52.7)	15 (50)	24 (55)	.04
Diabetes duration, years, median (IQR[a])	5.5 (5.2)	4.7 (6)	5.7 (6)	.05
HbA_{1c}[b] (mmol/mol), median (IQR[a])	48.0 (7)	47.0 (8)	48.0 (6)	.13
HbA_{1c} (%),median (IQR[a])	6.5 (0.6)	6.5 (1)	6.5 (1)	.13
LDL[c] cholesterol (mmol/L), median (IQR[a])	2.0 (0.7)	2.0 (1)	2.0 (1)	.95
Systolic blood pressure (mm Hg), median (IQR[a])	128 (18)	122 (18)	128 (15)	.06
BMI[d] (kg/m^2), median (IQR[a])	27.6 (5.8)	27.0 (5)	28.5 (6)	.07
Microvascular complications	33 (22.9)	8 (28)	25 (15)	.09
Cardiovascular disease	29 (18.8)	10 (18)	19 (20)	.75
Lifestyle advice only	31 (20.1)	10 (18)	21 (22)	.54
Oral diabetes medication use	121 (78.6)	47 (83)	74 (76)	.37
Statin use	115 (74.7)	38 (67)	77 (79)	.08
Insulin use	10 (6.5)	4 (7.0)	6 (6)	.84

[a]IQR: interquartile range.

[b]HbA_{1c}: hemoglobin A_{1c}.

[c]LDL: low-density lipoprotein.

[d]BMI: body mass index.

Treatment preference was motivated by 48.1 % of the eligible patients (74/154). The reason “monitoring at a convenient time” was mentioned most often (18 patients). The reasons mentioned most often for nonparticipation were “preference for personal contact or visiting nurse practitioner” (n=15 patients) and “no computer or problems working with computer” (n=14 patients; Figure 1).

Questionnaires

Of the 57 patients willing to participate, 45 returned the 3 questionnaires; from the 97 nonparticipants, 21 questionnaires were received. Nonparticipants less often thought that their disease would last their entire life (median 8.0 vs 10.0, *P*=.03) and they were more satisfied with their current treatment than participants. There was no significant difference in quality of life between the 2 groups (Table 4).

Table 4. Quality of life, illness perceptions, and treatment satisfaction.

Questionnaires	Participating patients (n=57)	Nonparticipating patients (n=97)	*P* value
Number of questionnaires returned, n (%)	45 (79)	21 (22)	
EQ-5D health state utility score, median (IQR[a])	1.0 (0.16)	0.89 (0.19)	.20
EQ VAS[b] (range 0-100), mean (SD)	75.9 (11.5)	77.2 (13.7)	.68
BIPQ[c] consequences (range 0-10) median (IQR[a])	3.0 (5)	1.0 (5)	.27
BIPQ timeline (range 0-10), median (IQR[a])	10.0 (2)	8.0 (4)	.03
BIPQ personal control (range 0-10), median (IQR[a])	8.0 (1)	6.0 (4)	.21
BIPQ treatment control (range 0-10), median (IQR[a])	8.0 (2)	8.0 (2)	.06
BIPQ identity(range 0-10), median (IQR[a])	2.0 (3)	2.0 (4)	.58
BIPQ concern (range 0-10), median (IQR[a])	4.0 (5)	2.0 (7)	.89
BIPQ understanding (range 0-10), median (IQR[a])	8.0 (2)	7.0 (3)	.16
BIPQ emotional response (range 0-10), median (IQR[a])	2.0 (4)	1.0 (3)	.33
DTSQ[d] total score (range 0-48), median (IQR[a])	40.0 (6)	44.0 (10)	.05

[a]IQR: interquartile range.

[b]EQ VAS: EQ visual analogue scale.

[c]BIPQ: Brief Illness Perception Questionnaire.

[d]DTSQ: Diabetes Treatment Satisfaction Questionnaire.

Multivariate analysis showed that older patients were more likely to not participate compared with younger patients (OR for each year 1.06, 95% CI 1.02-1.10, *P*<.01). The same held true for non–Western European ethnicity (OR 3.33, 95% CI 1.25-8.88, *P*=.02) and for those with a higher BMI (OR for each kg/m^2 1.11, 95% CI 1.02-1.22, *P*=.02).

Finally, only 30 patients started the Internet-based self-management support program (Figure 1). Predominantly, practical issues (such as problems related to Internet access) hindered implementation of the Internet-based self-management program. Other patients still preferred to visit the nurse practitioner.

Active Participation in the First Year of the Internet-based Self-Management Program

Patients started their first Internet-based support session 3 months after providing informed consent. Depending on their starting date, patients in the Internet-based self-management support program had completed one or more sessions by the date of the database lock. None of the patients stopped the Internet-based self-management monitoring sessions in the first year after implementation. Mean values of fasting blood glucose, SBP, and BMI remained stable during this study period.

Most patients used oral diabetes medication (80%). Antihypertensive medication was used by half of the patients and 67% (38/57) of the patients used a statin. In 4 cases, medication was changed in response to the Internet-based contact, twice during the first and twice during the second Internet-based contact. Furthermore, the following personalized advice was given:

1. In 83% of the self-management monitoring sessions the patient received a message that their entered data were within target.

2. In the 64 self-management monitoring sessions performed, 11 patients were advised to contact their PCP the next working day, either because of a very high self-reported blood pressure value (n=4) or because of reported diabetes-related health problems in the previous 3 months (n=7);

3. Two patients received a message to contact their PCP the same day, 1 patient because of an entered low blood pressure value and 1 patient because of diabetes-related health problems; both patients followed the advice.

Discussion

Principal Findings

This study explored the reach of an Internet-based self-management support program including a 75% decrease in personal contact, replaced by Internet-based personalized advice, in T2DM patients with good cardiometabolic control. Results showed that the PCPs perceived almost half of their own patients with well-controlled T2DM as ineligible for this approach, mainly because of cognitive impairment and language barriers. Of the 154 eligible patients, 37% (57/154) chose to participate. The main reason to participate was better time management, whereas the reasons mentioned most often for nonparticipation were a preference to visit the nurse practitioner and not having a computer. Older patients, patients with non–Western European ethnicity, and patients with a high BMI were less likely to participate. Of the 57 patients who chose to participate, only 30

patients started the Internet-based program, mostly because Internet and browser problems. Mean cardiometabolic values remained stable during participation in the Internet-based self-management support program.

Internet-based self-management support as a replacement for part of the regular care might facilitate patient centeredness and time-effectiveness. Patients can manage their disease—with personalized goals—and can perform the monitoring at home at a convenient time; they do not have to visit the health center and are not absent from work, sport, or family. Moreover, it enables PCPs to give more attention to patients with poorly controlled T2DM. However, the applicability of Internet-based self-management support showed to be limited, even in this group of people with well-controlled T2DM.

Participants of the Internet-based program were younger than nonparticipants, suggesting that older patients are less comfortable working with Internet-based self-management with their personal computer. This suggestion is supported by the main reason for nonparticipation as mentioned by the eligible patients. Previous research showed that elderly patients often have poor technical skills in this respect [25].

Our finding that T2DM patients with higher education were more willing to take over some monitoring duties is in concordance with previous research [26]. Patients who were less satisfied with their current treatment might have been more willing to participate in Internet-based self-management because they prefer a more active role in their own treatment.

Patient of Western European origin, in first instance based on the PCPs' selection but also based on the patients' own preference were more often among the participants than those with Non-Western European origin. Self-care behaviors differ by ethnicity and self-efficacy. Differences in perceptions have an impact on self-care behavior [27-29]. The reason that patients with non–Western European ethnicity seemed less motivated to participate might be due to ethnic differences in illness perceptions [30]. Non–Western European patients might perceive their diabetes more often as a harmless condition that could be cured, compared with Western European patients [31]. These findings suggest that culturally tailored messages about diabetes self-care might be needed. However, other reasons for nonparticipation should also be considered, such as health literacy.

A strong aspect of this study is the real-life setting in which the true reach of an Internet-based self-management support program with all the related difficulties of its implementation could be demonstrated. However, against that background this study had some limitations. First, patients were considered to have good cardiometabolic control based on data retrieved from the patient records in August 2014, whereas the patients were enrolled in 2015. The time interval between the "eligibility check" by the PCPs and the invitation resulted in a number of patients who could not participate anymore.

Second, one could state that the reach of the program was limited because patients with well-controlled T2DM were offered the opportunity to participate in the Internet-based self-management program only when their PCP judged them as eligible. Therefore, not all patients with well-controlled T2DM were asked to participate. This strategy was chosen for patient safety. However, the indications for selection by the PCPs, and afterward the patients' preferences, were rather similar: younger age, Western European ethnicity, and shorter diabetes duration. A shared decision-making process is a realistic and more elegant option to determine the eligibility of patients to participate in an Internet-based self-management program and to evaluate the preferences of all patients with well-controlled T2DM.

Third, the number of patients who actually started the Internet-based self-management support program was low. There were some Internet and browser problems with the implementation of the Internet-based self-management support program, leading to fewer participants to start the program. However, this represents implementation in a real-life setting.

Conclusions

This study showed that PCPs consider about half of all patients with well-controlled T2DM eligible for an Internet-based self-management support program and that about 1 out of 3 eligible patients is willing to participate. Almost half of the patients who chose to participate did not actually start the program, demonstrating that implementation of such a program is difficult and its applicability is limited. Although only 10% of all patients with well-controlled T2DM eventually started the program, this number is relevant, given the huge numbers of people with T2DM. For example, with about 800,000 people with T2DM in the Netherlands and 25%-30% with good control, the use of our Internet-based self-management support program could hypothetically result in a reduction of nearly 70,000 practice visits a year, which might diminish the diabetes burden on the health care system.

Authors' Contributions

HEH designed the study, collected data, and wrote the manuscript. EL and IETMG collected and researched data and wrote the first draft of the manuscript. GEHMR reviewed and edited the manuscript. RCV researched data, contributed to the discussion, and reviewed and edited the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BIPQ: Brief Illness Perception Questionnaire
BMI: body mass index
DSME: diabetes self-management education
DSME/S: diabetes self-management education and support
DTSQ: Diabetes Treatment Satisfaction Questionnaire
eGFR: estimated glomerular filtration rate
EQ VAS: EQ visual analogue scale
HbA1c: hemoglobin A1c
IQR: interquartile range
LDL: low-density lipoprotein
OR: odds ratio
PCP: primary care provider
SBP: systolic blood pressure
SCORE: Systematic Coronary Risk Evaluation
T2DM: type 2 diabetes mellitus

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