JMIR Research Protocols

Ongoing Trials, Grant Proposals, Formative Research, Methods, Early Results
Volume 9 (2020), Issue 11 ISSN: 1929-0748

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Twelve-Week Internet-Based Individualized Exercise Program in Adults With Systemic Lupus Erythematosus: Protocol for a Randomized Controlled Trial

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Abstract

Background: Systemic lupus erythematosus is a systemic autoimmune disease, which is associated with high cardiovascular risk, a predisposition to metabolic disorders, muscle wasting, and fatigue. Exercise therapy has become an important part of the long-term treatment of comorbidities in systemic lupus erythematosus. Exercise can lead to various benefits in patients with systemic lupus erythematosus such as increased aerobic capacity and exercise tolerance, resulting in an increased quality of life, decreased depression, and decreased fatigue. At the moment, no evidence-based treatment guidelines that recommend exercise for patients with systemic lupus erythematosus exist. Also, the efficacy of different training programs requires further investigation.

Objective: This study focuses on the feasibility, efficacy, and safety of an internet-based exercise program in patients with systemic lupus erythematosus. Furthermore, we investigate the feasibility and efficiency of anaerobic training compared to aerobic training.

Methods: Overall, patients with systemic lupus erythematosus from the Division of Nephrology, Rheumatology, and Immunology outpatient clinic of the University Medical Center Mainz who are clinically stable status are included and randomized in an aerobic exercise group (n=10), anaerobic exercise group (n=10), or treatment as usual group (n=10). After completing initial clinical testing and physical fitness tests, patients undergo supervised 12-week online exercise programs, receiving weekly individualized training plans adapted to their physical performance. The primary outcome is change in physical fitness (VO2 peak) after 12 weeks compared to baseline. Secondary outcomes are disease activity measured via laboratory results (complement, autoantibodies) and questionnaires, as well as changes in muscle mass (anaerobic exercise group), results of the Chair-Stand test, and measurements of circulating cell-free DNA and extracellular vesicles.

Results: The study was registered in May 2019. Enrollment began in May 2019. Of 40 patients who were initially screened, 30 patients fulfilled the inclusion criteria and were included in the study; 1 participant withdrew prior to the start of the exercise program. Among the 25 patients who completed the study, no serious adverse events have been reported; 3 participants withdrew during the program (due to frequent colds, n=1; Crohn relapse, n=1; physical strain, n=1), and 1 participant has not yet completed the program. Data analysis is ongoing, and results are expected to be submitted for publication in January 2021.

Conclusions: We expect the online exercise intervention to be a feasible and efficient tool to provide regular individualized exercise for patients with systemic lupus erythematosus.

Trial Registration: ClinicalTrials.gov NCT03942718; http://clinicaltrials.gov/ct2/show/NCT03942718.

International Registered Report Identifier (IRRID): DERR1-10.2196/18291

(JMIR Res Protoc 2020;9(11):e18291) doi:10.2196/18291

KEYWORDS

systemic lupus erythematosus; physical activity; internet-based exercise program, disease activity; fatigue

Introduction

Systemic lupus erythematosus is a chronic autoimmune disease that affects organs and tissues, such as skin, kidney, joints, lungs, and the central nervous system [1]. Its etiology is still unknown. Remarkably, nearly 90% of patients with systemic lupus erythematosus are females [2]. Its incidence in Germany in 2002 was 15.4 per 100,000 in males and 55.4 per 100,000 in females [3]. Worldwide, prevalence ranges from 20 to 70 per 100,000 [4]. Both geographical and racial differences seem to influence the prevalence of systemic lupus erythematosus [4].

Therapeutic approaches aim to ensure long-term survival by keeping disease activity low, reducing drug toxicity, and improving quality of life [5-7]. Due to improved drug therapies, the 10-year survival rate of patients with systemic lupus erythematosus increased remarkably from approximately 50% in the 1950s to >90% since 1990; however, long-term use of drugs and the inflammatory potential of the disease itself cause a host of comorbidities such as cardiovascular disease, end-stage renal failure, or osteoporosis [8]. Compared to the general population, the risk of death is still greater by approximately 5-fold [9,10]. It has been shown that cardiovascular disease is the main risk factor of increased death and organ damage [11].

In addition to classical therapy options, nonpharmacological interventions, which are well tolerated by the patient, are desirable. Between 67% and 90% of patients with systemic lupus erythematosus, depending on their ethnicity, report fatigue which leads to tiredness, inactivity, and thus, to a reduction of physical fitness [12,13]. This often accompanies a progressive reduction of muscle mass leading to sarcopenia [14]. Therefore, the effect of exercise in patients with systemic lupus erythematosus was investigated in several small case studies [14-20], and it was shown that exercise may be a promising augment treatment to counteract the negative effects caused by inactivity in patients with systemic lupus erythematosus (ie, fatigue, depression, disease activity, sarcopenia, and reduced aerobic capacity). Several studies have shown that physical exercise is well tolerated in systemic lupus erythematosus [21]. Cycling, running, and walking were shown to be effective and well tolerated in patients with systemic lupus erythematosus [14,18,21,22], while progressive resistance training with elastic bands is considered to be a safe method to improve muscle strength [23]; however, cardiovascular training seems to have a better effect on the quality of life of patients than resistance training does [24].

While previous studies [19,25,26] applied a supervised face-to-face exercise concept, which is very costly and time consuming due to a high staff load, more time- and cost-effective interventions are necessary to make this training concept accessible to as many patients as possible. Internet-based exercise interventions fulfill these requirements. Furthermore, individualized internet-based exercise programs, unlike group interventions, allow adjustments for each patient. There is also the possibility of a higher level of adherence, since patients are free to decide on which day and at what time they schedule their sports program, regardless of their different daily routines. Therefore, we developed an individualized internet-based exercise program. We hypothesized that patients will adhere to a 12-week exercise program and that the program will lead to a significant improvement in peak oxygen uptake, demonstrating an improvement in aerobic capacity, as well as a reduction of fatigue, depression, disease activity, and sarcopenia in patients with systemic lupus erythematosus.

Methods

Ethics

This study was approved by the ethics commission of the University Medical Center Mainz, Germany and the Medical Associations Rhineland-Palatinate (number 2018-13039) and conformed to the standards of the Declaration of Helsinki of the World Medical Association. Written consent was obtained from all participants at the beginning of the study.

Recruitment

Participants aged 18-65 years and diagnosed with systemic lupus erythematosus according to the 1982 American College of Rheumatology classification criteria and the new 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria were recruited [5,27]. Detailed inclusion and exclusion criteria are listed in Table 1.

Table 1. Inclusion and exclusion criteria.

Type	Criteria
Inclusion	1. Diagnosis of systemic lupus erythematosus by the classification criteria ACR[a] and the 2019 EULAR[b]/ACR Classification Criteria for systemic lupus erythematosus 2. Positive antinuclear antibody titer (≥1:80) or anti-dsDNA[c] (≥200 IU/mL) or positive anti-dsDNA autoantibody (≥30 IU/mL) 3. Systemic Lupus Erythematosus Disease Activity Index ≥4 4. For 30 day prior, stable immunosuppressive therapy with steroid (0-20 mg/day) or other immunosuppressive medication such as hydroxychloroquine, chloroquine, azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, belimumab, rituximab
Exclusion	1. Pregnancy 2. Active lupus nephritis, myocarditis, or pericarditis 3. Physical activity more than 2 times a week

[a]ACR: American College of Rheumatology.

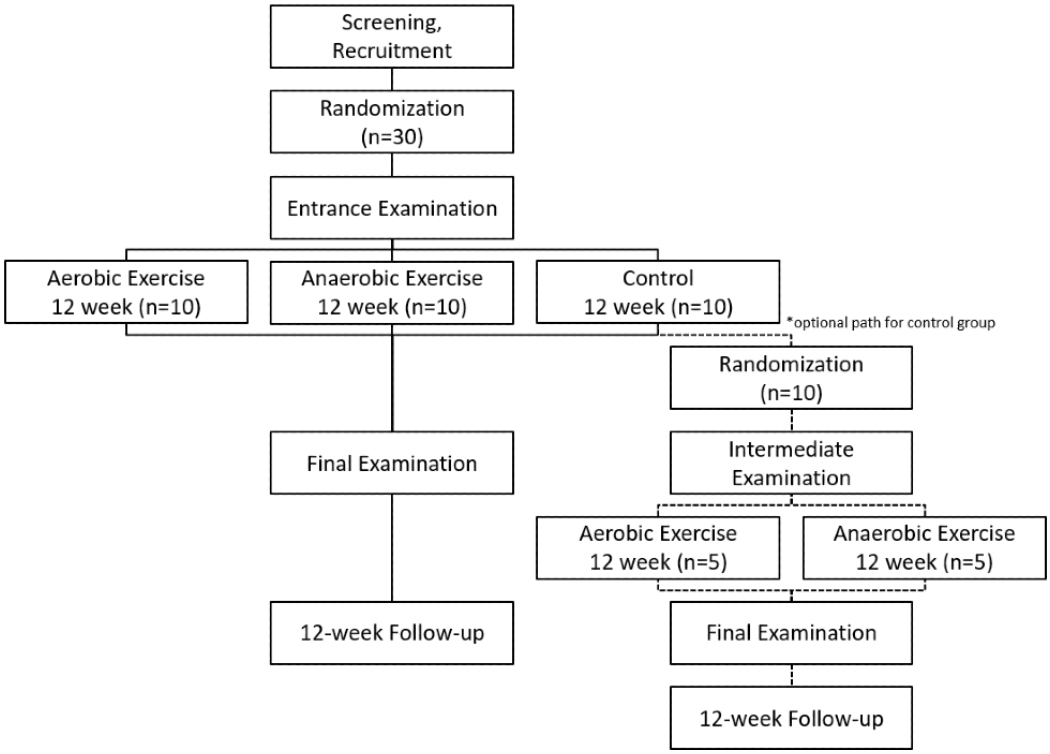
[b]EULAR: European League Against Rheumatism.

[c]dsDNA: anti–double stranded DNA.

Study Design

After recruiting and screening participants (n=30), they were randomized to 3 groups: mainly aerobic training (n=10), mainly anaerobic training (n=10), and control (treatment as usual; n=10). The patients in the control group have the option to participate in one of the exercise groups after 12 weeks of treatment as usual (Figure 1). By creating 2 different exercise groups, we wished to study whether there are different effect sizes and differences in feasibility. As far as we know, no data are available on anaerobic training conditions for patients with systemic lupus erythematosus.

Figure 1. Study design.



During the examinations and follow-up appointments, which take place in the Division of Nephrology and Rheumatology outpatient clinic of the University hospital Mainz and the Department of Sports Medicine of the University in Mainz, blood samples are taken, and questionnaires are filled out. During the outpatient visits, the patients are cared for by the study doctor and a doctoral student in sport medicine. Participants undergo preliminary examination, which includes bioelectric impedance analysis (InBody 3.0, InBody Co Ltd), a Chair-Stand test (as many complete sit-stand-sit cycles as possible, with a chair height of 43.2 cm, in 30 seconds) [23], resting electrocardiography (ECG) (AT-60; Schiller Medizintechnik GmbH), and a pulmonary function test (Bodybox 5500, Medisoft Group).

During physical fitness testing, patients undergo spiroergometry and ECG. To determine individual physical performance, participants undergo standardized stepwise exercise test on a laboratory treadmill (Saturn, H/p/cosmos Sports & Medical GmbH) until participative exhaustion, with a modified walking protocol (Table 2) that includes 14 steps of increasing velocity

and partially increasing slope [28]. Absolute and relative contraindications as well as stop criteria to terminate spiroergometry were defined according to the guidelines [29]. The same physical fitness tests are repeated at the end of the 12-week period to evaluate the effect of the training program of each participation.

Table 2. Modified walking protocol [28].

Stage	Time, minutes	Cumulated time, minutes	Velocity, km/h	Slope, %
1	3	3	3.0	1.5
2	3	6	3.7	3.0
3	3	9	4.4	4.9
4	3	12	5.1	6.3
5	3	15	5.8	7.4
6	3	18	6.5	8.2
7	3	21	6.5	9.8
8	3	24	6.5	11.4
9	3	27	6.5	13.0
10	3	30	6.5	14.6
11	3	33	6.5	16.2
12	3	36	6.5	17.8
13	3	39	6.5	19.4
14	3	42	6.5	21.0

Intervention

After exercise testing, patients in both intervention groups were given an individual account for the internet platform. In a personal introduction appointment after exercise testing, participants received information about the internet platform and all materials, such as the smartwatch (M430, Polar Electro Oy) and 3 different resistance bands (KG 67071, 67072, 67073, Trendy Sport GmbH & Co). The smartwatch was used to evaluate the physical strain of the patients (heart rate) and distance during exercise. Participants had the opportunity to enhance social contacts by using the smartwatch's internal message function. Training videos for home-based resistance training could be downloaded from the platform.

Every Monday, an individualized training schedule was sent to each patient in both intervention groups. Participants are given a weekly protocol, where all physical activities during the week, including all recommended (endurance and strength) and additional activities, should be recorded. After each week, a sports therapist analyzes the training data to adapt the schedule for the following week according to participant self-reported values of pain and training load (Table 3).

Table 3. Weekly individual training adjustment [28].

Pain[a]	Load[a]	Adjustment
If		
0-3	0-6	Increase
0-3	7	Maintain
0-3	8-10	Reduce
Else if		
4-6	0-7	Maintain
4-6	8-10	Reduce
Else		
7-10	0-10	Reduce

[a]Borg scale 0-10.

To determine the exercise program, we used the FITT-VP (frequency, intensity, type, time, volume, and progression) principle based on American College of Sports Medicine guidelines [30]. Therefore, 3 exercise sessions were recommended, and each exercise program was be adjusted (intensity or duration) by interpreting of the training data and the rating of perceived pain and load every week. The recommendations are based on heart rate in training zones

related to individual anaerobic threshold. The 12-week exercise program consists of 4 fixed mesocycles depending on the group (Table 4).

Table 4. Number of aerobic and anaerobic training sessions for each group.

Group and session	Mesocycle 1 Weeks 1-3	Mesocycle 2 Weeks 4-6	Mesocycle 3 Weeks 7-9	Mesocycle 4 Weeks 10-12
Aerobic exercise group				
Aerobic training sessions	3	3	3	3
Anaerobic training sessions	0	0	0	0
Anaerobic exercise group				
Aerobic training sessions	3	2	1	0
Anaerobic training sessions	0	1	2	3

Both intervention groups undergo the same aerobic exercise program in the first mesocycle. Afterward, differently structured mesocycles in both intervention groups are used to verify the effects of aerobic or anaerobic exercise, respectively. Each training session contains endurance exercise between 20 and 50 minutes, including a 5-minute warmup, and a 5-minute cooldown, depending on the current progression stage. Every patient can scale up, scale down, or remain on different progression stages from week 1 to week 12 according to individual training adjustments (Table 4). The aerobic exercise group performs aerobic training sessions for the whole program. In the anaerobic exercise group, more intense training sessions are progressively integrated (Table 5). For the anaerobic training sessions, we use an intermittent protocol with heart rate above the individual anaerobic threshold for 2-3 minutes per interval. The progression stages in the anaerobic exercise group range from 3 intervals (1 interval of 3 minutes + 2 intervals of 2 minutes each) up to 8 intervals (8 intervals of 3 minutes each) with a 2-minute walking break between intervals, a 5-minute warmup, and a 5-minute cooldown.

To assess the effect of the intervention program, the control group (treatment as usual) will participate in voluntary exercise that is assessed using a questionnaire for habitual physical activity [31]. These participants also received a smartwatch.

We recommended that walking or running should be the main part of endurance training sessions. Moreover, we suggested performing 1 to 2 strength training session weekly or integrating specified strength training exercises into the endurance training (eg, at the end of running or walking).

We created a compilation of 10 strength exercises for major muscle groups that can be trained separately with elastic resistance bands. We recommended 3 sets with 15 repetitions per exercise each week [32]. Furthermore, the compilation includes 10 relaxation exercises, recommended for after strength training sessions.

Table 5. Outcome parameters.

Outcome	Description	Measurement timepoint
Primary outcome		
VO_2 peak[a]	Using spiroergometry	Week 0, 12
Secondary outcomes		
Fatigue Scale for Motor and Cognitive Functions	This scale consists of 20 items using a 5-point Likert scale, from absolutely agree to absolutely disagree) to assess cognitive fatigue (10 items) and motor fatigue (10 items). The scores for cognitive and motor fatigue are added for the sum score. A cutoff value of 43 indicates mild fatigue, whereas higher values are associated with moderate fatigue (≥53) or severe fatigue (≥63) [33].	Week 0, 12, 24
Beck Depression Inventory	This questionnaire consists of 21 sets of statements, which are ranked in terms of severity from 0 to 3. The sum (range 0-63) indicates the severity of depression. The standardized scale is 0-8, no depression; 9-13, minimal depression; 14-19, mild depression; 20-28, moderate depression; 29-63: severe depression [34].	Week 0, 12, 24
Systemic Lupus Erythematosus Disease Activity Index	This index consists of 24 items including clinical and laboratory variables to measure disease activity within the previous 10 days. The maximum score is 105, scores >3 indicate a mild or moderate flare, and scores ≥12 indicate a severe flare.	Week 0, 12, 24
Disease Activity Score–28	The score indicates rheumatoid arthritis disease activity and treatment response. It is composed of 4 measures including the number of swollen or tender joints, C-reactive protein level, and patient's health assessment. A total score is calculated using the formula. Values range from 2.0 to 10, where a higher value indicates higher disease activity. The score is a valuable tool to assess the severity of joint involvement and activity in systemic lupus erythematosus.	Week 0, 12, 24
Work Ability Index	This self-assessment questionnaire is used to assess the work ability of the patients. The questionnaire covers 6 dimensions including current work ability, as well as past 2-year estimation among others: 7-27 points indicates poor, 28-36 points indicates moderate, 37-43 points indicates good, and 44-49 points indicates very good work ability.	Week 0, 12, 24
Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index	This scoring system includes a score to measure the activity of skin lesions and a score to measure the damage of skin lesions in patients with discoid lupus erythematosus and cutaneous lupus erythematosus. The score is used as a follow-up parameter. It has been shown that scores correlate well with the physicians and patient's global assessment of disease activity.	Week 0, 12, 24
Autoantibody titer	dsDNA[b] titer (standard value ≤20 IU)	Week 0, 12, 24
Complement level	C3c and C4 levels (standard values: C3c: 0.9-1.8 g/L; C4: 0.1-0.4 g/L)	Week 0, 12, 24
Circulating, cell-free DNA levels	The concentration of circulating, cell-free DNA (ng/mL) is measured before during and after laboratory standardized stepwise exercise test from capillary and venous blood samples. After centrifugation of the samples, the circulating cell-free DNA is determined by a direct quantitative real-time polymerase chain reaction method from plasma without previous DNA extraction [31] Compared to healthy participants patients with systemic lupus erythematosus show higher circulating cell-free DNA plasma levels.	Week 0, 12
Extracellular vesicles	The relative amount of extracellular vesicle subpopulations is analyzed using bead isolation and size exclusion chromatography followed by protein marker characterization.	Week 0, 12
Lactate levels	To estimate the lactate threshold, capillary blood samples are taken from the fingertips using end-to-end capillary with a defined volume of 20 µL (sodium heparin, EKF-Diagnostics GmbH). Erythrocytes are hemolyzed in glucose/lactate hemolyzing solution (EKF-Diagnostics GmbH) before analysis using the Biosen S-Line (EKF-Diagnostics GmbH). In this study, capillary blood samples are taken at the beginning of the test (pre), after each step of treadmill walking, as well as 3 minutes after exhaustion. All samples are quantified directly after the test. To define the anaerobic lactate acid threshold or individual anaerobic threshold the Dickhuth model (baseline +1.5 mmol/L model) is used [35].	Week 0, 12
Ventilatory threshold	Change in ventilatory threshold after 12 weeks compared to baseline.	Week 0, 12
Muscle mass	Muscle mass will be measured in absolute mass (kilograms) including internal organs using bioelectrical impedance analysis.	Week 0, 12
Chair-Stand test	Change of Chair-Stand test after 12 weeks compared to baseline.	Week 0, 12

Outcome	Description	Measurement timepoint
Borg scale	Ratings of perceived exertion with the Borg 15-grade scale (6-20) within the last 30 seconds of each stage of walking will be recorded [36].	Week 0, 12
Smartwatch data	Evaluation of the physical strain and performance during the weekly training sessions measured by heart rate and distance covered during running.	Week 0-12

[a]VO2 peak: peak oxygen uptake.

[b]dsDNA: anti–double stranded DNA.

Outcomes

Primary Outcome

The primary objective of this study is to examine changes in physical fitness in response to an internet-based exercise program with aerobic or anaerobic training protocols in patients with systemic lupus erythematosus. Therefore, the primary outcome is the change of VO_2 peak (after 12 weeks in comparison to baseline).

Secondary Outcomes

The secondary outcome parameters are summarized in Table 5. This table also shows at what timepoints parameters are measured.

Results

The study was registered in May 2019 (NCT03942718). Information brochures were laid out in the rheumatology outpatient clinic of the University Medical Center Mainz for the recruitment of patients. In addition, information brochures were sent by mail to patients with systemic lupus erythematosus treated in the rheumatology outpatient clinic. Out of 40 patients who contacted us, 30 patients fulfilled the inclusion criteria and were included in the study. One patient withdrew before the first performance test and before the start of the sports program due to a fracture, and 29 patients started the study. Among the 25 patients who completed the study, no serious adverse events were reported; however, 1 patient has not yet completed the study, and 3 patients withdrew from the study. One due to repeated colds, so that regular sport was not possible, another patient had a relapse of Crohn disease during the study period, and 1 patient stated that continuing to exercise was not possible due to physical strain.

Discussion

Previous studies [20,21] indicate that exercise can lead to various benefits in patients with systemic lupus erythematosus due to an increased aerobic capacity, exercise tolerance, and quality of life as well as decreased depressive symptoms and symptoms of fatigue. These positive effects were achieved in supervised as well as unsupervised exercise programs [15,17-19,22,37,38]. In addition, it has been repeatedly discussed whether physical activity leads to an increase in lupus disease activity—an increase in autoantibodies, an increase in the consumption of complement factors, and an exacerbation of clinical symptoms such as arthralgia and myalgia. However, several recent studies [18,20] have shown that physical activity is safe in patients with systemic lupus erythematosus and that there is no increase in lupus disease activity.

Nondrug therapy, especially exercise therapy, has become an important component of long-term treatment of comorbidities of systemic lupus erythematosus in recent years. Therefore, effective and efficient exercise programs need to be studied. In this study, we focus on the feasibility of an internet-based exercise program in patients with systemic lupus erythematosus. Similar concepts have already been successfully applied in other diseases such as major depressive disorder, fatty liver disease, Barrett carcinoma, cystic fibrosis, and psychiatric disorders [28,39-41].

To our knowledge, this is the first study in which exercise treatment in systemic lupus erythematosus is supervised via the internet, which has several benefits: (1) Patients with systemic lupus erythematosus can perform their individual exercise program at a self-chosen time point and do not need to participate in a presence program. Moreover, participants can fulfil their exercise program at home, which has several logistic benefits. (2) To reduce the risk of physical over- or underload, a weekly feedback protocol, which includes the rating of perceived exertion and the heart rate during the exercise sessions, is used. Based on these data, participants receive weekly-adapted exercise prescription, which allows adjustments in accordance with FITT-VP principles throughout the program. Moreover, we ensure a moderate beginning of exercise prescription to avoid injuries or dropout based on exercise overload. Other studies found a positive association between adherence, compliance, or persistence and treatment satisfaction [42] In this study, adherence can be evaluated by completed training sessions. (3) By using the platform, participants can benefit due to a chat and forum function. (4) This allows patients to communicate quickly with the sports therapist, gain insight into their own training sessions, and have the opportunity to communicate with each other. Through this exchange, there is a possibility of mutual motivation enabling social connection and lasting training bonds among participants. By using the internet to supervise the exercise program, resources are reduced, since one sports therapist can supervise participants in parallel.

Tench et al [14] showed that patients with systemic lupus erythematosus (n=93) have reduced oxygen uptake in comparison to that of healthy controls (n=41). Furthermore, Keyser et al [43] compared 16 healthy participants with 18 patients with systemic lupus erythematosus and found significant differences in their aerobic capacity (VO_2 peak). A meta-analysis showed an improvement of nearly 2 mL/kg/minute of oxygen uptake after exercise treatment (12-52 weeks) [21]. Wilson et

al [44] assume that low aerobic capacity leads to a significant restriction in daily life. Mostly all daily activities have a range of 10.5 mL/kg/minute to 17.5 mL/kg/minute of oxygen uptake. In addition, Pinto et al [45] showed that patients with systemic lupus erythematosus have impaired aerobic capacity when compared with the aerobic capacity of controls matched by physical inactivity, age, sex, and BMI. These findings reinforce the recommendation of physical activity in systemic lupus erythematosus treatment and were recently reconfirmed by a randomized one-year physical activity program for women with systemic lupus erythematosus [46].

However, patients with systemic lupus erythematosus frequently suffer from fatigue in their daily life, so the burden of being physically active is much higher than it is for healthy patients. But when the patients are physically active, a reduction in fatigue could already be observed after a walking program of 6 weeks [22]. Thus, an individually adapted training program (based on training status and time of training) could be continuously and easily used by patients and to positively support permanent use.

Nevertheless, there are some risks in using the internet as a supervision tool. First, we presuppose that all participants have an internet device and an email account to create a user profile. Research has shown that nearly 79.5% of the population in Germany has access to an internet account [47]. Second, it could be possible that patients need the presence of a personal coach to perform the exercise sessions correctly, even to reduce the risk of injury. Therefore, precise recommendations of exercise prescription will be used and controlled. It is also possible to watch the strength exercises as videos on the internet platform. Furthermore, it already has been outlined above that systemic lupus erythematosus progress is heterogeneous which could be a critical point of this study. Patients could suffer due to health-associated problems, which could lead to an early termination of the exercise program, as they have no personal contact person on site. However, our objective is to promote a frequent contact through the platform and that the patients will not have any inhibitions and will be able to report at any time. Complaints about health problems are always passed on to the study physician so that immediate contact with the patient is possible. In this way, we hope to achieve a reduction of the risk of premature termination of the program.

A selection bias due to (1) exercise affine people and (2) internet-based motivated people could be possible. Moreover, based on etiology, it is expected that (3) mostly female participants will participate. Furthermore, (4) only participants followed by the University Medical Centre Mainz will be recruited.

This study will allow us to assess the potential for internet-based exercise program in patients with systemic lupus erythematosus by comparing our internet-based exercise program in terms of changes in levels of physical ability (VO_2 peak, anaerobic exercise group, Chair-Stand test) in the treatment groups compared to those in the treatment as usual group. Furthermore, it will allow us to study the intensities of exercise recommendations that are feasible for patients with systemic lupus erythematosus without any disadvantages in terms of disease activity.

Acknowledgments

We thank the University of Mainz for maintaining the inner-university research grant, which made it possible to pay for a doctoral student from the field of sports medicine. Additionally, this study would not have been possible without the support of the nephrology and rheumatology outpatient clinic of the University Medical Center Mainz. Finally, we thank all the patients who participated in the study.

Conflicts of Interest

None declared.

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Abbreviations

BMI: body mass index
ECG: electrocardiography
FITT-VP: frequency, intensity, type, time, volume, and progression
VO2 peak: peak oxygen uptake

Edited by G Eysenbach; submitted 17.02.20; peer-reviewed by K Druce, G Jerome; comments to author 29.06.20; revised version received 04.08.20; accepted 11.08.20; published 03.11.20.

Please cite as:
Boedecker SC, Philippi KFA, Neuberger E, Schmidt S, Pfirrmann D, Haller N, Schwarting A, Simon P, Weinmann-Menke J
Twelve-Week Internet-Based Individualized Exercise Program in Adults With Systemic Lupus Erythematosus: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2020;9(11):e18291
URL: https://www.researchprotocols.org/2020/11/e18291
doi:10.2196/18291
PMID:33141101

Protocol

Effects of a Collective Family-Based Mobile Health Intervention Called "SMARTFAMILY" on Promoting Physical Activity and Healthy Eating: Protocol for a Randomized Controlled Trial

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Abstract

Background: Numerous smartphone apps are targeting physical activity and healthy eating, but empirical evidence on their effectiveness for initialization and maintenance of behavior change, especially in children and adolescents, is still limited.

Objective: The aim of this study was to conceptualize a theory-based and evidence-based mHealth intervention called SMART*FAMILY* (SF) that targets physical activity and healthy eating in a collective family-based setting. Subsequently, the app will be refined and re-evaluated to analyze additional effects of just-in-time adaptive interventions (JITAIs) and gamification features.

Methods: A smartphone app based on behavior change theories and behavior change techniques was developed and implemented and will be evaluated with family members individually and cooperatively (SF trial). Existing evidence and gained results were used to refine and will be used to re-evaluate the app (SF2.0 trial). Both trials are cluster randomized controlled trials with 3 measurement occasions. The intervention group uses the app for 3 consecutive weeks, whereas the control group receives no treatment. Baseline measurements (T_0) and postintervention measurements (T_1) include physical activity (ie, self-reported and accelerometry) and healthy eating measurements (ie, self-reported fruit and vegetable intake) as the primary outcomes. The secondary outcomes (ie, self-reported) are intrinsic motivation, behavior-specific self-efficacy, and the family health climate, complemented by an intentional measure in SF2.0. Four weeks following T_1, a follow-up assessment (T_2) is completed by the participants, consisting of all questionnaire items to assess the stability of the intervention effects. Mixed-method analysis of covariance will be used to calculate the primary intervention effects (ie, physical activity, fruit and vegetable intake) while controlling for covariates, including family health climate, behavior-specific self-efficacy, and intrinsic motivation.

Results: This study is funded by the German Federal Ministry of Education and Research and ethically approved by the Karlsruhe Institute of Technology. For both trials, it is hypothesized that the apps will positively influence physical activity and healthy eating in the whole family. Furthermore, SF2.0 is expected to produce stronger effects (ie, higher effect sizes) compared to SF. SF app development and piloting are completed. Data acquisition for the SF trial is terminated and discontinued due to the COVID-19 pandemic. SF2.0 app development and piloting are completed, while data acquisition is ongoing. Participant recruitment for the SF 2.0 trial started in February 2020. The results for SF are expected to be published in mid-2021, and the results of SF2.0 are expected to be published in mid-2022.

Conclusions: In this study, it is hypothesized that targeting the whole family will facilitate behavior change at the individual level and the family level, as the implemented strategies address changes in daily family life. Furthermore, subsequent app

development (SF2.0) with supplementary addition of motivation-enhancing features and a JITAI approach is expected to enhance positive intervention effects.

Trial Registration: German Clinical Trials Register DRKS00010415; https://tinyurl.com/yyo87yyu

International Registered Report Identifier (IRRID): DERR1-10.2196/20534

(JMIR Res Protoc 2020;9(11):e20534) doi:10.2196/20534

KEYWORDS

mobile app; telemedicine; behavior change; health behavior; family; primary prevention; exercise; food and nutrition; randomized controlled trial; accelerometer; wearable electronic devices; social cognitive determinants; just-in-time adaptive intervention; digital intervention; mobile phone

Introduction

Background

A lack of physical activity, too much sedentary behavior (eg, extended screen time and nonactive media usage), and an unhealthy diet are serious concerns of modern societies. These behaviors increase the risk of health conditions across all ages [1-4]. Research has shown that many children and adolescents do not sufficiently engage in physical activity [5] and frequently make unhealthy food choices [6,7]. Approximately 81% of the children and adolescents (and 23% of the adults) in the world do not meet the recommendations on physical activity levels and healthy eating, for example, fruit and vegetable intake [8]. In this regard, a dose-response relationship was detected, with even slight increases in physical activity leading to physiological and psychological health benefits in adults [9-11] as well as in children and adolescents [12]. Longitudinal studies have shown that behavioral patterns in adolescence have low-to-moderate influence on physical activity patterns in adulthood [13-16]; therefore, there is a need for interventions targeting children to promote a sustainable and healthy lifestyle.

Health-related behaviors such as physical activity and healthy eating are embedded in social contexts such as the family context and are affected by social relations and ties [17]. Therefore, addressing behavioral changes embedded in daily family life might be a promising avenue for facilitating an individual's behavior change. Family meals, for example, are often an important part of everyday life in families and there is accumulating evidence that this collective behavior is associated with a better overall diet quality and body mass index [18-20]. In a similar vein, there is some evidence that family-based physical activity is positively associated with individual physical activity levels [21]. It has been shown that supportive interactions within a family and shared values about health behavior affect children's physical activity engagement [22] and eating behavior [23]. Moreover, results of intervention studies indicate that social support is significantly associated with continuation of exercise programs [24-28] as well as participation in weight-loss interventions [29-31].

Mobile health (mHealth) technologies are increasingly used as a delivery mode for health behavior change interventions throughout the lifespan. Specifically, smartphone-based apps offer a great promise for enhancing physical activity and healthy eating as well as for making health care more accessible and scalable, more cost-effective, and more equitable [32,33]. Reviews and meta-analyses support the view that app-based mobile interventions are effective and highly promising for changing physical activity [27,34] and nutrition behaviors [35]. Moreover, a recent systematic review of economic evaluations of mHealth solutions found a consistent overall reporting of positive economic outcomes (eg, increase in life-years gained, cost savings, cost-effectiveness) [36].

Reviews on mHealth interventions indicate that the strategies or the central "building blocks" of app-based interventions mainly encompass 4 behavior change technique clusters [37], namely, goal setting, feedback and self-monitoring, information, and social support provision, which coincide with successful conventional individual and group-based interventions [35,38,39]. Setting goals, monitoring behavior, receiving feedback, and reviewing relevant goals in the light of feedback are central to self-management and behavioral control, as specified by control theories [40,41] and health behavior theories [42-44]. However, since mobile interventions distinguish themselves by being interactive, adaptive, time-sensitive, and intraindividually dynamic, more dynamic concepts, including the timing of feedback or tailoring tasks and goals to individual progress and capacities as specified in persuasive technology and gamification approaches, might be essential ingredients of effective focused mobile interventions [35]. Moreover, mobile interventions can be delivered within a social system so that all members, for example, of a family, can simultaneously and collectively take part in an intervention and share their goals and progress. However, currently available apps for health promotion are almost exclusively tailored to the individual person [45]. Motivation for behavior performance is higher when the individual is embedded in a social system of mutual appreciation and importance (see self-determination theory [46,47]), which was successfully used in physical activity interventions by enhancing autonomous motivation and fulfilling the 3 basic psychological needs, that is, "autonomy," "competence," and "relatedness" [46]. As healthy or unhealthy behavioral patterns are developed and maintained in social contexts, embedding an mHealth intervention in a family-based setting and targeting all family members might be promising and corresponds to assumptions of family-as-systems approaches [48]. Families represent natural social systems characterized by supportive interactions and common shared values and should therefore be targeted as a whole to implement sustainable behavior change on the individual as well as the family level. Therefore, the described trials aim at developing a smartphone

intervention app that targets the family as a social system of high relevance for its single members.

Objective

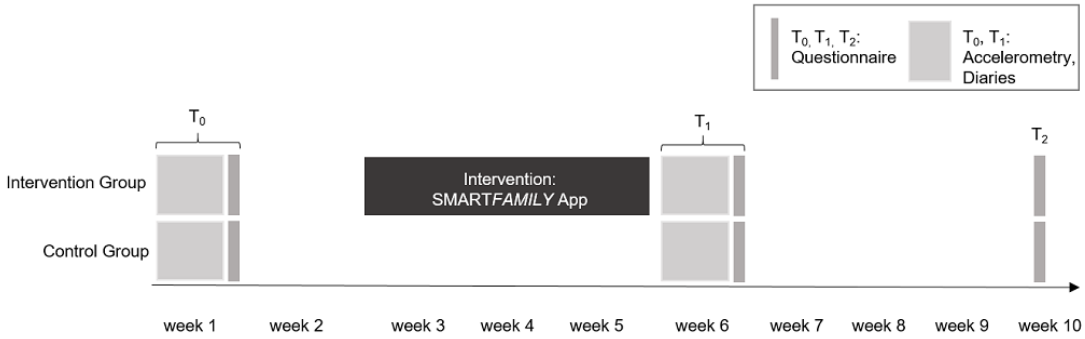
The aim of the SMART*FAMILY* project, consisting of SMART*FAMILY* (SF) and SMART*FAMILY*2.0 (SF2.0) is to develop, refine, and evaluate an mHealth intervention aiming to improve physical activity levels and healthy eating at the individual and family level. The development of the app is based on behavior change theories, including self-determination theory and the use of behavior change techniques. Extending the previous research, the behavior of children *and* parents is targeted in order to induce family-based and individual-based behavior changes. In particular, family members are using the SF app individually and cooperatively. Furthermore, SF and SF2.0 aim to deliver context-dependent interventions and provide support during time periods when needed the most. The first version of the app (SF) will be refined, and motivational and gamification features as well as a just-in-time adaptive intervention (JITAI) approach will be added (SF2.0). The effectiveness of SF and SF2.0 will be evaluated through 2 cluster randomized controlled trials consisting of families (parents and their children).

Methods

Study Design

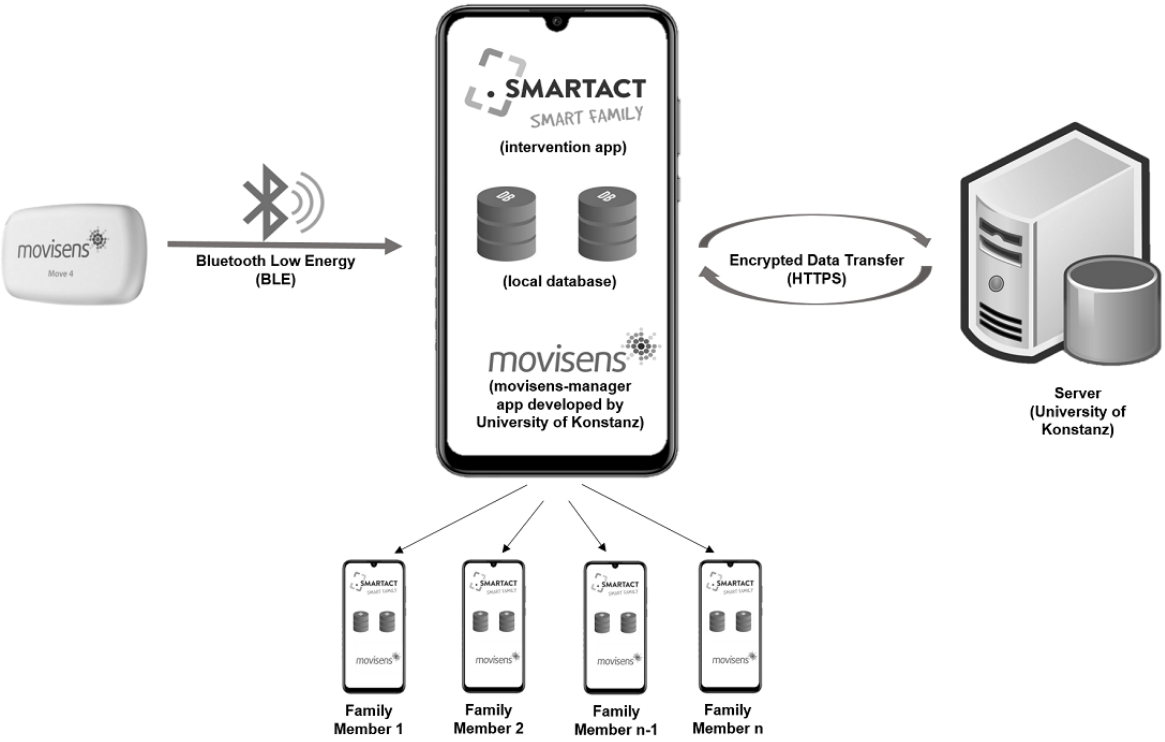
The studies are conducted and described according to the CONSORT-eHealth checklist [49], which can be found in Multimedia Appendix 1. The outline of the SF and SF2.0 trials is presented in Figure 1. In both trials, the assessment of outcomes is identical and is completed at baseline (T_0) after the 3-week intervention (or no intervention) period (postintervention, T_1), and 4 weeks after T_1 (follow-up, T_2). Each family (parents and children) is invited to the laboratory for an individual introductory session. Each family member receives an accelerometer for physical activity assessment and a daily paper-pencil–based diary assessing type, intensity, duration and joint activities as well as food intake (specifically fruit and vegetable intake) during the first assessment week (T_0, Figure 1). At the end of week 1 (end of T_0), they fill in a questionnaire (paper-pencil in SF, web-based questionnaire in SF2.0) and return all the materials to the laboratory. The completion of the questionnaire takes about 20 minutes. Both parents and children complete individual daily diaries and questionnaires. The data of the preintervention (baseline) assessment (T_0) are analyzed and they serve as the basis for the weekly goal set-up in the intervention group during the following intervention period.

Figure 1. Detailed study design. T0: baseline; T1: after 3 weeks of intervention; T2: Four weeks after T1.



Participants allocated to the intervention group receive smartphones with the preinstalled SF app (SF or SF2.0). We provide all study participants with a study smartphone in order to control for device effects (screen size, Android version, etc) and ensure that the app is fully functioning. Carrying an additional device might pose an additional burden for participants and therefore, great care will be taken to explain the need for a study device in the introductory session. Moreover, previous studies within the SMARTACT consortium, comparing participants who could either use their own smartphone or were provided with a study smartphone to record their diet, showed no differences in terms of engagement [50]. Each smartphone (Samsung Galaxy A5 for SF, Nokia 5 for SF2.0) is connected with an accelerometer (Move 3 [SF] and Move 4 [SF2.0], Movisens GmbH) via Bluetooth low energy. Different from similar mHealth studies, the accelerometer used for the preintervention and postintervention (primary outcome) measurement is also used within the intervention period and provides data used by the app. Since participants monitor their physical activities (based on the data from the accelerometer) and goal progress through the app, an additional commercial device is not necessary for motivating the participants. Data are stored in a local database on the smartphone by using an additional app (Movisens Manager app) developed by the Human-Computer Interaction Group of the University of Konstanz as part of the SMARTACT project. The SF and SF2.0 apps are notified by the Movisens Manager app once new sensor data are available (ie, when the accelerometer is in reach of the Bluetooth low energy connection of the smartphone) and processes this data, thus creating 2 new entries in the database: the received data from the accelerometer and the aggregated value for that day (including accelerometer data and manual input by the participants). The aggregated data are then sent via encrypted HTTPS to the server in Konstanz. From there, data are sent back to all family members' smartphones, so that individual and collective goal progress can be monitored. The control group does not receive any intervention. Please see Figure 2 for a depiction of the operation principles.

Figure 2. Detailed depiction of the operation principles of the SMARTFAMILY apps.



When starting the intervention, all families of the intervention group are asked to set a collective weekly goal for physical activities, which they want to achieve as a family within 1 week, that is, total steps and total time spent on physical activity per family. In addition, collective family goals are set for activities within the family and healthy eating, ie, the amount of fruit and vegetable intake per family and the number of family meals. It is important to note that every single family member is contributing to the collective family goal through his or her own behavior. In contrast to the set goals related to common recommendations such as 10,000 steps a day or 5 servings of fruits and vegetables per day for individuals, the family sets its own collective goals. In order to facilitate realistic goal-setting at the beginning of the intervention, the family members can rely on the analysis of their individual physical activity level and fruit and vegetable intake assessed during T_0. The goal-setting process is repeated every week during the intervention period. The only goal-setting instruction given to the participants is the recommendation to set collective family goals for the coming week, which are slightly higher than their current cumulative performance. In SF2.0, an interactive goal-setting coach assists with this decision. This procedure involves usage of behavior change techniques, which will be presented in detail below.

After 3 weeks of intervention (or no intervention) period, a 1-week postintervention measurement (T_1) with the same procedure as T_0 starts. Four weeks after completion of T_1, participants fill in the questionnaire for the last time (T_2) and return them to the study team in a prepaid reply envelope. In SF2.0, participants can complete all questionnaires pseudonymized on the internet. Validated measures and scales are used (if available), which were adapted from paper-pencil versions for web-based versions to make it easier for participants to complete the surveys. Ethical approval was obtained and data protection was ensured. A closed survey design was used and the usability and technical functionality of the electronic questionnaire were tested. Participants receive analyses of their individual activity patterns for study participation in SF and SF2.0, whereas families in SF2.0 are additionally provided with a 40€ (US $46.8) online shopping voucher and an activity tracker for every child of the family in order to further facilitate physical activity maintenance.

Eligibility Criteria and Ethical Approval

Families are eligible for inclusion if 1 parent or both parents and at least one child who is 10 years of age or older are living together in a common household. All siblings are invited to take part in the study. All participants have to be used to handle a smartphone and speak, read, and write German fluently. In order to ensure fairness, siblings who do not meet the age requirements in the inclusion criteria also receive the study materials, if deemed feasible.

Full ethical approval was obtained from the University of Konstanz (for the consortium SMARTACT) as well as from the Karlsruhe Institute of Technology (for SF and SF2.0). All participants, children, and legal guardians provide written informed consent prior to commencing the study by signing the informed consent form. Both trials are conducted in accordance with the Declaration of Helsinki.

Randomization and Blinding

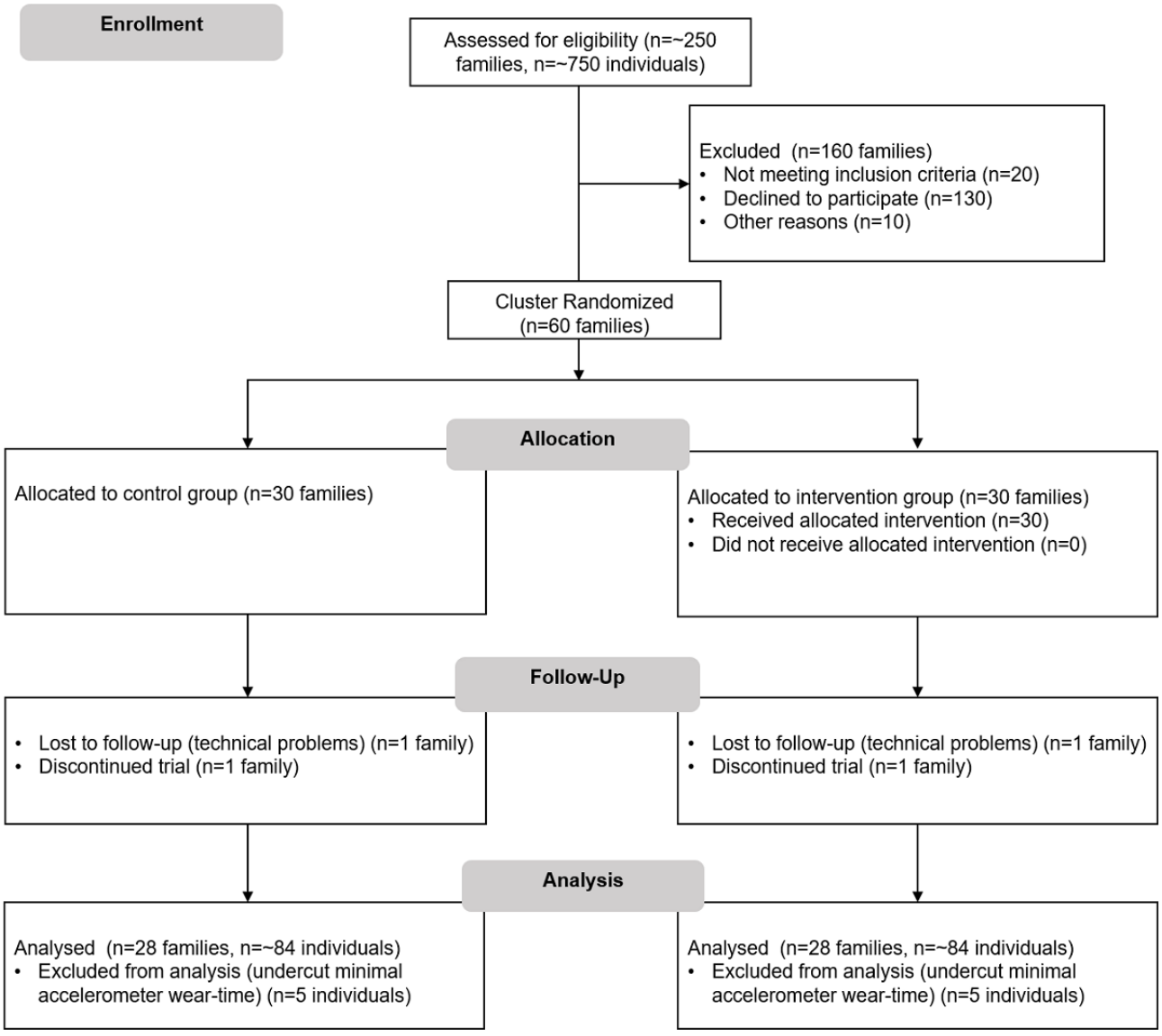
Both trials (SF and SF2.0) are cluster randomized controlled trials with 2 groups: (1) an intervention group receiving the SF or SF2.0 and (2) a nonintervention control group. Recruited families who provide informed consent are allocated to one of

the 2 groups prior to recruitment by using a simple randomization procedure for cluster designs [51]. Although the intervention group participants are told about the mHealth nature of the study, control group participants are only told to take part in an epidemiologic assessment of physical activity levels, making it essential to wear the accelerometers 2 times for 1 week and to answer several questions over the course of 10 weeks in order to gain reliable and valid results.

Participant Recruitment

Participants are recruited in schools, school holiday programs, music schools, and sports clubs via personal communication, newspapers, and email distribution lists of the Karlsruhe Institute of Technology. Power analyses for analysis of covariance with 2 groups and 4 covariates using G*Power [52] yields a total of 52 families with approximately N=156 participants (assuming 3 family members), to find a small-to-medium effect (α=.05, 1-β=.80, Cohen f=0.25). In order to increase power and to compensate for potential dropouts, we aim for a total of 60 families per trial. Please see Figure 3 for the planned participant flow for SF and SF2.0.

Figure 3. Planned participant flow and allocation pattern for the cluster randomized controlled trial for SMARTFAMILY and SMARTFAMILY2.0.



Development of SF Apps

Both SF and SF2.0 are developed as part of the SF project, which is part of the consortium project SMARTACT and its toolbox encompassing mobile interventions for promoting physical activity and healthy eating (see for example [53-57]). The multidisciplinary team includes professionals with expertise in sports and exercise science, nutrition, health psychology, neuroscience, economics, and human-computer interactions. SF and SF2.0 are devised in iterative processes, with input from target group members and experts as well as from previous SMARTACT project findings and behavioral theories. Programming of the apps is conducted by the Human-Computer Interaction Workgroup of the University of Konstanz as part of the SMARTACT project, which is responsible for all tasks related to computer science (ie, programming of apps, surveillance of data servers, etc). In general, all people with data access signed a confidentiality agreement. Both apps run

on Android and use the SMARTACT Toolbox, which is conceptually developed by the SMARTACT consortium partners [53] and programmed within the SMARTMOBILITY project led by the Human-Computer Interaction Group of the University of Konstanz. The appearance and content of SF and SF2.0 are adapted and changed in iterative processes throughout the invention phases and pilot studies but not throughout a trial. Both apps are piloted for probing usability and feasibility through standardized interviews (SF) and questionnaires (SF2.0).

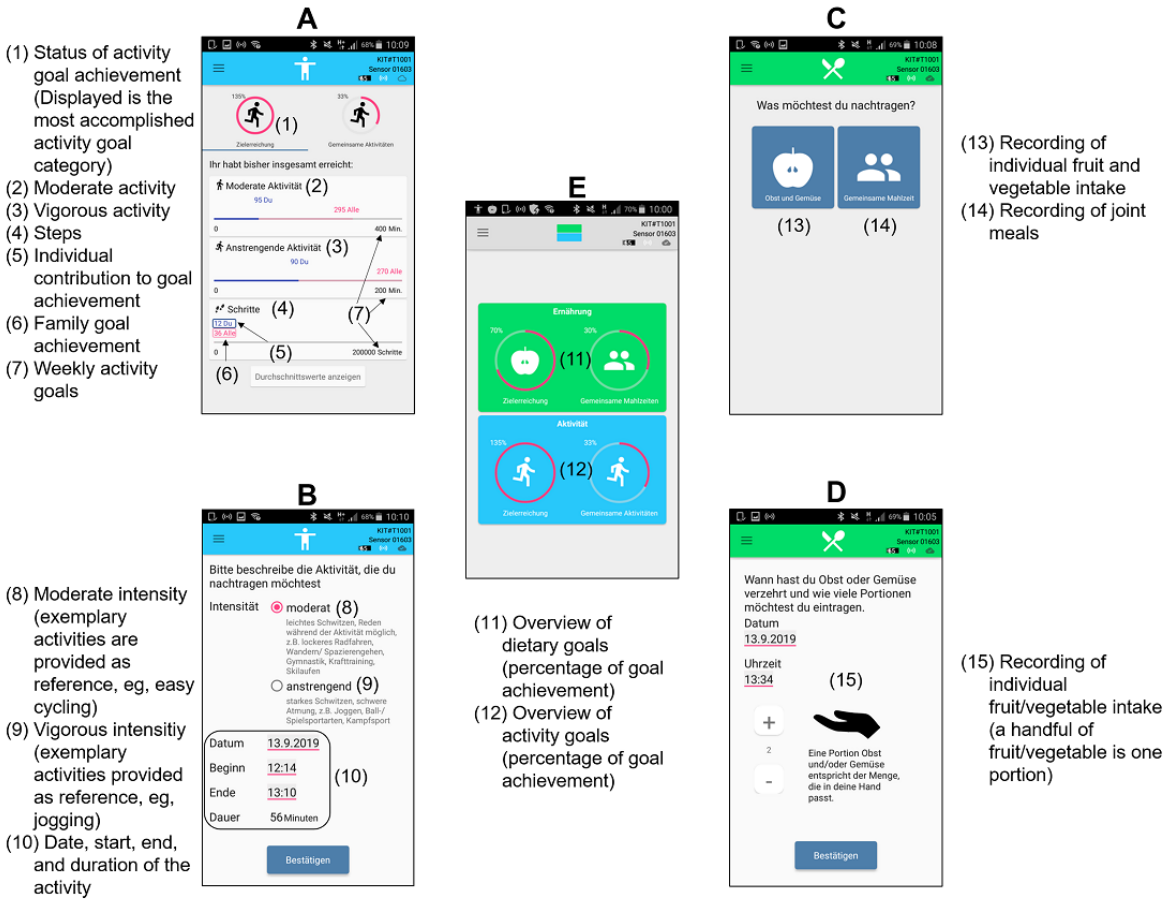
Intervention: SF and SF2.0 Apps

Overall, SF and SF2.0 aim to enhance physical activity levels and healthy eating at the family level, including parents and children. The apps are designed to be implemented autonomously by participants. Both apps (SF and SF2.0) are entitled to fulfil criteria of high quality regarding theoretical and empirical foundation [38,46,48]. The inclusion of 10 (SF) and 13 (SF2.0) behavior change techniques doubles the amount of behavior change techniques found in "average" mHealth intervention apps.

Features of the SF App

Examples of the SF app screens are shown in Figure 4. On the home screen, the app always displays the whole family's current status of goal achievement as well as individual family member's contribution (Figure 4, #11-12). During the course of 1 week, if milestones of 25%, 50%, 75%, and finally 100% of goal achievement is reached by the family, every family member receives a congratulatory message and a motivational reinforcement, that is, "Great! You've reached 75% of your goal. Go on, you are making a good progress." Moreover, the detailed goal achievements concerning moderate and vigorous physical activity and steps (Figure 4, #1-7) as well as fruit and vegetable intake (not displayed) on family and individual basis can be examined. The achieved values for specific days are also presented in the calendar function (not displayed). Although physical activity is recorded automatically by the accelerometer, fruit and vegetable intake has to be entered manually into the app (Figure 4, #15). In case of physical activity that is not assessed by the accelerometer because it cannot be worn (eg, swimming) or cannot be validly captured by the hip-worn accelerometer due to a lack of lower body movements (eg, upper body strength exercises or bicycling), the app incorporates a feature to manually enter the individual amount of time spent with moderate or vigorous activity (Figure 4, #8-10). As the family members' smartphones are connected with each other (via internet) and each smartphone is connected with its accelerometer (via Bluetooth low energy), all family members receive real-time feedback on individual and family-level physical activity behavior with respect to steps, moderate and vigorous physical activity, as well as on self-reported fruit and vegetable intake. This allows for continuous self-monitoring of behavioral goals of a family.

Figure 4. Examples of SMARTFAMILY app screens. A. Detailed status of activity goal achievement; B. Manual activity recording; C. Food recordings; D. Manual food recording; E. Start screen with overview of goal achievement.



Features of the SF2.0 App

Table 1 provides an overview of the behavior change techniques incorporated in the SF app and the additional behavior change techniques of SF2.0 (Figure 5), allocated to the basic psychological needs [47].

Figure 5 shows examples of the SF2.0 app screens. While SF focuses on elementary functions, SF2.0 includes a more comprehensive range of app features such as JITAIs [58] and an interactive, humanized goal-setting coach who interacts with the app user in a personal way, providing hints and facts to achieve a higher app (and therefore, health behavior) commitment (ie, gamification). In both apps, triggered and app-based ecological momentary assessment (EMA) [59] is used. Supplementary to EMA of physical activity and healthy eating in SF, EMA was extended in SF2.0 by the real-time measurement of behavioral and affective correlates of physical activity and fruit and vegetable intake, including current mood, stress, and exhaustion (see #14-16 in Figure 5) as additional control variables [54,55]. This assessment is prompted at least 4 times a day, paralleling inactivity prompts (see below). Inactivity-triggered prompts are sent when the participant is inactive for at least 60 minutes (neither <2 sensor values at >2 MET nor 100 steps). Push notifications regarding inactivity are inhibited for the remaining day if the participant reaches at least 60 minutes of moderate-to-vigorous physical activity on the respective day. Every evening at 7 PM, participants are asked if they recorded all the necessary manual information of physical activity and healthy eating. The last assessment of mood, exhaustion, and stress occurs when the participant presses the "going-to-sleep button" (if there has not been an inactivity trigger during the last 60 minutes). Sleep quality is assessed every morning after the participant pushes the "get-up button" in the app. Furthermore, EMA is used to evaluate the reasons for inactivity (see #18 in Figure 5).

To further increase motivation, SF2.0 comprises a more detailed gradation of goal achievement. Participants can gather stars for every 10% of goal achievement. If the family achieves their individual goal during 1 intervention week, they are instructed to set a higher goal for the next week. In SF2.0, the interactive goal-setting coach advises them about a promising goal for the following week. If the family does not achieve its individual goal, the coach instructs family members to set the same or even a slightly lower goal for the next week. For recording of the different parameters and operation principles of SF2.0, see SF. One additional feature included in SF2.0 is adapted from the SMARTACT Toolbox [53-55]. Here, users are instructed to take a picture of every single meal (including snacks), producing an exact timestamp of food consumption (Figure 5, #25). Furthermore, SF2.0 comprises a real-time assessment of mood,

exhaustion, and stress (Figure 5, #14-16), a gamification approach (visualized by the personal coach and collectable stars; Figure 5, #1), an inactivity-triggered ecological momentary intervention (Figure 5, #17,18), and a provision of up to 5 health-related facts by the interactive coach to improve health literacy [60]. These additional features are related to the inclusion of further behavior change techniques as shown in Table 1.

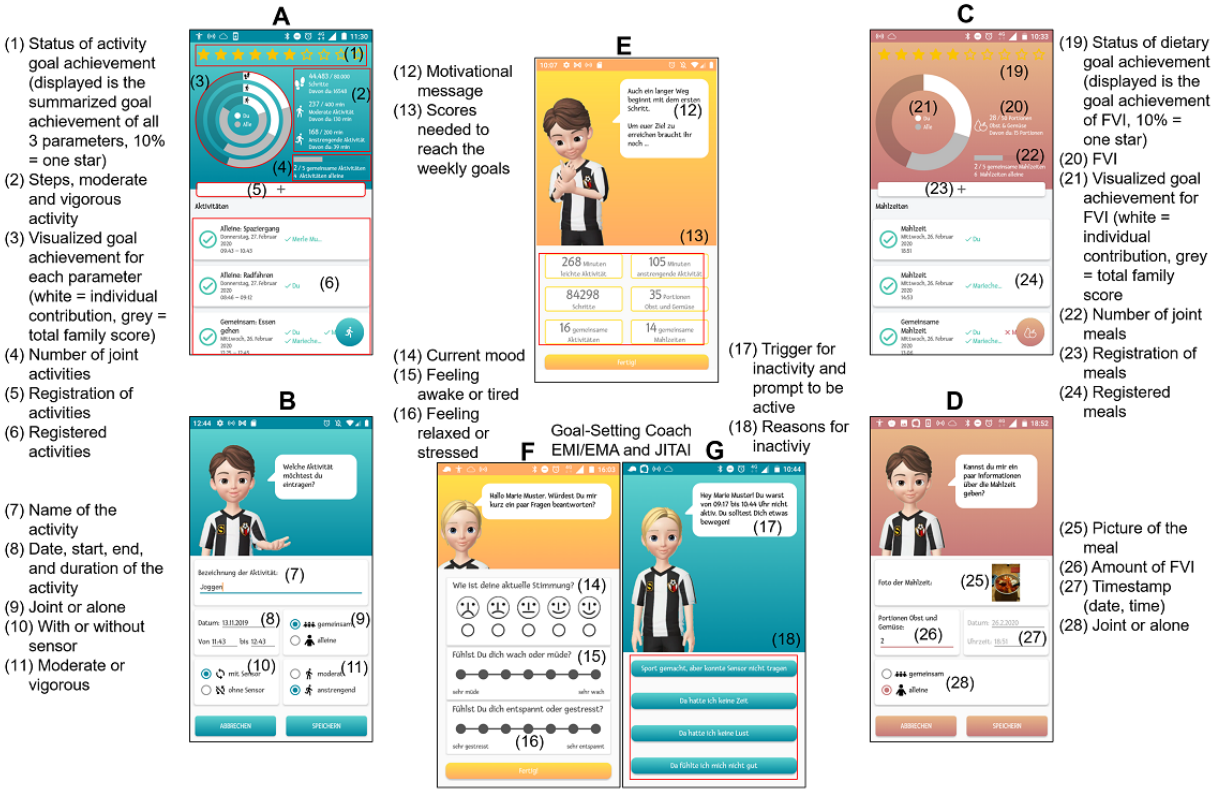
Table 1. Implementation of the basic psychological needs and behavior change techniques within the app features.

Self-determination theory, basic psychological needs	Autonomy	Relatedness	Competence
SF[a] app features and number of behavior change techniques (Michie et al [37])	Self-imposed weekly goal-setting (eg, steps, duration of moderate-to-vigorous activity, fruit/vegetable intake) (behavioral goal-setting, #5[b]) App displays current status on performance and goal achievement (prompt review of behavioral goals, #10, prompt self-monitoring of behavior, #16, provide feedback on performance, #19) Calendar displays overview on performance (provide feedback on performance)	App implemented in a family-based setting, encouraging social support (plan social support/social change, #29) and identification as a role model (prompt identification as role model/position advocate, #30)	Set slightly higher weekly goals than current performance (set graded tasks, #9); rewards are provided according to progressively set goals via motivation notifications (shaping, #14) Motivation notifications at a level of 25%, 50%, 75%, and 100% of goal achievement (prompt rewards contingent on effort or progress toward behavior; provide rewards contingent on successful behavior, #12, #13)
Additional app features in SF2.0	Includes all the features of the SF app.	Additional review of the common goals via daily notifications in the morning (prompt review of behavioral goals, #10)	Interactive goal-setting coach provides knowledge about physical activity and healthy eating (provide information on consequences of behavior in general, #1) Gathering stars when achieving goals for each 10% of goal achievement (prompt rewards contingent on effort or progress toward behavior; provide rewards contingent on successful behavior, #12, #13) Inactivity-based reminders for physical activity according to ecological momentary intervention principles (teach to use prompts/cues, #23) Ecological momentary assessment of sleep, mood, exhaustion, and stress (barrier identification/problem solving, #8)

[a]SF: SMART*FAMILY*.

[b]These numbers refer to the Behavior Change Techniques (BCTs) shown in Michie et al [37].

Figure 5. Examples of SMARTFAMILY2.0 app screens. A. Detailed status of activity goal achievement; B. Manual activity recording; C. Nutritional goal achievement; D. Manual food recording; E. Morning screen with an overview of the status quo and remaining physical activity and fruit and vegetable intake until goal achievement; F. Ecological momentary assessment and ecological momentary intervention; G. Just-in-time adaptive intervention. EMA: ecological momentary assessment; EMI: ecological momentary intervention; JITAI: just-in-time adaptive intervention; FVI: fruit and vegetable intake.



Outcomes

All self-reported measures and diaries are implemented in German language.

Primary Outcomes

Primary outcome measures are device-based measured physical activity (ie, amount of steps taken, minutes of moderate-to-vigorous physical activity) via accelerometers (T_0 and T_1) as well as self-reported assessed physical activity levels via questionnaires (T_0-T_2) and diary records (T_0 and T_1). Furthermore, healthy eating (fruit and vegetable intake) is assessed via questionnaires (T_0-T_2) and diary records (T_0 and T_1). Primary outcomes are similar for SF and SF2.0.

Device-Based Measured Physical Activity (Accelerometers)

Hip-worn accelerometers (Move 3/Move 4) are used to continuously record physical activity (3-axial acceleration, which is conveyed by algorithms into steps, time spent during moderate [3-6 MET]/vigorous [>6 MET] physical activity and sedentary time [1-1.5 MET]). The accelerometers are connected via Bluetooth low energy with the smartphone app to provide users direct feedback on their physical activity levels. The accelerometer's validity was tested in previous studies and is considered accurate for assessing physical activity [61,62]. Participants are instructed to wear the accelerometer during wake time and remove it only for taking a shower, swimming, or during certain sports involving bodily contact to minimize the risk of injuries. This nonuse time is added manually into the app. Device-based activity assessment takes place at T_0 and T_1.

Self-reported Physical Activity (Questionnaire and Diary)

Self-reported physical activity is measured using valid and reliable measures. In the SF trial, the International Physical Activity Questionnaire [63] was used at all 3 measurement points for adults [64]. For children, the 60-minute screening measure for moderate-to-vigorous physical activity is used. These measures were chosen in order to account for the requirements of different age groups. However, due to better comparability of results, an adapted version (referring to the activities of the last week and not of a typical week) of the General Physical Activity Questionnaire [65] is used in SF2.0 for children and adults. In both trials, all participants complete a diary complementary to accelerometers [66], indicating time and type of activity, duration and intensity on each single day of the measurement week, and if this activity is carried out as a family or alone.

Fruit and Vegetable Intake (Questionnaire and Diary)

Fruit and vegetable intake is assessed using a single item asking for the total amount of fruits and vegetables consumed within a typical week [67] in the questionnaire as well as using a description in a diary of detailed food consumption during 1 week by indicating the time of the meal, ingredients, portions

of fruit and vegetable intake, and whether the meal was consumed within the family or alone.

Secondary Outcomes

Demographics

In the T_0 questionnaire, demographic information of the participants is collected, including sex, age, height, weight, highest education level, and tobacco and alcohol use (parents, only in SF), and attended school level (children). Moreover, participants are asked to rate their perceived general health [68]. The remaining questions are kept consistent over the 3 measurement points and are similar for SF and SF2.0.

Intrinsic Motivation Toward Physical Activity

To assess activity-related intrinsic motivation, the Behavioral Regulation in Exercise Questionnaire [69] is used [70].

Intrinsic Motivation Toward Healthy Eating

For assessing dietary-related intrinsic motivation, the Regulation of Eating Behavior Scale [71] is used.

Self-efficacy for Physical Activity and Healthy Eating

Activity-related self-efficacy and dietary-related self-efficacy are assessed using the health specific self-efficacy scale [72].

Family Health Climate

The family health climate is assessed using the family health climate scale [73].

Additional Outcome Measures of SF2.0

Intention to Participate

The intention to participate in physical activity and to eat healthy is assessed by a single-item measure [74,75]. Additionally, these measures were adapted to capture the participants' intention to use smartphone apps for the promotion of physical activity and healthy eating.

Additional Measures in SF2.0

Healthy eating is assessed as fulfilment of the 10 guidelines of the German Nutrition Society [76] using the respective items of the Food Frequency Questionnaire [77,78] and diary information. Within the intervention, time and frequency of (shared) meals can be analyzed using timestamps of pictures taken [54]. Additionally, *adherence and user engagement* within the intervention are controlled for in SF2.0 by using app usage data stored on a server at the University of Konstanz (see Figure 2). Hence, app usage data (eg, recording of fruit and vegetable intake, achievement of physical activity and fruit and vegetable intake–related goals), and device-based measured physical activity are analyzed.

Data Analysis

First, the baseline characteristics of the study population are summarized within each cluster randomized group on individual and family levels for all measures to control for group differences. Then, all primary outcome data will be screened for normal distribution by using the Shapiro-Wilk test. Data will be checked for outliers. To further analyze changes in health behavior, mixed-model analysis of covariance with time (T_0 and T_1 for device-based physical activity; T_0, T_1, and T_2 for self-reported physical activity and healthy eating) as within-subjects and group (intervention group vs control group) as between-subjects factor will be conducted, with covariates being family health climate, self-efficacy, and intrinsic motivation (Behavioral Regulation in Exercise Questionnaire and Regulation of Eating Behavior Scale) as well as intention in SF2.0. Results of the Mauchly test will be checked for homoscedasticity of data and results will be corrected accordingly ($\varepsilon>0.75$ Huynh-Feldt, $\varepsilon<0.75$ Greenhouse-Geisser). Furthermore, homogeneity of the error variances will be checked, as assessed by Levene test. If this test does not reveal significance, a Box-Cox transformation will be applied to the data. Moreover, Tukey-corrected posthoc tests will be considered for detailed interpretation of results. Main effects will only be considered if the interaction is found to be significant. All analyses will be conducted using SPSS 26 statistical software (IBM Corp).

Results

This study is funded by the German Federal Ministry of Education and Research and ethically approved by the Karlsruhe Institute of Technology. For both trials, it is hypothesized that the apps will positively influence physical activity and healthy eating in the whole family. Furthermore, SF2.0 is expected to produce stronger effects (ie, higher effect sizes) as compared to SF. SF app development and piloting are completed. Data acquisition for the SF trial is terminated and discontinued due to the COVID-19 pandemic. SF2.0 app development and piloting are completed, and data acquisition is ongoing. The recruitment of the participants for the SF2.0 trial started in February 2020. The results for SF are expected to be published in mid-2021, and the results of SF2.0 are expected for mid-2022.

Discussion

Overview

The aim of the SF project is the development, implementation, evaluation, and refinement of an mHealth intervention to increase physical activity and healthy eating at individual and family level. Extending the previous research, the behavior of children *and* parents is targeted in order to induce individual behavior changes that are anchored in daily family life. Moreover, several behavior change techniques were included, which contribute to the fulfillment of the basic psychological needs according to the self-determination theory [46,47]. We examined whether (1) mHealth interventions (SF, SF2.0) elicit meaningful increases in physical activity levels and healthy eating in children as well as adults as compared to controls (no mHealth intervention), (2) changes are maintained after the intervention period, and (3) intervention effects can be strengthened by the addition of app-based features and JITAIs (SF2.0).

Innovative App Features: Strengths, Challenges, and Limitations

The SF and SF2.0 target the family as a whole. SF and SF2.0 aim to promote parents' as well as children's behavior by

focusing on family level behavioral goals that could only be achieved if all family members collaborate. Although most apps that aim to improve physical activity and healthy eating focus on an individual's behavior and comprise social features by the facilitation of social comparisons [79], both SF apps focus on collaborative group behavior and collective goal setting within a family-based setting. Furthermore, as known from sports psychological team theories, individual team members have the capacity to influence the behavior of other team members, thereby resulting in a state of team synergy, which can be loosely described as performance capacity that is more than the sum of its parts [80,81]. One advantage of using a group intervention is that studies have shown groups to work more effectively for a given goal (ie, aiming for a healthier lifestyle or increasing physical activity [82]). In one of the first studies in the field of social psychology, Triplett [83] found that people perform tasks better when the social context includes other people than when individuals complete a task alone. Subsequent findings validated Triplett's results, and other experiments have shown that the presence of others can increase performance in many types of tasks, including jogging, playing pool, lifting weights, and working on mathematics and computer problems [84-86]. The tendency to perform tasks better or faster in the presence of others is known as social facilitation. This study aims to take the advantage of the social facilitation theory by involving the whole family as a social system into the intervention.

A constraining factor might be that family sizes and ages within families may vary. As studies have shown that there is an inverse relationship between family size, parental resources, and children's educational performance [87], family size might also affect intervention success. However, there is currently a lack of knowledge about this relationship regarding behavior change or accomplishment of healthy lifestyles in families. Depending on family size distribution, families of different sizes will be compared if possible. However, future studies need to focus on and examine whether bigger families have advantages or disadvantages regarding intervention effects compared to smaller families. A further constriction might be the age range, especially of children and adolescents. Since this study includes the whole family, children of different ages and with different needs and perceptions are addressed in a similar way by the app, which might affect the intervention effects. Finally, SF and SF2.0 are based on sophisticated technical issues. EMA is used to assess physical activity (accelerometers), healthy eating (diaries), and psychosocial correlates. The inclusion of device-based and self-reported measures of physical activity provides a more comprehensive picture of the actual amount of physical activity. However, the synchronization of accelerometer-based data among multiple users also enhances the complexity of the app and is a potential source of problems caused by the Bluetooth low energy interface.

To the best of our knowledge, this is the first study implementing a mobile app to promote individual physical activity and healthy eating of children/adolescents and their parents in a family-based setting. Evidence-based strategies are integrated within a collaborative approach, which is characterized by setting family goals and collaborative striving for the achievement of these goals. This principle is contrary to several commercial apps or social media–based interventions, fostering a competitive environment through social comparisons among users. Further, the app in this study does not require external goal-setting but rather encourages the whole family to set their own goals and to plan joint activities and meals, which fosters communication within the family. Moreover, the additional inclusion of app features such as the interactive goal-setting coach, gamification, JITAIs, and EMAs in SF2.0 may exploit the potential of an mHealth intervention by means of its interactive and time-adapted nature [58,88]. Thus, JITAIs target to promote physical activity and healthy eating during those time periods when the individual is at high risk for physical inactivity and unhealthy eating patterns. Furthermore, user engagement will be monitored with these sophisticated tools, thus enabling the identification of the potential effects of regular app usage on the change of health habits.

Potential Methodological Issues

Based on literature regarding theories on behavior change (ie, the transtheoretical model [89,90]), an intervention duration of 3 weeks might not be sufficient [35]. This might also be true for the follow-up at 4 weeks following the intervention, which might not be an appropriate time point to measure the maintenance of behavior change. However, mHealth intervention studies have revealed significant behavior change effects even with intervention durations of only 1 [91], 2 [92], and 3 weeks [93]. In a similar vein, a recent meta-analyses on mobile apps for diet management showed that interventions with longer duration were not generally more effective [35]. To our knowledge, there is currently no common accepted standard and sufficient empirical evidence for devising an "ideal" intervention duration, although a dose-response relationship appears very plausible. Moreover, as we examine families in their natural setting, there are also practical constraints. In Germany, a continuous school period lasts for a maximum of 6 to 8 weeks, followed by a vacation period. In order to conduct the core assessments, including pretesting and posttesting accelerometry, during 1 continuous school period, we needed to condense the actual interventions per family to 3 weeks. Longer intervention periods would inevitably mean that there is a confounding between assessment periods (school time vs vacation). Another issue is that participants have to use an additional smartphone to run the SF and SF2.0 app while also wearing the accelerometer on the hip. This burden might limit user engagement, which, however, can be controlled for by analysis of app usage data.

Conclusion

Taken together, SF and SF2.0 expand on the existing body of evidence as they investigate the influence of a theory-based mHealth intervention targeting physical activity and healthy eating in a collective family-based setting. The major advantage of this smartphone app is that it facilitates behavior change at the individual level and the family level as the implemented strategies address changes in daily family life. Furthermore, motivation-enhancing features based on gamification strategies (ie, personal coach in SF2.0) and a JITAI approach matching interventions to individual needs is expected to induce positive

behavioral changes at the individual and family level. Project information, updates, and results can be found on the project homepage [57].

Acknowledgments

This research was supported by the Federal Ministry of Education and Research Grant FKZ 01EL1820A within the project SMARTACT.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1)
[PDF File (Adobe PDF File), 605 KB - resprot_v9i11e20534_app1.pdf]

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Abbreviations

EMA: ecological momentary assessment
JITAI: just-in-time adaptive intervention
mHealth: mobile health
SF: SMARTFAMILY

Edited by G Eysenbach; submitted 21.05.20; peer-reviewed by S Schoeppe, CQ Zhang; comments to author 14.07.20; revised version received 08.09.20; accepted 13.09.20; published 11.11.20.

Please cite as:
Wunsch K, Eckert T, Fiedler J, Cleven L, Niermann C, Reiterer H, Renner B, Woll A
Effects of a Collective Family-Based Mobile Health Intervention Called "SMARTFAMILY" on Promoting Physical Activity and Healthy Eating: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2020;9(11):e20534
URL: http://www.researchprotocols.org/2020/11/e20534/
doi:10.2196/20534
PMID:33174849

Protocol

REMOTION Blended Transdiagnostic Intervention for Symptom Reduction and Improvement of Emotion Regulation in an Outpatient Psychotherapeutic Setting: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Emotion regulation has been identified as an important transdiagnostic factor relevant to the treatment of mental health disorders. Many empirically validated psychotherapeutic treatments incorporate elements targeting emotion regulation. Most of these treatment approaches are conceptualized as standard face-to-face treatments not as blended treatments, which include an internet-based intervention.

Objective: The aim of this study is to examine, for the first time, a new internet-based intervention—REMOTION—that will be provided transdiagnostically, as an add-on to psychotherapy, to provide a blended treatment format.

Methods: A total of 70 participants will be assigned (1:1 allocation ratio) to either the intervention group (REMOTION + psychotherapy) or the treatment-as-usual group that receives psychotherapy alone. To maximize external validity, a typical outpatient treatment sample of patients diagnosed with a range of disorders such as depression, anxiety disorders, and adjustment disorder will be recruited from a university outpatient clinic. Patients with bipolar disorder, psychotic disorders, or acute suicidality will be excluded from the study. The feasibility and potential effectiveness of the intervention will be examined by assessing data at baseline, 6 weeks (post), and 12 weeks (follow-up). The primary outcome is general symptom severity, assessed with the Brief Symptom Inventory. Secondary outcomes are emotion regulation, depressive symptoms, anxiety symptoms, health related quality of life, well-being, and a variety of feasibility parameters. Quantitative data will be analyzed on an intention-to-treat basis.

Results: Participant recruitment and data collection started in February 2020, and as of November 2020, are ongoing. Results for the study are expected in 2022.

Conclusions: This pilot randomized controlled trial will inform future studies using transdiagnostic blended treatment.

Trial Registration: ClinicalTrials.gov NCT04262726; http://clinicaltrials.gov/ct2/show/NCT04262726

International Registered Report Identifier (IRRID): DERR1-10.2196/20936

(JMIR Res Protoc 2020;9(11):e20936) doi:10.2196/20936

KEYWORDS

blended therapy; internet-based intervention; emotion regulation; transdiagnostic; online therapy

Introduction

Emotion Regulation and Mental Health

According to Gross [1], emotion regulation refers to "the processes by which individuals influence which emotions they have, when they have them, and how they experience and express these emotions." Emotion regulation can describe how individuals modulate the intensity or duration of an emotion and or the quality of an emotional response; it is often a conscious process, however, can also be an unconscious one [2].

According to several theoretical frameworks, successful emotion regulation is associated with positive health outcomes [3]. In recent years, research has continually shown that emotion regulation is an important transdiagnostic factor relevant to the treatment of mental health disorders [3-5]. Emotion regulation deficits play a role in the development, maintenance, and treatment of a variety of mental health disorders [6]. A number of empirically validated psychotherapeutic treatments incorporate elements of emotion regulation. For example, elements concerning emotion regulation can be found in the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders [7], dialectical behavior therapy [8], accelerated experiential-dynamic psychotherapy [9], and emotion-focused therapy [10].

Treatments Specifically for Emotion Regulation

Over the past years, there has also been an increase in treatment programs which explicitly target emotion regulation in order to improve mental illness symptoms. Many of these treatments have been carefully developed, and effectiveness has been shown in a number of trials. Examples are acceptance-based emotion regulation group therapy [11]; affect regulation training [12]; emotion regulation therapy [13]; Managing Emotions: Emotions Under Control [14]; Group Therapy for the Improvement of Emotion Regulation Skills [15]; and Gross model–based emotion regulation strategies training on anger reduction [16].

Notably, some of these treatment concepts have also made links to findings from research in basic affective science. Berking and colleagues [17], for example, have integrated findings from affective neuroscience in affect regulation training; they present 7 neural "vicious cycles" important to emotion regulation which are then complemented with 7 skills that are trained in sequence for adaptive emotion regulation. The effects of affect regulation training have been shown in several studies [17,18]. Gratz and Gunderson [11] developed emotion regulation group therapy by using a definition that draws on theoretical literature on emotion regulation during childhood and development, and places emphasis on the control of behavior while experiencing an emotion instead of control of the emotion [11]. Emotion regulation group therapy has shown effectiveness in several studies, and mechanisms of change have also been studied [11,19,20]. Emotion regulation therapy [21,22] also includes links to affective science by targeting motivational awareness, the development of regulatory capacities, and contextual learning [23] while making reference to theory by Gross [1]. In line with Gross' differentiation of antecedent and response-focused strategies, emotion regulation therapy first teaches individuals adaptive response-focused strategies and then antecedent-focused strategies [24].

The Extended Process Model of Emotion Regulation

In 2015, Gross presented a valuable extension to the process model of emotion regulation, named the extended process model of emotion regulation [2], elaborating that emotion regulation is an interaction of valuation systems and identifying emotion regulation stages: identification, selection, and implementation. The identification stage is concerned with whether to regulate emotion, the selection stage is concerned with what strategy should be used to regulate emotion, and the implementation stage is concerned with implementing a specific tactic suited to the situation [2]. Furthermore, Gross [2] also mentions the importance of flexibility in emotion regulation, described as matching strategy to circumstance.

A valuable contribution by Gross et al [25] described how elements from the extended process model of emotion regulation pertain to mental illness; maladaptive affect regulation can arise from identification, selection, implementation, and monitoring decisions and individuals can benefit from different treatment aspects and exercises depending on which stage of the model is affected. The intervention in this study, REMOTION, aims to use the stages of emotion regulation of the extended process model of emotion regulation [2] as a general framework for a highly structured transdiagnostic intervention. This intervention aims to foster the use of emotion regulation strategies, while also addressing potential difficulties encountered at each stage of regulation and focuses on training flexibility in emotion regulation strategy use.

Over- and Underregulated Emotional States

In the field of psychotherapy research, the distinction between over- and underregulated emotional states and its relevance to psychotherapy have been made explicit [8,10,15,26]. According to Corcoran and colleagues [27], "one way to classify psychiatric disorders is to consider the degree to which emotions, reported within their syndromal presentation, are over or underregulated." Greenberg [28] states that one guiding factor for integrative psychotherapy interventions may be the type of affect dysregulation involved (too little or too much emotion). Moreover, "whether clients are under- or overregulated and which emotions are to be regulated and how are important issues in any treatment [29]" . In accordance with this view, the same patient can experience both over- and underregulated states, and also exhibit patterns linked more closely to one or the other. Linehan [8,30] developed, in detail, distress tolerance skills relevant to overwhelming underregulated states.

On the other hand, more recently, radically open dialectical behavior therapy was developed for individuals with disorders characterized by overcontrol [26,31,32]. Emotional loneliness is seen as an important problem in disorders characterized by overcontrol [31]. The treatment is aimed at increasing flexible responding, prosocial signaling, openness, and emotional expressiveness of patients while reducing rigid inhibitory control [32]. Within radically open dialectical behavior therapy, specific skills for individuals with overcontrol problems have been

developed [26]. REMOTION provides explicit strategies for both over- and underregulated states as described by Linehan [8] and Lynch [26], in a blended therapy format.

Internet-Based Interventions

Over the last decades, the use of internet-based interventions has increased rapidly in the health sector and also in psychotherapeutic treatment. Internet-based interventions have become a popular and effective treatment format for the treatment of a variety of mental health disorders in various countries [33-39]; this has been shown mainly for internet-based cognitive behavioral therapy interventions but also for other treatment contents [40]. Such treatments often allow for more flexibility and convenience in use for the patient [41]. With regard to internet interventions focusing on emotion regulation, González-Robles and colleagues [42] have very recently published a study investigating the effect of an emotion-focused, guided internet treatment in specialized care; the internet intervention was superior to treatment as usual on measures of depression, anxiety, and health-related quality of life.

Blended Treatment

The combination of internet interventions with conventional face-to-face therapy (blended treatment) is only in its early stages, and studies in a routine care setting are rare. Available studies on blended treatment in routine patient care show positive effects or positive trends for blended treatment [43-47]. For example, a study by Berger and colleagues [34] was able to show that a combination of psychotherapy and internet-based treatment was more effective than psychotherapy alone. Furthermore, Rizvi and colleagues [48], piloted an adjunct treatment for dialectical behavioral therapy called DBT Coach. DBT Coach was given to patients with borderline personality disorder and substance use for 10 to 14 days during outpatient treatment. A decrease of depressive symptoms and general distress was reported [48]. Moreover, Lukas and colleagues [49] piloted a blended therapy emotion regulation approach for individuals with elevated levels of alexithymia that showed positive effects on reducing alexithymia scores.

According to Erbe and colleagues [46], in comparison to purely internet-based treatments or purely face-to-face therapy, blended treatments could offer the following benefits: cost-effectiveness, increased effectiveness of treatment, improved transfer to everyday life, and ability to reach individuals for whom sole face-to-face or internet-based approaches are not suitable. A further benefit of providing interventions in a blended therapy format instead of solely internet-based is the argument that patient emotion regulation is assisted by the therapeutic relationship in session [10,50].

Study Objectives

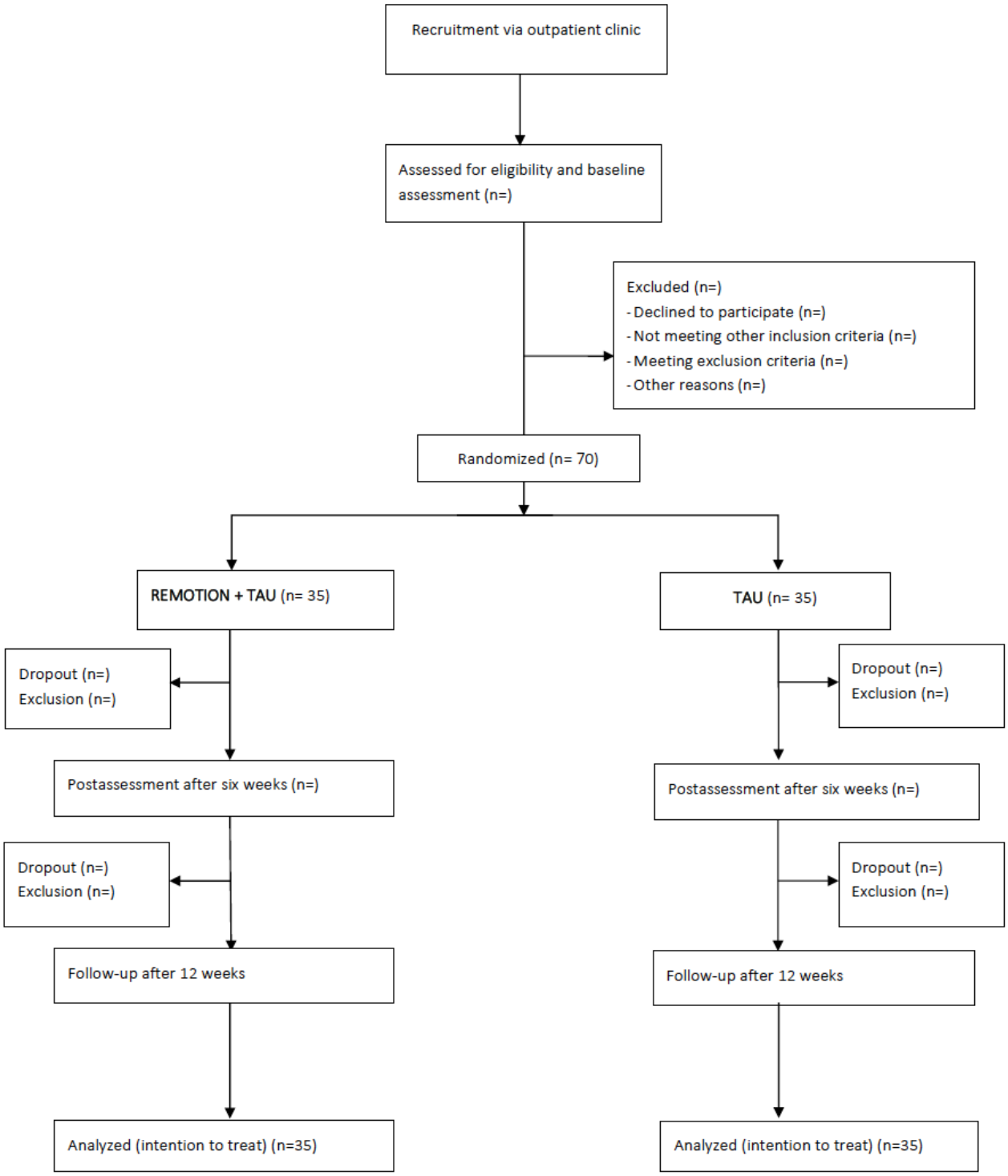
This study aims to pilot a blended treatment that uses an internet-based transdiagnostic program to improve emotion regulation (REMOTION) as an add-on to outpatient face-to-face psychotherapy. REMOTION aims to incorporate a variety of elements from effective treatment approaches into the emotion regulation framework provided by Gross [2], while also making explicit to patients specific strategies for over- and underregulated states [8,10,26]. The study aims to make use of the benefits of blended therapy format in order to convey emotion regulation skills to patients who are in psychotherapy. REMOTION aims to be a resource for both patient and therapist. This study aims to evaluate the feasibility and first effects of a transdiagnostic, blended treatment focused on emotion regulation in a mixed outpatient sample.

Methods

Study Design

The study is a 2-arm pilot randomized controlled trial comparing an intervention group (REMOTION + psychotherapy) with a treatment as usual group (psychotherapy alone). Participants in the intervention group will immediately be given access to REMOTION whereas participants in the treatment as usual group will receive access to REMOTION after 12 weeks. Assessments will occur at baseline, 6 weeks (post), and 12 weeks (follow-up) for all participants. Assessment at 6 and 12 weeks will occur irrespective of whether the patient is still in face-to-face treatment. Figure 1 depicts the design of the trial. The single center trial will take place at the outpatient clinic of the Department of Clinical Psychology and Psychotherapy at the University of Bern, Switzerland.

Figure 1. Participant flow. TAU: treatment as usual.



Sample Size

According to Sim and Lewis [51], 55 participants are the minimum necessary for a pilot trial. Moreover, according to Whitehead and colleagues [52], for a main trial designed with 90% power and 2-sided 5% significance, 25 participants per treatment arm are necessary in the pilot for standardized effect sizes that are small. Furthermore, previous unpublished data at the outpatient clinic for psychotherapy at the University of Bern has shown dropout rates of 15%. Therefore, a final sample size of 70 is planned for the study (35 per trial arm).

Eligibility Criteria

The inclusion criteria are age over 18 years, in psychotherapeutic treatment, with mental illness, with internet access, and who provide written informed consent. The exclusion criteria are current participation in another intervention specifically for emotion regulation, a current episode or a history of psychotic

disorders or bipolar disorder, acute suicidality, and not fluent in the German language.

Recruitment, Randomization, and Blinding

Patients registering at the outpatient clinic will be informed about the study. Interested patients receive an information sheet, are invited to ask questions, and can provide written informed consent if they wish to participate. After study eligibility is proven, participants are randomly assigned to 1 of 2 groups (intervention or treatment as usual). Participants are randomized using a computerized random number generator and randomly permuted block sizes. The allocation schedule is generated by a researcher not involved in the research process and is unknown to the investigators and participants. There is no blinding implemented in the study, consistent with recommendations for the conduct of pragmatic randomized controlled trials in routine practice [53], in which the focus is on external validity and generalizability of the results to routine practice.

Ethical Criteria and Ethics Committee

The study will be conducted according to local regulations and the Declaration of Helsinki. The study was approved by the ethics committee of the canton of Bern (ID 2019-01929). Written informed consent will be obtained from all patients. The trial is registered with clinicaltrials.gov (NCT04262726).

Intervention

REMOTION

REMOTION is an internet-based program that was created at the University of Bern (by LLB in collaboration TB and with input from FM). A more detailed description of the program can be found in Table 1. It is a 6-part program (introduction and 5 modules), and the general sequence and components of the modules are based on the stages of emotion regulation in the extended process model [2]. A variety of elements from different evidence-based psychotherapeutic treatment approaches—dialectical behavior therapy [8], emotion-focused therapy [10], cognitive behavioral therapy [54], mindfulness based cognitive therapy [55], radically open dialectical behavior therapy [26], and Unified Protocol [7]—are incorporated into each module of REMOTION. Furthermore, the focus placed on overregulated as well as underregulated states as described by Greenberg [10] and Lynch [26].

Table 1. REMOTION content.

Module	Content
Introduction	Information about the structure of the intervention, about the theoretical background, and a user guide are provided in this module.
Psychoeducation	Information is provided about what emotions are, what their functions are, and what types of emotional experiences there are. The concept of emotion regulation is introduced, and the relationship between emotion regulation and mental illness is explored.
Identification	Emotional awareness, which is identified as key to the perception substep of the identification stage of emotion regulation [2], is explored in this module. If and when to regulate emotions, along with information on the value of emotion regulation, are introduced in this module.
Selection	This module shows patients what types of emotion regulation strategies are available. The focus is on the selection of an emotion regulation strategy [2]. The strategies—situation selection or modification, attentional deployment, change of cognitions, and response modulation [1]—are introduced in this module. Furthermore, strategies specific to over- and underregulated states [10,26,30] are also introduced.
Implementation	This module shows patients how the previously introduced strategies can be implemented, for example, translated to different tactics [2]. Exercises are introduced for every emotion regulation strategy, and advice is provided as to how these exercises can be implemented into daily life.
Monitoring/flexibility	Being able to modify strategies, being able to apply them flexibly, maintaining, switching, and stopping [2,25] are discussed in this module. Patients are encouraged to flexibly use strategies, to apply them to different contexts, to practice, and to try sequences or blends of strategies that work for them as individuals.

The program is provided to study participants on a platform (hosted by the University of Bern) free of charge and uses text, video, and audio material along with various exercises (Figure 2). Additionally, every week for 6 weeks, individuals in the intervention group receive an email reminding them which module they should be working on. After 9 weeks, patients will receive another email as a reminder to work on the program. Patients will also take part in their routine psychotherapy sessions while using REMOTION. Also, along with the internet-based program given to the patients, the therapists will receive information about the content of REMOTION in the form of an information booklet. The information given to the therapists is meant to explain the content of the internet-based program and provide suggestions as to how elements from the program can be integrated in face-to-face sessions. A detailed description of the information given to the therapist can be found in Table 2.

Figure 2. REMOTION homepage.

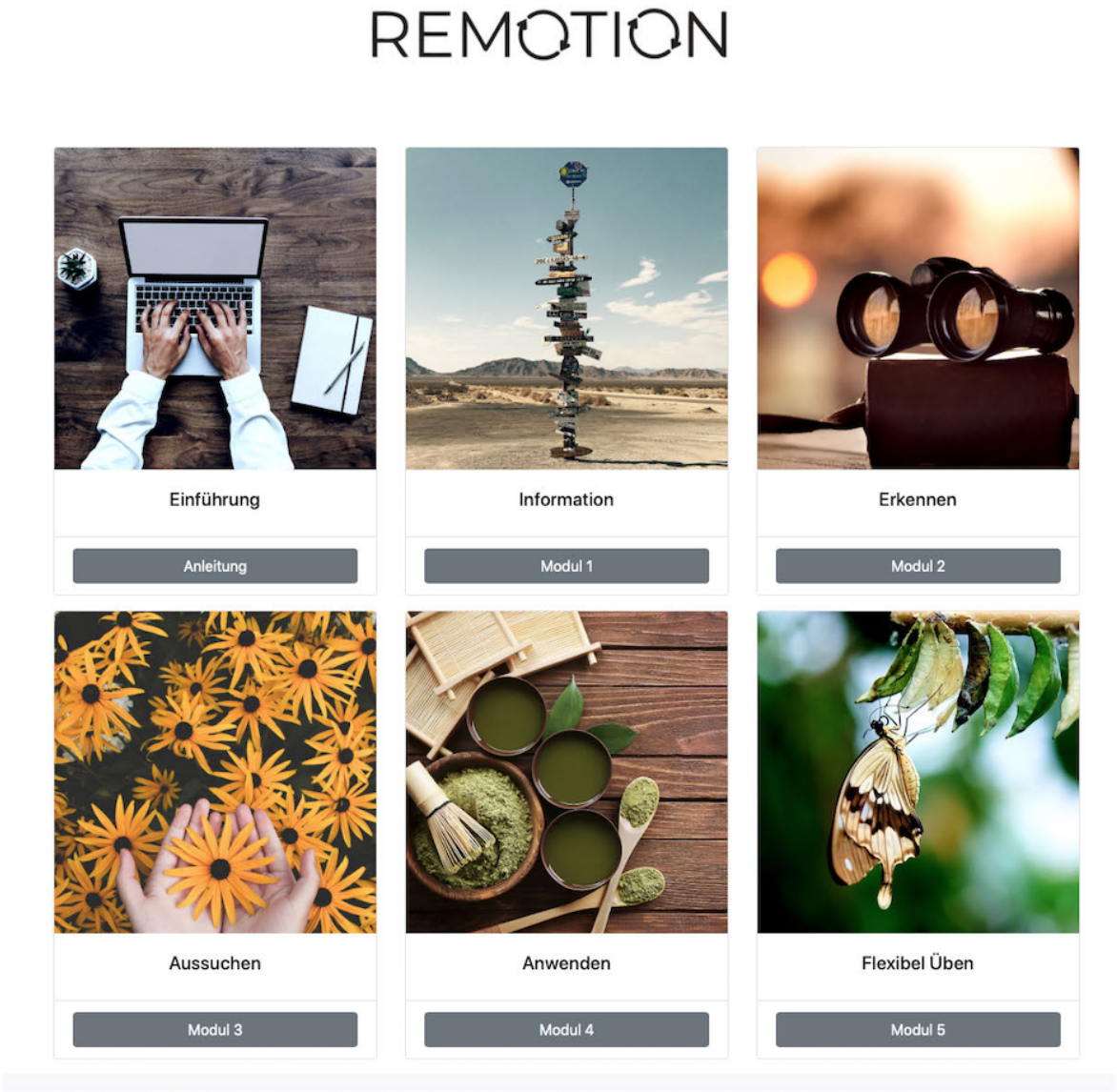


Table 2. Information provided to therapists.

Chapter	Content
Information about REMOTION	Information about the structure of REMOTION and theoretical background is provided for the therapists.
Information about each module	Each module and its content are outlined for the therapists. Therapists are informed about the exercises that patients complete in each module.
Information on using REMOTION exercises in face-to-face sessions	Therapists are provided with information as to how they can integrate specific exercises that patients have completed in the program, in their therapy sessions.

Treatment as Usual

Treatment as usual, in this study, consists of psychotherapy as administered in routine practice at the outpatient clinic of the Department of Clinical Psychology and Psychotherapy at the University of Bern. Psychotherapy at the outpatient clinic is an integrative form of cognitive behavioral therapy based on psychological therapy principles [56]. Individual case formulations are key in this treatment approach. This integrative form of cognitive behavioral therapy places a focus on empirically validated interventions and on the following general change factors in psychotherapy: clarification, resource activation, problem activation, and problem solving [57]. A further focus is placed on the analysis of problems and potentials for the therapeutic relationship, such as motive-oriented therapy relationship [58], and on plan analysis [59], which analyses the instrumental functions of patient behavior and experience. Patients in the treatment as usual group will not have access to REMOTION during the 12-week assessment period. Treatment sessions at the outpatient clinic usually take place once a week.

The exact number of treatment sessions during the 12-week assessment period will be recorded for each patient.

Therapists

Psychotherapy is administered by licensed psychotherapists who work at the outpatient clinic of the University of Bern and who have completed postgraduate training in psychotherapy at the University of Bern (Master of Advanced Studies in Psychotherapy), or by psychotherapists in said postgraduate training under regular supervision. All psychotherapists have master's degrees in psychology. Psychotherapists in training have been in training for at least half a year and are regularly supervised. Therapists will be allocated to patients according to capacity at the outpatient clinic, a within-therapist design is used in the study.

Measures

Overview

Items recording demographic information of patients will be recorded at baseline, post and follow-up. Also, as part of routine practice in the outpatient clinic, patient diagnostic status will be obtained during the study by conducting a Structured Clinical Interview I (German version) for Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) [60]. Furthermore, a qualitative interview with questions created specifically for the study will be conducted with a share of participants and therapists in the REMOTION group after 6 weeks. The purpose of this interview is to assess both experience and satisfaction with REMOTION, and thereby, should complement information from the questionnaires.

If deemed necessary, data collection will be aided by emails and phone calls in cases of poor data retention. A full description of all outcomes in the study is provided in the next sections. Unless stated otherwise, measures will be provided online.

Primary Outcome Measure

The primary outcome measure in this study is general symptom severity as measured with the Brief Symptom Inventory (German version) [61]. The Brief Symptom Inventory will be given to patients at baseline, post and follow-up. The Brief Symptom Inventory contains 53 items and is one of the most frequently used questionnaires to measure general symptom severity. A study [62] has shown that it has good psychometric properties, comparable with those of the Symptom Checklist-90-Revised instrument .

Secondary Outcome Measures

Emotion regulation will be assessed using 2 different instruments: (1) the German version [63] of Difficulties in Emotion Regulation Scale [64], a 36-item self-report questionnaire consisting of 6 subscales assessing difficulties in emotion regulation, and (2) Fragebogen zur standardisierten *Selbsteinschätzung emotionaler Kompetenzen* (SEK-27, *Emotion Competencies Questionnaire*) [65], a 27-item self-report instrument that addresses a range of emotion regulation skills, given to all patients in the study at baseline, 6 weeks, and 12 weeks. Moreover, therapists will also be asked to fill out ratings of patient emotion regulation. Good psychometric properties have been shown for the English [64] and German versions [63] of the Difficulties in Emotion Regulation Scale. The SEK-27 shows both good reliability and validity [65].

Depressive symptoms will be assessed with the German version [66] of the 9-item Patient Health Questionnaire, which is one of the most widely used self-report scales to assess depressive symptoms; criterion validity and change sensitivity have been reported [67].

Anxiety symptoms will be assessed with the German version [68] of the 7-item Generalized Anxiety Disorder Scale, a self-report measure that also shows good psychometric properties.

Health-related quality of life will be assessed with the German version [69] of the 12-item Short Form Health Survey, a frequently used, valid, reliable and change sensitive self-report questionnaire [69] used to assess both physical and psychological aspects of health-related quality of life.

Well-being will be assessed with the German version [70] of the World Health Organization Five Well-Being Index, a widely used economic instrument that shows excellent psychometric properties [70].

Feasibility parameters will be assessed in the study at different measurement timepoints: (1) The number of participants consenting to take part in the study and number of participants randomized will be recorded at the beginning of the study. (2) A previous study has shown that adherence may be an important factor in explaining the difference between effects of internet-based cognitive behavioral therapy in open recruitment and routine practice trials [71]; therefore, adherence to the program in this study will be assessed by number of modules completed at 6 weeks and 12 weeks for the REMOTION group, number of pages visited in the program at 6 weeks and 12 weeks for the REMOTION group, and number of exercises completed at 6 weeks and 12 weeks for the REMOTION group. (3) Usability of REMOTION will be assessed with the 10-item System Usability Scale [72] at 6 weeks and 12 weeks in the REMOTION group. (4) User experience of the REMOTION group will be recorded with the meCUE questionnaire [73], a self-report questionnaire that assesses user experience of products with 34 items at 6 and 12 weeks and with a qualitative interview that will be conducted with a share of the participants after the 6 week point, by telephone. (5) Patient attitudes toward online interventions will be assessed with the German version [74] of the Attitudes toward Psychological Online Interventions Questionnaire at baseline, 6 weeks, and 12 weeks for both study groups. (6) Satisfaction with the intervention will be assessed with the Client Satisfaction Questionnaire (in German [75] and adapted for internet interventions) at 6 and 12 weeks in the REMOTION group. Also, satisfaction will be assessed with qualitative interviews conducted with a share of the participants in the REMOTION group by telephone, after the 6-week point.

Other Measures

Therapeutic alliance measured with the German version [76] of the Working Alliance Inventory—short revised, a 12-item self-report scale that has shown good psychometric properties [76] will be given to all patients at 6 and 12 weeks. Patient self-compassion will be assessed with the German version [77]

of the Self-Compassion Scale, a 26-item self-report scale that is both reliable and valid and will be given to all patients at baseline, 6 weeks, and 12 weeks. In order to assess negative effects of the intervention, an adapted version of the Inventory to Assess Negative Effects of Psychotherapy [78] for internet intervention will be used. Only 15 out of 21 items will be used; 6 items geared specifically at conventional psychotherapy will be exempt. The questionnaire is a self-report and will be given to REMOTION group patients at 6 and 12 weeks.

A variety of therapist variables will be recorded in the study, also including demographic data (experience, background, etc) and individual items on general use of emotion regulation interventions in therapy and general use of online interventions in therapy. In the REMOTION group, therapists perceived effect of REMOTION on therapy (attitude toward the intervention, use, satisfaction with the intervention, etc) will also be assessed with a set of items created specifically for the study. An interview will be conducted with a share of the therapists in the REMOTION group after the 6 week timepoint in order to further assess perceived effect of REMOTION on therapy. This interview will also collect data on therapist experience and satisfaction with REMOTION. It will be conducted per telephone.

Patient difficulties in emotion regulation and patient emotion compentencies will be rated by therapists using versions of the Difficulties in Emotion Regulation Scale (original [64], German version [63]) and SEK-27 [65], adapted specifically for this study, at the same measurement timepoints as patients. The wording of the questions is changed as little as possible from the original, but the questions are from an observer's perspective about their patient.

Control of contamination between REMOTION and treatment as usual due to within-therapist design will be controlled in the following ways: the number of therapists who provide both REMOTION and treatment as usual therapies will be recorded, therapists who provide both conditions will be asked explicitly not to talk about REMOTION or use the REMOTION exercises provided in the REMOTION therapist booklet during treatment as usual therapy (a strategy utilized by studies in a review by Magill and colleagues [79]). Adherence to this condition will be recorded with items at post and follow-up for the therapists.

Planned Analysis

Data will be analyzed on an intention-to-treat basis, meaning that all randomized patients will be included in the outcome analyses and missing data be handled accordingly. The primary outcome measure, general symptom severity, will initially be analyzed descriptively. Within- and between-group effect sizes will be calculated, and linear mixed models will be calculated. These models use all available data on a participant and estimate parameters of missing values. The various secondary outcomes will also be analyzed descriptively, then analyzed with linear mixed models, where applicable. With regard to feasibility parameters, the data will be characterized by descriptive statistics (means, standard deviations, and confidence intervals) in order to allow for comparison with other studies in the field. For categorical data, amount or percentage will be reported. The qualitative interviews generated for this study, will be analyzed using qualitative content analysis as recommended by Mayring [80]. Results will be reported in accordance with CONSORT (Consolidated Standards of Reporting Trials) [81] and CONSORT-EHEALTH [82].

Results

The study was approved by the regional ethics committee in January 2020 and was registered with clinicaltrials.gov in February 2020. Participant recruitment and data collection started in February 2020, and as of November 2020, are ongoing. Results for the study are expected in 2022.

Discussion

General

This study aims to evaluate the benefit of adding a new transdiagnostic treatment tool, REMOTION, to outpatient psychotherapy. The study aims to provide a tool to improve emotion regulation transdiagnostically and to make use of the benefits of blended therapy as described, for example, by Erbe and colleagues [46]. More generally speaking, the results of this study could be used to improve transdiagnostic treatments of mental illness for patients and provide valuable information on the provision of blended therapy. Although many studies on internet-based and blended treatments are conducted in Switzerland, corresponding intervention formats are not implemented and available in routine practice. With regard to the concept of emotion regulation, to our knowledge, this is the first time an emotion regulation intervention structurally based on the stages of emotion regulation as specified in the extended process model of emotion regulation [2] is used with a clinical population in a blended psychotherapy setting. The application of a basic theoretical concept to a clinical psychotherapy context is a further strength of the study.

Limitations

The following limitations of the study need to be considered. First, as this is a pilot trial, the number of patients examined in the study is small and thus only preliminary results on the effects of the treatment can be provided. However, this pilot trial can inform future larger studies that would be necessary to examine the efficacy or effectiveness in the future. Also, as this is a pilot study, no conclusions on specificity or mechanisms of change can be made. Moreover, most of the outcomes assessed in the study will be measured via self-report. In emotion regulation literature, the fact that self-report may be limiting has been described [64]. We have, as a result, tried to also include an observer rated assessment of emotion regulation by the therapist. Also, it should be considered, that unlike therapists for treatment as usual, therapists in the intervention group are encouraged to integrate elements of the REMOTION program into their psychotherapy sessions therapy. This may also lead to differences between the 2 study groups. Furthermore, it currently remains unclear what impact the COVID-19 pandemic may have on patient recruitment and data collection.

Conclusions

REMOTION is a pilot randomized controlled study, assessing for the first time the feasibility and potential effectiveness of an internet-based emotion regulation treatment (REMOTION) as an add-on to psychotherapy in the form of a blended treatment. The study aims to make emotion regulation tools accessible to a broad range of patients and will provide insight into ways to improve psychotherapy for patients by the provision of internet-based tools. The strength of the approach lies in the application of the theoretical framework in a psychotherapy context and in the use of the treatment modality (blended).

Acknowledgments

We would like to thank Dania Spagnuolo and Noé Weigl for their contributions to programming the internet-based version of REMOTION. Funding for the study is provided by the Department of Clinical Psychology and Psychotherapy, University of Bern, Switzerland.

Authors' Contributions

LLB wrote the initial version of the manuscript. All authors contributed to further drafts of the manuscript. TB is the principal investigator of the study.

Conflicts of Interest

None declared.

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Abbreviations

SEK-27: Fragebogen zur standardisierten Selbsteinschätzung emotionaler Kompetenzen (Emotion Competencies Questionnaire)

Edited by G Eysenbach; submitted 02.06.20; peer-reviewed by J Apolinário-Hagen, D Erbe; comments to author 14.07.20; revised version received 10.08.20; accepted 27.10.20; published 12.11.20.

Please cite as:
Bielinski LL, Krieger T, Moggi F, Trimpop L, Willutzki U, Nissen C, Berger T
REMOTION Blended Transdiagnostic Intervention for Symptom Reduction and Improvement of Emotion Regulation in an Outpatient Psychotherapeutic Setting: Protocol for a Pilot Randomized Controlled Trial
JMIR Res Protoc 2020;9(11):e20936
URL: http://www.researchprotocols.org/2020/11/e20936/
doi:10.2196/20936
PMID:33180026

Protocol

A Self-Administered Multicomponent Web-Based Mental Health Intervention for the Mexican Population During the COVID-19 Pandemic: Protocol for a Randomized Controlled Trial

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Abstract

Background: The COVID-19 pandemic has become a public health emergency of international concern; it has not only threatened people's physical health but has also affected their mental health and psychological well-being. It is necessary to develop and offer strategies to reduce the psychological impact of the outbreak and promote adaptive coping.

Objective: This study protocol aims to describe a self-administered web-based intervention (Mental Health COVID-19) based on the principles of positive psychology supported by elements of cognitive behavioral therapy and behavioral activation therapy to reduce the symptoms of anxiety and depression and increase positive emotions and sleep quality during and after the COVID-19 outbreak through a telepsychology system.

Methods: A randomized controlled clinical superiority trial with two independent groups will be performed, with intrasubject measures at four evaluation periods: pretest, posttest, 3-month follow-up, and 6-month follow-up. Participants will be randomly assigned to one of two groups: self-administered intervention with assistance via chat or self-administered intervention without assistance via chat. The total required sample size will be 166 participants (83 per group).

Results: The clinical trial is ongoing. This protocol was approved by the Research Ethics Board of the Free School of Psychology-University of Behavioral Sciences (Escuela libre de Psicología-Universidad de Ciencias del Comportamiento). The aim is to publish the preliminary results in December 2020. A conservative approach will be adopted, and the size effect will be estimated using the Cohen *d* index with a significance level (α) of .05 (95% reliability) and a conventional 80% power statistic.

Conclusions: The central mechanism of action will be to investigate the effectiveness of an intervention based on positive psychology through a web platform that can be delivered through computers and tablets, with content that has been rigorously contextualized to the Mexican culture to provide functional strategies to help the target users cope with the COVID-19 pandemic.

Trial Registration: ClinicalTrials.gov NCT04468893; https://clinicaltrials.gov/ct2/show/NCT04468893

International Registered Report Identifier (IRRID): DERR1-10.2196/23117

(JMIR Res Protoc 2020;9(11):e23117) doi:10.2196/23117

KEYWORDS

e-health; positive psychology; cognitive behavioral therapy, behavioral activation therapy, COVID-19; internet; intervention; telepsychology, Mexican sample

Introduction

Background

The outbreak of COVID-19 has been declared a Public Health Emergency of International Concern (PHEIC) [1]. It has also affected people's mental health and has had consequences for their psychological well-being. In a study conducted in China to determine the impact of the initial phase of the COVID-19 outbreak on people's mental health, more than half of the respondents evaluated the negative psychological impact of the outbreak as moderate or severe. Moreover, the participants reported depressive symptoms (16.5%), anxiety (28.8%), and moderate to severe stress levels (8.1%) [2]. Subsequently, increases in negative emotions (eg, anxiety, depression, and irritability) and sensitivity to social risks have been observed, as well as a decrease in positive emotions and life satisfaction after the official declaration of the epidemic of COVID-19 in China [3]. During this pandemic, public health measures have been implemented to mitigate the spread of the virus, such as physical distancing and confinement worldwide. However, although these measures can be critical to mitigate the spread of the disease in the general population, the separation from loved ones, the perception of loss, and the uncertainty of the evolution of the disease could cause adverse psychological effects both in the short and long term [4]. Due to the outbreak control measures, it has been observed that confinement, loss of normal routine, and reduction of social and physical contact with others frequently resulted in feelings of boredom, frustration, and isolation, which were perceived as distressing to the participants [5].

In Mexico, at the time of the writing of this manuscript, as of July 18, 2020, 324,041 cumulative cases of COVID-19 have been reported and 37,574 deaths have been confirmed [6], and it is estimated that the pandemic may continue to have devastating effects considering the structural conditions of poverty and lack of access to physical and psychological health assistance. Although published research articles about the impact of COVID-19 in Mexico are still scarce, it was identified that just one week after the national health emergency was declared in Mexico, 50.3% of a total sample of 1105 participants rated the psychological distress of the outbreak as moderate to severe, followed by 15.7% participants who reported moderate to severe depressive symptoms and 22.6% who reported moderate to severe anxiety symptoms [7]. Another study with a sample of 3932 participants identified that 14.8% of the participants reported moderate and 7.8% reported severe intrusive thoughts, 15.9% reported moderate and 6.4% reported severe avoidance symptoms, 9.8% reported moderate and 2.4% reported severe symptoms of hyperarousal, and 27.7% reported clinically significant symptoms of posttraumatic stress [8].

The pandemic presents a double challenge because not only is it necessary to design and develop interventions to meet the demand for mental health services, but these interventions must also be adapted to the requirements of a population that is currently in confinement and cannot attend in-person sessions to receive psychological support. Thus, the development of remote psychological care services that provide service to the general population is of extreme relevance. Therefore, there is an emerging need to develop cost-effective mental health prevention interventions, not only to cover the demand for care existing after the COVID-19 pandemic but also to reduce risk factors that increase the possibility of either developing mental health problems or exacerbating the symptoms of pre-existing mental disorders [9,10]. The purpose is to strengthen these factors with individual tools such as positive thinking, interpersonal effectiveness skills, and problem-solving [9], among other mechanisms that enable the general population to positively adapt to adversity. Positive psychology is one of the approaches that focuses on promoting such tools.

Psychological Intervention Based on Positive Psychology

Positive psychology is a movement within psychology that strives to better understand meaning in life, character strengths, and how these can be developed [11]. It is defined as the scientific study of positive experiences, positive individual traits, and institutions that facilitate the development of these experiences and traits, as well as programs that improve the quality of life of individuals while preventing or reducing the incidence of psychopathology [12-14]. Positive psychology seeks to complement traditional psychology; it does not deny suffering and negative aspects in people and seeks to correct the imbalance that affects the homeostasis of daily life [15]. Individuals can intentionally strengthen their ability to experience and maximize positive emotions, which has been shown to improve their physical, emotional, and social health [16]. People are happier and have fewer depressive symptoms after receiving positive psychology [17]. Seligman et al [18] considered it necessary to distinguish at least three access routes to happiness: positive emotions and pleasure (pleasant life); commitment (committed life); and meaning (life with meaning). Furthermore, positive and negative affect usually exist in the same continuum [19]. Positive psychology is oriented toward the prevention and treatment of emotional problems such as anxiety, depression, and stress, among others [20-24]. The objective of the professionals who conduct positive psychology interventions with adults is to increase the emotional well-being of said adults [25].

Efficacy of Interventions Based on Positive Psychology

The topics treated in interventions based on positive psychology, such as strengths, positive emotions, and emotional regulation, produce positive effects on happiness levels, therefore reducing worry, increasing the construction of personal resources, and improving general well-being [19,25,26]. Positive psychology interventions drive happiness through the activation of positive emotions [27], increase aspects of positive body image, and have a significant impact on health and well-being [28]. In

interventions based on gratitude for aspects related to well-being and mental health, increments of subjective happiness and life satisfaction as well as reduction of negative affect and depression symptoms were observed [29]. Moreover, research into new approaches using positive psychology interventions is increasing, such as a randomized controlled trial with three groups [30]. Sin and Lyubomirsky [31] carried out a meta-analysis of 51 interventions involving 4266 participants, and the results revealed that positive psychology interventions did significantly improve well-being (mean r=0.29) and decrease depressive symptoms (mean r=0.31). The efficacy and effectiveness of positive interventions that aimed at cultivating pleasure, commitment, and meaning have also been demonstrated [32]. Although the efficacy of positive psychology has been studied during the last 40 years, it is necessary to be more exhaustive and include more studies in meta-analyses and better effect sizes. This will allow significant analyses to be performed to determine the efficacy of the various interventions based on positive psychology, particularly whether individual interventions are more effective than group interventions and whether longer interventions are more effective than shorter ones [33].

It is also interesting to note that cognitive behavioral therapy (CBT) and positive psychology are compatible, and sometimes one can nurture the other. Both approaches involve analyzing thoughts and behaviors while taking emotions into consideration, while always pursuing the psychological well-being of people [34]. Thus, it has been proven that the application of behavioral activation therapy can be an effective approach to reduce anxiety and depression because it can help people become reinvolved in their lives [35]. In addition, in some studies, it has been pointed out that behavioral activation therapy can be useful for the prevention and treatment of emotional disorders; it can modify dysfunctional patterns by increasing the involvement of the person in what is valuable for them and thus reinforce their efforts. It should be noted that there this research still involves heterogeneity and limitations, and there is insufficient evidence for its use as a sole therapeutic approach [35].

Efficacy of Web-Based Positive Psychology Interventions to Enhance Mental Health in Adults

Web-based interventions through digital platforms offer the possibility of two-way communication and therapeutic approaches [36] and are recommended by official psychological colleges, such as the Official College of Psychology of Madrid. In their Guide to Telepsychological Intervention [37], they state that web-based interventions provide advantages such as accessibility to people who otherwise would not request psychological assistance; in addition to these factors and benefits, they provide quick and easy recording of information to justify the integration of information and communications technology into the therapeutic process. Similar recommendations can be found in the guides of the Colombian College of Psychologists [38] and the College of Professionals in Psychology of Costa Rica [39]. Web-based therapy is advantageous at times when it is difficult or complicated to attend a therapy center, such during as the COVID-19 outbreak; web-based approaches can help avoid the spread of the disease caused by the SARS-CoV-2 virus [40]. The internet can be useful to carry out self-administered psychological interventions [41] and enhance accessibility to therapy for all those who need it [42]. It is important to note that in different reviews, self-administered treatments via the internet and computer-based treatments have been found to be effective [43-45]. Studies have affirmed that the substantial effect of the intervention in positive psychology occurred when it is applied on the internet [46]. In addition, web-based positive psychology therapy with exercises designed to promote positive emotions, behavior, thoughts, strengths, and virtues was found to be effective in reducing symptoms related to depression or other emotional problems [47]. Furthermore, studies have evaluated web-based treatment programs for sleep disorders in adults [48], reporting a significant improvement in participants who received the intervention based on positive psychology [49,50]. Web-based positive psychology therapy has shown significant improvements in both well-being and depressive symptoms [51,52]; significant improvements were obtained in the life satisfaction and general well-being of the participants.

Technology plays a fundamental role in the transmission of positive attitudes. However, there is insufficient knowledge about the factors that influence acceptance and compliance with web-based interventions [53]. It is too early to draw conclusions regarding the psychological consequences of the COVID-19 outbreak in the population. Professionals are conducting research to determine the influencing factors, and as mentioned above, it is estimated that interventions in positive psychology can provide benefits and improve the well-being of the population during the COVID-19 outbreak.

The aim of this study is to describe a randomized controlled trial to evaluate the efficacy of a web-based self-administered positive psychology intervention program based on a telepsychology system (Mental Health COVID-19) for the reduction of anxious and depressive symptoms and the increase of positive emotions and sleep quality during and after the COVID-19 outbreak.

Hypotheses

Primary Hypothesis

The self-administered web-based intervention with psychological assistance via chat will show greater statistical gains in the reduction of anxiety and depression symptoms and greater improvement in positive psychological functioning than an intervention program without support.

Secondary Hypotheses

Higher rates of acceptance and satisfaction will be reported by the participants in the web-based intervention program with psychological support via chat compared to the intervention without assistance; coping strategies and acceptance and satisfaction will be found to function as moderating variables of clinical change; and the changes will be maintained for three and six months after the end of the intervention programs with and without psychological support via chat.

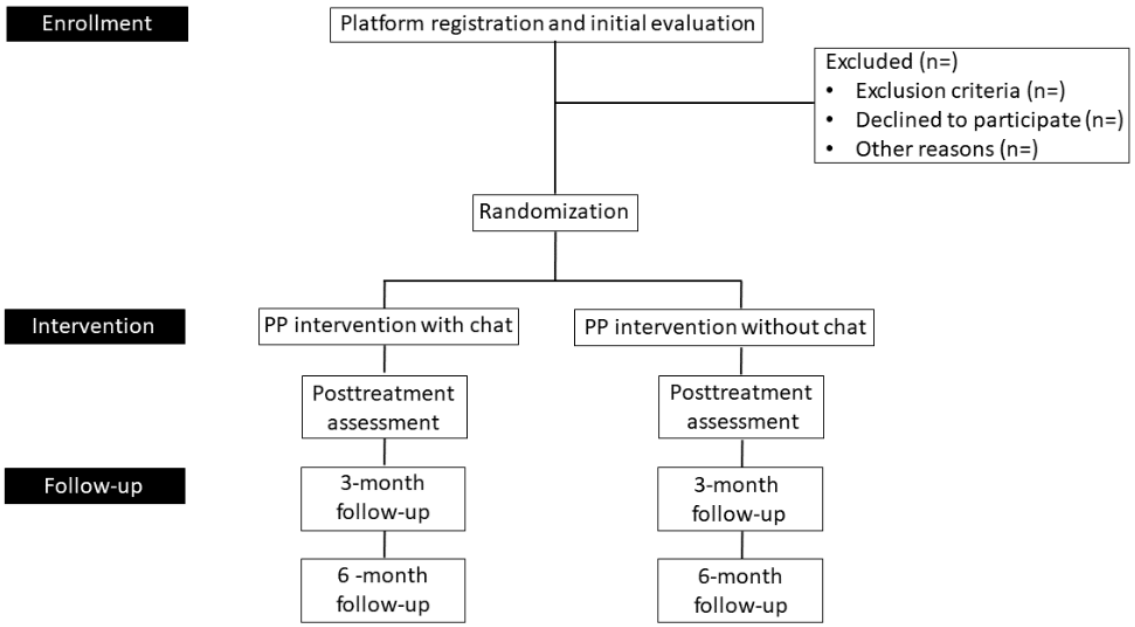
Methods

Study Design

A randomized controlled study will be carried out according to the guidelines set forth in the Consolidated Standards of Reporting Trials (CONSORT) statement [54] and CONSORT eHealth checklist [55].

A randomized controlled clinical superiority trial with two independent groups will be used, with intrasubject measures at four evaluation periods: pretest, posttest, follow-up at 3 months, and follow-up at 6 months [56]. Participants will be randomly assigned to one of two groups: self-administered program based on positive psychology (Mental Health COVID-19) with assistance via chat or self-administered program based on positive psychology (Mental Health COVID-19) without assistance via chat. Figure 1 shows a detailed description of the study design.

Figure 1. Flowchart of the study design for the Mental Health COVID-19 platform. PP: positive psychology.



Study Setting

Sampling

Nonprobabilistic, intentional, subject-type sampling will be conducted in the Mexican population according to the following criteria:

Eligibility Criteria

The inclusion criteria are age ≥18 years; voluntary participation; access to a technological device (computer, tablet, mobile phone, etc) with an internet connection; a valid email address; basic digital skills in the use of an operational system; and access to an internet browser to answer the initial assessment instruments.

The exclusion criteria are having a psychotic disorder and receiving psychological or pharmacological treatment during the study.

The first removal criterion is not accepting the conditions of the informed consent. Due to the enormous and sudden impact on mental health related to the COVID-19 outbreak, no participants will be excluded from the intervention in terms of the results of their applied psychometric tests. However, the results of the participants who did not fulfill the criteria for any of the measured disorders at the premeasure will be excluded from the statistical analysis. The second removal criterion is absence from the web-based platform for more than 20 days.

Sample Size

The sample size was considered based on the effect sizes in controlled clinical studies in which the efficacy of web-based psychological interventions based on positive psychology was evaluated. For the present study, the Cohen *d* index will be used, assuming that the variances of the two groups will be homogeneous; if not, the Hedges *g* index will be used.

Furthermore, the study will include two experimental conditions; a priori analysis was conducted to compare the means between the two independent groups. A conservative approach was adopted, including an effect size with an average magnitude of 0.25 (Cohen *d*, equivalent to g=0.5), a significance level (α) of .05 (P<.05, which corresponds to 95% confidence) and a conventional statistical power of 80% ($1 - \beta = 0.8$). For the analysis, the software G*Power version 3.1.6 [57] was used, and a required sample size of 128 participants was obtained (64 per group).

However, the number of participants will be increased by 30% to control the variable related to dropping out of participants during the treatment; this rate is reported in the literature on

web-based treatments [58,59]. Thus, the total required sample size will be 166 participants (83 per group).

Participant Recruitment

Participants will be recruited through advertisement in digital media (eg, notes in news magazines), as well as through dissemination on social networks. The intervention program will be aimed at adults who can connect via the internet from any part of Mexico. Potential participants can make contact through registration in the Mental Health COVID-19 platform.

Randomization

Once the evaluation is completed, the users will be randomly assigned to one of the study conditions. The randomization will be performed by an independent researcher using web-based randomization software [60] at a ratio of 1:1 using the method of randomly permuted blocks.

The Mental Health COVID-19 Web-Based Intervention

The Mental Health COVID-19 web-based intervention aims to provide the target population with a self-administered intervention based primarily on positive psychology; the intervention is aimed at the recognition and development of strengths and virtues through a well-being approach. In addition, it is supported by elements of CBT such as the definition of emotions and the 3-component model of emotional experience. The three components of this model are (1) physiological (what does the person feel in their body that is related to their emotional state); (2) cognitive (what does the person think, where these thoughts are often related to or caused by their emotional state); and 3) behavioral (what does the person do or feel an impulse to do in response to their emotional state) [61,62]. The Mental Health COVID-19 intervention is also supported by the antecedent-response-consequence (ARC) model of emotions [62]. In this model, the antecedent is the event or situation that triggers emotional experiences; these triggers can be something that is happening in the present moment or even something that occurred in the past. Response refers to the responses to emotional experiences, including thoughts, feelings, physical sensations, and behaviors. Finally, consequence can refer to short- or long-term consequences that occurred due to the antecedents and responses [62].

The elements of behavioral activation therapy are also included, such as the importance of physical exercise and the relationship between physical anxiety and its effects on anxiety and depression [63]. The intervention is composed of 15 modules that are adapted to the symptoms that the population may experience during the global pandemic caused by the COVID-19 outbreak. In addition to the positive psychology contents, a module with psychoeducation on grief and loss was added; although this module is not directly related to a positive psychology intervention, the authors considered that these contents will be helpful in providing psychoeducation to patients who suffered the death of a loved one due to COVID-19 or during the outbreak. The combination of components of positive psychology and CBT in a single intervention has demonstrated effectiveness in decreasing the symptomatology of negative affect, depression, and anxiety and in increasing positive affect [64].

A detailed description of each of the modules, as well as the theory and objectives on which each module is based, can be found in Table 1.

Table 1. Module objectives of the web-based Mental Health COVID-19 intervention.

Intervention module	Theory	Main objective
1. Understanding our emotions during the COVID-19 outbreak	CBT[a]	Learn about the importance of emotions, including anxiety and why it is experienced [61,62,65]
2. Reflection on preventive measures regarding COVID-19	Positive psychology	Recognize the importance of staying home for the common good [61,66,67]
3. Time for gratitude	Positive psychology	Focus attention on gratitude to reduce the negative impact caused by the outbreak [68-70]
4. To the rhythm of life	Positive psychology	Recognize the importance of a healthy lifestyle [71]
5. Resilience, facing adversity	Positive psychology	Provide tools and recognize personal abilities to recover after a stressful event [72]
6. Helping my mind	Positive psychology	Provide information on the importance of focusing on the present moment with the aim of improving or maintaining emotional balance [73]
7. Taking control	CBT	Define achievable goals to regain a sense of self-control and increase satisfaction during the outbreak as much as possible; decrease avoidance of relevant activities [74]
8. Smile and laugh	Positive psychology	Recognize the importance of laughing and its positive effects on mental and physical health [75]
9. Share concerns	Positive psychology	Recognize the importance of communication with one's family, friends, and partner and the importance of expressing concerns to loved ones
10. Separated but together	Positive psychology	Recognize the importance of technologies as means of communication to stay connected through telephone calls, chats, and video calls
11. Time to start	Positive psychology	Propose activities that are usually not performed due to lack of time [76]
12. Exercising my mind and body	Behavioral activation therapy	Perform physical exercise involving motor skills of the body and mental exercises that enable the person to stay busy in personal aspects; recognize the importance of sleep hygiene [63]
13. Spirituality	Positive psychology	Provide tools that help develop a level of spirituality to serve as a tool for positive coping with the outbreak of COVID-19 [77]
14. How to deal with grief over the loss of a loved one during the COVID-19 outbreak	Behavioral activation therapy	Provide information about how to cope with the loss caused by COVID-19 or other losses during this time period [78]
15. My inner strength	Positive psychology	Provide support to help the participants focus on their own strengths and know their areas of opportunity [79,80]

[a]CBT: cognitive behavioral therapy.

Module Delivery Procedure

The contents will be delivered through 15 videos. Each module contains a video with a duration of 10 to 20 minutes, plus homework. The process to generate each of the modules consisted of writing a script based on the theory stated in Table 1 for each module; afterward, the script was narrated by a clinical psychologist with experience in recording video clips and audio capsules. Subsequently, the audio narration was converted to a video clip that included illustrations, short clips, and in some cases, text with explanations of the psychoeducational content. All the videos had the same recording format, in which the narrator provided most of the audio presence and a very small amount of background music was provided without any lyrics. Finally, the videos were uploaded to YouTube, and the privacy option was selected to prevent the videos from being publicly available while they remained accessible with the links integrated in the Mental Health COVID-19 platform. In addition to the videos, the participants could download the exercises indicated in the video as a PDF that could be printed or accessed on the internet; these formats were provided only as review materials for the participants. Video and text elements are among the most common ways to deliver psychological interventions through the internet and can be implemented for a broad range of adult participants; therefore, these two methods were selected. At the end of each video, the participant is asked to answer a 5-question quiz with true-and-false or multiple choice answer options, with the contents observed at the end of each video. It is necessary to complete the quiz with a score of 60% (3 correct questions) to advance to the next module.

The engineering team worked on the usability and accessibility of the platform prior to allowing access to the platform by the general population in terms of responsive design; this ensures that the system has flexibility across both mobile and nonmobile platforms, enabling ease of use across multiple devices [81]. It was confirmed that it is possible to access the intervention through mobile phones, computers, and tablets and properly visualize the contents.

The modules will be delivered to the participants with a frequency of at least 1 day between modules to give the participants time to integrate the contents and perform the

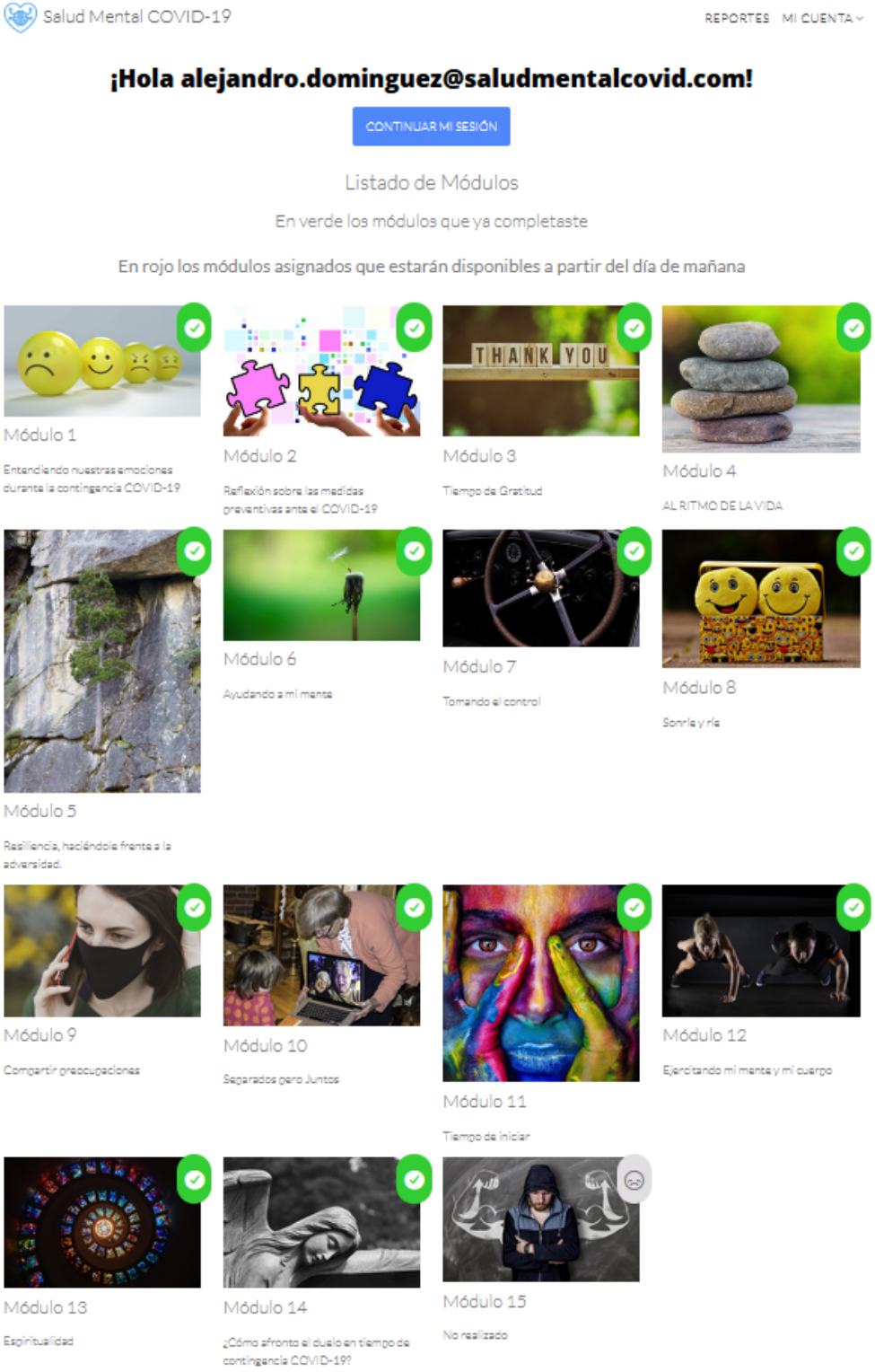
activities assigned to them. Figure 2 shows how the modules will be presented to the participants.

In addition, the COVID-19 Mental Health platform will include an option enabling the participant to observe their progress and review any modules they have already finished. The modules they have completed will be marked in green. The modules available for completion are marked in gray, and modules that are upcoming or available the next day will be marked in red (Figure 3).

Participants in the Intervention With Chat group may use this tool with unlimited access whenever they log in to the web-based platform, that is, 24 hours per day, 7 days per week. The chat service will be provided through the Tawk app, in which participants will be able to receive help from trained, supervised, and clinically experienced psychologists. The main purpose of the chat is to provide emotional containment in cases of emotional distress; give technical guidance on the platform's operation; provide psychoeducation in case the participant has doubts about the content of the modules; support the participants in solving problems or encourage them to finish the modules; and provide a referral whenever a participant shows a need for specialized intervention after an assessment, such as substance abuse, depression, self-harm, suicidal behavior, or psychosis. In these cases, the participants will be provided with contact information they can use. Furthermore, a follow-up will be scheduled with anyone using the chat to determine if they have any doubts about the module's content or about the suggested solutions as well as to explore if they were able to establish contact with the guidance provided.

Figure 2. Screenshot of a module of the Mental Health COVID-19 platform (in Spanish).

Figure 3. Menu showing the modules completed by the participant.



Technical Details of the Platform

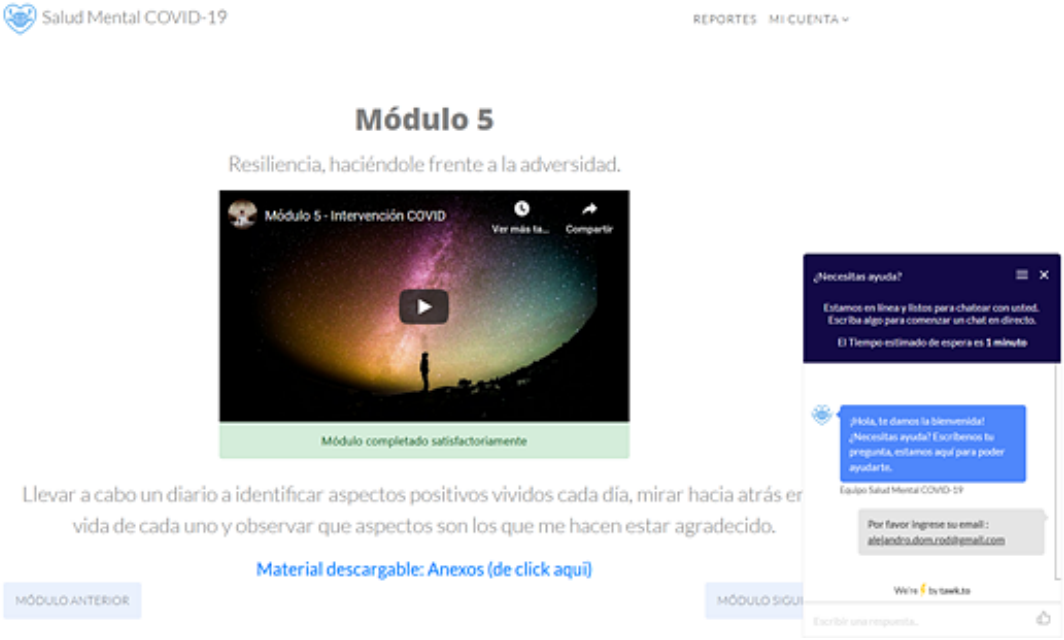
The main technical objectives of this platform were to separate the parts that make up the system, achieve better code administration, implement the best security techniques, and achieve efficient development; therefore, the web-based system was developed in Visual Basic .NET language under the paradigm of object-oriented programming. The platform is composed of classes and data structures that are assembled in a three-layer architecture. The visualization layer managed through the HTML markup language supports the dynamism offered by jQuery and different support libraries, and communicating with the "Business Rules" layer through asynchronous calls; the platform takes advantage of the facile integration offered by the Active Server Pages (ASP) ASP.NET language and its benefits as a simple syntax language that, in turn, manages all interaction with the data layer, which is managed by a Microsoft SQL server with a relational database.

All development was managed with the Git version manager, and the continuous integration and continuous delivery methodology was used to ensure the quality of the code at the time of its deployment in the production environment and, finally, its availability on the internet.

Synchronous Writing Conversation Assistance and Monitoring of Psychological Counselors

In the case of the intervention condition with synchronous writing conversation assistance, also known as chat, each user will be assigned to a trained psychologist with experience in clinical practice, who will receive prior training on the Mental Health COVID-19 intervention. The function of the psychological advisors is to motivate, guide, and listen to the questions and comments of each participant, providing support with the modules of the applied intervention or brief counseling. Previous studies have shown positive postintervention gains using this resource [82]. An example of the synchronous writing conversation integrated in this platform can be found in Figure 4.

Figure 4. Screenshot showing the integrated chat in the Mental Health COVID-19 platform (in Spanish).



Measures

All instruments used over the course of the study are self-report questionnaires that are completed on the internet and have psychometric properties regarding the evaluated population. Table 2 gives an overview of all the questionnaires with the time points of the assessments.

Table 2. SPIRIT (Standard Protocol Items: Recommendations for International Trials) table displaying the schedule of enrolment, interventions, and assessments in the study.

Time point	Study period					
	Enrollment	Allocation	Postallocation			
	t0	0	t1: Pretest	t2: Posttest	t3: Follow-up 1	t4: Follow-up 2
Enrolment						
Eligibility criteria	✓					
Informed consent	✓					
Allocation		✓				
Interventions						
Positive psychology intervention with chat						
Positive psychology intervention without chat						
Assessments						
Primary outcome measures						
Scale of Posttraumatic Stress Traits	✓			✓	✓	✓
Widespread Fear Scale	✓			✓	✓	✓
Urban Strategies Coping Strategies Scale	✓			✓	✓	✓
State-Trait Anxiety Inventory	✓			✓	✓	✓
Scale for Suicide Ideation	✓			✓	✓	✓
GAD-7[a]	✓			✓	✓	✓
BDI-II[b]	✓			✓	✓	✓
Pittsburgh Sleep Quality Index	✓			✓	✓	✓
Positive Psychological Functioning Scale				✓	✓	✓
Secondary outcome measures						
Opinion questionnaire about the treatment				✓		
System Usability Scale				✓		

[a]GAD-7: Generalized Anxiety Disorder 7-Item Scale

[b]BDI-II: Beck Depression Inventory second version

Primary Outcome Measures

1. Scale of Posttraumatic Stress Traits in Mexican Youth Exposed to Social Violence, validated by Pineda et al [83] and Chávez-Valdez et al [84]. This scale measures posttraumatic stress disorder (PTSD) symptomatology based on version 5 of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) criteria. This brief scale consists of 24 items that assess traits that support a diagnosis of PTSD. It is answered through a self-report process. It has internal consistency, with a Cronbach α coefficient of .97.
2. Widespread Fear Scale [85], adapted by Chávez-Valdez and Ríos Velasco [86]. This scale measures fear of adversity in a particular context and the feelings it disseminates, as well as other economic and social fears; in this case, it has been adapted for the COVID-19 pandemic. The scale is composed of seven items with options from 0 (nothing) to 3 (a lot), and it has shown an acceptable internal consistency of α=.90.
3. CIU (Cuestionario de Inseguridad Urbana) Urban Strategies Coping Strategies Scale [87], adapted by Chávez-Valdez and Ríos Velasco [86]. This scale is composed of four factors: affective components, physiological activation, cognitive confrontation, and behavioral promotion. In a reliability analysis using the Cronbach alpha coefficient performed by Vuanello [87] in Argentina, a Spanish-speaking country, a Cronbach alpha of .92 was found. A validation of this scale with the Mexican population has been performed by the authors in this manuscript and has been submitted for publication.
4. State-Trait Anxiety Inventory (Spanish version by Spielberger and Díaz-Guerrero) [88]. This instrument measures the symptoms related to anxiety in general (anxiety trait) or how respondents experience anxiety at a certain time (anxiety state). It is composed of 40 items, 20 for state, and 20 for trait.
5. The Scale for Suicide Ideation [89]. This scale aims to assess the frequency of attitudes, behaviors, and plans to commit suicide. It is divided into 19 items with response

options of 0-2, giving a total of 0-38, where a score ≥10 indicates an existing risk of suicide. This scale has been validated by González-Macip et al [90] in the Mexican population, obtaining a Cronbach alpha of .84. For the purpose of the analysis, the last item was removed because it evaluates suicide attempts and not ideation; however, with only 19 items, the same Cronbach alpha of .84 was obtained [91].

6. The Generalized Anxiety Disorder 7-Item (GAD-7) scale [92]. This is a brief scale consisting of 7 items designed to measure the severity of symptoms of generalized anxiety disorder. The answers are based on the symptoms perceived during the last week. The questions in this scale are answered in a Likert format with scores from 0-3, where the maximum total score is 21. A score between 0 and 4 points indicates that anxiety is not perceived, and a score between 15 and 21 is an indicator of perceived severe anxiety. The version by García-Campayo et al [93] was used for this study.
7. Beck Depression Inventory second version (BDI-II) [94]. This self-administered scale measures the presence and severity of depression symptoms in adolescents and adults. It contains 21 items with response options on a Likert scale from 0-3, except for items 16 and 18, which have seven response options each. The score ranges from 0-63, where a total of 0-13 indicates minimal depression, 14-19 indicates mild depression, 20-28 indicates moderate depression, and 26-63 indicates severe depression. Studies of the psychometric properties of the Spanish version of the BDI for the Mexican population were conducted by Jurado et al [95] and González et al [96] for version II (Cronbach alpha values between .87 and .92).
8. The Pittsburgh Sleep Quality Index [97]. This instrument evaluates sleep patterns that differentiate people with poor sleep quality from people with good sleep quality. In this scale, seven areas are evaluated: sleep duration, sleep disturbance, sleep latency, daytime dysfunction due to drowsiness, sleep efficiency, overall quality of sleep, and use of sleep medication [97]. The evaluation in the Mexican population showed solid reliability (α=.78) [98].
9. The Positive Psychological Functioning scale. This scale consists of 11 psychological resources: autonomy, resilience, self-esteem, purpose in life, enjoyment, optimism, curiosity, creativity, humor, environmental mastery, and vitality. All of these resources are grouped into a second order factor called Positive Psychological Functioning. This measure has adequate validity and reliability in the Mexican population (α=.91) [99].

Secondary Outcome Measures

Acceptance, Satisfaction, and Usability Measures

1. Opinion about the treatment [42]. This questionnaire is composed of four questions that report the participants' level of satisfaction with the treatment and if they would recommend the treatment to a friend or family member, if they consider the treatment useful, and if they think that the treatment was difficult to manage or aversive. The questions are answered on a scale from 1 (nothing) to 10 (very much).
2. System Usability Scale [100]. This instrument is designed to validate the usability of a system; it is composed of 10 items, which are answered on a 5-point Likert-type scale with respect to the degree of conformity of the product (1, completely disagree to 5, completely agree). To obtain the global score of this scale, all the obtained values must be added together and multiplied by 2.5; this will result in a number between 0 and 100, which will be the global value of this scale.

Data Collection and Management

Due to the structure of how the platform is built, it is possible to know if the participants have not logged in to the platform in more than 3 days. For this purpose, we will consider sending a generic email to all the participants reminding them about the benefits of continuing with the intervention [101].

All the participants may withdraw from the treatment at any time for any reason they consider relevant to interrupt the intervention. The participants will not need to notify any member of the project about their withdrawal from the intervention; however, the main contact points such as email or therapists in the chat will record any notification received about the withdrawal of any participant, and this will be analyzed at the end of the study. Moreover, the structure of this web-based intervention provides data about the users' behavior on the platform in terms of how often they use it, for how long, and which modules they review, while respecting the confidentiality and anonymity of the users at all times because sensitive data are not requested, nor is it possible to identify the users. These data will allow the researchers to identify if variables such as education level, age, gender, or symptomatology are related to a higher or lower frequency of use of the platform.

Statistical Analysis

Descriptive analyses will be carried out to characterize the study sample based on demographic variables such as age, sex, occupation, and residence. The abandonment data based on experimental condition, region of the country, and sociodemographic characteristics will be considered. To analyze the clinical indicators, the intensity of symptoms, their duration, and comorbidity with other psychological problems will be reviewed, as well as measures focused on the enhancement of positive emotions, strengths, and virtues.

To determine the differences in sociodemographic and diagnostic variables that could affect the efficacy of the study between the two treatment groups (assisted by psychological counselors via chat or without assistance), statistical analysis will be performed before the intervention.

The Kruskal-Wallis test, with a level of significance of $P \leq .05$, will be calculated for categorical variables through chi-square test analysis. The results will be presented in three sections. The first section is contrast analysis to measure the efficacy of the interventions. In this regard, specific measures of anxiety and depression symptoms and positive psychological functioning will be analyzed before and after the COVID-19 Mental Health treatment program. The second section analysis of moderating

variables (coping strategies), and the third section measures the acceptance and satisfaction as well as the usability of the system.

Power

To determine the efficacy of the intervention program, a repeated-measures analysis of variance will be computed using SPSS (IBM Corporation), in which we will compare the pretest measures against the posttest measures in the two experimental conditions. The results will be assessed by performing effect size analyses for each intervention group and between treatment groups (unassisted and therapist-assisted) using the G*Power version 3.1.6 software [57]. A conservative approach will be adopted, and the size effects will be estimated using the Cohen *d* index with a significance level (α) of .05 ($P<.05$, which corresponds to 95% reliability), which will be estimated with a conventional 80% power statistic ($1 - \beta = .8$).

Confidentiality and Ethical Conditions

This study will strictly adhere to the guidelines expressed in the American Psychological Association Code of Ethics for Psychologists [102]. The project supervisors will protect user confidentiality and interaction records during chat support. All participants must read and accept the informed consent, which details the objectives of the study, and then proceed to respond to the evaluation instruments that will provide support to evaluate the effectiveness of the intervention. These instruments are included within the Mental Health COVID-19 platform; therefore, it will not be necessary to provide access to links to other servers, thus protecting the identity and data of each user. At all times, the participants' rights to confidentiality and privacy of personal data will be respected. The personal data of the participants will be protected for consultation only by the study researchers, and the users may request that their data be removed from the registry and abandon the study at any time. Participation is voluntary, and the intervention will be free of charge for all members of the adult Mexican population who meet the inclusion criteria for the study.

The platform includes a section on privacy policy and privacy rights, which can be found on the website [103]. This section describes the objectives of the platform and provides information regarding the uses of the collected data, use of cookies, links to third parties, and control of personal information. This study received approval from the *Escuela Libre de Psicología, Universidad de Ciencias del Comportamiento* (Ethics Committee of the Free School of Psychology University of Behavioral Sciences) in Chihuahua, Mexico (reference number Folio 2008) on May 1, 2020.

Results

The clinical trial is ongoing. As of July 2020, enrollment has been completed. We aim to publish the results of the study in December 2020.

Discussion

Primary Considerations

This study focuses on addressing the psychological repercussions of the COVID-19 pandemic, and its objective is to test the effectiveness of a self-administered web-based intervention based on the principles of positive psychology for people who are psychologically affected by the pandemic. The intervention is also supported by elements of CBT, and components of behavioral activation therapy were added. Some reviews have shown that web- and computer-based treatments for depression are effective interventions [43-45,51,52].

The objective of this intervention is to enable the participants to internalize and consolidate what they have learned in each module, improve their sleep quality, decrease the anxious depressive symptoms characteristic of the posttraumatic stress generated by the pandemic, and use the learned content as coping strategies and skills on a day-to-day basis. It is important to note that it is possible to apply evidence-based treatments through the internet [41]. These treatments reduce the contact time between the patient and therapist; also, due to confinement during the pandemic, this treatment would not be possible otherwise.

Thus, with the implementation of positive psychology modules, it is expected that the participants' negative affect and anxiety will decrease significantly and that their positive affect will increase; this would be in accordance with the study by Mira et al [104], in which they suggest that positive psychology techniques can have an impact on clinical symptoms and highlight the need to include these techniques to achieve changes in measures of positive functioning. Also, in interventions based on gratitude, improvements in anxiety, depression, and optimism have been found [29,105].

Particularly, the behavioral activation modules can help users pay attention to the activities they perform daily and realize how this affects their emotional state with regard to their stress level and coping capacity. Quintana et al [106] affirm that strategies to increase physical activity can increase adherence to healthy lifestyles and improve some psychological variables, such as quality of life, quality of sleep, and anxiety. In the same way, the aim of the CBT modules with components of emotion will be to decrease sleep disorders, such as insomnia and nightmares, and decrease the symptoms of PTSD present in the study sample [107] as well as reduce their symptoms of anxiety and depression [108].

The discussion of the study will be in line with the considerations highlighted by Botella et al [109] when evaluating a psychological intervention. When considering the results, attention will be paid to both the axis of efficacy and internal validity. This will enable analysis of the available evidence from the study against alternative explanations and in the axis of effectiveness implied by the generalization or external validity of the intervention, in terms of the feasibility of applying the intervention in various social and cultural contexts of individuals as well as the associated benefits of its dissemination in the context of the health crisis derived from the COVID-19 outbreak.

To summarize, this platform will offer the possibility of reaching a large number of people, reduce costs because it will be administered at home, and offer useful tools for the mental health care of the Mexican population. The web-based methodology offers the possibility of interacting creatively with

vignettes, videos, audios, etc; therefore, it is more attractive than traditional interventions.

Limitations

It should be noted that this study has some weaknesses, such as the lack of ease of internet management for some people, especially older people; also, the dropout rate may be higher than in traditional therapy [41]. In addition, a high dropout rate is observed in web-based interventions performed by the participants themselves, and the influencing factors on treatment adherence and sabotage that may appear during the course of therapy are unknown [41]. It is to be hoped that web-based self-administered treatment will become a generality in the therapeutic community.

Acknowledgments

For their contributions, the authors would like to thank Sarah Margarita Chávez, Arantza Mariel Solis Nicolas, Karen Ochoa, Ana Marisa Colmenero Guadián, Oscar Armando Esparza-Del Villar, Flor Rocío Ramírez-Martínez, Jasshel Teresa Salinas-Saldívar, Delia Isa Silva, Alma Leonor Alvarado, José Cruz Ramírez Holguín, and Marco Antonio Sáenz. This research did not receive any funding.

Authors' Contributions

ADR and ADLRG conceived the study, and ADR, ADLRG, MJHJ, and PAL developed the methodology. JAS, JEGH, and ADR developed the web platform. ADR, ADLRG, MJHJ, PAL, SCML, CAS, and VAG wrote the original draft of the manuscript. ADR, ADLRG, MJHJ, PAL, SCML, CAS, VAG, JAS, and JEGH reviewed and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed module contents.
[DOCX File , 21 KB - resprot_v9i11e23117_app1.docx]

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Abbreviations

ARC: antecedent-response-consequence
ASP: Active Server Pages
BDI-II: Beck Depression Inventory second version
CBT: cognitive behavioral therapy
CIU: Cuestionario de Inseguridad Urbana
CONSORT: Consolidated Standards of Reporting Trials
DSM-5: Diagnostic and Statistical Manual for Mental Disorders version 5
GAD-7: Generalized Anxiety Disorder 7-Item Scale
PTSD: posttraumatic stress disorder

Edited by G Eysenbach; submitted 01.08.20; peer-reviewed by N Johnson, M Heilemann; comments to author 02.10.20; revised version received 24.10.20; accepted 27.10.20; published 16.11.20.

Please cite as:
Dominguez-Rodriguez A, De La Rosa-Gómez A, Hernández Jiménez MJ, Arenas-Landgrave P, Martínez-Luna SC, Alvarez Silva J, García Hernández JE, Arzola-Sánchez C, Acosta Guzmán V
A Self-Administered Multicomponent Web-Based Mental Health Intervention for the Mexican Population During the COVID-19 Pandemic: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2020;9(11):e23117
URL: http://www.researchprotocols.org/2020/11/e23117/
doi:10.2196/23117
PMID:33196449

Protocol

Digital Support for Healthier Eating Habits Among Patients With Type 2 Diabetes: Protocol for a Randomized Clinical Trial Within Primary Care (HAPPY Trial)

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Abstract

Background: Despite the large impact that dietary habits have in the management of diabetes, few tools for supporting healthy eating habits are available for persons with diabetes.

Objective: The aim of this randomized clinical trial is to evaluate the effect of a 12-week, mobile health (mHealth), app-based intervention promoting healthy eating habits among patients with type 2 diabetes.

Methods: The HAPPY (Healthy eating using APP technologY) trial is a randomized clinical trial with two arms aiming to include 200 patients, 18 years of age or older, with type 2 diabetes. Both women and men are eligible for inclusion. Study participants are randomized 1:1 to an intervention group, where they are instructed to use a smartphone app promoting healthy eating, or to a control group, where they receive standard primary care only, for a period of 12 weeks. Each week a new topic (eg, vegetable intake) is introduced via the app. After an introduction text, the user is given a topic-related activity to perform (eg, eat one additional serving of vegetables per day during that week). The app records daily progress and sends automatic reminders or feedback to the user. Dietary intake, body composition, clinical variables, and biomarkers are measured at baseline and at 3- and 6-month follow-ups. An extensive web-based questionnaire comprising several validated questionnaires assessing a number of lifestyle factors is distributed via email at baseline and at 3-, 6-, and 12-month follow-ups; lifestyle factors include, for example, sleep, physical activity, eating behavior, and health-related quality of life. The effect of the intervention on dietary intake (primary outcome) and on glycated hemoglobin and blood lipid levels, body composition, blood pressure, other lifestyle factors, and overall health (secondary outcomes) will be assessed.

Results: Data collection is ongoing. Recruitment of participants started in January 2019. Findings from the study are expected to be published by the end of 2021.

Conclusions: Technology development provides new ways to promote and support long-term adherence to healthier eating habits. mHealth-based approaches allow for real-time interaction and the delivery of an intervention at any time. Further, focusing on overall diet allows the user to apply new knowledge to current eating patterns, creating an individualized approach. In this study, we evaluate the effect of using a new smartphone app promoting healthy eating habits on dietary intake, clinical markers, and lifestyle factors among patients with type 2 diabetes.

Trial Registration: ClinicalTrials.gov NCT03784612; https://clinicaltrials.gov/ct2/show/NCT03784612

International Registered Report Identifier (IRRID): DERR1-10.2196/24422

(JMIR Res Protoc 2020;9(11):e24422) doi:10.2196/24422

KEYWORDS

body composition; diabetes; dietary intake; HbA1c; metabolic health; mHealth; obesity; randomized clinical trial; serum lipids; smartphones

Introduction

Background

The prevalence of type 2 diabetes is increasing in Sweden, as well as in the rest of the world. Today, over 400 million adults have diabetes [1]. It has long been known that persons with type 2 diabetes have an increased risk of cardiovascular disease (CVD) and premature death, in large part due to an increased prevalence of risk factors for CVD (eg, obesity, dyslipidemia, and hypertension) [2].

More than 80% of patients with type 2 diabetes in Sweden are overweight or obese [3]; excess adiposity, in particular visceral obesity, as well as insulin resistance are strongly associated with an increased risk of both type 2 diabetes and CVD [4]. A healthy diet is the key factor in both prevention and management of type 2 diabetes. Patterns of vegan, vegetarian, and Mediterranean diets have been shown to improve glycemic control in patients with type 2 diabetes in randomized clinical trials [5]. An unhealthy lifestyle (eg, with poor dietary habits and physical inactivity), on the other hand, increases the risk of developing the disease, as well as the risk of complications [1]. In addition to CVD, complications can be serious and may include kidney failure, blindness, and amputation of lower extremities, and could lead to premature death.

Despite the large impact of dietary habits in the management of type 2 diabetes, few tools for supporting dietary changes and maintenance of a healthy diet are available. One strategy to improve health is regular visits to health clinics [6]. This may not always be a feasible strategy given the large number of patients in need of support. To meet both the needs of the patients and the capacity of the health care system, new strategies must be developed. Mobile health (mHealth) (ie, the use of mobile devices, including smartphones, to promote health) is one way to bridge the gap between what patients need and what health care can offer.

In Sweden, over 90% of adults own and use a smartphone [7], making an app-based intervention feasible for implementation in the general population of patients with type 2 diabetes. Technology-driven diabetes prevention programs (ie, utilizing, for example, text messages, email, automated phone calls, websites, etc) focusing on diet and/or physical activity have been evaluated in several intervention studies focusing on weight loss with promising results [8]. Michaelides et al [9] also showed that a fully mobile diabetes prevention program including a dietary component could facilitate weight loss and weight maintenance. Further, results from two recent reviews summarizing smartphone apps targeting diet have also shown promising results with regard to dietary intake in particular, although none of the apps had been developed for, or evaluated in, patients with type 2 diabetes specifically [10,11]. Nevertheless, among patients with type 2 diabetes, an automated web-based program to support healthy diet has been shown to improve dietary habits when assessed using a quality dietary score [12], and improvements in adherence to the Mediterranean diet and in diet quality overall have been shown after the use of a smartphone app during a period of 3 months [13]. Thus, mHealth strategies show potential as a tool to promote and support healthy eating habits, including among type 2 diabetes patients.

Aim

We are conducting a randomized clinical trial called the HAPPY (Healthy eating using APP technologY) trial, which is a 12-week mHealth intervention (ie, includes the use of a smartphone app). The main aim of the trial is to evaluate its effect in promoting and improving healthy eating habits (primary outcome) and in improving levels of glycated hemoglobin (HbA_{1c}), blood lipids, body composition, and blood pressure, as well as other lifestyle factors and overall health (secondary outcomes) in patients with type 2 diabetes. The aim of this paper is to describe the study design and methodology of the HAPPY trial.

Hypothesis

Our hypothesis is that participants randomized into the intervention group, who will use the smartphone app, will have improved their dietary habits, cardiovascular risk factors, and other lifestyle factors after 12 weeks of active intervention compared to the control group, who will receive standard care. Further, we hypothesize that improved habits will be maintained after an additional 12 weeks of follow-up.

Methods

Study Design

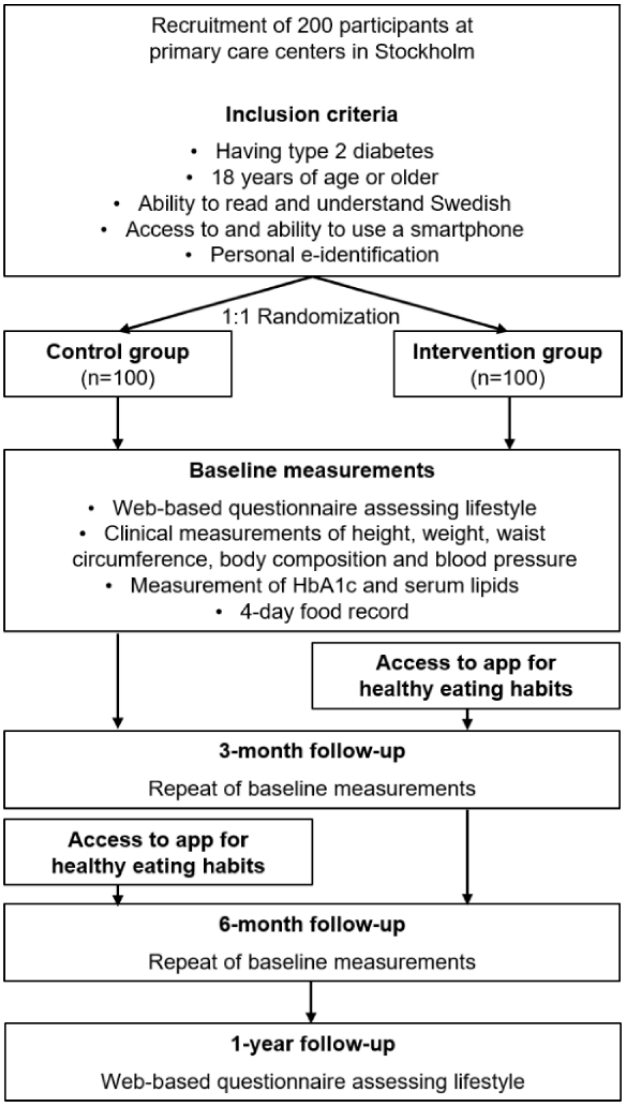
The HAPPY trial is a randomized clinical trial with two arms. The research team behind the design of the smartphone app and the study includes nutritionists, epidemiologists, statisticians, and clinicians. The intervention is described according to the CONSORT (Consolidated Standards of Reporting Trials) statement [14] and the CONSORT-EHEALTH (Electronic and Mobile HEalth Applications and onLine TeleHealth) checklist developed specifically for eHealth and mHealth interventions [15].

Patients with type 2 diabetes who volunteer to participate are recruited from primary health care centers in the center and suburbs of Stockholm. Data collection is performed in collaboration with clinicians and nurses at the centers, where they give a brief introduction of the study to their patients. Information about the study is also available in the waiting rooms of the centers, and patients can contact study personnel directly if they are interested in participating. The included primary care centers differ in size, and the number of eligible patients can vary. Those interested in participating in the study are contacted by phone by study personnel and are given more information. Patients that fulfill inclusion criteria and agree to participate are sent an email with a link to the baseline questionnaire, including a web-based consent form. They are

thereafter scheduled for a meeting with study personnel. During this meeting, participants sign an additional written informed consent form in order to verify that they fully understand the web-based information. Thereafter, baseline measurements are performed and patients are then randomized 1:1 to the intervention or control group. All participants are followed up after 3, 6, and 12 months.

Baseline and follow-up assessments at 3 and 6 months include an extensive web-based questionnaire including assessment of lifestyle factors; a 4-day food record; clinical measurements of height, weight, waist circumference, blood pressure, and body composition; and blood sampling for measurement of HbA_{1c} and serum lipids. After 12 months, participants are followed up with a final web-based questionnaire. All participants continue to receive usual care by their primary caregiver (ie, they visit their primary caregiver as planned as if they had not been part of the study). Participants randomized to the intervention group use the smartphone app during the 12 weeks of the active intervention from baseline, while participants in the control group will use the app during the 12 weeks after the first follow-up at 3 months. Participants are encouraged to use the app daily, but there is no requirement of how often participants should use the app. The study design is presented in Figure 1.

Figure 1. Study design of the randomized clinical intervention, the HAPPY trial, aiming to evaluate the use of an app-based program for healthy eating habits. HAPPY: Healthy eating using APP technologY; HbA_{1c}: glycated hemoglobin.



Ethical Approval, Trial Registration, and Consent to Participate

The trial was approved by the ethics committee of the Regional Ethical Review Board, Stockholm, Sweden (2018/652-31; 2018/1094-32; 2018/2393-32). The trial was registered at ClinicalTrials.gov (NCT03784612). All study participants receive oral and written information about the study and give their written informed consent prior to study start.

Inclusion and Exclusion Criteria

Inclusion criteria are having type 2 diabetes diagnosed by a physician; being 18 years of age or older; having the ability to read and understand Swedish; having access to, and the ability to use, a smartphone; having a personal e-identification (ie, a secure, digital citizen e-identification solution to enable personal and secure identification in the app); and giving informed consent for participation. Both women and men are eligible for inclusion. No specific exclusion criteria apply.

Randomization and Blinding

Study participants are randomized to either the intervention group (ie, standard care and use of the smartphone app at study start) or the wait-listed control group (ie, standard care and use of the smartphone app after 3 months). Randomization is done by study personnel (AD and LS) at baseline at a 1:1 ratio using an allocation sequence list generated in Stata, version 14.0 (StataCorp LP). Women and men are randomized separately in blocks of 4 within each participating primary care center in order to assure an even distribution between the intervention and control groups. Due to the nature of the intervention, participants are not blinded to their allocation.

Intervention

Development and Content of the HAPPY Smartphone App

The primary aim of the intervention is to achieve an improvement in dietary intake and subsequent improvements in clinical variables and lifestyle factors through the use of a smartphone app for healthy eating habits among patients with type 2 diabetes. The content of the HAPPY smartphone app and the healthy eating behavior program is built into an existing digital platform developed by FRISQ AB. The program with its contents has been developed by researchers with experience in behavior change interventions (eg, physical activity), nutritionists, and active clinicians within primary and specialist care. It is based on a theoretical framework including the health belief model and the stages of change model, as well as on social cognitive theory [16]. Several techniques for behavior change, including general information, goal-setting strategies, self-monitoring, and feedback on performance, are included in the program [17]. The specific features of the HAPPY smartphone app are described below. The app is available both for iOS (version 11.4 and higher) and Android (version 5.0 and higher).

The HAPPY Smartphone App

Each week the user will be introduced to a new topic on healthy eating habits (eg, vegetable intake). The specific topics for each of the 12 weeks of the active intervention are outlined in Table 1. Following a short written introduction to the current topic, the user is given an activity to perform (eg, to add one portion of vegetables per day during that week or replace sugar-sweetened beverages with water during a week). Daily progress is recorded in the app, and automatic reminders (eg, notifications if the user has not responded to an activity) or feedback on the activity (eg, “Thank you for participating in the activity”) will be given. All study participants receive the same introduction and activity to perform. Reminders and feedback depend on the actions taken by the user.

Table 1. Topics of the healthy eating program for each week of the intervention.

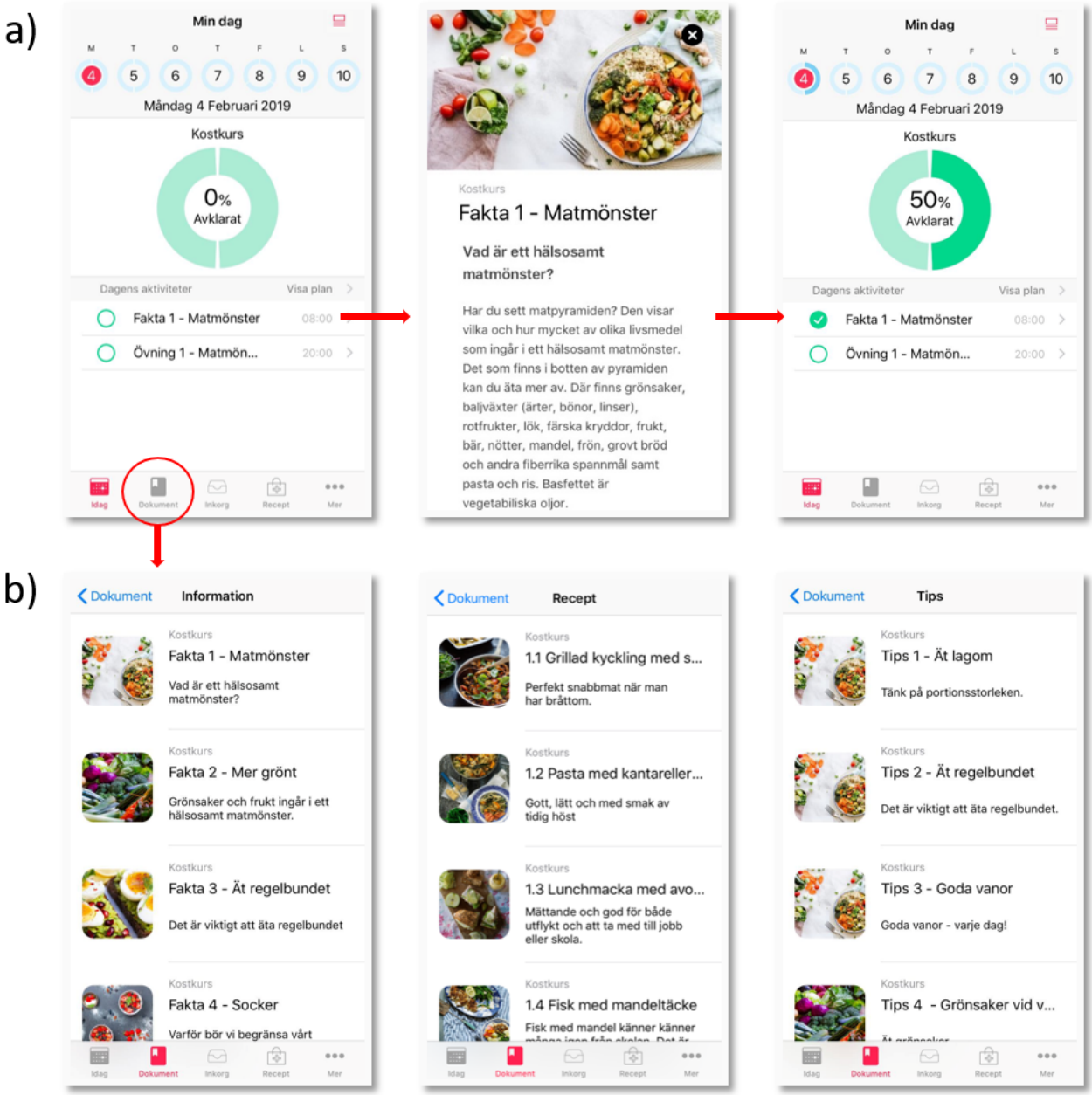
Week	Topic
1	Healthy food patterns
2	Vegetable intake
3	Regular eating habits
4	Sugar intake
5	More on vegetable intake
6	Slow and fast carbohydrates
7	Whole grains and fibers
8	Legumes
9	Saturated fat
10	Unsaturated fat
11	Salt intake
12	Beverages

Each topic (ie, each week) comprises information, recipes, short fun facts, or advice (ie, edutainment and an activity related to the topic). Every Monday, information and an activity that is linked to the theme of the week are available in the app. Recipes to inspire healthy cooking and facts or advice on healthy eating habits are introduced during the week on Tuesday, Wednesday, Friday, and Saturday. Every Thursday, the user receives a reminder of the activity, and at the end of the week, an evaluation about the activity is sent to the user. Each action (ie, reading the information text, recipes, short facts, or advice, and then performing the activity) is marked as read or completed in the app by the user. The status of an action in the app (ie, read vs not read or completed vs not completed) is also visible to study personnel. This information, together with information on each time a user has logged on to the app, is saved within the system. The structure of one week in the healthy eating program is presented in Table 2. Examples from the HAPPY smartphone app are shown in Figure 2.

Table 2. Structure of weekly activities in the app.

Day	Content
Monday	Information and activity introduction
Tuesday	Recipe 1 and recipe 2
Wednesday	Short fact or advice 1
Thursday	Activity reminder: “How is it going?”
Friday	Recipe 3, recipe 4, and recipe 5
Saturday	Short fact or advice 2 and short fact or advice 3
Sunday	Activity evaluation: “How did it go?”

Figure 2. Examples of screenshots from the HAPPY smartphone app. a) Each day, the specific activities for that day are displayed to the user. Before completing an activity, 0% of the activities for that specific day have been performed, as indicated by the large circle. By touching the screen where an activity is listed, the user is taken to a new page showing the activity in question. When an activity has been completed, this is indicated in the large circle as well as to the left of the activity in the list below the circle. b) At the bottom of the first page in the app, the user can choose the document symbol to display information (left-hand image), recipes (middle image), or short facts and advice (right-hand image). The user can access the documents at any time; for example, they can return to reread information or find favorite recipes. HAPPY: Healthy eating using APP technologY.



Download

At baseline, participants in the intervention group will download and be connected to the digital platform, where the study personnel (ie, trained nutritionists) can follow the individual progress of the user during the 12-week course on healthy eating habits in the app. Participants in the control group will be offered to download and be connected to the app at the 3-month follow-up. To avoid overlap with the 4-day food record, the app will be activated on the first Monday following the meeting with study personnel (ie, at baseline or the 3-month follow-up) and the intervention will thereafter follow for 12 consecutive weeks. An individual user account on the digital platform will be created for each participant by study personnel. Users will identify themselves in the app using a personal e-identification .

Sample Size and Power Calculations

A total of 168 patients (84 per group) will provide 80% power at a 5% significance level to detect a clinically significant change of 4 mmol/mol in HbA_{1c} [18]. A standard deviation of 11.8 mmol/mol was estimated based on the average HbA_{1c} level (mean 53.4 mmol/mol, 95% CI 53.3-53.5) in Stockholm County in 2016 using data from the National Diabetes Register [19]. Based on earlier intervention studies within similar populations, a dropout rate of around 20% is expected. To cover for potential dropout, we will recruit a total of 200 patients (100 per group).

Outcome Measures

Overview

A web-based questionnaire including assessment of lifestyle factors; a 4-day food record; clinical measurements of height, weight, waist circumference, blood pressure, and body composition; and blood sampling for measurement of HbA_{1c} and serum lipids will be given to all participants at baseline and at follow-up assessments at 3 and 6 months. At the 12-month follow-up, participants will respond to a final web-based questionnaire.

Dietary Intake From the 4-Day Food Record

Dietary intake is measured using a 4-day food record over 4 consecutive days, including at least one weekend day. Participants are given a paper diary and instructed by the study personnel, who are trained nutritionists, to write down everything they eat and drink during the period of recording. Type of meal (ie, breakfast, snack, lunch, dinner, etc) is also recorded. The estimated amount of food and beverages consumed can be recorded in different units, including number of items (eg, number of potatoes), weight (eg, 125 g chicken), or unit of volume (eg, 2 dL of milk or 1 cup of coffee). The participants are requested to maintain their usual diet during the days of recording. The software program Dietist Net (Kost och Näringsdata AB) is used by study nutritionists to calculate nutrient intake from the food records; the nutritionists also check the dietary recordings for completeness when they are returned. In the event of items being recorded in an unspecified way (eg, “fish” or “yogurt” without further specification), information on the most commonly consumed fish or yogurt is obtained from nationwide data [20] and entered into the nutrient calculations. Standard portion sizes available for each food item in the Dietist Net software are used if the amount of food was not specified.

The participants complete the food records, as well as respond to a food frequency questionnaire (FFQ), at baseline and follow-up after 3 and 6 months. While the food records will give detailed information on types of food items, portion sizes, and frequency and timing of intake during the day, data from the FFQs allow for comparison to other studies as well as to follow-up of study participants in this study after 12 months.

Body Composition

Weight, height, waist circumference, and body composition are measured by study personnel at baseline and at 3- and 6-month follow-ups. Weight is measured to the nearest 0.1 kg in light clothing without shoes, and height is measured to the nearest cm in a standing position. Waist circumference is measured around the waist, approximately 2 cm above the umbilicus, to the nearest cm. Body weight and waist circumference are measured once on each occasion. Body composition, including body fat and fat-free mass, is measured using a digital body composition analyzer, Model BC-418 (Tanita). The scale utilizes an 8-electrode bioelectrical impedance analysis with current going from foot to hand and from hand to foot on both sides of the body.

Blood Pressure

Blood pressure—systolic and diastolic—is measured by the study personnel using the M7 Intelli IT automatic electronic monitor with Bluetooth technology (Omron). Measurements are done with each participant in a seated position with legs uncrossed after the participant has been sitting for at least 5 minutes.

Biomarkers

Biomarkers are measured in fasting blood samples at baseline and at 3- and 6-month follow-ups. Study participants visit their closest primary care unit to have the blood samples taken. All samples are sent for analysis to the same lab connected to the Karolinska University Hospital in Stockholm, Sweden. HbA_{1c} (mmol/mol) is measured using the IFCC (International Federation for Clinical Chemistry and Laboratory Medicine) reference measurement procedure [21,22]. Triglycerides (mmol/L), total cholesterol (mmol/L), and high-density lipoprotein (HDL) cholesterol (mmol/L) are measured using the enzymatic method. Low-density lipoprotein (LDL) cholesterol (mmol/L) is calculated using the Friedewald equation:

$$\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - (0.45 \times \text{triglycerides})$$

The ratio of LDL cholesterol to HDL cholesterol is calculated from the levels of these lipoproteins.

Web-Based Questionnaire

Study participants respond to a web-based questionnaire at baseline and at follow-up after 3, 6, and 12 months. A link to the questionnaire is emailed to study participants on each occasion. A first reminder is sent if the participant has not

responded within 1 week, and an additional reminder is sent 1 week after that if there is still no response. Each questionnaire takes approximately 30-45 minutes to complete and is comprised of several different sections as specified below. If not otherwise specified, the web-based questionnaire is comprised of the questions below.

Background information on marital status, education, and tobacco use (ie, smoking and snuff use) is assessed. Participants are also asked to report the year that they were diagnosed with type 2 diabetes; medication use related to hypertension, hyperlipidemia, and diabetes (ie, insulin or other treatment); and if they have changed their medication during the past 30 days. Background information is only collected from the baseline questionnaire.

Dietary intake is assessed using a 94-item semiquantitative FFQ. The FFQ has been validated previously in a random sample of Swedish men [23]. Spearman correlation coefficients for macronutrients comparing intake assessed using the FFQ, for an average of 14 24-hour recalls spread out over 1 year, were .44 (protein), .70 (total fat), .73 (carbohydrates), and .81 (alcohol). Participants report how often, on average, they consume each included food and beverage, including alcohol. An additional six questions developed by the Swedish National Food Agency, that are used in clinical practice, assessing overall dietary habits and risk use of alcohol are also included [24].

Eating behavior is assessed using the 21-item Three-Factor Eating Questionnaire [25]. The questionnaire includes questions related to cognitive restraint (six questions), uncontrolled eating (nine questions), and emotional eating (six questions).

Physical activity and *sedentary behavior* are assessed using general questions commonly used in clinical practice, regarding time spent doing physical activities at a moderate-intensity level or higher and sitting time [24], using the Active-Q questionnaire [26,27]. Active-Q includes 48 items and assesses habitual activity in four different domains: daily occupation, transportation, leisure time, and regular sports activities.

Health-related quality of life is assessed using the RAND-36, a questionnaire developed by the RAND Corporation [28]. RAND-36 comprises 36 questions within eight domains: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy and fatigue, emotional well-being, social functioning, pain, and general health. Responses from the individual domains are summarized into an overall physical component summary score and an overall mental component summary score. Additionally, a Swedish translation of the Life Engagement Test comprised of six questions is used to assess purpose in life [29].

Sleeping habits are assessed using a 13-item version of the Karolinska Sleep Questionnaire [30,31]. Participants report the time of going to bed the previous evening, time of waking up in the morning thereafter, and time from going to bed to falling asleep. They are also asked to report on sleep quality.

Stress level is assessed using a 14-item version of the Perceived Stress Scale developed by Cohen et al [32]. Participants are asked to respond to how often they perceive themselves to react in different, potentially stressful situations on a 5-point Likert scale, ranging from “Never” to “Very often.”

Diabetes self-efficacy and *distress* are assessed using the 20-item Swedish translation of the Problem Area in Diabetes Questionnaire [33]. Participants are asked to rate their distress with having diabetes on a 5-point Likert scale, ranging from “Not a problem” to “A serious problem.”

Perceivedsocialsupport for healthy eating habits is assessed by three questions regarding general support and support from friends and family. The questions were developed for this study and were based on the Physical Activity Social Support Scale [34]. Participants are asked to rate the statements “I experience support and encouragement to eat healthy food from *people around me*,” “*...my friends*,” and “*...my family*” using four response alternatives, ranging from “Agree completely” to “Do not agree at all.”

Evaluation questions about the usability of the app [35] and the contents of the healthy eating program are included in the 3-month follow-up questionnaire for participants in the intervention group and in the 6-month follow-up questionnaire for participants in the control group. This is done so that participants respond to the evaluation directly after having used the app. In total, users are asked to respond to 12 statements about the usability of the app (eg, “The app was easy to use”) and 12 statements regarding the content in the healthy eating program (eg, “The healthy eating program has made me reflect upon my dietary habits”) using a 5-point scale, ranging from “Do not agree at all” to “Completely agree.” In addition, users are also asked to leave a free-text comment regarding (1) what was good about the app and (2) what could be improved.

Statistical Analysis

All data from clinical assessments, the questionnaires, and the app are anonymized and continuously stored at secure servers. Descriptive statistics will be summarized to describe participant characteristics at baseline and follow-up. Data will be checked for outliers and normality. Results will be stratified by control and intervention group. Baseline results will be tested to assess the success of the randomization in balancing characteristics. Differences between groups will be assessed using Student *t* tests, analyses of variance, and logistic regression. Any detected differences in baseline characteristics between the intervention and control groups will be taken into account as potential confounders in further analysis.

Testing for trends over time in outcomes will be conducted using statistical methods for longitudinal data. Generalized estimation equations will be used to assess the effect of both time and the intervention itself on outcomes. We will control for any unbalanced baseline characteristics. Testing for interactions will be conducted in the models, and intention-to-treat analysis will be performed to account for effects of crossover and dropout. Sensitivity analysis to account for missing data will be done. To further study if the effect of the intervention differs based on participant characteristics, stratified analysis will be performed.

Lastly, we will analyze user satisfaction and user statistics, including number and length of visits to the platform via the

app. The number of completed actions during the active intervention will also be analyzed to assess user engagement with the app. Associations between use of the platform and characteristics of participants will be investigated.

Results

The first study participants were recruited in January 2019. Data collection is ongoing. Recruitment is planned to continue until a total of 200 study participants have been included or up to the end of June 2021, whichever comes first. Data collection, including follow-up assessments, will be complete 1 year after recruitment of the last study participant. We expect to publish findings from the study by the end of 2021.

Discussion

In the HAPPY trial, we aim to evaluate the effect of an mHealth intervention (ie, use of a smartphone app) promoting healthy eating habits in patients with type 2 diabetes. We know that a healthy diet is a key factor in the management of type 2 diabetes. However, implementing new habits (eg, healthier eating habits) and maintaining them is difficult. Nevertheless, interventions focusing on promoting healthier eating have been shown to lead to improvements in food habits [36]. Focusing on diet overall, instead of, for example, specific nutrients or energy intake, allows the individual to modify their existing dietary habits according to new advice, increasing the chance of successfully implementing new habits [37].

In a comprehensive review article by Ley et al [37], the authors concluded that the overall diet quality should be emphasized in dietary recommendations to patients. This was based on the gathered evidence showing that a higher intake of whole grains, fruits and vegetables, legumes, and nuts; moderate alcohol consumption; and a lower intake of refined grains, red and processed meats, and sugar-sweetened beverages were associated with a reduced risk of diabetes, as well as improved glycemic control and blood lipid levels in patients with type 2 diabetes. These results have also been supported in a later review [38]. The mHealth smartphone app evaluated in the HAPPY trial focuses on healthy eating habits in general, rather than the energy intake of specific nutrients.

Previous mobile- or app-based intervention studies targeting dietary intake or eating behavior have been summarized in two recent reviews, showing promising results [10,11]. Schoeppe et al [10] summarized results from studies using app strategies to target different lifestyle behaviors, including diet. Most apps targeting diet in adults were shown to be successful in improving dietary intake. Several of the included studies showed an increased fruit and/or vegetable intake or a decreased intake of sugar-sweetened beverages in the intervention groups compared to the control groups. The average duration of the intervention studies included in the review was 10 weeks (range 1-24). Further, Mandracchia et al [11] found that mHealth apps using self-monitoring were effective in increasing fruit and vegetable intake among adults or young adults with overweight. However, none of the apps targeting diet or eating behavior that were included in the two above reviews had been developed for, or evaluated among, patients with type 2 diabetes specifically.

In a study by Holmen et al [39], the authors showed good feasibility of using a mobile phone–based self-management system, including a dietary component, among patients with type 2 diabetes. After 1 year of using a mobile phone–based self-management system, between 30% and 40% of the individuals randomized to one of two groups using the system were substantial users of the app (eg, they had at least 50 interactions with the app during the past 6 months). Using an automated web-based program to support healthy diet has also been shown to improve dietary habits among this group of patients [12]. Further, a recent randomized controlled trial including patients with type 2 diabetes showed improvement in adherence to the Mediterranean diet and in diet quality overall after the use of a smartphone app over 3 months [13].

Noteworthy strengths of the HAPPY trial include the randomized design, a large sample size, objective assessment of outcomes (eg, measured clinical and anthropometric variables), and a priori calculation of statistical power. Further, the content of the HAPPY smartphone app was developed in collaboration with researchers, clinicians from primary care, and specialists from endocrinology clinics. The digital platform allows the patient and care provider to work together. This increases the chance of effectiveness, as interventions including both the health care system and patient have been found to be more effective than those targeting only one or the other [40]. Nevertheless, a limitation to our study is the lack of a pilot study testing feasibility and acceptability of the app among users. However, the healthy eating program is built into an existing digital solution that has been rigorously tested and is continuously updated to allow for the rapid development of iOS and Android systems. The stability of the digital solution is a strength, as users are less likely to stop using the app due to technical malfunctions. The use of various behavioral change techniques from different theoretical domains may also increase user engagement and decrease attrition in our study. Within the HAPPY trial, we are also collecting data on user engagement with, and usability of, the app and the healthy eating program.

A 4-day food record is used to assess dietary intake at baseline and follow-up. Although most dietary assessment methods are subjective and susceptible to social desirability, a food record has the advantages of being prospective (ie, does not rely on memory) and open ended with no limitation on what items can be reported. In the event of potential missing data in the food records (ie, unspecified food items being recorded or information on portion size is missing), this information will be added using data from a nationwide study of dietary intake in Sweden [20] or replaced by a standard portion size. This may affect results from the food records. However, such missing information is likely random. To enable long-term follow-up of dietary intake as well as comparison to other studies, participants also respond to an FFQ at baseline and follow-up after 3, 6, and 12 months.

Recruitment of study participants is performed at a number of different primary care centers located in areas with different populations and socioeconomic statuses. This increases the generalizability of our results to different groups of patients.

However, the inclusion criteria of being able to communicate in Swedish and having access to a smartphone may be a limitation of the study. Type 2 diabetes is more common with increasing age. This could be a limitation, as knowledge of how to use a smartphone may be limited among older individuals, leading to a younger study population. Nevertheless, over 75% of individuals aged 66-75 years in Sweden use the internet on their phone [7]. While patients with limited knowledge of Swedish are more prevalent in areas of lower socioeconomic status, smartphone usage in Sweden is independent of socioeconomic status, and over 90% of all adults in Sweden own and use a smartphone [7]. The smartphone app was developed for usage on both Android and iOS devices, meaning that most smartphone users can download and use it.

To conclude, the app-based mHealth solution evaluated in the described randomized clinical trial has been developed taking into account the needs of patients, who request mHealth solutions to support a healthy lifestyle, as well as the health care system, which is in need of new, feasible solutions to meet the needs of increasing numbers of patients. Using mHealth strategies, real-time interaction with users is possible and health interventions can be delivered at any time. Further, focusing on diet quality, rather than on specific nutrients, food items, or energy intake, allows the user to apply new knowledge regarding healthy eating habits to his or her current eating patterns, as well as personal and cultural food preferences [41]. Such an individualized approach could be a key factor in promoting and supporting long-term adherence to healthier eating habits among persons with type 2 diabetes.

Acknowledgments

We would like to thank the personnel at participating primary care centers for their hard work in recruiting study participants. This work is supported by the Strategic Research Area Health Care Sciences (SFO-V) at Karolinska Institutet (SB) and by funds from the regional agreement between Stockholm County Council and Karolinska Institutet (AD, LS, and YTL). The funders had no role in the design of the study, nor have they any role in the data collection, analysis, or interpretation, or in writing of this manuscript.

Conflicts of Interest

Non declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth
CVD: cardiovascular disease
FFQ: food frequency questionnaire
HAPPY: Healthy eating using APP technologY
HbA_{1c}: glycated hemoglobin
HDL: high-density lipoprotein
IFCC: International Federation for Clinical Chemistry and Laboratory Medicine
LDL: low-density lipoprotein
mHealth: mobile health
SFO-V: Strategic Research Area Health Care Sciences

Edited by G Eysenbach; submitted 18.09.20; peer-reviewed by L Tarro, AA Dumas; comments to author 05.10.20; revised version received 15.10.20; accepted 20.10.20; published 16.11.20.

Please cite as:
Trolle Lagerros Y, Dahlgren A, Sjöblom L, Bonn SE
Digital Support for Healthier Eating Habits Among Patients With Type 2 Diabetes: Protocol for a Randomized Clinical Trial Within Primary Care (HAPPY Trial)
JMIR Res Protoc 2020;9(11):e24422
URL: http://www.researchprotocols.org/2020/11/e24422/
doi:10.2196/24422
PMID:33196448

Protocol

Family Members' Perspectives on Family and Social Support Available to Suicidal Patients, and Health Systems' Interactions and Responses to Suicide Cases in Alberta: Protocol for a Quantitative Research Study

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Abstract

Background: Suicide is a major cause of preventable death globally and a leading cause of death by injury in Canada. To support people who experience suicidal thoughts and behaviors and to ultimately prevent people from dying by suicide, it is important to understand individual and familial experiences with the health care system.

Objective: We present the protocol for a study, the objective of which is to explore how people who died by suicide, and their family members, interacted with the health care system.

Methods: This is a quantitative research study. Data will be collected through a self-administered paper-based or online survey of the family member of patients who died by suicide. The sample size was calculated to be 385 (margin of error ±3%).

Results: Data collection will start in October 2020 and results will be available by March 2021. We expect the results to shed light on the experiences of individuals who died by suicide and their family members with the health care system. The study has received ethical clearance from the Health Ethics Research Board of the University of Alberta (Pro00096342).

Conclusions: Our study may inform practice, policy, and future research. The findings may shape how members of the health care system respond to people who are at risk of suicide and their families.

International Registered Report Identifier (IRRID): PRR1-10.2196/19112

(JMIR Res Protoc 2020;9(11):e19112) doi:10.2196/19112

KEYWORDS

suicide in Alberta; suicide; family members' perspectives; social support; health systems interactions

Introduction

Background

Suicide is a serious global public health problem, with an estimated 800,000 people reported to die by suicide every year [1]. In Canada, suicide remains the 9th leading cause of death and the second leading cause of death among children, youth, and young adults [2]. Suicide impacts people of all ages and backgrounds in Canada. Every day, an average of more than 10 Canadians die by suicide. There are close to 6000 emergency department visits and 2000 hospitalizations every year for self-inflicted injuries [3]. For every person lost to suicide, many more experience thoughts of suicide or suicide attempts. For every death by suicide, a large circle of survivors are significantly affected by the loss. Each suicide results in 135 people exposed (ie, who knew the person), who may need clinician services or support following exposure [4].

There were 4000 suicides in Canada in 2018 [5], with more than 500 of these deaths occurring in Alberta. Suicide is consistently a leading cause of death among Albertans. Suicide claims more lives annually than other causes such as motor vehicle collisions and homicides. Over 75% of those deaths occur among men, most between the ages of 30-69 years [6]. Health care systems play a vital role in suicide prevention. One study in Alberta, for instance, found that the majority of people who died by suicide used a health service in the year prior to their death. They were also more likely to use the emergency department, in-patient services, or community mental health services than those who died from other causes; they typically used health services for mental disorders as well [7].

In Alberta, which is the site of this study, suicide prevention initiatives, including Living Hope, are underway to enhance aspects of the health care system, as evidenced by the Implementation Plan for the Edmonton Suicide Prevention Strategy [8]. Living Hope promotes a comprehensive preventative approach that seeks to enhance access to the protective factors that decrease the risk of suicide. The implementation plan upholds the inherent value of every person and recognizes that residents of Alberta, both as service providers and as community members, can offer the compassion, respect, and hope needed to increase resilience and nurture hope for those contemplating suicide [8].

The Mental Health Commission of Canada, in collaboration with the Canadian Association for Suicide Prevention, the Centre for Suicide Prevention, the Public Health Agency of Canada, alongside an Advisory Committee comprising people with lived experience related to suicide, have developed toolkits to support individuals who have been impacted by suicide. One toolkit is tailored for people who have attempted suicide, and the other is focused on resources for people who have lost someone to suicide [9].

Beyond stakeholder engagement [10] and an understanding of the dimensions of service quality [11], little is known locally about the personal, family, and social circumstances of people who died by suicide in Alberta. Similarly, little is known about how individuals who died by suicide and those close to them experienced the health care system. The current mechanism by which Alberta Health Services (AHS) investigates suicide is through the Quality Assurance Review (QAR). A QAR of an adverse event utilizes the Systems Analysis Methodology, which aims to determine what happened, how it happened, and what can be done to improve care for future patients. This type of review generally involves engaging a multidisciplinary team to examine all of the health care system components (eg, environment, task, policy, etc) as they relate to an event (or group of similar events). This process often results in recommendations aimed at improving the quality and safety of health care delivery. The focus is on improving structures, processes, and/or practices within AHS [12]. QARs are done following a suicide on a case-by-case basis, and the results are not shared beyond those directly involved. The privacy of the QAR limits case comparison and knowledge translation. Additionally, an understanding of the context of death by suicide is needed, as it is thought to differ from the context of a suicide attempt. QARs usually focus on the health systems' contributions to the suicide and do not place much emphasis on examining the personal, familial, and societal factors that also contribute to deaths by suicide. One study found that while individuals who attempt suicide generally exhibited similar levels of depression, those who died by suicide were significantly more likely to have experienced significant job stress and financial problems, left a suicide note, and used alcohol and drugs prior to the act [13]. AHS is committed to patient- and family-centered care [14], which highlights the importance of talking to families about both their own and their relatives' experiences with the health care system. Ultimately, insight into the experiences of people who died by suicide, and their family members, has the potential to inform policy and practice, and shape how members of the health care system, and AHS specifically, respond to individuals who are at risk of suicide.

Objectives

The purpose of this study is to understand better the family and social circumstances of individuals who died by suicide, and how those who died by suicide and their family members interacted with the health care system. This study extends the knowledge to be gained from a recently completed qualitative study that examined family members' perspectives on health system interactions with those who died by suicide [15].

Our specific quantitative research questions are:

1. What factors related to family, society, and health systems contribute to death by suicide in Alberta?
2. How do individuals impacted by the suicide of a family member perceive their own interactions with the health care system?

To the best of our knowledge, no previous province-wide study has examined the personal, familial, societal, and health systems factors that contribute to suicide deaths in Canada. One study was conducted by Schaffer et al [16] to investigate the population-based analysis of health care contacts among suicide decedents prior to death by suicide. It was a systematic extraction of data from records at the Office of the Chief Coroner of Ontario of each person who died by suicide in the

city of Toronto from 1998 to 2011 [16]. Consequently, this work, the first of its kind in Alberta and in Canada, could help identify important factors that are associated with deaths by suicide in the province of Alberta.

Methods

Study Design

This study utilizes a quantitative research design. Data will be collected through a self-administered paper-based or online survey of the family members of patients who died by suicide (Multimedia Appendix 1). A sample size of 385 was predetermined on the assumption that with an annual average of 500 people dying by suicide in Alberta, a 95% CI, and one family member per suicide decedent completing the survey, the sample size needed to estimate family members' perspectives on health system interactions, as well as family and social support for suicidal patients, with the margin of error ±3%, is 385. Data will be collected via both paper format and online. Prospective participants will be provided with paper-based or online information leaflets.

Participants

Participants will be adults; they should also have a close family member who has died by suicide in the previous 12 months and had regular contact with this family member prior to their suicide, such that they are reasonably aware of their personal, family, and social situation prior to their suicide as well as their interaction with the health care system. Participants do not have to identify themselves and their submission of the survey implies their consent.

Data Collection

We initially designed a survey form that reflected risk factors for dying by suicide identified in the published literature as well as additional factors to help answer our research questions. The draft survey questions were reviewed by the Canadian Mental Health Association (CMHA), Alberta Division, and the Centre for Suicide Prevention, and changes were made based on the feedback received. The survey was then pretested on two volunteer family members of patients who had died by suicide before being further revised and finalized for use in the study. The survey questions take 10-55 minutes to complete, and no incentives will be offered to participants who complete the survey. Paper-based recruitment will be done in collaboration with the CMHA regional offices in Alberta. The association runs focus groups for family members of people who died by suicide, with hundreds of people attending annually. Information leaflets and posters advertising the study will be distributed among prospective participants attending these focus groups. Those interested in participating in the study will be provided with guidance on how to access the survey questions.

In addition, online versions of the survey will be promoted through the websites and social media feeds of AHS, the CMHA, the Centre for Suicide Prevention, the Edmonton Mental Health Foundation, and the University of Alberta's Faculty of Medicine and Dentistry. The online survey is designed in accordance with the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) checklist [17]. Prospective participants will be invited to review the online version of the information leaflet and proceed to complete the survey. Information identifying participants will not be collected for the online survey, and completion and submission of the survey denotes consent. The study will be conducted in accordance with the Declaration of Helsinki (Hong Kong Amendment) and Good Clinical Practice (international guidelines). Informed consent will be obtained from each participant. The study has received ethical clearance from Health Ethics Research Board of the University of Alberta (Pro00096342).

Data Analysis

Quantitative data will be analyzed using SPSS, version 26 (IBM Corp), using descriptive statistics and correlational analyses [18]. A chi-square test will be used to explore differences in responses between demographic variables of the suicide decedent and the respondent.

Results

Data collection is expected to commence in October 2020. Results will be available by March 2021. Findings from the study will help illuminate factors related to family, society, and health systems, and the role they play in death by suicide in Alberta.

The study results will be disseminated at several levels, including to participants, practitioners, academics/researchers, and health care organizations.

Our team will plan an organizational engagement strategy to advance discussions about feasibility and effectiveness prior to the conclusion of the trial. This will help ensure the findings are a relevant part of decision-making processes. In addition, this may facilitate the planning of a larger study that is endorsed at both leadership and operational levels so that the potential benefits of the study results can reach participants in a timelier fashion.

Discussion

The main objective of this study is to investigate the familial, societal and health systems–based support available to individuals who die by suicide in Alberta. It also aims to examine the support offered by the health care system in Alberta to family members of patients who die by suicide.

Studies in other jurisdictions suggests that personal, familial, and social factors such as stigma [1], public education [19,20], psychiatric illness [21,22], age [23,24], gender [1,23], marital status [25], positive support [26,27], familial history of suicide [28-31], and alcohol consumption [32,33] are associated with death by suicide. Similarly, health system factors such as staff attitude toward suicidal persons [19], recency of hospitalization for suicide attempt and recent health care contact [19,21,34-37], underdiagnoses of mental disorders and major depressions [38], brevity of interactions with medical staff [39], ignoring suicide-related warning signs by health care providers [40], lack of trust in health care services [41], and relatives' feelings of exclusion from information on treatment [42] have all been positively associated with deaths by suicide in studies conducted

in other jurisdictions. The results of our study will provide us with information on familial, societal, and health systems–related influences in Alberta as well as aspects of care in need of further improvement and refinement. The recommendations arising from this study have the potential to lead to significant system enhancements and reductions in suicide rates in Alberta and beyond.

Acknowledgments

This study is supported by Alberta Health Services, the Centre for Suicide Prevention, and the Canadian Mental Health Association.

The authors received no financial support for the research, authorship, and/or publication of this paper.

Authors' Contributions

RMAE-M, contributed to the study design and drafted the initial and final versions of manuscript. LU, SS, DL, AG, MG, LM, IC, DG, and RO contributed to the study design and reviewed the initial and final drafts of the manuscript. VA conceived and designed the study and contributed to drafting the initial and final versions of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Quantitative research study survey.
[DOCX File , 36 KB - resprot_v9i11e19112_app1.docx]

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Abbreviations

AHS: Alberta Health Services
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
CMHA: Canadian Mental Health Association
QAR: Quality Assurance Review

Edited by G Eysenbach; submitted 04.04.20; peer-reviewed by E Kleiman, K Fox; comments to author 12.06.20; revised version received 02.08.20; accepted 18.08.20; published 24.11.20.

Please cite as:
Abou El-Magd RM, Urichuk L, Surood S, Li D, Greenshaw A, Grunau M, MacNeil L, Challborn I, Grauwiler D, Olson R, Agyapong VIO
Family Members' Perspectives on Family and Social Support Available to Suicidal Patients, and Health Systems' Interactions and Responses to Suicide Cases in Alberta: Protocol for a Quantitative Research Study
JMIR Res Protoc 2020;9(11):e19112
URL: https://www.researchprotocols.org/2020/11/e19112
doi:10.2196/19112
PMID:33231553

Protocol

The Effect of Question Order on Outcomes in the Core Outcome Set for Brief Alcohol Interventions Among Online Help-Seekers: Protocol for a Factorial Randomized Trial

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2021/2/e26578

Abstract

Background: A core outcome set (COS) for trials and evaluations of the effectiveness and efficacy of alcohol brief interventions (ABIs) has recently been established through international consensus to address the variability of outcomes evaluated.

Objective: This is a protocol for studies to assess if there are order effects among the questions included in the COS.

Methods: The 10 items of the COS are organized into 4 clusters. A factorial design will be used with 24 arms, where each arm represents 1 order of the 4 clusters. Individuals searching online for help will be asked to complete a questionnaire, and consenting participants will be randomized to 1 of the 24 arms (double-blind with equal allocation). Participants will be included if they are 18 years or older. The primary analyses will (1) estimate how the order of the clusters of outcomes affects how participants respond and (2) investigate patterns of abandonment of the questionnaire.

Results: Data collection is expected to commence in November 2020. A Bayesian group sequential design will be used with interim analyses planned for every 50 participants completing the questionnaire. Data collection will end no more than 24 months after commencement, and the results are expected to be published no later than December 2023.

Conclusions: Homogenizing the outcomes evaluated in studies of ABIs is important to support synthesis, and the COS is an important step toward this goal. Determining whether there may be issues with the COS question order may improve confidence in using it and speed up its dissemination in the research community. We encourage others to adopt the protocol as a study within their trial as they adopt the ORBITAL (Outcome Reporting in Brief Intervention Trials: Alcohol) COS to build a worldwide repository and provide materials to support such analysis.

Trial Registration: ISRCTN Registry ISRCTN17954645; http://www.isrctn.com/ISRCTN17954645

International Registered Report Identifier (IRRID): PRR1-10.2196/24175

(JMIR Res Protoc 2020;9(11):e24175) doi:10.2196/24175

KEYWORDS

order effects; question order bias; brief alcohol intervention; outcomes; factorial trial; randomized trial; online intervention; alcohol; protocol; effectiveness; efficacy

Introduction

Alcohol brief interventions (ABIs) have been widely used, researched, and disseminated over the past 60 years [1,2], in both face-to-face [3-5] and digital [6-8] settings and in a variety of populations such as primary care patients [5], emergency health care patients [9,10], college students [11,12], and veterans [13]. Defined by the World Health Organization (WHO) as "practices that aim to identify a real or potential alcohol problem and motivate an individual to do something about it" [3], ABIs encompass a broad range of actions that aim to help individuals change their drinking behavior. At their core, ABIs assess and provide feedback on alcohol use, and can be delivered as a single session or multiple sessions over time, designed to motivate and encourage alcohol change [1,2].

However, the variety of outcome measures used in trial evaluations of ABIs' effectiveness and efficacy is a limiting factor in evidence synthesis across all modes of intervention delivery (eg, face-to-face and online). Comparisons across trials and synthesis of outcomes as evidence are sometimes impossible despite the use of similar interventions. The ORBITAL (Outcome Reporting in Brief Intervention Trials: Alcohol) project [14] was established to overcome this issue through the determination of an international, consensus-derived core outcome set (COS). The aim was to prioritize the key outcomes to be measured in all online, digital, and otherwise delivered ABIs designed for adult drinkers who are at risk or currently experiencing harm, but who are not seeking treatment. This consensus was derived using the established COMET (Core Outcome Measures in Effectiveness Trials) Methodology [15], including a systematic review that quantified the diversity in outcomes and measurement reporting on 2641 different outcomes, measured in 1560 different ways, in 405 trials of ABIs [16]. This was followed by two e-Delphi (online method to reach consensus) rounds [17], a consensus meeting, and psychometric evaluation to decide the final COS and how outcomes should be measured [18]. The COS established 10 outcomes, which are (1) frequency of drinking, (2) typical number of drinks consumed on a drinking day, (3) frequency of heavy episodic drinking, (4) combined consumption measure, (5) hazardous or harmful drinking, (6) standard drinks consumed in the past week, (7) alcohol-related consequences, (8) alcohol-related injury, (9) use of emergency health care services, and (10) quality of life.

The first 5 outcomes in the COS are measured using the WHO's Alcohol Use Disorders Identification Test - Consumption (AUDIT-C) tool [19]. Outcome 4 is measured by the total AUDIT-C score, and for outcome 5 a clearly outlined and justified cutoff point of the AUDIT-C score suitable for the country and population should be used. Outcome 6 is measured by asking how many standard drinks were consumed each day of the last week and reported in grams to allow for intercountry comparison.

Alcohol-related problems or consequences (outcome 7) are measured using the Short Inventory of Problems [20,21], with a 3-month time frame. Outcome 8 is measured by asking a single question about injuries inflicted while drinking or being intoxicated, and outcome 9 is similarly measured by a single question about the number of visits to an emergency room or urgent care treatment facility. Finally, quality of life (outcome 10) is measured using PROMIS (Patient-Reported Outcomes Measurement Information System) global health items [22].

This is the first Question Order Bias Core Outcome Set (QOBCOS-1) study, which aims to assess if there is question order bias among the outcomes of the COS. Question order bias occurs when an individual's response to a question is affected by previously asked questions, and is a well-known phenomenon that has been studied, and perhaps abused, in marketing and political science for some time [23,24]. Recently, it was discovered that question order bias may affect measures of alcohol consumption [25], as individuals who were asked to first report weekly alcohol consumption were then less likely to be screened as risky drinkers, in comparison to individuals who were first screened and then asked about weekly alcohol consumption. However, these findings conflict with previous research that found no evidence of such order effects [26]. Further investigation into this phenomenon is therefore necessary in order to provide better guidance on this potential bias.

This protocol contains the relevant SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) items [27] and describes a trial that aims to estimate order effects among the questions within the COS for ABIs. In addition, this trial will investigate patterns of abandonment of the questionnaire, as including questions that participants find less relevant may lead to increased attrition [28]. The trial findings will apply in the context of self-completion of the COS using digital questionnaires among online help-seeking individuals. We encourage others to contact the lead author and replicate this protocol in their studies, so that we can collect data for a meta-analysis across different contexts and with different interventions (with due credit).

Methods

Trial Design and Interventions

A double-blind randomized factorial design trial will be employed to investigate question order bias among the outcomes of the COS for ABIs. The 10 COS outcomes will be divided into 4 clusters [18]: (1) *average drinking measures:* frequency of drinking, typical number of drinks consumed on a drinking day, frequency of heavy episodic drinking, combined summary consumption measure, hazardous or harmful drinking; (2) *recent drinking measures:* standard drinks consumed in the past week; (3) *quality of life:* health-related quality of life; and (4) *alcohol problems:* alcohol-related problems or consequences, alcohol-related injury, use of emergency health care services.

The order of these clusters will be permuted to create 24 order combinations (Table 1).

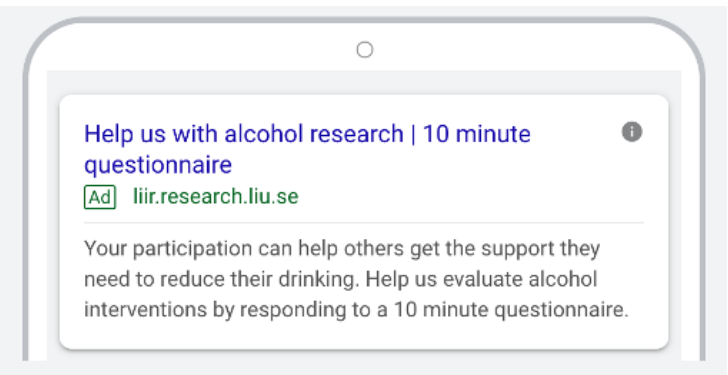
Table 1. Order combinations of the 4 item clusters creating 24 trial arms.

Arm	Cluster 1	Cluster 2	Cluster 3	Cluster 4
1	1	2	3	4
2	1	2	4	3
3	1	3	2	4
4	1	3	4	2
5	1	4	2	3
6	1	4	3	2
7	2	1	3	4
8	2	1	4	3
9	2	3	1	4
10	2	3	4	1
11	2	4	1	3
12	2	4	3	1
13	3	1	2	4
14	3	1	4	2
15	3	2	1	4
16	3	2	4	1
17	3	4	1	2
18	3	4	2	1
19	4	1	2	3
20	4	1	3	2
21	4	2	1	3
22	4	2	3	1
23	4	3	1	2
24	4	3	2	1

Setting and Participants

This trial received ethical approval on July 1, 2020, from the Swedish Ethical Review Authority (Dnr 2020-01799). English-speaking individuals searching online for information on how to drink less or quit drinking will be recruited using Google Ads with language targeting. Language targeting is an automated process in which Google's algorithms will display the advert to individuals using their products (eg, search and Gmail) in the specified language. Examples of search queries targeted are "How do I drink less," "I drink too much," and "Support for drinkers." The recruitment information will be framed as an invitation to take part in a study that aims to improve alcohol intervention research, and it will be made clear that participants should not expect to receive support. An example of an advert is shown in Figure 1, and study information presented to individuals who click on the advert can be found in Multimedia Appendix 1.

Figure 1. Example of online advertisement used to recruit trial participants.



Individuals will be asked to read the study information presented when the advert is clicked on and confirm that they are at least 18 years old and consent to take part in the trial (see Multimedia Appendix 1). Participants consenting to take part in the trial will be randomized to one of the arms of the trial (Table 1). Thus, there will be no explicit exclusion criteria; however, analyses will exclude participants reporting having not consumed any alcohol during the past 3 months (ie, answering *Never* to the first AUDIT-C question and having consumed 0 drinks in the past week). Questions will be presented to participants in the order that corresponds to their group allocation. Participants will be allowed to go back and change their responses to previous questions (to make the experiment similar to regular surveys and trials; see Discussion). Once all questions have been answered, participants will be thanked and recommended to read more about alcohol and health on a selection of websites. No further contact will be made with the participants.

Outcomes

The primary outcomes are the 10 outcomes of the COS measured using the recommended questionnaires [18], and the proportion of participants abandoning the questionnaire.

The secondary outcomes are the proportion of participants visiting the provided links at the end of the questionnaire, and time spent on the questionnaire among completers and abandoners.

The first primary outcome (ie, the responses to the COS) will facilitate the primary analysis of question order effects. As the COS is new, we also wish to measure the abandonment rate in order to guide both future trials utilizing the COS and further development of the COS for online and digital settings.

Measuring the proportion of participants visiting the provided links at the end of the questionnaire is an opportunistic decision to gather some data on the degree to which responding to the COS satisfies participants' intentions to seek help online. Assessment has been found to affect alcohol outcomes [11,29,30]; thus, differentiation between those who visit the links at the end of the questionnaire with respect to responses to the COS will generate hypotheses for future trials aimed at understanding who is affected by the assessment. The final outcome, time spent on the questionnaire, is captured primarily to guide future research on the anticipated participant burden of completing the COS.

Randomization and Blinding

Block randomization (random block sizes of 24 and 48) will be used to achieve equal allocation among arms. The randomization sequence and allocation will be fully automated and computerized. Since no identifiers are collected for individuals, we will use web browser cookies and HTML5 storage to store allocation information on the participants' web browsers (see Discussion). Participants who have not completed the questionnaire and return to the trial website will be presented with the cluster order according to their assignment. Participants who have completed the questionnaire and return to the trial website will be thanked for their participation, but not offered an opportunity to answer the questions again.

Participants will be aware that they are taking part in a research study; however, the true nature of the study will not be revealed to them, since this would interfere with the effect being studied. Therefore, participants will not be aware of which arm they are in, and hence will be blinded to allocation. Researchers will also be blind to participant allocation.

Analysis

Preliminary

All analyses will be conducted according to intention-to-treat principles, with all participants analyzed in the groups to which they were randomized. Analyses will exclude participants who report not having consumed any alcohol the past 3 months (ie, answering *Never* to the first AUDIT-C question and having consumed 0 drinks in the past week). Analyses will initially be done using complete cases, and sensitivity analyses with imputed values will be used to assess robustness of results under different assumptions of the missing data. Estimates for model parameters will be interpreted by inspecting marginal posterior distributions using Bayesian inference (see Sample Size for prior specification) [31-33] and complemented by null hypothesis testing (at the .05 significance level).

Primary Analysis

The primary analysis of question order bias will be conducted through regression models in which each outcome in each cluster will be regressed against a dummy variable representing whether each of the other clusters was asked before or after the outcome. For instance, standard drinks consumed in the past week (which is part of Cluster 2), will be regressed against 3 dummy variables, representing Cluster 1, Cluster 3, and Cluster 4, respectively. The dummy variables will take value 0 if the cluster was asked after Cluster 2 and value 1 if the cluster was asked before Cluster 2. For each outcome, 1 regression model will be created, yielding a total of 10 models, using negative binomial regression for counts (outcome 6 and outcome 9), logistic regression for hazardous or harmful drinking (outcome 5, using AUDIT-C scores of 5+ as the cutoff), and normal regression for scores (all other outcomes, possibly log-transformed if found to be skewed).

We will investigate 2- and 3-way interactions among the cluster dummy variables in order to explore if the order of a combination of clusters affects outcomes (eg, if the order of Cluster 1 and Cluster 2 in combination creates a question order bias on the outcomes in Cluster 3).

The proportion of participants abandoning the questionnaire will be analyzed in two ways: (1) using a logistic regression model with allocated arm as a covariate, to identify orders that are more (or less) likely to result in abandonment, and (2) using a logistic regression model with the cluster that was abandoned and the number of questions responded to as covariates, to identify clusters that are more (or less) likely abandoned (adjusted for number of questions responded to).

Secondary Analysis

The proportion of participants visiting the provided links at the end of the questionnaire will be analyzed using a logistic

regression model with the COS outcomes as covariates under both standard normal priors and shrinkage priors [34].

Time spent (in seconds) on the questionnaire will be reported among completers and abandoners and analyzed in two ways: (1) using normal regression with arm as a covariate (completers and abandoners, possibly log-transformed) and (2) using normal regression with the COS outcomes as covariates (completers only, possibly log-transformed). Both analyses will be conducted under standard normal priors, and the second analysis will also be conducted using shrinkage priors [34].

Exploratory Analysis

Patterns among individuals with respect to going back and changing responses to previous questions will be investigated in exploratory analyses using a combination of regression and clustering models. We will also run sensitivity analyses to see if the primary findings change when using the first response option that participants chose.

Sample Size

The trial will use a Bayesian group sequential design [35-37] to monitor recruitment, with interim analyses planned for every 50 participants completing the questionnaire. Responses to each of the 10 COS outcomes will be modelled following the primary analyses, and each dummy variable representing cluster order will be assessed for evidence of effect or futility. Let $ß_{k,i}$ represent the coefficients for each dummy variable (i=1,2,3) in each model (k=1...10) and D represent the data available at the interim analyses. Then, the target criteria will be (1) *effect:* $p(ß_{k,i} > 0 \mid D) > 97.5\%$ or $p(ß_{k,i} < 0 \mid D) > 97.5\%$ (ie, if the question order effect is greater or less than 0 with a probability greater than 97.5%); (2) *futility (normal regression):* $p(-0.1 < ß_{k,i} < 0.1 \mid D) > 95\%$ (ie, if the question order effect is close to 0 with a probability greater than 95%); and (3) *futility (negative binomial and logistic regression):* $p(\log(1/1.2) < ß_{k,i} < \log(1.2)) > 95\%$ (ie, if the question order effect is close to 0 with a probability greater than 95%).

For the effect criterion, we will use a skeptical normal prior for dummy covariates (mean 0, SD 1.0), and a wider prior will be used for the futility criterion (mean 0, SD 2.0).

The criteria should be viewed as targets; thus, at each interim analysis, we will evaluate each criterion for each covariate and decide if we believe that recruitment should end. We will only make decisions to stop recruitment entirely, not drop or modify any of the arms. Simulations indicate that we will require a sample size in the range of 1500 to 2500 participants. Recruitment will not exceed 24 months.

Results

Recruitment will commence in November 2020. Findings from this study are expected to be disseminated in peer-reviewed journals and presented at relevant international conferences during 2021-2023, after which all data will be made available on the Open Science Framework. Protocols and standard operating procedures will be developed to promote replication, including in modes other than online, and all models will be hosted on the Open Science Framework [38].

Discussion

Overview

This study will be the first to assess question order bias in the COS for ABIs, and will help guide future trials in how to ask the COS. It is clear that the research field as a whole would benefit from reducing heterogeneity in the outcomes used in trials; thus, the findings from this study may help increase confidence in using the COS.

Limitations and Generalizability

Respondents will be able to go back and change their responses to previous questions as they progress through the items; if the aim of the study was to capture causal connections among constructs represented by the clusters, a method used in other studies [39], then this process of changing responses would have been inappropriate. However, the aim of the study is to capture question order bias among the items as they would be used in a regular survey or trial; thus, not allowing participants to change previous responses would reduce generalizability. However, if this trial finds evidence of question order bias, then future trials should test not allowing previous responses to be changed with the aim of testing causal connections.

There is no reason to collect and verify any unique identifiers or means of contact for each participant (eg, phone number of email), since this trial does not require any follow-up. This, however, also means that there is no way of connecting group allocation to such a unique identifier. Instead, we will use HTML5 storage and cookies in participants' web browsers to store group allocation information, such that when participants return to the study website, they will not be rerandomized. However, participants could be rerandomized if they join using a different computer or web browser. This is a limitation of this trial that we find necessary in order to retain interested individuals in the trial, as confirming email addresses and phone numbers would increase participant burden and reduce the participation rate. We will, however, keep track of the number of times each participant visits our website using the same device. A high rate of return from the same device would increase the likelihood that participants also visit from other devices, and vice versa. Therefore, we can use this measure to help judge the risk of bias from double randomization. In addition, the links to websites with alcohol information at the end of the survey aim to satisfy the need of participants to search for this material again, reducing the risk that they revisit the study website.

As is often the case in online studies, participants sign up to the trial on their own. We have no screening questions to exclude participants who are not seeking help with their alcohol consumption, as this may interfere with the study of the order effects. Therefore, some may participate because they are curious about the study or seeking help for others. A single question at the end of the survey (not part of the factorial allocation) will explore participants' intentions ("Was the aim of your participation in this study to get help to reduce your

alcohol use?"). We will also analyze the search strings used by those clicking on the advert to capture the intentions of the study sample. We will not, however, make any adjustments to our primary analyses, but rather consider this uncertainty a limitation of generalizability of the findings of the trial.

Other limitations of this trial include clustering of certain outcomes in the COS. Alternative clustering may reveal different findings, and it would also be possible to randomize the order of each question without clusters; however, the number of arms would exceed what is feasible for factorial trials. The findings may also not apply to modes other than online data collection (eg, order effects may not hold in paper-based or face-to-face administration).

Acknowledgments

This project is funded by the Lifestyle Intervention Implementation Research group at Linköping University, for which MB is the research group leader.

Conflicts of Interest

MB owns a private company (Alexit AB) that develops and distributes digital lifestyle interventions to the general public and for use in health care settings. Alexit AB had no part in funding, planning, or execution of this trial. GWS was the lead researcher on the development of the ORBITAL effectiveness and efficacy outcome set. The core outcome set is free, and GWS receives no financial reward for its use. All other authors declare no conflicts.

Multimedia Appendix 1
Informed consent materials.
[DOCX File , 16 KB - resprot_v9i11e24175_app1.docx]

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Abbreviations

ABI: alcohol brief intervention
AUDIT-C: Alcohol Use Disorders Identification Test – Consumption
COMET: Core Outcome Measures in Effectiveness Trials
COS: core outcome set
ORBITAL: Outcome Reporting in Brief Intervention Trials: Alcohol
PROMIS: Patient-Reported Outcomes Measurement Information System
QOBCOS-1: Question Order Bias Core Outcome Set
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WHO: World Health Organization

Edited by G Eysenbach; submitted 07.09.20; peer-reviewed by D Leightley; comments to author 29.09.20; revised version received 08.10.20; accepted 13.10.20; published 26.11.20.

Please cite as:
Bendtsen M, Garnett C, Toner P, Shorter GW
The Effect of Question Order on Outcomes in the Core Outcome Set for Brief Alcohol Interventions Among Online Help-Seekers: Protocol for a Factorial Randomized Trial
JMIR Res Protoc 2020;9(11):e24175
URL: http://www.researchprotocols.org/2020/11/e24175/
doi:10.2196/24175
PMID:33242024

Protocol

Posttraumatic Stress Disorder and Neuroprogression in Women Following Sexual Assault: Protocol for a Randomized Clinical Trial Evaluating Allostatic Load and Aging Process Acceleration

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Abstract

Background: Posttraumatic stress disorder (PTSD) is a prevalent, chronic, and severe disorder related to traumatic events. Women are disproportionately affected by PTSD than men and are more at risk in the occurrence of sexual assault victimization. Estimates suggest that 50% of women develop PTSD following sexual assault and successful clinical management can be challenging. Growing evidence has implicated neural, immune, and endocrine alterations underpinning PTSD, but only few studies have assessed the evolution of acute PTSD in women.

Objective: This study aims to measure whether the onset of PTSD is associated with accelerated aging in women following sexual assault. We hypothesize that the increase of allostatic load caused by PTSD leads to neuroprogression. We will implement a randomized clinical trial to compare responses to treatment with either interpersonal psychotherapy adapted for PTSD (IPT-PTSD) or the selective serotonin reuptake inhibitor sertraline.

Methods: We will include women between 18 and 45 years of age, who experienced sexual assault from 1 to 6 months before the initial evaluation, and present with a Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) diagnosis of PTSD. Baseline evaluation will comprise clinical and psychometric assessments, structural and functional magnetic resonance imaging, neuropsychological testing, polysomnography, evaluation of immune and endocrine parameters, and genetic analyses. Age-matched female healthy controls will be included and subjected to the same evaluation. Patients will be randomized for treatment in 1 of the 2 arms of the study for 14 weeks; follow-up will continue until 1 year after inclusion via treatment as usual. The researchers will collect clinical and laboratory data during periodic clinical assessments up to 1-year follow-up.

Results: Data collection started in early 2016 and will be completed by the end of the first semester of 2020. Analyses will be performed soon afterward, followed by the elaboration of several articles. Articles will be submitted in early 2021. This research project has obtained a grant from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP 2014/12559-5).

Conclusions: We expect to provide insight into the consequences of recent sexual assault exposure in women by investigating the degree of neuroprogression developing from an early stage of PTSD. We also expect to provide important evidence on the

efficacy of a non-exposure psychotherapy (IPT-PTSD) to mitigate PTSD symptoms in recently sexually assaulted women. Further, we aim to obtain evidence on how treatment outcomes are associated with neuroprogression measures.

Trial Registration: Brazilian Clinical Trials Registry RBR-3z474z; http://www.ensaiosclinicos.gov.br/rg/RBR-3z474z/

International Registered Report Identifier (IRRID): DERR1-10.2196/19162

(JMIR Res Protoc 2020;9(11):e19162) doi:10.2196/19162

KEYWORDS

PTSD; neuroprogression; allostatic load; sexual assault; trauma; thematic research; randomized clinical trial; aging

Introduction

Background

Posttraumatic stress disorder (PTSD) is a psychiatric disorder triggered by an external traumatic event that exposes a person to an imminent life-threatening situation [1]. PTSD is characterized by intrusive memories and thoughts about the traumatic event, avoidance of trauma-related reminders and feelings, negative alterations in cognition and mood, and hyperarousal [2]. Although trauma is a necessary condition for PTSD diagnosis, not all traumatized individuals will develop the disorder [3]. Those who develop PTSD may show elevated risk of health decline (eg, diabetes, cardiovascular disease, autoimmune diseases, hypertension, and dementia) and comorbidity with other psychiatric disorders [4,5]. PTSD is a significant societal burden, with increased likelihood of hospitalization, suicide, drug abuse, and aggressive behavior [6-8].

PTSD etiology is complex and is underpinned by the integration of endogenous and environmental factors. Molecular genetics–based heritability and epigenetic influences associated with adversities during childhood reflect this integration [9,10]. Women are more likely than men to develop PTSD following trauma in a female-to-male ratio of approximately 2:1 [11,12]. Women also have more prolonged and poorer PTSD outcomes than men regardless of threat or injury event–related factors [13]. The reasons for this gender discrepancy remain unclear, but evidence suggests that psychosocial, cultural, and biological factors play significant roles in the increased vulnerability of women to disorder onset and progression [14,15]. Among traumatic events that may challenge individuals in their lifetime, sexual trauma appears a major instigator of developing PTSD. Approximately half of women will develop PTSD following sexual assault [16].

Allostatic Load and Neuroprogression in PTSD

PTSD has evolved its concepts in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) to include a complex heterogeneity of symptom profiles that may impede successful clinical management [17,18]. Despite decades of research, there remains a lack of consensus on the optimal treatment of this disorder [19]. Some guidelines recommend psychotherapeutic and drug-based interventions; however, remission and relapses persist, often leading to chronicity [20,21]. This is particularly concerning, as an estimated 50% of PTSD cases followed up in long-term studies evolve to chronicity [22,23]. The concept that “time heals wounds” only holds true for a limited number of individuals with PTSD, which strengthens the notion that important biological abnormalities predate the traumatic event and predispose to disorder severity [24].

The occurrence of trauma leading to PTSD and elevated stress may cause deviations in homeostasis, leading to pathogenic biological alterations. Persistent stress triggers an adaptive response termed “allostasis,” in which the organism attempts to cope and restore homeostatic balance through hormonal and physical dynamic changes [25]. However, allostasis is insufficient to explain the consequences of stress in an organism. The term “allostatic load” was thus coined to define the costs of chronic stress exposure associated with elevated or oscillating biological responses [26]. The “costs” of allostatic load are reflected in numerous alterations in endocrinal and immune reactivity, neural circuitry dysregulation, and molecular and physiological deterioration described in the PTSD literature [27].

As stress and challenges involved in PTSD may accumulate allostatic load in the organism and cause dysregulation of biological systems, it is crucial to investigate parameters of neuroprogression in individuals affected by the disorder. Neuroprogression, a term initially developed to describe impairment and neuroanatomical alterations in patients with bipolar disorder, is defined as a pathological brain reorganization that occurs concomitant with the decline in clinical health over the course of the disease, typically reflecting patterns consistent with accelerated biological aging [28]. As previously mentioned, substantial evidence supports the association of PTSD with adverse health outcomes. Only recently has PTSD begun to be more closely linked to biological markers of accelerated aging via measurement of telomere shortening [29] and DNA methylation [30], and in analyses of inflammation [31] and immune responses [32].

Objectives

We designed a thematic research project to evaluate whether the traumatic events and onset of PTSD are associated with accelerated aging in individuals in the early stages of PTSD who are not chronically ill (medically and psychiatrically). We aim to enroll women in the study to better understand the effects of PTSD in this sex, given the high prevalence and severity of PTSD following sexual violence against women.

At baseline we will compare data from the PTSD group with a healthy non-PTSD control group of women with no sexual trauma history. We hypothesize that the toxicity of the increased allostatic load caused by PTSD symptoms leads to

neuroprogression, even if the onset of PTSD is recent (less than 6 months). We hypothesize that we will observe:

- Poor treatment outcomes associated with neuroprogression measures.
- Reduced corpus callosum, hippocampus, and anterior cingulate cortex volume associated with increased allostatic load, suggesting that neuroprogression occurs in the early stages of PTSD.
- Alterations in telomere length and in methylation profile of long interspersed nuclear element-1 (LINE-1) regions.
- Downregulation of gene expression.
- Worse sleep quality, reduced rapid eye movement (REM) sleep, and alterations in the heart rate variability during sleep.
- Impairment of executive functions, memory, and attention associated with PTSD severity and negative outcomes.
- Hypothalamic–pituitary–adrenal imbalance, with unregulated cortisol and adrenocorticotrophic hormone levels.
- Persistent inflammatory response with increased levels of inflammatory markers.

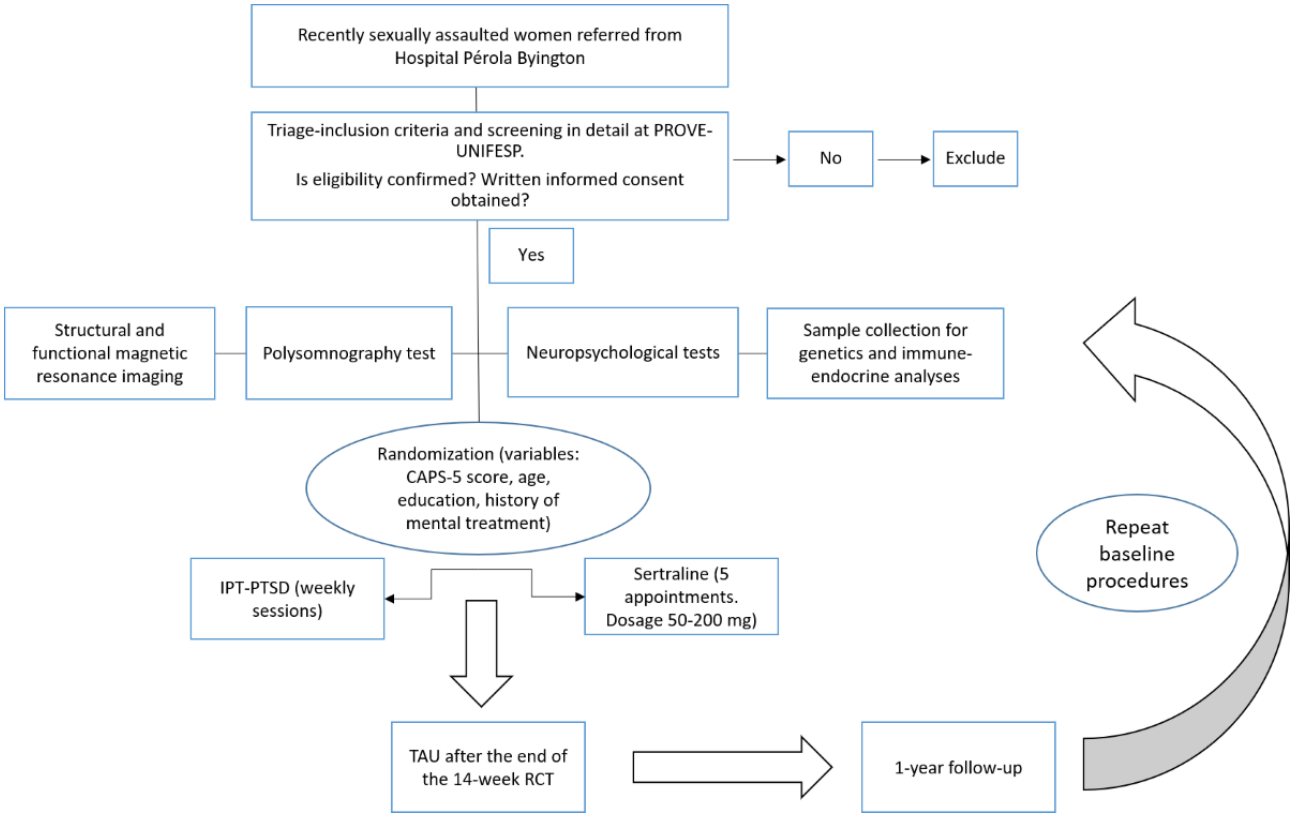
Further, we aim to implement a randomized clinical trial (RCT) to compare 2 therapeutic interventions: interpersonal psychotherapy adapted for PTSD versus sertraline. In comparing the 2 interventions, we aim to verify whether treatment response is associated with neuroprogression measures.

Methods

Overall Study Design

The thematic research project has a cross-sectional and longitudinal study design with multiple time-point assessments. Hospital Pérola Byington (HPB), the largest public health center facility in São Paulo that offers gynecological care for women following sexual assault, will refer all women eligible to participate in the research. Sexually assaulted women admitted to HPB will initially be requested by HPB staff to complete the National Stressful Events Survey Short Scale for PTSD-Short Scale (NSESSS-PTSD), a brief self-report PTSD screening scale. The Universidade Federal de São Paulo (Federal University of São Paulo) (UNIFESP) team will contact women by telephone to assess initial eligibility criteria. Medical records at HPB will be assessed. An appointment for screening with trained psychologists and psychiatrists at UNIFESP will be scheduled. If eligibility is confirmed, participants will be requested to undergo the following procedures: (1) structural and functional magnetic resonance imaging (MRI); (2) neuropsychological testing; (3) in-laboratory polysomnography; (4) saliva and blood sample collection for inflammatory and immune marker analyses; (5) blood sample collection for genetic analyses. After completing these procedures, all women will be randomized to receive intervention (either ITP-PTSD or sertraline) in a 14-week RCT. At the end of the 14-week RCT, women will undergo treatment as usual. After completing 1 year of treatment in the project, patients will be invited to repeat all baseline procedures, that is, the examinations and testing 1-5 described above (1-year follow-up; Figure 1).

Figure 1. Research process flowchart. IPT: interpersonal psychotherapy; PROVE-UNIFESP: Service for Research and Care on Violence and PTSD; PTSD: posttraumatic stress disorder; RCT: randomized clinical trial; TAU: treatment as usual; UNIFESP: Universidade Federal de São Paulo (Federal University of São Paulo).



The thematic research project has obtained a 5-year grant from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP 2014/12559-5). The research will be conducted at the Service for Research and Care on Violence and PTSD (PROVE-UNIFESP) in the Department of Psychiatry at Escola Paulista de Medicina, UNIFESP. It will rely on the cooperation of different UNIFESP departments: the RCT and screening will occur at PROVE-UNIFESP; MRI will be conducted in the Department of Diagnosis in Neuroimaging; saliva and blood sample collection for genetic and inflammatory investigations, as well as the neuropsychological testing, will occur at the Associação Fundo de Incentivo à Pesquisa (AFIP-UNIFESP). The Department of Morphology and Genetics will perform DNA extraction and all genetic analyses. The Instituto do Sono-AFIP will perform in-laboratory polysomnography testing.

Participants

Patient Recruitment

We estimate inclusion of 100 patients and 100 matched healthy controls who fulfill inclusion criteria. All participants must sign an informed consent form approved by the UNIFESP Committee Board, in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Participation in the study will be voluntary without financial compensation. Participants will be compensated only for their public transportation expenses. If at any point in this research, any participant experiences severe symptomatic worsening, or no longer wishes to participate in the study, we will offer immediate standard treatment in our outpatient service.

Inclusion Criteria

Eligible women are those 18-45 years old with a definite diagnosis for PTSD according to DSM-5, who experienced nonpartner sexual violence between 1 and 6 months prior to study inclusion and developed PTSD following this particular traumatic event. We conceptualized sexual assault as rape (through force or threat), attempted rape, and drug-facilitated rape. Comorbidity with major depression, anxiety disorders, and borderline personality disorder will not be considered exclusion criteria.

Exclusion Criteria

Women excluded from study participation are those outside the study age range. Further exclusion factors are infection with HIV or other sexually transmissible diseases, acute clinical illness, unstable medical condition, neurological disorders, schizophrenia, bipolar disorder, current use of corticosteroid medication, menopausal symptoms, and substance abuse or dependence not in remission for the last 6 months. We will carefully select patients who are not undergoing any psychological/psychiatric treatment or taking psychotropic medication. Pregnant women will be excluded from the study.

Selection of Healthy Controls

We intend to enroll 100 female age-matched healthy controls selected from the community with no PTSD and no history of sexual assault who voluntarily comply with study participation. Educational level and socioeconomic characteristics will be taken into consideration to match the PTSD group. All controls will be assessed for eligibility at PROVE-UNIFESP and will undergo the same baseline procedures as the PTSD group: that is, psychometric assessments, MRI, neuropsychological testing, polysomnography, evaluation of immune and endocrinal parameters, and genetic analyses. We will exclude controls diagnosed with psychiatric disorders, currently using psychotropic medication(s), or undergoing psychotherapy. Controls will not undergo treatment and will not be followed up. Controls must not have familial relation to enrolled study patients. The same exclusion criteria for patients will be applied to controls.

Measures

Full Sociodemographic Inventory and History of the Sexual Assault Episode

We developed a detailed sociodemographic inventory to collect relevant sociodemographic characteristics of our participants. We aim to collect the following data on the sexual violence episode: (1) type of violence (rape, attempted rape, or drug-facilitated rape); (2) whether the perpetrator(s) was (were) known (family member, friend, or acquaintance) or unknown; (3) location of the assault (eg, home, public place, working place), precise date, and time of the assault; (4) whether the victim chose to notify the police authorities, and if so, whether an investigation is ongoing; and (5) detailed description of the assault. We will also monitor whether participants adhere to gynecological treatment offered at HPB.

Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

This assessment is the gold standard to assess PTSD diagnostic status and symptom severity. The clinician administers this instrument as a structured interview, comprising 30 items assessing both the frequency and the intensity of PTSD symptoms and trauma-associated variables using a frequency/severity scale varying from 0 (never/not severe at all) to 4 (most of the time/severe). Based on a large-scale psychometric study, its authors state that the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) presented substantial evidence of both its validity and reliability as a measure for PTSD symptoms; it has been adapted to Brazilian Portuguese [33,34].

Mini International Neuropsychiatric Interview (MINI)

This structured diagnostic interview is designed for clinical practice and research in psychiatric and primary care settings. The Mini International Neuropsychiatric Interview (MINI) provides accurate psychiatric diagnoses (psychosis, mood, anxiety, personality, and PTSD) and is widely used in international psychiatry [35].

Beck Depression Inventory (BDI)

This self-report instrument is a 21-item questionnaire measuring clinical depression. Each of the 21 multiple-choice questions presents 4 alternatives varying in level of depressive severity (minimal, mild, moderate, and severe). The score consists of the sum of the most severe alternative chosen for each question [36,37].

Beck Anxiety Inventory (BAI)

This 21-item self-report inventory assesses anxiety symptoms. Patients must evaluate how much each anxiety symptom applies to their condition on a severity scale from 0 to 3. The score sums the individual items, classifying the severity of anxiety as minimum, mild, moderate, or severe [38].

Childhood Trauma Questionnaire (CTQ)

This self-report instrument for adults and adolescents investigates 5 early stage abuse and negligence experiences. It investigates physical, emotional, and sexual abuse, as well as physical and emotional neglect in childhood. The respondent indicates, on a 5-point Likert scale, the frequency of 28 different childhood situations [39].

Peritraumatic Dissociative Experiences Questionnaire (PDEQ)

This is a 10-item measure of dissociative symptoms experienced during or immediately after a traumatic event. The self-rated Peritraumatic Dissociative Experiences Questionnaire (PDEQ) uses a 5-point Likert scale from 1 (not at all true) to 5 (extremely true) [40].

The Clinical Global Impression—Severity Scale (CGI-S) and Clinical Global Impression—Improvement Scale (CGI-I)

These 7-point scales reflect the clinician's evaluation. The GCI-S requires the clinician to rate the severity of the patient's mental illness based on the clinician's experience with patients with the same diagnosis. Patients are assessed for disease severity rated from 1 (normal) to 7 (extremely ill). The GCI-I requires the clinician to assess how much the patient's condition has improved or worsened relative to the baseline of the intervention. It is rated from 1 (very much improved) to 7 (very much worse) [41].

PTSD Checklist for DSM-5 (PCL-5)

This 5-point Likert scale is a 20-item self-report assessing the 20 DSM-5 PTSD symptoms. Responses vary according to how much each symptom of PTSD has bothered the individual in the last 4 weeks, rated from 0 (not at all) to 4 (extremely) [42].

Life Event Checklist for DSM-5 (LEC-5)

This self-report measure assesses the occurrence of traumatic events in an individual's lifetime. The Life Event Checklist for DSM-5 (LEC-5) assesses exposure to 16 events that may potentially lead to PTSD. An additional item encompasses a further extremely stressful event not captured by the other 16 items. The LEC-5 yields no total score and lacks a recognized interpretation protocol, but the instrument is commonly used in combination with other measures, such as the CAPS-5 or PTSD Checklist for DSM-5 (PCL-5), to establish actual occurrence of DSM-5 criterion A traumatic events [43].

Tonic Immobility Scale (TIS)

This self-report instrument was originally designed specifically to evaluate the presence and severity of tonic immobility in sexually assaulted women. The Tonic Immobility Scale (TIS) reflects physiological and behavioral features that accompany tonic immobility during the traumatic event and comprises 2 parts. The first part assesses multiple dimensional tonic immobility responses; the second assesses victim behaviors in contextual assault circumstances [44].

Structured Clinical Interview for DSM-5 for the Diagnosis of Borderline Personality Disorder (SCID-5)

This is a semistructured interview administered by the clinician or a trained mental health professional to assess the major DSM-5 diagnoses and symptom severity dimensions of both current and lifetime occurrence of mental disorders [45]. Specific segments for borderline personality disorder, common comorbidity with PTSD, and influential aspects of PTSD treatment outcomes will be used.

World Health Organization's Quality of Life Assessment (WHOQOL-BREF)

This abbreviated self-rated questionnaire, designed with international cooperation for global cross-cultural use, assesses quality of life. Its 25 facets are scored in environmental, social, physical, and psychological domains [46].

The Revised Adult Attachment Scale (RAAS)

This 5-point Likert scale measures adult attachment and assesses close interpersonal relationships. The 18 items range from 1 (not at all characteristic) to 5 (very characteristic of me) and are classified into 3 subscales: closeness, dependency, and anxiety [47].

The Sheehan Disability Scale (SDS)

This brief 3-item self-report measures the impairment and disruption caused by symptoms to work, family, and social functioning. Patients self-rate on a scale from 0 (not at all) to 10 (extremely) [48].

Modified Fatigue Impact Scale (MFIS)

This 21-item scale assesses the perceived effects of fatigue on quality of life in physical, cognitive, and psychosocial domains. It is mainly used in patients with chronic diseases. The Modified Fatigue Impact Scale (MFIS) uses a 5-point Likert scoring system from 0 (never) to 4 (almost always) [49].

Pittsburgh Sleep Quality Index (PSQI)

This self-administered, reliable tool evaluates sleep quality and possible disturbances in the previous month. It is used in both clinical practice and research. The 19 Pittsburgh Sleep Quality Index (PSQI) individual items generate 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction [50]. We will use an addendum of the PSQI designed explicitly to measure PTSD-related sleep dysfunction [51].

Epworth Sleepiness Scale (ESS)

This self-report questionnaire measures the occurrence and intensity of daytime sleepiness. The Epworth Sleepiness Scale (ESS) evaluates the probability of falling asleep in 8 situations involving daily activities. Total score ranges from 0 to 24; scores over 10 suggest excessive daytime sleepiness [52].

Insomnia Severity Index (ISI)

This brief self-report instrument measures patient perception of his or her insomnia. The Insomnia Severity Index (ISI) targets the subjective symptoms and consequences of insomnia. The ISI also measures the degree of concerns or distress caused by those difficulties. The ISI comprises 7 items assessing the severity of sleep-onset and sleep maintenance difficulties, satisfaction with current sleep patterns, interference with daily functioning, noticeability of impairments attributed to sleep problems, and degree of distress or concern caused by the sleep problems. Each item is rated on a scale from 0 to 4, and the total score ranges from 0 to 28 [53].

Alcohol Use Disorders Identification Test (AUDIT)

This 10-item questionnaire was developed by the World Health Organization to identify patients with recent heavy drinking or alcohol dependence. The Alcohol Use Disorders Identification Test (AUDIT) score ranges from 0 to 40. An AUDIT score of 8 indicates a pattern of harmful alcohol consumption; 16 to 19 indicates alcohol abuse, and 20 shows probable dependence [54].

Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

This interview developed by the World Health Organization identifies history and current (past 3 months) use of substances. The Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) assesses cannabis, cocaine, amphetamine-type stimulants, inhalants, sedatives, hallucinogens, opioids, other miscellaneous drugs, and alcohol or tobacco use. After responding regarding the lifetime use of all substances investigated, participants respond regarding recent use on a 5-point scale (frequency) ranging from “never” to “daily or almost daily” [55].

Detailed Procedures

Magnetic Resonance Imaging

Brain MRI scans will be performed using a 3T Philips Achieva scanner with a 32-channel head coil. The MRI protocol consists of a localizer; coronal T2; volumetric T1 (repetition time [TR] = 2000 ms; echo time [TE] = 3 ms; inversion time = 1100 ms; field of view = 240 × 240 × 180 mm^3; matrix size = 240 × 240 × 180); axial fluid-attenuated inversion recovery; diffusion tensor imaging (weighted images acquired using a single-shot, spin-echo, echo - planar imaging with b=1000 s/mm^2 with 31 uniformly distributed, noncolinear direction images, plus 1 additional image acquired with nondiffusion weighting [b=0 s/mm^2]); 2D multislice gradient echo sequence with magnitude and phase images (TR = 500 ms, TE = 2.0 and 4.3 ms; flip angle = 30°, fat saturation = off, water fat shift = 0.3 pixels, bandwidth (BW) = 1446.8 Hz/pixel); resting-state functional MRI (isotropic resolution 3 × 3 × 3 mm^3, TR = 2 s, TE = 30 ms, 300 volumes); and 3 MRI spectroscopy sequences: (1) in the anterior cingulate gyrus using chemical shift imaging (multivoxel spectroscopy) with a 2D PRESS sequence (TE/TR = 45/2000 ms, 1024 samples, BW = 2 kHz, voxel size = 10 ×10 × 15 mm, matrix = 8 × 8 voxels, oversampled to 13 × 12 to avoid aliasing, average = 1, total scan time = 3:30 min); (2) multiecho single-voxel PRESS (TR = 2000, TE = 30, 40, 50, 60, ..., 250, 260 ms [24 TEs in total], 2048 samples, BW = 2 kHz, voxel size = 20 × 20 × 20 mm, average = 8, total scan time = 8:48 min) according to a protocol by Hurd and colleagues [56]; and (3) conventional long TE single-voxel PRESS (TE/TR = 144/2000 ms, 2048 samples, BW = 2 kHz, voxel size = 20 × 20 × 20 mm with the same positioning as that in [2], average = 96, total scan time = 3:48 min). All MRI protocols include the acquisition of an unsuppressed water reference spectrum. Details on imaging preprocessing and analyses will be provided in specific studies from this cohort.

Neuropsychological Testing

Application of a neuropsychological battery will be composed of the following subtests: Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary and Matrix Reasoning, Digit Subtests of the Wechsler Adult Intelligence Scale (WAIS-III), Rey Auditory Verbal Learning Test (RAVLT), Spatial Span Subtest of the Wechsler Memory Scale (WMS), III Edition, abbreviated version of the Wisconsin Test, Concentrated Attention Test (D2), Prospective Memory Subtest of the NEUPSILIN Scale, Five-Digit Test, and the Stroop Test (Trenerry’s version).

Polysomnography

Participants will undergo 1 night of polysomnography recording in the Instituto do Sono-AFIP at UNIFESP. Recordings will be conducted using Embla N7000 (Embla Systems, Inc.). In the polysomnography test, we will measure brain activity using electroencephalogram electrodes, monitor eye movements using electrooculography electrodes, measure muscle tone using electromyography electrodes, measure heartbeat using electrocardiograph electrodes, and monitor rate of respiration using respiratory monitors. The following sleep variables will be determined: REM sleep latency; sleep onset latency; total sleep time; wake after sleep onset; sleep efficiency; percentages of total sleep composed of N1, N2, N3, and REM sleep; arousal index; number of arousals per hour; periodic limb movements in sleep indices with and without arousal; number of limb movements per hour with and without arousal; apnea–hypopnea index; number of apneas and hypopneas per hour; and REM sleep density. A power spectral analysis of heart rate variability will be performed from the electrocardiogram signal collected throughout sleep and will assess the quantitative contribution of high frequency (0.15-0.4 Hz), low frequency (0.04-0.15 Hz), and very low frequency (0.003-0.04 Hz) components to the total variance.

Immune and Endocrinal Parameters

Results for interleukin-6, interleukin 1-β, monocyte chemoattractant protein-1, tumor necrosis factor-α, and C-reactive protein will be obtained from blood samples of the participants at the AFIP-UNIFESP at 7:00 am after the polysomnographic examination. We will use ethylenediaminetetraacetic acid (EDTA) tubes, and the plasma will be stored at –20°C.

Salivary cortisol samples will be collected using the Salivette kit with a synthetic swab. All participants will be provided instructions according to the kit protocol. Saliva will be collected

at home 4 times: at 10 p.m. before sleeping and the next day at 6:30 a.m., 7 a.m., and 7:30 a.m.

A second collection of salivary cortisol will be performed at the Instituto do Sono-AFIP at UNIFESP. Professionals will collect saliva at 10 p.m. (prepolysomnographic examination), 6:30 a.m., 7 a.m., and 7:30 a.m. (postpolysomnographic examination).

For C-reactive protein, adrenocorticotrophic hormone, vasopressin, aldosterone, and cortisol analyses, we will use a high-sensitive enzyme-linked immunosorbent assay kit (ELISA). The MILLIPLEX MAP panel based on the Luminex xMAP technology will be used to obtain cytokine results.

Genetics

Peripheral blood of the participants will be collected in 2 EDTA tubes for DNA isolation and 2 PAXgene RNA tubes for RNA analysis. DNA and RNA extraction will be performed using Gentra Puregene (Qiagen) and PAXgene blood RNA isolation kits, respectively, according to the manufacturer's instructions.

The DNA samples will be used to perform different genetic/epigenetic analyses such as genotyping, measurement of telomere length, and methylation profile over LINE-1 regions. The genotyping of individuals will be performed using the Infinium Global Screening Array BeadChip (Illumina) with approximately 640,000 markers, including rare, common variants, and exonic, intronic, nonsense, missense, indel markers. Telomere length will be measured by quantitative polymerase chain reaction, according to a protocol previously described by Cawthon [57], which consists of determining the relative ratio between the telomere region copy number (T) and a single-copy gene (S – albumin gene) using a relative standard curve. The methylation profile of LINE-1 transposable elements was verified by quantification of global methylation of these fragments using polymerase chain reaction followed by sequencing using Pyrosequencing technology.

The RNA samples will be used to investigate the blood transcriptome by sequencing using the NextSeq 500/550 High Output Kit (version 2.5; Illumina).

Randomized Clinical Trial: Interpersonal Psychotherapy Adapted for PTSD Versus Sertraline

We designed a 14-week RCT comparing IPT adapted for PTSD to sertraline. Our plan is to evaluate the relative efficacy of both interventions, comparing treatment outcome, patient adherence, and tolerability for women in the early stages of PTSD following sexual trauma. Sertraline is a widely used, usually well-tolerated selective serotonin reuptake inhibitor (SSRI) effective as an antidepressant and anxiolytic, and one of the 2 SSRIs FDA approved to treat PTSD [58,59]. However, several guidelines consider antidepressants to be of secondary importance to psychotherapy for the treatment of PTSD [60], and many SSRI-treated patients do not achieve remission [61].

Interpersonal psychotherapy adapted for PTSD is a non-exposure, nontrauma-focused brief therapy designed to minimize the high attrition rates observed in patients undergoing exposure therapies. Many traumatized individuals refuse or are unable to tolerate treatments such as prolonged exposure, as they require facing reminders of the traumatic event(s), which often trigger fear, avoidance, and intolerable stress [62]. The aversive aspects of exposing patients to their traumatic memories and cues may elevate attrition, reducing treatment efficacy. Interpersonal psychotherapy adapted for PTSD explores interpersonal and commonly severe social aftereffects of trauma, not the trauma itself [63]. In one RCT, interpersonal psychotherapy adapted for PTSD produced superior results to prolonged exposure in treatment retention and symptom improvement in chronic sexual assault survivors [64].

Interpersonal psychotherapy adapted for PTSD is delivered in 3 phases: (1) assessment of PTSD diagnosis and patients' interpersonal context, including meaningful past and present relationships. The therapist offers a life crisis formulation that provides the therapeutic focus (2-3 sessions); (2) the therapist helps patients to resolve the focus, eliciting and validating patients' thoughts and feelings and encouraging them to take appropriate social risks to improve abilities to assert wishes and needs in relationships (8-9 sessions); (3) the therapist terminates treatment, calling attention to patients' gains during the process, and reinforces positive roles (eg, as a survivor rather than a victim). Positive and painful aspects of the intervention are addressed to help patients finalize the psychotherapy process (3 sessions) [63,65]. Part of adapting IPT for PTSD involves helping numbed patients attune to their emotions, and to recognize them not as dangerous but as helpful interpersonal signals.

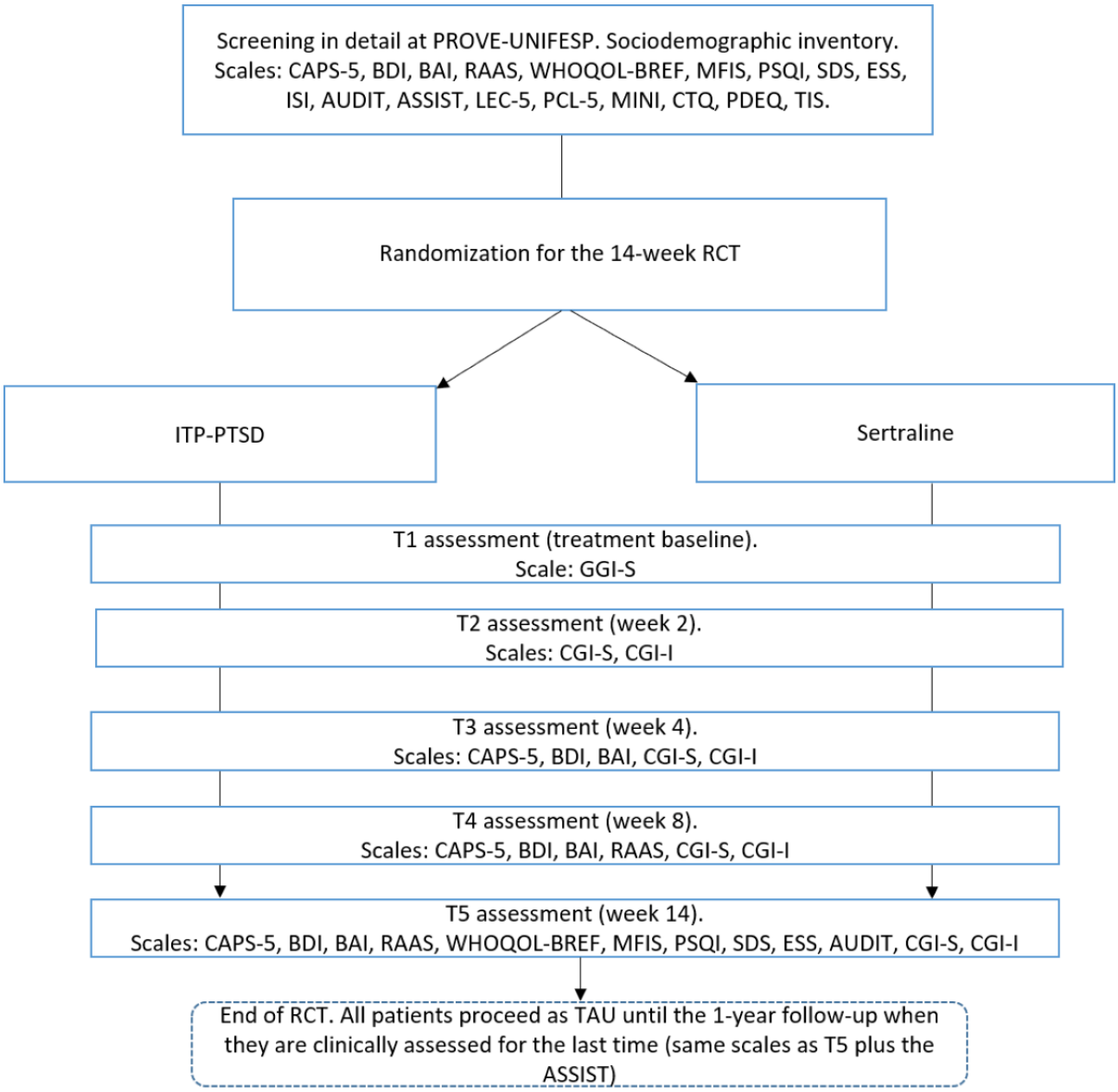
In the pre-enrollment consent process, patients will be told about the study design, and that they may not choose between the treatments. Both arms will have a 14-week duration and will be conducted entirely at PROVE-UNIFESP. Patients nonresponsive to treatment will not be crossed over to the other arm, and will be excluded from the research if they become suicidal or if their symptoms become more severe. A brief description of the methods applied in both arms is as follows:

- Interpersonal psychotherapy adapted for PTSD will comprise weekly 50-minute sessions with an experienced, well-trained therapist who will be supervised every week by 2 expert interpersonal psychotherapy adapted for PTSD therapists. The sessions will be audiotaped with patient consent, and the interpersonal psychotherapy adapted for PTSD team will study the recordings to assess therapy quality by rating therapist verbalizations rather than patient responses. Patients will be seen briefly 5 times during the 14-week treatment by a psychiatrist, who will have the option to introduce low dosage of the following sedative medications: quetiapine (25-50 mg), risperidone (1-2 mg), or zolpidem CR (12.5 mg). Interpersonal psychotherapy adapted for PTSD therapists and clinicians will maintain confidentiality.
- Sertraline will be administered using an initial dosage of 50 mg that may be increased to 200 mg over the 14-week treatment. Patients will be seen 5 times during the 14-week trial by psychiatrists experienced in treating patients with PTSD. Additional dosages of quetiapine (25-50 mg), risperidone (1-2 mg), or zolpidem CR (12.5 mg) may be used.

Different psychiatrists will evaluate the patients in either arm of the trial. The additional drugs mentioned above (quetiapine, risperidone, and zolpidem CR) will be prescribed only if patients exhibit high levels of anxiety, fear, or severe insomnia.

The clinical assessments of the study are presented in Figure 2. Longitudinal assessments will occur at week 2 (CGI-S and CGI-I), week 4 (CAPS-5, Beck Depression Inventory [BDI], Beck Anxiety Inventory [BAI], CGI-S, and CGI-I), week 8 (CAPS-5, BDI, BAI, The Revised Adult Attachment Scale [RAAS], CGI-S, and CGI-I), and week 14 (CAPS-5, BDI, BAI, RAAS, WHOQOL-BREF, MFIS, PSQI, SDS, ESS, AUDIT, CGI-S, and CGI-I). The CGI-S and the CGI-I will be used by the clinicians in all appointments. The research team will administer the other scales in a separate meeting with patients. Assessors will be blind to treatment condition and will not provide any treatment. The same measures will be repeated at 1-year follow-up with the addition of the ASSIST.

Figure 2. Clinical assessment flowchart. ASSIST: Alcohol, Smoking and Substance Involvement Screening Test; AUDIT: Alcohol Use Disorders Identification Test; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; CAPS-5: The Clinician-Administered PTSD Scale for DSM-5; CGI-I: The Clinical Global Impression—Improvement Scale; CGI-S: The Clinical Global Impression—Severity Scale; CTQ: Childhood Trauma Questionnaire; ESS: Epworth Sleepiness Scale; IPT: interpersonal psychotherapy; LEC-5: Life Event Checklist for DSM-5; MINI: Mini International Neuropsychiatric Interview; MFIS: Modified Fatigue Impact Scale; PCL-5: PTSD Checklist for DSM-5; PDEQ: Peritraumatic Dissociative Experiences Questionnaire; PROVE-UNIFESP: Service for Research and Care on Violence and PTSD; PSQI: Pittsburgh Sleep Quality Index; PTSD: posttraumatic stress disorder; RAAS: The Revised Adult Attachment Scale; RCT: randomized clinical trial; SDS: The Sheehan Disability Scale; TAU: treatment as usual; TIS: Tonic Immobility Scale; WHOQOL-BREF: World Health Organization's Quality of Life Assessment.



Sample Size Power Calculation for the RCT and Randomization

A sample size of 84 patients with PTSD (42 in each group) could be adequate considering a difference between 2 independent proportions. To obtain the sample size, we fixed a probability of a type I error of .05 (level of significance), and the power of the test of 0.8 (probability of type II error of .2) for a bicaudal test. In addition, we considered an index of 0.6 (60%) of response for active treatment for PTSD, and a placebo effect of 0.3 (30%). We increased the number by 20% in anticipating dropouts (n=102) and we will use sequential randomization to prevent an imbalance between treatment groups for known factors (symptom severity, age, educational level, history of previous treatment) that influence prognosis or treatment responsiveness. The sequential randomization also prevents type I error and improves the power of the test for small trials (<400 patients).

We will randomize eligible patients to either interpersonal psychotherapy adapted for PTSD or sertraline using a method developed to balance prognostic factors in psychiatric clinical trials [66]. This method allows allocation into 2 homogenous groups. Randomization will be performed by an independent statistician who will generate an allocation sequence and will keep the assignment schedule in a separate computer. The following variables will be used: CAPS-5 total score, age, educational level, and whether there is history of prior psychological/psychiatric treatment.

Statistical Analyses Planned for the RCT

We will use a generalized estimating equation [67] to evaluate the effects of time and group randomization (ie, sertraline or interpersonal psychotherapy adapted for PTSD) on 4 different outcomes: CAPS-5 score, BDI, BAI, and CGI-I. Each patient in the RCT will receive 4 time-point longitudinal assessments. We will apply a first-order autoregressive effect working correlation to consider carryover effects of the PTSD symptoms across time [68]. The first-order autoregressive working correlation matrix will be used to deal with the within-subject effect, as it is expected that measurements taken further apart are less correlated than those taken closer together.

Patient attrition is commonly observed and expected in multiple time-point assessment clinical trials. To minimize the impact of patient dropout, an intention-to-treat analysis must be performed [69]. We will use 2 different techniques to deal with missing data when estimating time and group allocation, which are our main covariates of interest. The first technique will be a full-information maximum likelihood, which is the default estimator (maximum likelihood) to accommodate missingness when doing generalized estimating equation. This approach is important due to the long format of the data set and when (at least) baseline measures are available in the outcome. The second technique is a flexible approach to deal with missing data when implementing clinical trials [70]. It replaces missing data with one or more specific values, to allow statistical analysis that includes all participants and not just those who do not have any missing data. We will run all analyses using SPSS (version 24; IBM).

Ethics Approval and Consent to Participate

The clinical trial of this study was registered at Brazilian Clinical Trials Registry (registration number RBR-3z474z; registration date: March 24, 2015).

The Institutional Review Board of the UNIFESP approved the study protocol. Written informed consent will be obtained, following statement of compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards of the Review Board and granting agency.

Results

Data collection started in early 2016 and will be completed by the end of the first semester of 2020. Analyses will be performed soon afterward, followed by the elaboration of several articles. Articles will be submitted in early 2021.

Discussion

Sexual violence against women is a great concern to society and among health providers. It often leads to prolonged and severe mental health consequences such as PTSD. Most studies of the associations between PTSD and neuroprogression evaluate alterations in chronic patients, particularly older male veterans. More research is warranted to investigate the neurobiology of recent PTSD in women. With this thematic research project, we will investigate the occurrence of accelerated biological aging in our patients by assessing markers associated with aging through neuroimaging, genetics, neuropsychological testing, sleep disturbances, immune and inflammatory alterations, and how they relate to clinical outcomes and treatment response.

The main study strength is that it addresses important knowledge gaps in understanding the extent to which PTSD triggered by recent exposure to sexual assault affects neuroprogression in young women. To the best of our knowledge, this is the first thematic research to investigate accelerated aging as a consequence of sexual assault–related PTSD in women from a developing country. Sexual assault in Brazil has reached staggering numbers. Although there is a lack of studies to estimate more precisely the prevalence of sexual assault in the Brazilian population, previous evidence pointed to half a million women being sexually assaulted every year [71]. As sexual assault often leads to PTSD, and violence against women is on the rise in many countries, this is a global public health concern.

Another study strength is its investigation of the effectiveness of interpersonal psychotherapy adapted for PTSD, a non-exposure psychotherapy, in a sample of sexually assaulted Brazilian women. As successful treatment of PTSD can be challenging, we expect our contribution will deepen the discussion of treatment options through implementing an RCT contrasting sertraline with interpersonal psychotherapy adapted for PTSD. This is the first RCT to compare IPT to SSRI for PTSD. Following up our research patients will also permit to assess correlations between treatment response and neuroprogression measures.

The study has limitations. As published evidence on biological markers in the early stages of PTSD is lacking, we are unable

to calculate the sample size to power the eventual biomarker alterations found in our sample. Based on the previous literature on PTSD interventional studies, we can provide a sample size calculation for the RCT, but not for all investigations that will be conducted in the thematic research project. Furthermore, investigation of aging markers in the early stages of PTSD and in a relatively youthful patient sample may prove too early to be detectable. However, it is warranted to investigate whether PTSD following sexual assault may accelerate deterioration of biological health parameters in young women. Our approach may fuel further research to investigate initial biological alterations in patients with PTSD before evolution to chronicity that could be used as biomarkers in the near future. Another limitation is that social stigma may discourage women from seeking mental treatment following sexual assault. Accordingly, refusal to participate in the study may be high and impede achieving the hoped-for quantity of patients we aim to enroll. Another concern is the possible elevated attrition rates, a common problem in the treatment of PTSD. A high attrition rate could limit the performance of the RCT, and weaken the longitudinal analyses of neuroprogression in our sample and its associations with treatment response.

Acknowledgments

The authors thank the social workers, psychologists, and gynecologists of Hospital Pérola Byington for their enormous contribution to the development of this research. We gratefully acknowledge UNIFESP team members Cecilia Proença, Cecilia Zylberstajn, Bruna Nicoletta, Thauana Oliveira-Watanabe, Nina Valente, Luciana Porto, Thays Mello, Euthymia Prado, Rosaly Braga, Samara Hipolito Nitzsche, Flavia Strumpf, Roberta Constantino, Camila Matsuzaka, Nathalia Balloni, Fernanda Gomes, Tania Camargo, Paula Maria Serafim, Magda Bignotto, Vinicius Calsavara, and Fernando Rodrigues Grecco. We also thank Dr John Markowitz for his contribution to the design of the RCT. The research is sponsored by FAPESP grant number 2014/12559-5. Additional grant support comes from CNPq 303389/2016-8, CNPq 312464/2018-5, and FAPESP 2015/26473-8. This study is financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001. The funders had no role in study design or decision to publish this protocol article.

Conflicts of Interest

None declared.

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Abbreviations

ASSIST: Alcohol, Smoking and Substance Involvement Screening Test
AUDIT: Alcohol Use Disorders Identification Test
BAI: Beck Anxiety Inventory
BDI: Beck Depression Inventory
CAPS-5: The Clinician-Administered PTSD Scale for DSM-5
CGI-I: The Clinical Global Impression—Improvement Scale
CGI-S: The Clinical Global Impression—Severity Scale
CTQ: Childhood Trauma Questionnaire
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ESS: Epworth Sleepiness Scale
GEE: generalized estimating equation
HPB: Hospital Pérola Byington
ISI: Insomnia Severity Index
LEC-5: Life Event Checklist for DSM-5
LINE-1: long interspersed nuclear element 1
MFIS: Modified Fatigue Impact Scale
MINI: Mini International Neuropsychiatric Interview
MRI: magnetic resonance imaging
NSESSS-PTSD: National Stressful Events Survey Short Scale
PCL-5: PTSD Checklist for DSM-5
PDEQ: Peritraumatic Dissociative Experiences Questionnaire
PROVE-UNIFESP: Service for Research and Care on Violence and PTSD
PSQI: Pittsburgh Sleep Quality Index
PTSD: posttraumatic stress disorder
RAAS: The Revised Adult Attachment Scale
RCT: randomized clinical trial
REM: rapid eye movement

SDS: The Sheehan Disability Scale
SSRI: selective serotonin reuptake inhibitor
TIS: Tonic Immobility Scale
UNIFESP: Universidade Federal de São Paulo (Federal University of São Paulo)
WHOQOL-BREF: World Health Organization's Quality of Life Assessment

Edited by G Eysenbach; submitted 07.04.20; peer-reviewed by S Mukherjee, B Smith; comments to author 29.06.20; revised version received 20.08.20; accepted 20.10.20; published 18.11.20.

Please cite as:
Coimbra BM, Yeh M, D'Elia AT, Maciel MR, Carvalho CM, Milani AC, Mozzambani A, Juruena M, Belangero SI, Jackowski AP, Poyares D, Mello AF, Mello MF
Posttraumatic Stress Disorder and Neuroprogression in Women Following Sexual Assault: Protocol for a Randomized Clinical Trial Evaluating Allostatic Load and Aging Process Acceleration
JMIR Res Protoc 2020;9(11):e19162
URL: http://www.researchprotocols.org/2020/11/e19162/
doi:10.2196/19162
PMID:33206061

Protocol

Mass Drug Administration With High-Dose Ivermectin and Dihydroartemisinin-Piperaquine for Malaria Elimination in an Area of Low Transmission With High Coverage of Malaria Control Interventions: Protocol for the MASSIV Cluster Randomized Clinical Trial

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Abstract

Background: With a decline in malaria burden, innovative interventions and tools are required to reduce malaria transmission further. Mass drug administration (MDA) of artemisinin-based combination therapy (ACT) has been identified as a potential tool to further reduce malaria transmission, where coverage of vector control interventions is already high. However, the impact is limited in time. Combining an ACT with an endectocide treatment that is able to reduce vector survival, such as ivermectin (IVM), could increase the impact of MDA and offer a new tool to reduce malaria transmission.

Objective: The study objective is to evaluate the impact of MDA with IVM plus dihydroartemisinin-piperaquine (DP) on malaria transmission in an area with high coverage of malaria control interventions.

Methods: The study is a cluster randomized trial in the Upper River Region of The Gambia and included 32 villages (16 control and 16 intervention). A buffer zone of ~2 km was created around all intervention clusters. MDA with IVM plus DP was implemented in all intervention villages and the buffer zones; control villages received standard malaria interventions according to the Gambian National Malaria Control Program plans.

Results: The MDA campaigns were carried out from August to October 2018 for the first year and from July to September 2019 for the second year. Statistical analysis will commence once the database is completed, cleaned, and locked.

Conclusions: This is the first cluster randomized clinical trial of MDA with IVM plus DP. The results will provide evidence on the impact of MDA with IVM plus DP on malaria transmission.

Trial Registration: ClinicalTrials.gov NCT03576313; https://clinicaltrials.gov/ct2/show/NCT03576313

International Registered Report Identifier (IRRID): DERR1-10.2196/20904

(JMIR Res Protoc 2020;9(11):e20904) doi:10.2196/20904

KEYWORDS

ivermectin; dihydroartemisinin-piperaquine; mass drug administration; malaria; cluster randomized trial; The Gambia

Introduction

Between 2000 and 2015, the burden of malaria decreased substantially in sub-Saharan Africa following the scale-up of insecticide-treated bed nets (ITNs), indoor residual spraying (IRS), and artemisinin-based combination therapy [1,2]. In The Gambia, between 2003 and 2007, the proportion of blood slides positive for malaria decreased by 74%, and hospital admissions for malaria by 81% [3,4]. Nevertheless, despite the high coverage of control interventions, malaria transmission has become increasingly heterogeneous [5-7]. Innovative interventions and tools to further reduce transmission and eliminate malaria are needed.

Mass drug administration (MDA), a full antimalarial treatment to all inhabitants of target communities regardless of their infection status, has been identified as a potential tool to further reduce transmission where coverage of vector control interventions is already high [8,9]. MDA with artemisinin-based combination therapy (ACT) reduces transmission by clearing asexual infections and early-stage gametocytes in asymptomatic, infected individuals [8,9]. Dihydroartemisinin-piperaquine (DP), thanks to its simple dosing schedule, long posttreatment prophylaxis period, good safety profile [10,11], and the fact that it is not used as a first-line antimalarial treatment in The Gambia, is a promising candidate for MDA. However, the effect of MDA with ACT on malaria is limited over time [12,13]. This limited impact is largely attributed to incomplete coverage and the persistence of malaria parasites in the mosquito population, with a smaller contribution to residual transmission of gametocytes remaining after ACT administration [14].

Combining an antimalarial treatment (DP) with an endectocide treatment able to reduce vector survival, ivermectin (IVM), could increase the impact of MDA and offer a new tool to reduce malaria transmission [15,16]. IVM is a broad-spectrum antiparasitic endectocidal drug, active against a wide range of parasites, including ectoparasites [17]. It reduces the lifespan of mosquitoes that feed on treated individuals [16], with conflicting data on a possible effect on parasite development in surviving mosquitoes [18-20]. A major advantage of IVM is that, since malaria vectors feed on more than one person, the effective coverage may exceed MDA coverage, especially if its mosquitocidal effect can be extended by repeated treatments. Repeated IVM dosing increases the duration of time that IVM concentration remains above the lethal concentration that kills 50% of mosquitoes [17]. A 3-day regimen of IVM 300 µg/kg is safe and has a mosquitocidal effect for *Anopheles gambiae s.s.* lasting approximately 28 days post treatment [16].

The community administration of IVM could reduce malaria transmission [19,21], providing a synergistic effect compared to MDA with ACTs alone [15]. Furthermore, IVM can reduce the prevalence of other parasitic infections, including ectoparasites and soil-transmitted helminths, which could be an important additional benefit and improve the cost-effectiveness of this intervention.

The mass drug administration of ivermectin and dihydroartemisinin-piperaquine as an additional intervention for malaria elimination (MASSIV) study is a cluster randomized trial that aims to evaluate the impact of MDA with IVM plus DP on malaria transmission in an area with high coverage of malaria control interventions, eg, ITNs, IRS, and seasonal chemoprevention (SMC). The trial was implemented in Basse, Upper River Region (URR) in The Gambia.

Study Objectives

Clinical

The clinical objective is to determine whether three monthly rounds of MDA with IVM plus DP implemented over two malaria transmission seasons will reduce malaria transmission in communities with high coverage of malaria control interventions.

Entomological

The entomological aim is to determine whether three monthly rounds of MDA with IVM plus DP implemented over two malaria transmission seasons will reduce vector parity, a proxy for vector survival, in communities with high coverage of malaria control interventions.

Social Science and Health Economics

The social science and health economics aims are to (1) identify the most socially acceptable and sustainable way of achieving and maintaining high coverage of MDA with IVM plus DP, and (2) determine the costs and cost-effectiveness of this intervention compared to standard malaria control measures.

Methods

Study Design

The study is a cluster randomized trial (ClinicalTrials.gov, NCT03576313) that included a total of 32 villages (16 control

and 16 intervention), located at least 3 km from each other. A buffer zone of ~2 km was created around all intervention clusters in a modified fried-egg design [22]. No buffer zone was created around control villages. MDA with IVM plus DP was implemented in all intervention villages and the buffer zones; control villages received standard malaria interventions according to the Gambian National Malaria Control Program's (NMCP) plans.

Study Setting

The study was conducted in the eastern part of The Gambia in the Upper River Region (URR). The region is open Sudanese savanna and covers an area of 1995 km^2 [23]. Most of the residents are subsistence farmers. The climate is characterized by a long dry season from mid-October to mid-June, followed by a single short rainy season. Malaria transmission is highly seasonal, with most malaria cases occurring during the rainy season and immediately afterward, until December-January [23,24]. Malaria transmission has decreased substantially in The Gambia; however, it is higher in URR than in other regions [24]. The URR is also characterized by low vector density and high vector parity rate, indicating high vector survival, suggesting the existence of populations (or subpopulations) of mosquitoes able to escape standard vector control interventions [24].

Selection of Villages and Informed Consent

A cross-sectional survey was carried out in November 2017, at the peak of malaria transmission, in 47 medium-sized (200-600 inhabitants) villages to select study villages with a baseline malaria prevalence of at least 10%. Following the survey, 32 villages with malaria prevalence determined by qPCR of at least 10% were included in the trial and randomly assigned to either the intervention or control arm using STATA, version 15; randomization was constrained such that the mean baseline prevalence in the intervention clusters was within ±10% of the prevalence in the control clusters.

After explaining the study objective and methods of the trial to the local authorities and the populations of the study villages through sensitization meetings in the local language, a census of the study population was carried out in November 2017. This was followed by individual consent procedures to obtain written informed consent for all willing residents in the study villages. Consent for children was provided by their parents/guardians; assent was sought for adolescents 12-17 years old.

Consent and enrolment procedures were carried out throughout the trial to obtain written informed consent from new residents and individuals missed previously by the research team due to absence at the time of the initial consenting and enrolment procedures.

A list of all residents in the study villages, by compound, including consent status, were generated and made available to the study team.

Eligibility Criteria

The target population for MDA was all eligible individual residents in the intervention villages. During each MDA round, residents were (re)assessed for eligibility to receive IVM and DP. Participants had to meet all inclusion criteria and none of the exclusion criteria. Inclusion criteria were: (1) age/anthropometry, for IVM: weight ≥15 kg; for DP: age >6 months, (2) willingness to comply with trial procedures, and (3) individual written informed consent. The exclusion criteria for both IVM and DP were known chronic illnesses such as HIV, tuberculosis, hepatitis, and severe malnutrition. Additionally, for IVM only, exclusion criteria were (1) pregnancy (any trimester) or breastfeeding, (2) hypersensitivity to IVM, and (3) travel to *Loa loa* endemic countries (Central Africa); for DP, these were: (1) first-trimester pregnancy, (2) hypersensitivity to DP, and (3) taking drugs that influence cardiac function or prolong QTc interval.

Trial Medication and Intervention

DP (Guilin Pharmaceuticals, China) was available as tablets of 320/40 mg and 160/20 mg piperaquine/dihydroartemisinin per tablet. DP was administered orally, once daily for three days, according to body weight per manufacturer's guidelines. For participants unable to swallow the tablets, such as infants and young children, DP was crushed and mixed with water. The mixture was used immediately after preparation. If a participant vomited within 30 minutes of taking DP, the full dose was readministered; if a patient vomited within 30-60 minutes, half the dose was readministered. IVM (Laboratorio Elea SACIF y A, Argentina) was available as 6 mg tablets. It was given at 300-400 µg/kg/day once daily for three days (15.0-25.9 kg one tablet, 26.0-40.9 kg two tablets, 41.0-60.9 kg 3 tablets, 61.0-80.9 kg four tablets, 81.0-95.9 kg five tablets, ≥96 kg 6 tablets). Therefore, the total dose of IVM for each round was 900-1200 µg/kg. Before treatment, women of reproductive age (15-49 years) were asked to provide a urine sample to test for pregnancy. All treatments were supervised.

MDA was implemented each year and for two consecutive transmission seasons as three-monthly rounds starting from July (end of the dry season) to August and September (rainy season). The choice of implementing the intervention for two consecutive years was taken to estimate its cumulative effect and to monitor community participation over repeated intervention rounds.

Standard malaria control interventions were implemented in both intervention and control villages. These consisted of ITNs, IRS with pirimiphos-methyl (Actellic 300CS) done in mid-July 2019, just before the first MDA round of IVM and DP, prompt diagnosis and treatment with artemether-lumefantrine, SMC, and intermittent preventive treatment during pregnancy (IPTp). During the three rounds of MDA, SMC was not administered to children in the intervention villages eligible for MDA with IVM plus DP to avoid double antimalarial treatment. In these villages and during the MDA period, only children aged 3-6 months received SMC as they were not eligible for DP treatment. Nevertheless, all children aged 3-59 months received SMC one month after completing the last MDA round in intervention villages. The implementation of these malaria control interventions was done by the Regional Health Team and documented at the level of individual participants. Eligible children in control villages received SMC as planned by the NMCP.

Outcome Measures

Clinical

The primary clinical endpoint was the prevalence of malaria infection measured by qPCR in all age groups [25] via a yearly cross-sectional survey at the peak of the transmission season in November.

Secondary endpoints included (1) incidence of clinical malaria estimated by passive case detection by recording all clinical cases from study villages (both intervention and control) attending the local health facilities or the community health worker when present; (2) prevalence of drug-resistant markers such as Pfcrt and Pfmdr-1 mutations [26], in malaria-positive blood samples collected during the annual cross-sectional survey; (3) serological markers of recent malaria infection and recent Anopheles exposure, both determined by detecting relevant antibody responses in blood samples collected during the annual cross-sectional survey; (4) intervention coverage as the proportion of eligible individuals having taken the investigational products.

Tertiary endpoints were the prevalence of bedbugs, headlice, scabies, and soil-transmitted helminths. Surveys were done yearly, before and after the MDA campaign.

Entomological

The primary entomological endpoint was the parous rate of *An. gambiaes.l.* females in each study group, determined on extracted ovaries [27]. The secondary endpoint was the duration of the IVM mosquitocidal effect, determined by the mortality of insectary colonized *An. coluzzii* after feeding on IVM-treated individuals on days 7, 14, and 21 post treatment. *An. coluzzii* mortality was recorded over 14 days after feeding.

Social Sciences and Economics

The economics and social sciences endpoints included: (1) MDA participation and acceptability, and (2) MDA costs and cost-effectiveness. For participation and acceptability, quantitative and qualitative research methods were used. For the former, in each intervention village, a cross-sectional survey was conducted between MDA years 1 and 2. For qualitative methods, in-depth interviews and focus group discussions with MDA participants, MDA decliners, village leaders, MDA field staff, and others were carried out throughout all trial activities. Information on the costs of malaria episodes to households and their management and the intervention costs was collected to estimate costs and cost-effectiveness. From these, the incremental cost-effectiveness ratio of the intervention versus control was calculated as costs per malaria-related DALY averted. Moreover, policy considerations around translating and scaling up the intervention were explored.

Statistical Considerations

The sample size was based on two primary endpoints: malaria prevalence determined by qPCR at the peak of the malaria transmission season and the vector population's parous rate. For malaria prevalence, we assumed the mean malaria prevalence in the control arm at peak transmission would be 15%; this is a conservative assumption, as, in November 2013, the prevalence in villages in eastern Gambia varied between 21.3% and 44.3% [24]. Based on an initial prevalence of 15% and assuming 95%, 86%, and 63% of eligible individuals receive 1, 2, or 3 courses of DP+IVM each year, prevalence would decrease by >90% assuming "ideal conditions" such as the absence of population movement, perfect adherence and no cluster spillover effects (human/vector movement from control to intervention clusters). However, such factors may influence the effect size of the intervention. Therefore, we used a more conservative effect size of 50% or prevalence from 15% to 7.5%. Assuming a conservative coefficient of variation of 0.5, 16 clusters per arm, 200 individuals per cluster recruited in the yearly cross-sectional survey, would have 90% power to detect a significant difference between study arms.

For the vector parous rate, the assumption was that the parous rate of *An. gambiae s.l.* would be 85% because, in 2013, it was 90.7% and 81.1% in the North Bank and South Bank of the URR, respectively [24]. Therefore, assuming the intervention would decrease parity from 85% to 75%, and a coefficient of variation of 0.25, dissecting 50 *An. gambiae s.l* per village would have 90% power to find a significant difference between arms.

Randomization and Blinding

The unit of randomization was the village. Randomization to the intervention or the control arm was done by computer-based randomization. To prevent imbalance for potential confounding factors, restricted randomization to balance the arms on factors such as baseline prevalence, ITN coverage, and distance from health facilities was used [22].

Considering the nature of the trial (cluster randomized), the primary endpoint (malaria prevalence), and the logistical and ethical (treating thousands of individuals with placebo) challenges, we chose not to blind participating individuals. All laboratory staff involved in processing samples and evaluations contributing to any clinical or entomological endpoints were blinded to the allocation arm.

Study Procedures and Evaluations

Clinical Evaluation

Passive case detection was established at local health facilities and the village level if community health workers were present. All suspected malaria cases, such as patients with fever or history of fever in the last 24 h without any other apparent illness, were investigated with an RDT (SD BIOLINE Malaria Ag Pf Standard Diagnostics); if positive, the patient was treated with artemether-lumefantrine, the first-line treatment in The Gambia. Axillary body temperature was measured using an electronic thermometer; a blood slide and blood spots were collected for later molecular analysis. Randomly selected individuals, regardless of temperature or history of symptoms, were included in the cross-sectional surveys to collect blood samples by finger prick and administer a short questionnaire on demographic characteristics, area of residence, recent travel history, and use of malaria control interventions and recent history of clinical malaria.

A cross-sectional survey to estimate the prevalence of ectoparasites, scabies, and helminths was carried out. In each cluster, 30 children aged 4-13 years, the age group at highest

risk of these infections, were selected. Bedbugs were detected by visual inspection of the child's bed using torchlight, and headlice were detected by visual search of the scalp. Scabies was identified by a complete physical examination of the body. A stool sample was taken to identify the presence of helminths, including *Strongyloides stercoralis*, *Trichuris trichiura*, *Necator americanus*, *Ancylostoma duodenale*, and *Ascaris lumbricoides* using PCR.

Entomological Evaluations

Both intensive and routine entomological surveys were performed. Intensive surveys were carried out 7-14 days after each MDA in all the intervention villages and for a similar period in 8 control villages randomly selected at the beginning of the study. The same control villages were sampled throughout the transmission season. Collections were carried out over three consecutive nights in six randomly selected houses. Monthly human landing catches (indoor and outdoor) were carried out in three houses for two nights (6 nights/month) to determine the landing rate, parity rate, sporozoite rate, and the entomological inoculation rate, and their potential reduction by IVM. Four collectors rotated between indoor and outdoor sites every 2 hours, from 7:00 pm to 7:00 am, in four selected villages per study arm. Routine surveys were carried out monthly, after the intensive surveys, between October and December, in all intervention and control villages using CDC light traps. [28]. In each village, six trapping nights/month with six indoor CDC light traps were positioned 1 m above the ground at the foot end of the bed (1 per house and protected by ITN) to obtain estimates of vector density, parity, and sporozoite rates. Parity was determined by dissecting 60 unfed *An. gambiae s.l.* (10 per trap per village) in droplets of phosphate-buffered saline (PBS) and read with a microscope at 10× field magnification. Sporozoite rate was determined by ELISA on the head and thorax of *An. gambiae s.l.*

To monitor the duration of the IVM mosquitocidal effect and potential host characteristics associated with lower efficacy, 40 randomly selected adults and 40 randomly selected children (2-10 years old) were recruited in one intervention and one control village near Basse field station, which has an insectary. Children were included in this component of the study because linear dosing based on total body weight may not achieve similar drug exposure in children as in adults, possibly a consequence of age-related changes in gastrointestinal motility, pH, or prehepatic expression of metabolic enzymes or transporters, resulting in increased absorptive capacity with age [29,30]. Only IVM-treated individuals were selected in intervention villages; all selected participants were asked to provide additional written informed consent. A 3-mL blood sample was collected at 7, 14, and 21 days post MDA. This blood sample was placed in a glass membrane feeding system and 2 cups (250 ml, covered at the top with netting), each containing 50 insectary-reared *An. gambiae s.s.* mosquitoes, were presented to the membrane feeder for 20 minutes [31]. The number of mosquitoes with an engorged abdomen was counted and those with unfilled/partially filled abdomens discarded. Mosquito survival was monitored daily until 14 days post feeding. To further understand heterogeneity in mosquito mortality, participants across different age groups, gender, and varying body mass index (BMI) were selected for these membrane feeding assays. Membrane feeding assays were performed using insectary-reared *An. coluzzii* at different age ranges.

Social Sciences Evaluations

A mixed-methods social science study was carried out prior to and throughout the trial. This study used ethnographic, qualitative, and quantitative methods to assess MDA coverage, potential bottlenecks to implementation, adherence, and acceptability among potential MDA participants. Before the initial MDA campaign, potential bottlenecks for the intervention were assessed, and recommendations were made to improve implementation in the first phase. These data helped fine-tune the intervention to local realities and engaged stakeholders to assure participation and long-term sustainability. In the second phase, exploratory research was conducted in all intervention and control villages to assess the MDA's socio-cultural effects. Methods included observations of all trial components, in-depth and key-informant interviews, and focus group discussions. These methods were carried out in both the first and second years of the MDA. A quantitative household survey was conducted between years to assess findings from the first intervention year in more detail; these findings were then explored by additional qualitative and ethnographic work, including surveys, interviews, and focus group discussions in the second year.

Laboratory Evaluations

A finger prick blood sample was collected from all selected individuals; 40-50 µL (3 droplets) were blotted onto Whatman 3 MM filter paper and stored with a desiccant at 4°C. For the molecular detection of *P. falciparum* parasitemia, three 6-mm punches of dried blood spot, each representing approximately 8 µL blood, were added to a 96-deep well plate and used for DNA extraction. Extracted DNA was analyzed with varATS qPCR using 5 µL of extracted DNA per assay [24]. All qPCR output was analyzed using the BioRad CFX Manager software. Each plate contains two rows of *P. falciparum* standard dilution, used to make the quantification curve and allow quality control. For the serological analysis, serum was eluted from one 6-mm punch (~4 µL serum) from the filter paper. This punch was eluted in 200 µL PBS/azide to have one 1:50 predilution from which 10 µL were used on the Luminex plate. As controls for the immunoassay, BSA-coupled beads, a pool of negative sera (malaria naïve European sera), and positive sera (highly exposed Gambian sera from previous surveys) were added to each plate. Plates were analyzed and read using the MAGPIX [32]. Results were presented as the median fluorescence intensity.

Data Capture, Management, and Analysis

Data for each participant were captured on electronic case report forms. Informed consent, demography, medical history, physical examination, vital signs, drug administration, adherence to study drugs, adverse events including serious adverse events, and laboratory evaluations were recorded.

All trial data were stored and managed within the REDCap trial database system, an application specifically designed to collect and store clinical trial data and customized for electronic data capture at the trial site. Analytical results for samples from the

prevalence surveys were linked to the main trial database. When inconsistencies were found, these were checked against the original forms and subsequently amended in the dataset. All staff involved in the trial was trained on their specific tasks.

Statistical Analysis

The primary clinical endpoint, malaria prevalence at the end of the second transmission season, will be compared between arms using random-effects logistic regression, and a random effect for study village will be included to account for clustering. An odds ratio, 95% CI, and *P* value will be presented. Malaria prevalence at the end of the first transmission season will be analyzed separately and in the same way.

The primary entomological endpoint, vector parity, will be compared between arms using random-effects logistic regression, and a random effect for study village will be included to account for clustering. A fixed effect for study month and year will be included. An odds ratio, 95% CI, and *P* value will be presented. Incidence will be compared between arms using random-effects Poisson regression, and a random effect for study village will be included to account for clustering. An offset for village population and a fixed effect for the study year will be included. A rate ratio, 95% CI, and *P* value will be presented. Mosquito mortality, a secondary entomological endpoint, will be determined by Kaplan-Meier estimates. Kaplan-Meier plots of mosquito survival will be presented for each age group and timepoint. A comparison between the arms will be made using survival analysis with an exponential survival model. A random effect (shared frailty) will be included for each human participant to account for correlated outcomes on mosquitoes fed on the same participant.

Other entomological endpoints: (1) Mosquito density will be compared between arms using random-effects negative binomial regression, and a random effect for study village will be included to account for clustering. A fixed effect for study month and year will be included. An odds ratio, 95% CI, and *P* value will be presented; (2) Sporozoite rates in field-caught mosquitoes will be compared between arms using random-effects logistic regression, and a random effect for study village will be included to account for clustering. A fixed effect for study month and year will be included. An odds ratio, 95% CI, and *P* value will be presented.

Quality Management

An independent data and safety monitoring board (DSMB) was appointed to advise the sponsor and investigators on the trial's safety issues. Study physicians and nurses were trained to monitor and report all adverse events, including serious adverse events associated with treatment. Before each dose, adverse events that occurred were systematically documented by medical terms, start and end date, severity and seriousness, relation to the study drug, and outcome. The relationship to the study drugs was determined based on temporal association and clinical judgment. The study nurses visited each household in intervention villages 7 days after starting treatment to monitor and document any adverse events in the study population. Serious adverse events were reported to the DSMB, the local ethics committee, and the London School of Hygiene and Tropical Medicine (LSHTM) Ethics Committee. Analysis of adverse events was restricted to the intervention arm because the study population in the control arm was not treated with the investigational products.

Ethical Approval

The protocol, informed consent documents, and patient information sheets have been reviewed and approved by The Gambia Government/MRC Joint Ethics Committee (ref number: 1593) and the London School of Hygiene and Tropical Medicine Ethics Committee (ref number: 15823).

Results

The MDA campaigns were carried out from August to October 2018 for the first year and from July to September 2019 for the second year. Statistical analysis will commence once the database is completed, cleaned, and locked.

Discussion

Principal Findings

IVM is a promising tool to complement the current effort to interrupt malaria transmission. It targets malaria vectors regardless of biting behavior (it kills exophagic and exophilic mosquitoes, including early biting vectors) and reduces vectorial capacity [15,33]. Research has shown that IVM is a potentially valuable addition to the existing tools to decrease malaria transmission [15,16,18,33,34]. Modeling showed that three monthly rounds of MDA with IVM at 300 µg/kg/day daily for three days with 70% coverage would reduce clinical incidence by 70% and prevalence by 34% in a highly seasonal moderate transmission setting [15]. The magnitude of the impact is predicted to be higher for MDA of IVM plus DP, resulting in a reduction of clinical incidence by 75% and prevalence by 64% [15]. Nevertheless, this trial compares MDA of IVM plus DP to standard malaria control interventions and cannot distinguish the IVM effect from the DP effect. The proposed trial will evaluate the impact of MDA with IVM plus DP.

Cluster randomized trials are the gold standard design to assess the community-level effect of an intervention [22]. Key considerations for the design are cluster size, spatial separation, and movement of individuals between intervention and control clusters [35,36]. Individual movement could lead to contamination or spillover, which would affect the interpretation of the intervention's efficacy [35]. We have defined a buffer zone around intervention clusters to reduce the spillover effect and ensure that intervention and control clusters are spatially well separated. The intervention (MDA with IVM plus DP) was carried out in intervention clusters and buffer zones to minimize contamination of the intervention villages. The entomological endpoint was one of the trial's primary objectives, and buffer zones were created to minimize contamination of intervention villages by vectors from control villages.

Measuring and detecting changes in malaria transmission requires appropriate metrics to assess the community-wide impact of an intervention [37]. Several metrics measuring different facets of malaria transmission have been proposed,

including entomological inoculation rate, slide positivity rate, parasite prevalence, disease incidence, sporozoite rate, vectorial capacity, and serological markers of mosquito and malaria exposure [37-39]. All these metrics have intrinsic limitations to their precision and accuracy [38]. Nevertheless, parasite prevalence is a suitable direct estimate of malaria infection in low transmission settings [37,38].

Parasite prevalence, the metric designed to measure the proportion of individuals found with parasites in their blood, varies by the methods used [37], including microscopy, RDT, and PCR [37,39]. Microscopy and RDTs may miss infections of low parasite density that represent a large proportion of infections in a low-transmission setting. Parasite prevalence at the peak of the transmission season and determined by PCR can provide an accurate estimate of the community's parasite reservoir and the effect of the intervention [38,40]. This trial's primary endpoint is parasite prevalence by PCR in all age groups through a community-based random sampling survey at the peak of the transmission season.

Successful MDA campaigns require high coverage and good compliance [41]. Understanding the local context and attitudes within the trial communities, including the communities' acceptability of the intervention, is key to achieving the necessary coverage and compliance to meet the desired clinical and epidemiological results. For example, healthy individuals, some of whom may be malaria-infected but asymptomatic, may not be ready to accept medications for a disease they are currently not affected by, and this could negatively impact trial coverage. Engaging communities to establish the most effective, ethical, and sustainable ways to implement these community-targeted interventions is vital. Therefore, community acceptance was assessed using a mixed-method design. During and after each round of MDA, acceptability was evaluated, and the findings informed the implementation of subsequent rounds.

To our knowledge, this is the first cluster randomized trial with a 3-day regimen of 300 µg/kg IVM (high-dose regimen). Strengths of the study include its design as an adequately powered cluster randomized trial, the setting in an area with high coverage of ITNs, IRS, and SMC, and where there is prompt and effective treatment with ACTs. Another major strength is the provision of safety data for the high dose IVM administered with DP. The trial is limited by its inability to determine the impact of IVM alone as this treatment is administered with DP, and there is no DP-only arm.

Conclusion

This study will be the first cluster randomized clinical trial of MDA with IVM plus DP. The results will provide evidence on the effect of MDA with IVM plus DP on malaria transmission.

Acknowledgments

We acknowledge the contribution of Thomas Mendy (data management) and Abdoulie Sillah (project management). Thanks to Guilin Pharmaceuticals for donating the dihydroartemisinin-piperaquine and to Elea Laboratories for providing ivermectin.

The trial is jointly funded under the Joint Global Health Trials Scheme by the Medical Research Council (United Kingdom), the Department for International Development (DFID), and the Wellcome Trust. The funding institutions have not had nor will have any role in the study's design, the collection, analysis, and interpretation of data, or writing the manuscript.

Authors' Contributions

UDA and JA conceived the study. EDD drafted the manuscript. KPG, JMR, AEF, CNS, HB, and CK designed the social science, health economics, and ectoparasite study work plans. HMS supervised the entomological work package. JB provided statistical expertise. UDA, JA, EDD, HS, SWL, BC, FC, JB, CK, HMB, BK, AEF, CNS, JMR, KPG, MRS, CD, and TB contributed to the refinement of the study protocol and approved the final version. All authors read and approved the final manuscript before submission.

Conflicts of Interest

None declared.

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Abbreviations

ACT: artemisinin-based combination therapy
CDC: Centers for Disease Control and Prevention
DP: dihydroartemisinin-piperaquine
DSMB: data and safety monitoring board

IPTp: intermittent preventive treatment during pregnancy
IRS: indoor residual spraying
ITN: insecticide-treated net
IVM: ivermectin
LSHTM: London School of Hygiene and Tropical Medicine
MDA: mass drug administration
PBS: phosphate-buffered saline
PCR: polymerase chain reaction
qPCR: quantitative polymerase chain reaction
QTc: rate corrected QT interval on an electrocardiogram
RDT: rapid diagnostic test
SMC: seasonal chemoprevention
URR: upper river region
varATS: var Gene acidic terminal sequence

Edited by G Eysenbach; submitted 03.06.20; peer-reviewed by F Brian, K Kobylinsky; comments to author 07.07.20; revised version received 28.07.20; accepted 03.08.20; published 19.11.20.

Please cite as:
Dabira ED, Soumare HM, Lindsay SW, Conteh B, Ceesay F, Bradley J, Kositz C, Broekhuizen H, Kandeh B, Fehr AE, Nieto-Sanchez C, Ribera JM, Peeters Grietens K, Smit MR, Drakeley C, Bousema T, Achan J, D'Alessandro U
Mass Drug Administration With High-Dose Ivermectin and Dihydroartemisinin-Piperaquine for Malaria Elimination in an Area of Low Transmission With High Coverage of Malaria Control Interventions: Protocol for the MASSIV Cluster Randomized Clinical Trial
JMIR Res Protoc 2020;9(11):e20904
URL: https://www.researchprotocols.org/2020/11/e20904
doi:10.2196/20904
PMID:33211022

Protocol

Integrating a Mobile Health Device Into a Community Youth Mental Health Team to Manage Severe Mental Illness: Protocol for a Randomized Controlled Trial

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Abstract

Background: Symptoms of mental illness are often triggered by stress, and individuals with mental illness are sensitive to these effects. The development of mobile health (mHealth) devices allows continuous recording of biometrics associated with activity, sleep, and arousal. Deviations in these measures could indicate a stressed state requiring early intervention. This paper describes a protocol for integrating an mHealth device into a community mental health team to enhance management of severe mental illness in young adults.

Objective: The aim of this study is to examine (1) whether an mHealth device integrated into a community mental health team can improve outcomes for young adults with severe mental illness and (2) whether the device detects periods of mental health versus deterioration.

Methods: This study examines whether physiological information from an mHealth device prevents mental deterioration when shared with the participant and clinical team versus with the participant alone. A randomized controlled trial (RCT) will allocate 126 young adults from community mental health services for 6 months to standard case management combined with an integrated mHealth device (ie, physiological information is viewed by both participant and case manager: unWIRED intervention) or an unintegrated mHealth device (ie, participant alone self-monitors: control). Participants will wear the Empatica Embrace2 device, which continuously records electrodermal activity and actigraphy (ie, rest and activity). The study also examines whether the Embrace2 can detect periods of mental health versus deterioration. A variety of measurements will be taken, including physiological data from the Embrace2; participant and case manager self-report regarding symptoms, functioning, and quality of life; chart reviews; and ecological momentary assessments of stress in real time. Changes in each participant's Clinical Global Impression Scale scores will be assessed by blinded raters as the primary outcome. In addition, participants and case managers will provide qualitative data regarding their experience with the integrated mHealth device, which will be thematically analyzed.

Results: The study has received ethical approval from the Western Sydney Local Health District Human Research Ethics Committee. It is due to start in October 2020 and conclude in October 2022.

Conclusions: The RCT will provide insight as to whether an integrated mHealth device enables case managers and participants to pre-emptively manage early warning signs and prevent relapse. We anticipate that unWIRED will enhance early intervention by improving detection of stress and allowing case managers and patients to better engage and respond to symptoms.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12620000642987; https://www.anzctr.org.au/ACTRN12620000642987.aspx

International Registered Report Identifier (IRRID): PRR1-10.2196/19510

(JMIR Res Protoc 2020;9(11):e19510) doi:10.2196/19510

KEYWORDS

electrodermal activity; anxiety; psychosis; mHealth device; actigraphy

Introduction

Overview

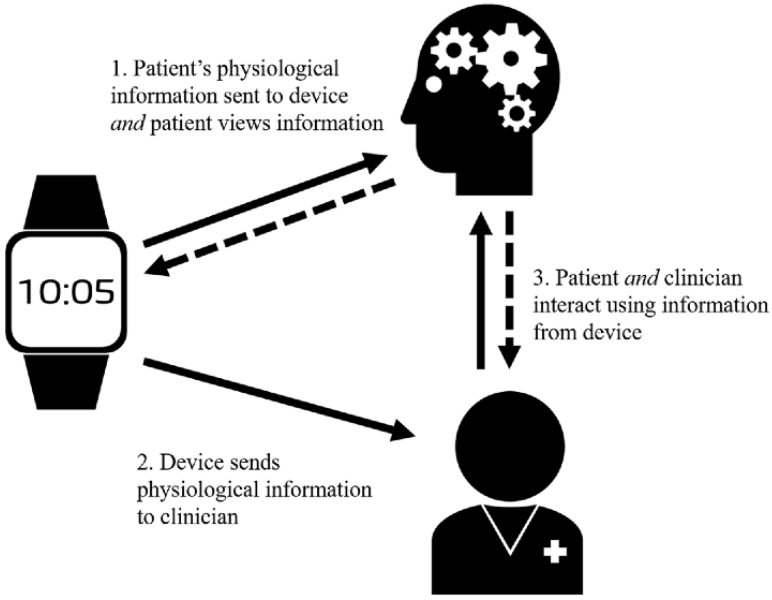
Severe mental illnesses, such as schizophrenia, bipolar disorder, and borderline personality disorder are associated with considerable burden and have their peak onset during early adulthood [1,2]. These disorders are highly disruptive in terms of functioning, impairing a young adult's ability to maintain close relationships, educate themselves, and find employment [1,3]. For example, youths at risk of psychotic illnesses often experience significant functional decline alongside the onset of symptoms [4,5]. The extent to which a mental illness prevents functioning is often the threshold for a psychiatric diagnosis [6,7]. Severe mental illness is also associated with high levels of distress and high rates of suicide compared to the general population [8]. While there is typically no cure for severe mental illness, symptoms can be managed in the community with combinations of medications and/or psychosocial treatments [9,10]. Effective case management requires collaboration between patient and clinician, as well as rapid identification and treatment of early warning signs [3,11]. Yet case management faces several challenges, including patients having limited insight into emerging symptoms and case managers not being able to respond promptly [3,9]. Even small delays prior to intervention could mean the difference between a minor relapse and a lengthy hospitalization.

A potential means to enhance early intervention and engagement is through the use of an inexpensive mobile health (mHealth) device that measures physiological indicators of stress and returns this information to patients and case managers. Across the spectrum of mental disorders, elevated stress levels are known to increase risk of relapse. The body and mind have systems that maintain a homeostatic state and these can be disrupted by acute or chronic stress [12,13]. For example, stress can impact upon the autonomic nervous system and circadian rhythms, causing changes in arousal and sleep patterns, respectively. While small amounts of stress can be beneficial, acute or prolonged stress is harmful, and individuals with mental illness are particularly sensitive to these effects. An mHealth device can be worn like a wristwatch that can reliably and continuously measure physiological signs of stress. For example, mHealth devices can measure arousal through electrodermal activity (EDA). An mHealth device can also measure actigraphy, which is a noninvasive method of monitoring human rest and activity cycles [14]. A small actigraphy unit has an accelerometer that measures gross motor activity across three axes. These measurements can be converted into variables of interest, such as step counts and periods of rest. Changes in these measures may indicate an individual is experiencing a level of stress that could be harmful. For example, a combination of high arousal and poor sleep suggests a stress response associated with greater risk of relapse. Less activity could be associated with a depressive state and greater levels could be associated with a manic state [15]. Physiological data from an mHealth device can also be combined with other related variables to predict relapse [15,16]. For example, an ecological momentary assessment (EMA) [17] involves taking subjective measurements of an individual's current mental state, which can be used in conjunction with physiological data from an mHealth device.

mHealth devices have been used effectively for managing and monitoring physical conditions such as cardiovascular disorders, diabetes, and obesity [18]. More recently, continuous data from an mHealth device has shown promise in predicting signs of stress and mental deterioration. For example, Sano and colleagues [19] examined whether physiological and behavioral measures collected by wearable sensors and mobile phones could predict stress and poor mental health in a large student sample (N=201). They used machine learning, a subfield of artificial intelligence, to analyze the multimodal data. The mHealth devices classified students into high- or low-stress groups 78.3% of the time and as experiencing high or low mental health 87% of the time. Cella and colleagues [20] used an mHealth device to compare heart rate, EDA, and movement for 30 participants with schizophrenia in the community and 25 controls. Compared to controls, participants with schizophrenia showed lower heart rate variability, movement, and functioning, consistent with autonomic dysregulation. Positive symptoms were also correlated with parasympathetic dysregulation. Most recently, Cella and colleagues [21] asked participants with first episode psychosis to wear an mHealth device to continuously measure their heart rate variability and EDA while self-reporting psychotic symptoms. They found higher EDA during periods where participants were experiencing psychosis.

The use of an mHealth device in younger adults with mental illness over extended periods has yet to be tested. This age group is more likely to be "tech savvy" and they are at high risk of developing severe mental illness. Pilot data indicate 15 out of 19 young adults with severe mental illness wore an mHealth device for greater than two weeks, and information regarding each participant's activity, sleep, EDA, and subjective stress was reliably collected during this period [22]. The next challenge is establishing if this information is clinically useful and predicts relapse. This protocol describes using information from an mHealth device streamed to both case managers and patients to allow them to independently monitor and then collaborate to manage any early warning signs (see Figure 1).

Figure 1. Information flow between patient, clinician, and integrated mobile health device.



Aims and Hypotheses

The aims of this study are to (1) examine whether case management augmented by an mHealth device integrated into a youth mental health team can improve treatment outcomes for young people with a severe mental illness and (2) examine whether the mHealth device can predict mental deterioration versus health for those allocated to the integrated arm of the trial. We hypothesize that (1) case management for a severe mental illness enhanced by an mHealth device integrated into a youth mental health team will result in better outcomes than case management with an unintegrated device and (2) physiological data from an mHealth device will identify periods of mental deterioration.

Methods

Overview

The trial design is a parallel-group randomized controlled trial (RCT) predicting the superiority of case management for severe mental illness with an integrated mHealth device over case management with an unintegrated device. It will examine outcomes both between subjects (ie, case management with an integrated vs unintegrated mHealth device) and within subjects (ie, repeated measures of participants with the integrated device to determine if it predicts mental deterioration). The conditions vary regarding whether information from the mHealth device is shared with participants and clinicians *or* with participants alone. Participants will be randomly allocated to either (1) the integrated (unWIRED) condition, where information from the mHealth device is shared with both participant and clinician, or (2) the unintegrated condition, where information from the mHealth device is sent to the participant alone. Participation in the study will last for 6 months. The design and reporting of this study will follow the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) guidelines [23]. This protocol was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) (ACTRN12620000642987).

Participants

The study will recruit 126 youths aged 18-25 years with a severe mental illness drawn from youth community mental health services in Western Sydney and Sydney Local Health Districts in New South Wales (NSW), Australia, where BK, JS, and AH are senior psychiatrists. Admission to these services is determined by participants experiencing moderate to severe mental illness that impairs functioning. All participants at these sites will be receiving case management for their mental illness, including regular medication monitoring and/or psychosocial treatments consistent with Australian and New Zealand College of Psychiatry guidelines. Participants will not be paid; however, they can be reimbursed for costs associated with participation, such as travel expenses or mobile phone credit.

Inclusion criteria are (1) being a current community mental health service patient, (2) aged 18-25 years, (3) having a confirmed diagnosis of serious mental illness, including schizophrenia spectrum disorders, bipolar affective disorder, severe major depressive disorder, anxiety disorder, and/or personality disorder, and (4) having the capacity to consent to the study.

Exclusion criteria are (1) being non-English speaking, (2) having greater than mild developmental disability, and (3) having an inability to comply with either the requirements of informed consent or the treatment protocol.

Substance use will not be an exclusion criterion, as the effects of stress due to substance withdrawal and self-medication are important factors in relapse. It is also important to keep the study population ecologically similar to the clinical population.

Equipment

The Empatica Embrace2 [24] will be used as the mHealth device in the study. The Embrace2 is an mHealth device that can be worn like a wristwatch. It has a wearable biosensor that captures,

stores, and wirelessly transmits EDA and motion data. The Embrace2 is paired to a mobile phone via Bluetooth, where information is displayed on the Mate App (Empatica Inc) of the participant's phone. The Mate App is a free app developed for the Embrace2 device. Data from the Embrace2 are uploaded to a secure Empatica cloud server. The device will be worn continuously to monitor physiological state, day and night. It requires charging every 48 hours using a USB and dock. In addition to the Embrace2, the young person will need to own a compatible mobile phone that runs on either the Apple iOS or Android operating system. Basic Android phones will be lent to participants who do not have a suitable phone. The mobile phone will have the free Mate App downloaded for the Embrace2 device. The phone can display activity-related information to the participant through the app. The Mate App also allows participants to log *events*, or make digital diary entries, that can be time stamped against their physiological data.

Interventions

Overview

All participants will receive standard treatments, including case management for their severe mental illness. This involves assessment followed by combinations of medication-based and/or psychosocial treatments. There is a strong emphasis on early intervention in these services. Prospective participants are initially assessed by a multidisciplinary team before being admitted according to standard inclusion criteria. The main criterion for admission is that they are experiencing a moderate to severe mental illness that impairs functioning. Participants are assigned a core case manager; however, their treatment is managed within a team of psychiatrists, nurses, psychologists, occupational therapists, and/or social workers. Treatments offered include case management, medication, psychotherapy, cognitive remediation, vocational interventions, and group programs (eg, psychoeducation). After consenting to the trial, participants at these services will be randomly allocated to one of two interventions that vary with respect to who receives information from the mHealth device.

Integrated mHealth Device: unWIRED Intervention

Participants will receive case management for their mental illness as well as wearing the Embrace2 device. This device sends physiological measurements to the Empatica Research Portal, which can then be relayed to health service computers for the treating case manager to view. A dashboard generated by the program Splunk [25] provides case managers with information regarding each participant's arousal, sleep, and activity from the previous day. Splunk captures, indexes, and correlates real-time data and generates graphs, reports, dashboards, and visualizations. The dashboard provides a visualization of the participant's EDA and activity over a 24-hour period, as well as representing activity through *speed meters*, which present the participant's level of activity. The program provides password-protected weblinks allowing clinical staff to view the dashboard from their clinical site. Each participant will also have access to activity-based information, which will be transmitted to their mobile phone's Mate App. Based on the information provided, case managers and/or participants may choose to alter their management plan. For example, periods of high arousal and/or poor sleep may indicate a need for a medication change or a more assertive intervention. Continuous data will be visually inspected for significant deviations in physiological measures and the *speed meters* will be used to alert clinicians of significant change. Physiological information relayed to both the case manager and participant will be regularly reviewed and discussed during team meetings. Where possible, the use of the dashboard will be recorded in electronic medical records. Adherence to the device will be monitored through a portal that shows if the device is being worn and the data are streaming. If there are consecutive days of nonadherence, the research psychologist (SB) will contact the participant to find out the reason for the disconnection and attempt to troubleshoot. For example, the psychologist may ask participants to remember to wear or charge the device and insure it is paired with their phone.

Unintegrated mHealth Device: Control Condition

Participants in the control condition will receive their standard care in addition to being given an Embrace2 to self-monitor their activity levels. This device will provide information to each participant regarding their activity; however, unlike in the integrated condition, information will not be returned to their treating case manager—the device will not be integrated with the mental health team. The device can be used at each participant's discretion, without prompting or oversight from their case manager.

Randomization

Randomization will be conducted by an independent statistician not associated with the study. Randomly permuted blocks of 4 participants will be centrally generated using a computer-generated algorithm. The randomization sequence will be managed by staff independent of the project who will notify the clinical researcher of the randomization allocation. Participants, case managers, and clinician researchers at any one site will not be blinded as to allocation, as those in the integrated condition will regularly discuss the intervention with their case manager.

Measurements

Overview

The primary outcome for the RCT is the extent to which the integrated mHealth device can prevent mental deterioration. The within-subjects components of the trial will examine if differences in activity, sleep, and EDA predict mental deterioration versus stability. A variety of measurements will be taken, including self-report, case manager report, biometric measures from the Embrace2, EMAs of stress, chart reviews, as well as qualitative reports from case managers and participants regarding the acceptability of the device. Multimedia Appendix 1 shows a summary of the measurements taken at each time point.

Assessments of Mental Deterioration

Case managers and blinded clinical staff will make monthly assessments of participants using the Clinical Global Impression

Scale (CGI) [26], the Social and Occupational Functioning Assessment Scale (SOFAS) [6], and chart reviews.

The Clinical Global Impression Scale

The primary measures are consensus scores on the CGI severity and treatment response scales. Assessments are made by blinded clinicians, taking into account all relevant information to make ratings on two 7-point scales. The CGI is a brief, valid measure of symptom severity and treatment response, which has shown utility in measuring mental state as compared to similar scales [27,28].

The Social and Occupational Functioning Assessment Scale

The SOFAS is an overall measure of social and occupational functioning used in psychiatric assessments. The SOFAS describes functioning of the participant at the time of the assessment. Its ratings are based on a 0-100 scale, reflecting excellent to grossly impaired functioning, with higher scores indicating better functioning.

Chart Reviews

Clinical research staff will primarily conduct chart reviews using electronic medical records to make CGI and SOFAS assessments of participants in the trial. Charts will be examined for information including diagnosis, medication histories, and occasions of service (ie, treatment-as-usual information); the period between emergence of symptoms and intervention; evidence of illicit substance use; hospitalizations; indications of relapse; and evidence of case manager use of the portal.

Participant Self-Report, With Time Point

Demographics

Demographic information includes gender, date of birth, and ethnicity and is collected at baseline only.

The 10-Item Big Five Inventory

The 10-item Big Five Inventory (BFI-10) [29] is a personality measure based on the 44-item Big Five Inventory [30]. The BFI-10 focuses on five broad personality domains, including openness, conscientiousness, neuroticism, extraversion, and agreeableness. It is rated on a 5-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). The BFI-10 retained validity compared to the original version and its test-retest reliability was .75. This inventory is administered at baseline only.

The 21-Item Depression Anxiety and Stress Scale

The 21-item Depression Anxiety and Stress Scale (DASS-21) [31] is a measure of depression, anxiety, and stress over the previous week. Respondents rate each item on a 4-point Likert scale, ranging from 0 (not at all) to 3 (almost always). The DASS-21 has high reliability, a factor structure consistent with its subscales, and high convergent validity with other measures of anxiety and depression [32]. This scale is administered at baseline and 6 months.

The Behaviour and Symptom Identification Scale-24

The Behaviour and Symptom Identification Scale-24 (BASIS-24) [33] measures psychiatric symptoms and functional difficulties over the previous week. Items are rated from 0 (no difficulty/symptom never present) to 4 (extreme difficulty/symptom always present). It has adequate reliability (coefficient α from .75 to .91 for subscales), validity, and responsiveness to change (effect size for change=0.56). The scale is administered at baseline and 6 months.

Activity and Participation Questionnaire

The Activity and Participation Questionnaire (APQ6) [7] is a measure of the participant's capacity to conduct their usual activities over the previous month. Consumer feedback and test-retest reliability indicates good construct validity. This questionnaire is administered at baseline, 3 months, and 6 months.

The Assessment of Quality of Life-8 Dimension

The Assessment of Quality of Life-8 Dimension (AQoL-8D) [34] is a health-related, multi-attribute, quality-of-life measure, which has 35 items measuring independent living, happiness, mental health, coping, relationships, self-worth, pain, and senses over the previous week. Results indicate it has strong validity, reliability, convergent validity, and predictive validity compared to other measures of quality of life. This measure is administered at baseline and 6 months.

The Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) [35] is a 19-item self-report measure of sleep quality and disturbances over the previous 7 days. The PSQI was used to measure seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. The domains are rated from 0 (no difficulty) to 3 (severe difficulty). A PSQI score above 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% (κ=0.75, P<.001) in distinguishing between good and poor sleepers. Generally, good psychometric properties have been established for the PSQI, with acceptable internal homogeneity, test-retest reliability, and validity. This measure is administered at baseline and 6 months.

The Working Alliance Inventory–Short Form Revised

The Working Alliance Inventory-Short Form Revised (WAI-SR) [36] measures therapeutic alliance, assessing agreement on the tasks of therapy, goals of therapy, and development of an affective bond. For example, item 1 asks "As a result of these sessions, I am clearer as to how I might be able to change." The WAI–Short Form Revised (WAI-SR) demonstrated good psychometric properties in an initial validation, with internal reliability (α>.80) and convergent validity with related measures being good [37]. This measure is administered at baseline and 6 months.

Other Measurements

Measurements From the Embrace2 Device

Participants will have their physiological measurements continuously recorded, including EDA, actigraphy, and temperature, as described in the Interventions section. Actigraphy can be converted into resting time (ie, an approximation of sleep) and step counts. Reports of physiological measures from Empatica are in the form of CSV (comma-separated values) files that can be converted into

dashboards and visual files using Splunk. Data transmitted to the research portal can also be examined for participant adherence to the device.

Ecological Momentary Assessment

Participants in the integrated mHealth intervention will be asked to report their stress levels in real time to identify periods when they are stressed or becoming unwell. Participants will receive a text message asking, "How stressed are you feeling now?" to be answered on a scale from 0 (not at all stressed) to 10 (very stressed), what they are doing, and/or how they are feeling. Participants will not respond to the text message, rather they will record their response on the Empatica Mate App, which is downloaded onto their phone. Text messages will be sent both according to an automated schedule and manually by the research psychologist. The event will be given a time stamp and recorded alongside participants' physiological data.

Qualitative Interviews Regarding Attitudes Toward the unWIRED Intervention

Feedback will be obtained from participants and their case managers as to the acceptability and usefulness of the approach. For example, participants and case managers will be asked what they found helpful or challenging about using the mHealth device. This information will be sought either from focus groups or individual interviews. The transcribed responses will be thematically analyzed according to Braun and Clarke [38] by members of the research team.

Case Manager Report

A monthly report of participant engagement and use of the device will be recorded by the case manager.

Outline of Study Processes

The following is an outline of the major components in administering the trial: recruitment, consent and initial assessment, administration, and trial conclusion.

Recruitment

Recruitment will primarily be managed by the research psychologist, who will explain and provide information to case managers and service managers at the clinical sites. Case managers will ask potential participants if they are interested in being involved. If they indicate interest, the research psychologist will contact them and answer any questions they may have regarding the project.

Consent, Randomization, and Initial Assessment

If a participant indicates interest in being involved, the research psychologist will ask for their written consent. Randomization will be determined by an external party who will communicate treatment condition to research staff. After consent and randomization, participants will be asked to complete a series of self-report questionnaires (see the Participant Self-Report, With Time Point, section). The psychologist will ask all participants to download the Empatica Mate App onto their phone and they will set up an Empatica account using a QR (Quick Response) code from the research portal. The Embrace2 device will be paired with the participant's phone using Bluetooth. They will give the participant some basic instructions on how to operate the device, including how to charge it and keep it connected.

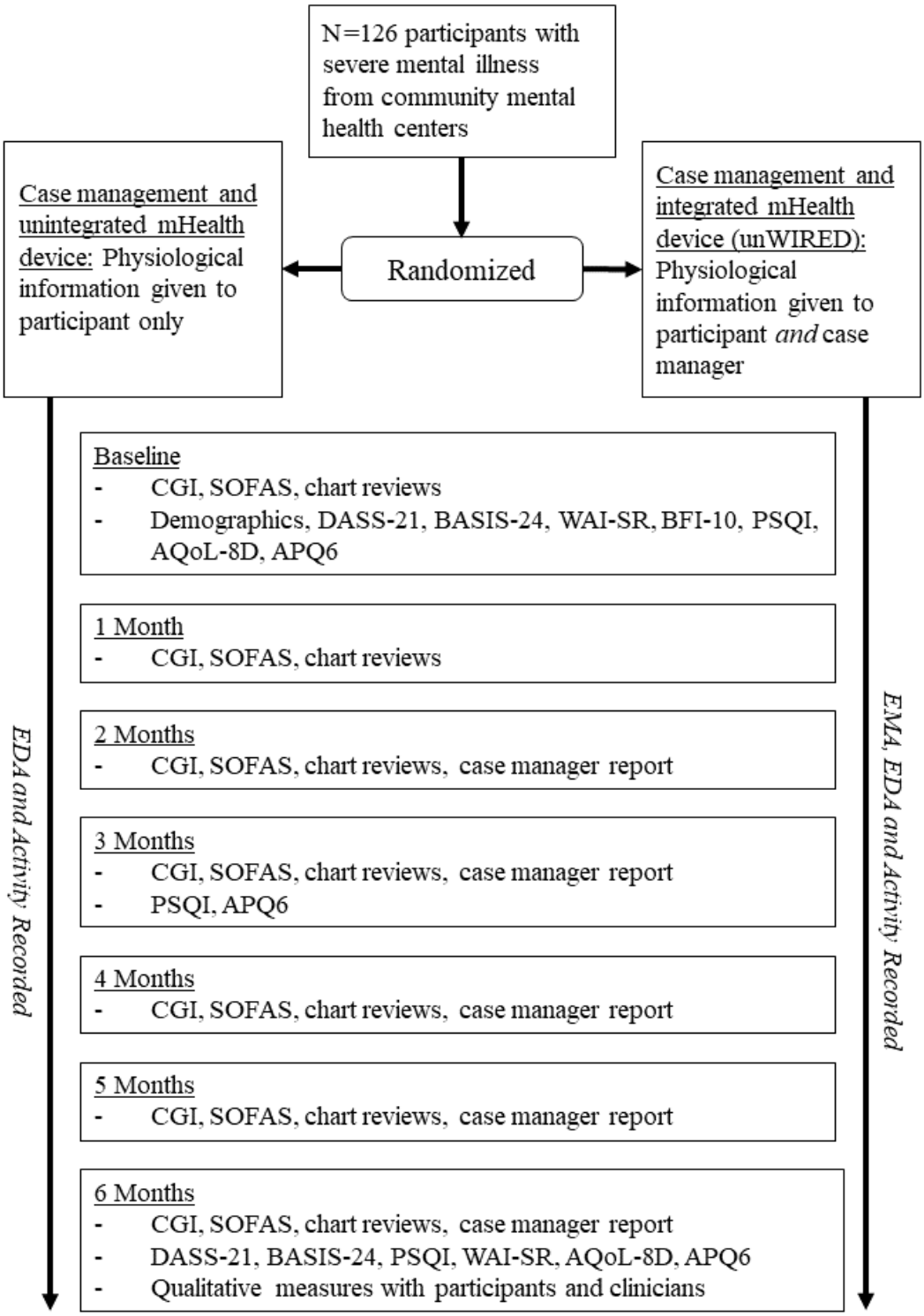
Trial Administration

Data will be collected from the Embrace2 in a continuous and ongoing manner for all participants. Case management and treatment will continue as per usual in the community mental health services. Case managers of participants in the integrated unWIRED arm will receive training on how to use the mHealth device and dashboard to monitor a participant's mental state. Research staff will monitor the extent to which there are data uploaded from the device based on the Empatica Research Portal. If unWIRED participants are observed to have minimal adherence over consecutive days, the research psychologist can contact each participant to determine the reason for the disconnection and attempt to restore the device. During the trial, the research psychologist may send EMA text messages to the unWIRED participants to determine stress levels and their responses will be visible on the Empatica Research Portal. EMA messages will be sent according to a schedule and can also be sent manually by the research psychologist. Physiological data from each unWIRED participant's previous day will be displayed on the Splunk dashboard, showing their activity, rest, and EDA. A link to the dashboard will be provided to case managers so they can view the information on their work computer. Case managers will use the information from the dashboard to enhance their clinical decisions. Clinical staff and participants will be encouraged to discuss data recorded from the device during their meetings and to include this information in their collaborative care plan. Case managers will be provided with a basic manual for interpreting the dashboard; however, a clinical response will be left to their clinical judgement. Throughout the trial administration, clinical staff will be asked to report on their participant's ongoing functioning and distress, as described in the Assessments of Mental Deterioration section. The research team can provide support to case managers as needed.

Trial Conclusion

After the 6-month enrollment in the study, or earlier if a participant asks to withdraw, all participants will once again be asked complete the self-report questionnaires that were administered during the initial appointment (see Participant Self-Report, With Time Point, section). Researchers will ask participants to remove their devices and return them to administrative staff at their clinical site. Each participant will be registered as having "completed" the trial on the Empatica portal, and clinical staff will be informed that they are no longer in the trial. Qualitative interviews may be used after the trial to examine both participant and case manager experiences with the integrated mHealth device. See Figure 2 for the RCT CONSORT-EHEALTH flow diagram.

Figure 2. Outline of measurements for the randomized controlled trial. APQ6: Activity and Participation Questionnaire; AQoL-8D: Assessment of Quality of Life-8 Dimension; BASIS-24: Behaviour and Symptom Identification Scale-24; BFI-10: 10-item Big Five Inventory; CGI: Clinical Global Impression Scale; DASS-21: 21-item Depression Anxiety and Stress Scale; EDA: electrodermal activity; EMA: ecological momentary assessment; mHealth: mobile health; PSQI: Pittsburgh Sleep Quality Index; SOFAS: Social and Occupational Functioning Assessment Scale; WAI-SR: Working Alliance Inventory–Short Form Revised.



Safety Monitoring

This study will be overseen by senior psychiatrists (AH, BK, and JS) who have extensive clinical experience in youth mental health. The participants will have case managers who are mental health professionals working with them on a weekly basis. Adverse events can be reported by either the participants or their case managers and reviewed by an investigational team. Participants will be prompted to report any adverse events. All adverse events will be recorded in the adverse event log in the participant case report form, including the seriousness, severity, relationship to study product, duration, and outcome. Steps will

be taken according to the adverse reaction decision tree. In all cases, researchers will maintain contact with participants who experience an adverse event until it has been resolved and symptoms disappear. If required, they will also be asked to notify their general practitioner or primary care doctor. Standard Operating Procedures will be in place to insure the trial is conducted in accordance with Good Clinical Practice. The project will have an independent data safety monitoring board (DSMB) composed of health professionals, researchers, and IT experts who will meet every 4 months. The project will have regular reviews and meetings to determine the safety and integrity of the data.

Data Collection, Use, and Privacy

Data will be collected by the research team and will be coded so that they will not be identifiable to anyone other than the research team. Data will be collected manually through self-report, interview notes, and EMAs and automatically through the mHealth device. The physiological data will be transmitted to the Empatica interface and downloaded to the project system within a day of recording. However, all data going to Empatica will be deidentified and coded. All data, once converted to electronic format where applicable, will be backed up on a password-protected computer hard drive. Source documents will be kept in participant files, which will be stored in a locked cabinet in a locked room. Data from measures will be entered into a password-protected electronic database on a secure health network drive and backed up onto a password-protected University of Sydney system. No uncoded or identifiable data will be stored outside of the hospital research site. A DSMB, composed of researchers in eHealth, psychiatrists, and information officers will meet to discuss the data management processes associated with this study.

Physiological data will be uploaded onto the secure website of Empatica Inc via its website in the United States. Data will then be retrieved and downloaded onto a University of Sydney server and analyzed within the secure university environment. Information will be returned to treating clinicians operating within NSW Health firewalls. The initial data are controlled by Empatica; they will then be transferred to University of Sydney and ESE (Engineering Und Software-Entwicklung GmbH) servers, which are assisting with data management. Data flow through servers domiciled in either the United States or the European Union is allowed in NSW Health [39] and does not breach the NSW Health Records and Information Privacy Act 2002 [40].

Power Calculations and Statistical Analysis

The primary outcome for this study is to compare changes in treatment-related outcomes before and after the intervention for participants enrolled in the integrated versus unintegrated conditions. There are currently no trials examining the augmentation of treatment with an mHealth device, so sample size estimations are made using general calculations. Assuming a moderately sized advantage of the integrated (ie, unWIRED) versus unintegrated device on outcomes (effect size=0.5, 80% power, and a 2-tailed α of .05), we will require 63 participants per group.

The RCT component generally compares measures of mental health, distress, and functioning between the conditions, adjusted for baseline scores. For example, this analysis may focus on an intent to treat using a hierarchical linear model (HLM) to test the differential effects of the two treatment conditions, because this method allows the number of observations to vary between participants and handles missing data by calculating estimates of trajectories using maximum likelihood estimation. Fixed effects could be tested for intervention condition and time of assessment. Random effects in the unstructured models provide an index of the relative effects of the treatments over time. Fixed effects parameters may be tested with the Wald test (*t* test, $P<.05$, 2-sided) and 95% confidence intervals. Analyses will focus on the primary outcomes (ie, CGI scores) and secondary outcomes (eg, APQ6, BASIS-24, DASS-21, PSQI, and AQoL-8D) between the unWIRED group and the active control group, with the main outcome points being at the 6-month follow-up relative to baseline. All results are based on estimated mean values derived from HLM analyses. The within-subjects analysis will be comprised of linear fixed effects models using physiological measurements (ie, sleep, activity, and EDA) to predict measures of mental health, distress, and functioning. Baseline variables may be used as covariates when analyzing individual and between-group differences (eg, age, illness severity, treatments, and personality differences). Thematic analysis [38] will be used to examine individual and group qualitative feedback regarding the acceptability of the mHealth device and the unWIRED intervention for participants and case managers; there will be approximately 10-20 participants in the patient and clinician groups.

Results

The study received scientific and ethical approval at Western Sydney Local Health District. It is due to start in October 2020 and conclude in October 2022.

Discussion

This study will determine whether integrating an mHealth device into clinical care is useful and effective in managing severe mental illness in young adults in the community. We plan to test this approach in a frontline community mental health setting, where we can examine its feasibility, acceptability, and efficacy for patients and case managers. While previous studies use mHealth devices for participants to self-monitor, this is among the first to stream information to both a patient and the treating mental health team. We hypothesize that the device will identify periods of increased stress and risk of mental deterioration.

A strength of this design is that it examines both between- and within-subjects components. An RCT is a gold standard in determining treatment efficacy, and the within-subjects design can control for individual differences. This study also takes several types of measurements regarding evidence of mental deterioration, symptoms, and functioning. Potential limitations with this protocol should also be noted. This study intends on using participants with a variety of diagnoses, with varying severities, and with psychosocial difficulties. While this increases its ecological validity, the variation may make it more

difficult to detect group differences. This limitation highlights the importance of controlling for relevant variables as well as studying within-subjects variation. Furthermore, even severely unwell patients are more often stable than deteriorating, providing fewer opportunities to test the efficacy of the unWIRED approach. Hence, examining process variables is important, as is the mixed methods approach employed in this study. Finally, the design incorporates several measures to detect an effect; however, this increases the likelihood of type I error.

While ambitious, this project's clinical implications are potentially significant. Any treatment that improves collaboration and early intervention may have a far-reaching impact on the treatment of severe mental illness in the community. The intervention could allow clinicians to remotely and unobtrusively monitor severely unwell patients in the community and provide an effective means to augment treatment.

Acknowledgments

Funding for this project was provided by the Balnaves Foundation and Western Sydney Local Health District.

Authors' Contributions

AH, BK, and FR are responsible for securing the research funding, oversight of the study, and submission of research papers. SB and JS are research clinicians responsible for conducting the study and submission of research papers. AC is the biometric analyst responsible for conducting the analysis and the submission of research papers.

Conflicts of Interest

AH has received consultancy fees from Janssen Australia, Lundbeck Australia, and Seqirus. He has received payments for educational sessions run for Janssen Australia and Lundbeck Australia. He has developed educational material for Servier. He is the recipient of an investigator-initiated grant from the Balnaves Foundation and Takeda Pharmaceutical Company. He owns shares in CSL and Ramsay Health. He is the recipient of funding from the Australian Research Council and the National Health and Medical Research Council. He is the chair of One Door Mental Health. The remaining authors declare no conflicts of interest.

Multimedia Appendix 1
Randomized controlled trial measurements, measurement reporter, and time points.
[DOCX File , 22 KB - resprot_v9i11e19510_app1.docx]

Multimedia Appendix 2
Scientific approval and reviewer reports from the authors' institution.
[PDF File (Adobe PDF File), 696 KB - resprot_v9i11e19510_app2.pdf]

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Abbreviations

ANZCTR: Australian New Zealand Clinical Trials Registry
APQ6: Activity and Participation Questionnaire
AQoL-8D: Assessment of Quality of Life-8 Dimension
BASIS-24: Behaviour and Symptom Identification Scale-24
BFI-10: 10-item Big Five Inventory
CGI: Clinical Global Impression Scale
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
CSV: comma-separated values
DASS-21: 21-item Depression Anxiety and Stress Scale
DSMB: data safety monitoring board
EDA: electrodermal activity
EMA: ecological momentary assessment
ESE: Engineering Und Software-Entwicklung GmbH
HLM: hierarchical linear model
mHealth: mobile health
NSW: New South Wales
PSQI: Pittsburgh Sleep Quality Index
QR: Quick Response
RCT: randomized controlled trial
SOFAS: Social and Occupational Functioning Assessment Scale
WAI: Working Alliance Inventory
WAI-SR: Working Alliance Inventory–Short Form Revised

Edited by G Eysenbach; submitted 12.06.20; peer-reviewed by Y Perry, C Kaylor-Hughes; comments to author 12.09.20; revised version received 02.10.20; accepted 09.10.20; published 02.11.20.

Please cite as:
Byrne S, Kotze B, Ramos F, Casties A, Starling J, Harris A
Integrating a Mobile Health Device Into a Community Youth Mental Health Team to Manage Severe Mental Illness: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2020;9(11):e19510
URL: https://www.researchprotocols.org/2020/11/e19510
doi:10.2196/19510
PMID:33136053

Protocol

Efficacy of an Online Physical Activity Intervention Coordinated With Routine Clinical Care: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Most adults are not achieving recommended levels of physical activity (150 minutes/week, moderate-to-vigorous intensity). Inadequate activity levels are associated with numerous poor health outcomes, and clinical recommendations endorse physical activity in the front-line treatment of obesity, diabetes, dyslipidemia, and hypertension. A framework for physical activity prescription and referral has been developed, but has not been widely implemented. This may be due, in part, to the lack of feasible and effective physical activity intervention programs designed to coordinate with clinical care delivery.

Objective: This manuscript describes the protocol for a pilot randomized controlled trial (RCT) that tests the efficacy of a 13-week online intervention for increasing physical activity in adult primary care patients (aged 21-70 years) reporting inadequate activity levels. The feasibility of implementing specific components of a physical activity clinical referral program, including screening for low activity levels and reporting patient program success to referring physicians, will also be examined. Analyses will include participant perspectives on maintaining physical activity.

Methods: This pilot study includes a 3-month wait-listed control RCT (1:1 ratio within age strata 21-54 and 55-70 years). After the RCT primary end point at 3 months, wait-listed participants are offered the full intervention and all participants are followed to 6 months after starting the intervention program. Primary RCT outcomes include differences across randomized groups in average step count, moderate-to-vigorous physical activity, and sedentary behavior (minutes/day) derived from accelerometers. Maintenance of physical activity changes will be examined for all participants at 6 months after the intervention start.

Results: Recruitment took place between October 2018 and May 2019 (79 participants were randomized). Data collection was completed in February 2020. Primary data analyses are ongoing.

Conclusions: The results of this study will inform the development of a clinical referral program for physical activity improvement that combines an online intervention with clinical screening for low activity levels, support for postintervention behavior maintenance, and feedback to the referring physician.

Trial Registration: ClinicalTrials.gov NCT03695016; https://clinicaltrials.gov/ct2/show/NCT03695016.

International Registered Report Identifier (IRRID): DERR1-10.2196/18891

(JMIR Res Protoc 2020;9(11):e18891) doi:10.2196/18891

KEYWORDS

physical activity; online intervention; clinical translational research

Introduction

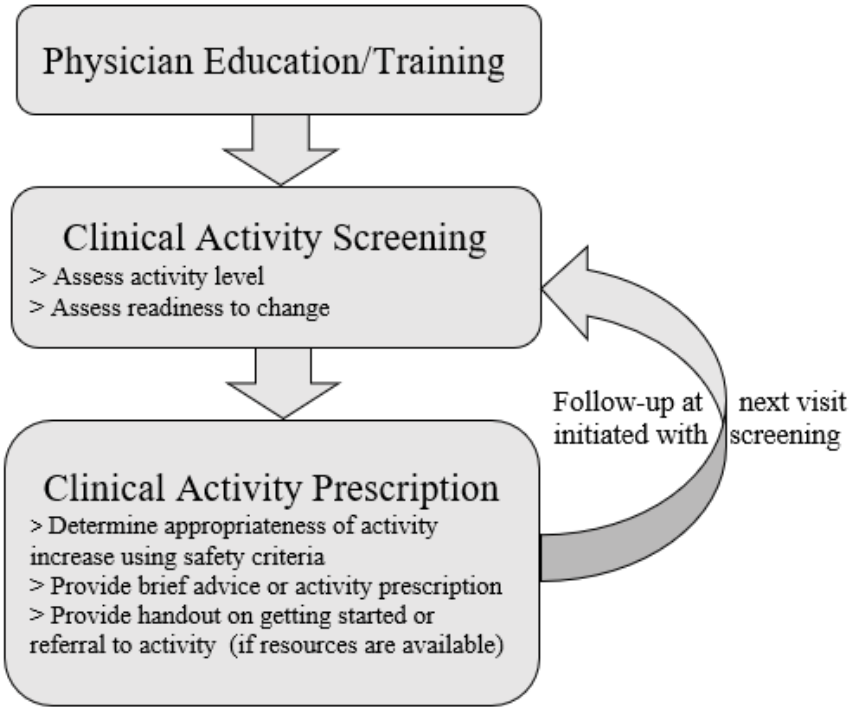
More than 20 years ago, the Surgeon General's report on physical activity summarized the health effects of inadequate physical activity, suggesting that inadequately low activity was associated with an increased risk for numerous poor health outcomes, including all-cause mortality, cancer, cardiovascular disease, and type 2 diabetes [1,2]. The report concluded with a recommendation for all adults to achieve at least 150 minutes of moderate-to-vigorous physical activity (like brisk walking) each week [3]. Unfortunately, less than half of US adults are currently meeting this recommendation [4-7], and the existing prevalence of inadequate activity levels has resulted in an estimated US $53 billion in health costs/year worldwide [8].

Clinical recommendations from the American Heart Association, the American Diabetes Association, and the US Preventive Services Task Force endorse physical activity in the treatment of common health problems, including obesity, diabetes, dyslipidemia, and hypertension [9-12]. It has been suggested that clinical referral for increasing physical activity has the potential to improve patient outcomes and lower health care costs [13-15]. Furthermore, advice from clinicians has been shown to greatly influence lifestyle behaviors and increase patient satisfaction with clinical care [16,17]. However, treating low activity levels is typically not currently part of routine clinical care [18-21]. Commonly cited reasons for this omission in routine care include lack of physician education and training on activity recommendations or referral options and lack of time and resources [22,23].

To enhance the incorporation of physical activity assessment and referral in standard disease prevention and clinical treatment, in 2007, the American College of Sports Medicine and the American Medical Association launched the Exercise is Medicine (EIM) initiative [13,24]. The EIM initiative provides support for clinical referral to physical activity by providing a framework and materials for physicians (eg, educational materials on physical activity recommendations, sample conversations with patients, and physical activity prescription pads) to facilitate a dialogue between providers and patients regarding physical activity participation.

EIM-based programs typically involve identification of patients with low activity levels using a simple questionnaire, advice from a health professional to increase physical activity, and suggestions for follow-up inquiries at the next routine visit (Figure 1) [13]. Clinical advice on physical activity can also be reinforced by referral to an exercise professional in the community or to an evidence-based physical activity intervention program [25]. However, published studies suggest that most existing programs involving clinical referral to physical activity for generally healthy adults are limited to physical activity screening and brief clinical advice to increase physical activity with a physical activity prescription, but without problem-solving support, gradual goal setting, or follow-up contact between visits [13,25-28], despite the fact that these are key components of effective behavioral change programs [13,25].

Figure 1. Existing process for physical activity prescription and referral, based on the American College of Sports Medicine's Exercise is Medicine program.



In addition to addressing factors that are relevant to the clinical setting, physical activity programs for patient populations should incorporate evidence-based aspects of successful behavior change programs [13,14,24]. Yet, recent meta-analysis findings suggested that only three of the 13 referenced clinical physical activity programs included theory-driven behavioral interventions and only one of the three had more than three sessions [25,29-31]. Furthermore, no programs provided support for maintenance of physical activity behavior change. This is despite the fact that the Centers for Medicare & Medicaid Services (CMS) is now reimbursing lifestyle interventions based on that developed and evaluated as part of the Diabetes Prevention Program (DPP). These highly successful translations of the theory-driven DPP behavioral intervention include weight loss and physical activity goals. These programs typically offer 12 to 16 core sessions that include key components of social-cognitive theory followed by a maintenance phase [32-34]. The lack of both theory-driven behavior change strategies and support following an initial behavior change intervention may explain the lower success with participants maintaining physical activity that has been reported for clinical physical activity programs, compared with programs delivered in other settings (community, workplace, and university) [25].

This manuscript describes the protocol for the ActiveGOALS Study. The primary aim of the study is to implement and evaluate an EIM-based approach that builds on successful translational lifestyle interventions [14,35,36]. This study involves developing and piloting the behavior change core intervention sessions (first 3 months) of a proposed 1-year intervention program. In contrast to traditional EIM programs, this program will include an internet-based physical activity intervention for the general adult patient population with remote coach support that is rooted in social-cognitive theory.

Methods

Study Design Overview

The ActiveGOALS Study was designed to develop, implement, and evaluate a 3-month, one-on-one, online intervention for promoting behavior change related to physical activity improvement in adult primary care patients (study sample of 80 participants, including 40 aged 21-54 years and 40 aged 55-70 years) with low activity levels using a randomized controlled trial (RCT) design with a wait-listed control group. Patients with low activity levels were recruited through several means, including self-referral and referral by their physician. Participants were required to be able to perform unsupervised moderate-intensity physical activity (eg, brisk walking), with a physician referral form required to confirm eligibility.

The use of an online platform improves convenience for patients and facilitates communication among the patient, referring physician, and ActiveGOALS coach (Figure 2). Patient participants accessed all ActiveGOALS program materials (13 weekly sessions, tracking tools, and workbook pages) through the online platform (Figure 3). Trained coaches tracked participant progress and communicated with participants through a secure messaging system within the platform to provide brief weekly advice and support or to answer questions related to physical activity. Participant progress was also reported to referring physicians.

Figure 2. ActiveGOALS program delivery process showing communication between the providers and patient (arrows indicate the direction of communication for each activity).

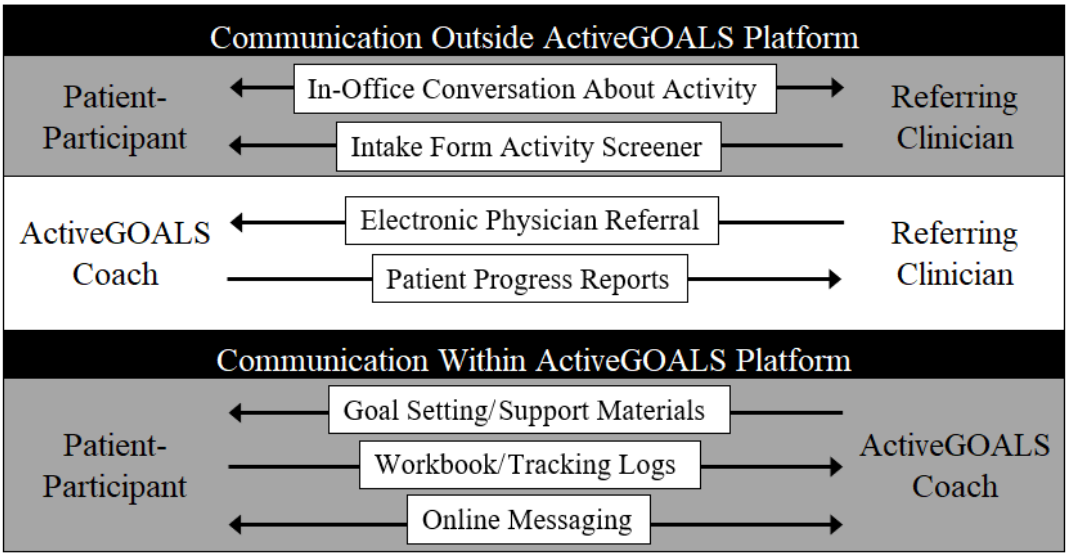
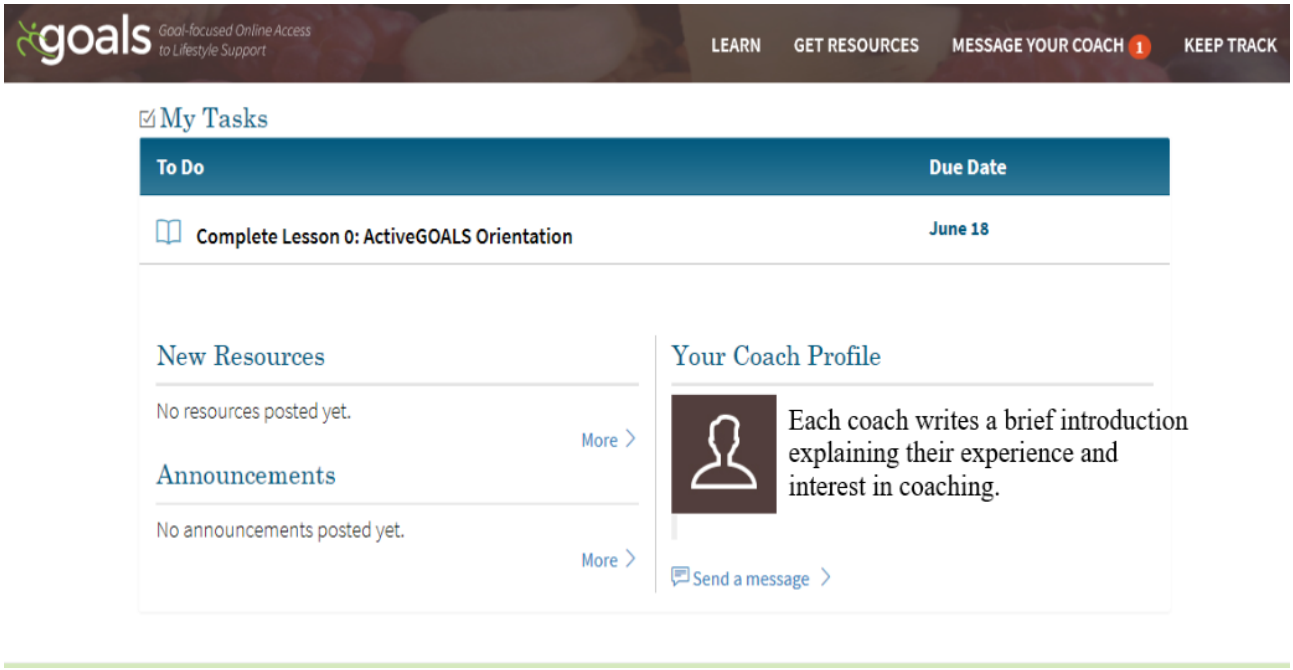


Figure 3. Screenshot of the ActiveGOALS intervention platform home page.



All enrolled participants were randomized to receive the intervention immediately (*immediate*) or after a 3-month waiting period (*wait-listed*). Assessments for the RCT were conducted at baseline and after 3 months when the *immediate* participants should have completed the 13 weekly ActiveGOALS program sessions and before the *wait-listed* participants were offered the ActiveGOALS program. We hypothesized that participants randomized to receive intervention immediately would have much larger (1) increases in steps/day and moderate-to-vigorous physical activity (minutes/day) and (2) decreases in sedentary behavior (minutes/day) between baseline and 3 months when compared to the wait-listed control group participants. To evaluate whether the effects of the intervention lasted beyond the weekly sessions, all participants were followed for 6 months after the start of their intervention (Figure 4). This study was approved by the Institutional Review Board at the University of Pittsburgh (STUDY19080212).

Figure 4. ActiveGOALS study timeline (only the wait-listed control group had the second preintervention assessment).

	Prerandomization	Baseline	Waitlisted Preinterventon	Interventon	Postintervention 3 months	6 months
Screening	X					
Information video	X					
Physician referral	X					
Online consent	X					
Randomization		X				
Measures:						
Activity monitor: GT3Xbt		X	X		X	X
ActiveGOALS platform usage				X	X	X
Questionnaires:						
Lifestyle/health		X	X		X	X
Self-efficacy/confidence		X	X		X	X
Quality of life		X	X		X	X
Participant cost		X	X		X	X
Participant experience					X	X
Activity maintenance						X
Referring physician survey						X

Patient-Centered Outcomes Research

We used a patient-centered research approach, engaging key stakeholders as members of the research team, using PaTH Clinical Research Network stakeholder engagement resources [37,38]. The research team included a patient partner and a community-based certified exercise specialist with an interest in helping others develop healthier lifestyles. The study partners were invited to participate in research meetings, and they provided guidance on intervention design and delivery, as well as the need for any additional patient-centered outcomes. They were compensated for each meeting attended.

Physician referral that included a confirmation that moderate physical activity was medically appropriate for the patient was required for study participation. A new physician referral form was required before returning to the program if an injury, illness, or surgery was reported during the study. Referring physicians also received two patient progress reports. The first progress report informed physicians of the participant's reason for joining the program, participant's baseline activity levels, program engagement (such as logging in, session completion, and tracking activity), and participant's success in meeting the goals in the first half of the program. The second progress report provided information on engagement throughout the program and included graphs of average step counts and time spent in moderate-to-vigorous activity for the participant in each week of the program. Referring physicians were also mailed a brief five-question survey regarding the utility of the physician reports.

Study Procedures

Intervention Development

ActiveGOALS intervention materials were adapted from existing lifestyle intervention materials involving social-cognitive behavior change theory and related strategies specific to supporting physical activity change and reducing sedentary behaviors, including barrier recognition and problem solving [14,36,39]. Materials were further refined with input from key stakeholders and assembled into structured lessons with interactive workbook pages (20-25 minutes long). Two technical lessons were also included, which provided help with using the ActiveGOALS platform and tracking, inputting, and viewing activity data in ActiveGOALS.

In all, 11 of the 13 intervention sessions were modified from the existing GOALS (Guided Online Access to Lifestyle Support) lifestyle intervention materials. The GOALS materials were developed as an individually focused online translation of the DPP, and like the DPP, it provided support for weight loss and physical activity goal achievement (150 minutes of at least moderate intensity physical activity per week) [14,35,40]. The GOALS platform was designed to be modified for use with lifestyle interventions that may have healthy lifestyle program goals not included in the original GOALS program.

For this study, GOALS sessions were redesigned to focus specifically on increasing physical activity to 150 minutes/week of moderate-to-vigorous activity, increasing daily step counts, and reducing daily sedentary time (without a weight-loss goal). In order to achieve the goal of reducing sedentary time, participants were guided to take short breaks from sedentary behaviors throughout the day as well as to take larger (10 minutes or more) breaks from sedentary behavior several times a day. Social-cognitive theory–based strategies, including barrier recognition and problem solving, were retained. A session on reducing sedentary behavior and tracking tools for sedentary time were adapted from materials developed for the Group Lifestyle Balance Program, an in-person group-based intervention developed for community use (CDC recognized/CMS reimbursable) by members of the team that created the original DPP lifestyle intervention [36,39,41]. Finally, one session on *maintaining physical activity while traveling* was developed specifically for ActiveGOALS. The modified intervention materials were presented through the online platform and delivered along with self-monitoring tools, links to reputable web-based materials that may support physical activity, and personalized e-coaching.

Participant Eligibility and Recruitment

To reduce participant burden, the study was designed to be conducted remotely, with no in-person participant visits. Study information was conveyed to potential participants by phone, through email, and via an online video describing the study. Recruitment took place between October 2018 and May 2019 through a local primary care office (University of Pittsburgh Physicians-General Internal Medicine-Oakland [UPP-GIMO], Pittsburgh, Pennsylvania) and through an online recruitment tool "Pitt+Me." The Pitt+Me system is a registry of over 200,000 patient volunteers interested in participating in research studies. A continuous (rolling) enrollment strategy was used to recruit men and women aged 21 to 70 years.

Women currently pregnant or planning a pregnancy in less than 6 months and individuals who were nonambulatory or planning a procedure that would cause them to be nonambulatory in less than 6 months were not eligible. A sixth grade literacy level and access to a computer and the internet were required for participation. Ability to safely perform physical activity at a moderate intensity (like a brisk walk) for bouts of 10 minutes without direct supervision was required (per both participant self-report and primary care physician referral).

We aimed to recruit a sample that reflects the general patient population within UPP-GIMO for sex (68% female) and race/ethnicity (25% minority; mostly African American people). No individual was excluded from the study on the basis of race or gender. Some previous studies suggested that readiness to change and technology adoption may differ between older and younger adults [42,43]. Although there were no targeted recruitment strategies by age group, to guarantee participation by older and younger adults, recruitment was stratified by age group (80 participants, including 40 aged 21-54 years and 40 aged 55-70 years).

Recruitment strategies at UPP-GIMO included the implementation of a two-question physical inactivity screener [44], which was used to identify potential participants (those reporting <150 minutes of planned physical activity per week) at the beginning of annual physical visits. The ActiveGOALS Study principle investigator also attended a UPP-GIMO departmental physician meeting and introduced the study to

attending physicians and clinical staff. Study fliers and brochures were distributed in the waiting room and exam rooms at UPP-GIMO. Patients with low activity levels could ask their physicians for a study referral at their office visit or could reach out to the study directly to complete the screening before reaching out to their physicians. Physicians were also encouraged to identify potentially eligible patients, confirm patient interest, and refer them to the study. Referrals were mailed or faxed to study staff (within UPMC, referral could take place via a standard electronic referral through the Epic Electronic Health Record [EHR]).

Study materials were posted to the Pitt+ME online portal and a targeted email was sent out to approximately 3500 adults aged 21 to 70 years, who expressed interest in lifestyle programs. This targeted email provided study information and a link to the portal where interested individuals could be prescreened by Pitt+ME staff. Interested or eligible individuals were referred to ActiveGOALS Study staff for confirmatory phone screening. Individuals without a primary care physician to complete the required referral, could be referred to UPP-GIMO (if they reported having insurance), student health (if they reporting being a student at a local university or college), and/or a local free clinic (if they reported having no insurance).

Screening

After referral by EHR or Pitt+ME, screening for eligibility was conducted by phone, during which participants were asked to verify their activity levels and answer a series of questions to determine eligibility. These questions included a three-question disability screener that has been previously used in conjunction with activity assessments to identify individuals with disability that could affect their ability to safely ambulate [45]. Additional safety screening was not required owing to the acquisition of a physician referral prior to enrollment.

Individuals were informed whether they were eligible for the program, provided with detailed study information at the end of the screening call, and given time to ask questions. Eligible and interested individuals were emailed a link to a short informational video, a copy of the consent form to read over, and a doctor's referral form that they were required to have signed. The brief video provided enrollment requirements, the study purpose/history, and information on program expectations.

Consent and Randomization

Study staff followed-up with the interested/eligible participants prior to consent to answer questions. Only individuals who returned a doctor's referral were forwarded a personalized link to an online consent form developed using REDCap, a Health Insurance Portability and Accountability Act (HIPAA) compliant web application for building and managing online surveys and databases. Participants were randomized 1:1 in REDCap to receive the ActiveGOALS intervention immediately or after a 3-month waiting period. Block randomization in groups of four was conducted within each age strata. Study staff did not have access to the assignment list. Staff were required to verify completeness of a record before the randomized group assignment would become visible in REDCap. Each participant was informed of their assignment as soon as it became known to the staff.

Intervention Delivery

The ActiveGOALS intervention was accessed online. The weekly behavior change curriculum was presented through the online platform. Participants were also provided with self-monitoring tools and links to reputable web-based physical activity materials. A trained lifestyle coach with a background in exercise physiology or physical activity and health communicated weekly with participants via a secure messaging system. They also provided feedback on participant workbook pages and worked with participants to set goals and develop individualized strategies for increasing and maintaining physical activity levels.

Participants were given a body-worn step counter as an intervention tool. Participants randomized to immediate intervention were given an Omron Alvita monitor. To examine whether a monitor with additional features might add to the success of the program (examined as change in activity and program satisfaction), after the RCT ended and the wait-listed participants were offered the full ActiveGOALS program, they were given a Fitbit Alta monitor instead of the Omron monitor. They could also print tracking logs for recording time spent in moderate-to-vigorous activities and breaks from sedentary behavior. All tracked activity was entered by hand into the online intervention platform.

Additional contact was used to promote adherence to the intervention and ensure high rates of follow-up. Participants who did not log in for over 14 days received an extra message in ActiveGOALS from their coach. If there was no response within several days, the coach would send an email or call the participant. Calls were used to re-establish contact and were not used as a supplementary coaching tool. Postcards could be sent via postal mail if, after 21 days, there was still no contact with the participant. Postcards were also sent to acknowledge milestone achievement. After sessions were completed, participants retained access to the ActiveGOALS platform, including completed session materials, tracking software, and supplementary materials (until after their final study assessment). However, coaching support was no longer provided.

Wait-Listed Control Group

Participants randomized to the wait-listed control group received the full ActiveGOALS intervention program after a 3-month waiting period. During the waiting period, they received monthly health fliers on general health topics unrelated to the ActiveGOALS intervention (sleep and hydration). The *wait-listed* participants also had one additional preintervention assessment (physical activity monitoring and online questionnaires).

Outcome Measures

To ensure accurate and objective measurement of physical activity, the outcomes of moderate-to-vigorous physical activity (minutes/day), steps/day, and sedentary minutes/day were assessed with ActiGraph GT3Xbt research grade monitors. The

primary outcome of interest was the change between baseline and the 3-month postbaseline follow-up visit (postintervention for the *immediate* group and the second preintervention for the *wait-listed* group; Figure 4).

Participants were mailed a monitor and received video and paper instructions for wearing an ActiGraph accelerometer on their waist at each assessment time point. They were instructed to wear the monitor during waking hours for the 10 days following receipt of the monitor. Based on previous research, a minimum of 4 days of recording with at least 10 hours of wear time is required for an accelerometer recording to be representative of a person's "typical" activity levels [46].

For the examination of secondary outcomes related to program success over 6 months, additional assessments were conducted for all participants at 3 and 6 months after program start (Figure 4). At all assessments (pre- and postintervention participation), participants were emailed a link providing access to an online portal to complete the lifestyle/medical/weight, self-efficacy/confidence, quality of life (European Quality of Life Visual Analogue Scale [EQVAS] from the European Quality of Life 5 Dimension [EuroQol5D] questionnaire and the Promis-29 questionnaire) [47,48], and program cost survey questionnaires. All questionnaires have been previously validated [36,47-49].

A participant satisfaction survey was also provided at the 3-month postprogram assessment (within 2 weeks of completing the 13-week program). The questionnaire was designed to provide feedback on patient-centered aspects of program utility/success and focused on the ActiveGOALS platform, coaching, session materials, and tracking/goal-setting materials. Questions developed to identify facilitators and barriers to program usage and success were also included.

Questions related to the maintenance of physical activity were given to participants with their final assessment (approximately 3 months after the 13-week program was completed) toward informing the design of physical activity maintenance session materials that would follow the existing 13 sessions. Participant perceptions of activity maintenance were assessed, along with their general attitudes and opinions toward their ability to maintain their current activity levels.

To minimize missing data, participants were alerted to incomplete answers in REDCap. Project staff members checked all questionnaires for completeness, notified participants via email if a questionnaire was not complete, and provided a link to complete the questionnaire.

Research staff communicating with participants regarding assessments were blinded to patient assignment. To ensure high rates of follow-up, participants received email reminders of each outcome assessment plus mail or telephone reminders if needed (up to five contacts). Reasons for missing data and participant withdrawal or drop-out were collected. Additional outcomes will include information from the ActiveGOALS platform related to lesson completion and tracking physical activity and sedentary breaks.

Incentives

Participants were compensated US $20 for completing each assessment (wearing a research activity monitor for 10 days and completing online questionnaires). Compensation was not provided for participation in the ActiveGOALS program (eg, session completion, tracking of activity, contacting their coach, and meeting physical activity goals).

Power and Sample Size

This pilot study was powered with enrollment of 80 participants (assuming approximately 20% attrition; n=64) to identify mean differences between randomized groups at 3 months (two-sided; $P<.05$) of 5 minutes/day moderate-to-vigorous physical activity ($\beta=.97$), 1500 steps/day ($\beta=.92$), and 75 minutes/day sedentary behavior ($\beta=.82$). Reference mean (SD) values were calculated from available baseline waist worn accelerometer data for participants with below recommended activity levels in another study being conducted by members of this study group.

Analyses

To ensure rigor and reproducibility, the primary analyses will be based on between-group comparisons for the 3-month RCT data (intention-to-treat), and linear mixed effects regression models will be used to assess differences across treatment groups (immediate intervention and wait-listed control) for primary outcomes collected from the accelerometers. Secondary analyses to inform the development of additional "maintenance phase" program materials (pre- to postintervention changes across 0, 3, and 6 months) will be conducted. Linear mixed models will be used to determine relationships between sessions completed, time to program completion, tracking frequency from the ActiveGOALS platform, quality of life, self-efficacy and confidence, and self-reported weight and the primary study outcomes. These results will be analyzed and presented for all participants combined, controlling for the study arm.

Comparisons across important subgroups, including randomized assignment, and across the two age groups (21-54 and 55-70 years) will be conducted to assess differences in change across groups for all outcomes. Results may also be examined across other important subgroups identified during analyses (although subgroup analyses may be fully powered). Descriptive statistics on patient satisfaction and cost will be determined. An evaluation of missing data will be conducted to determine the amount/type of missing data. Based on the findings, sensitivity analyses will be conducted using an appropriate imputation method (mean of other group or multiple imputation).

Results

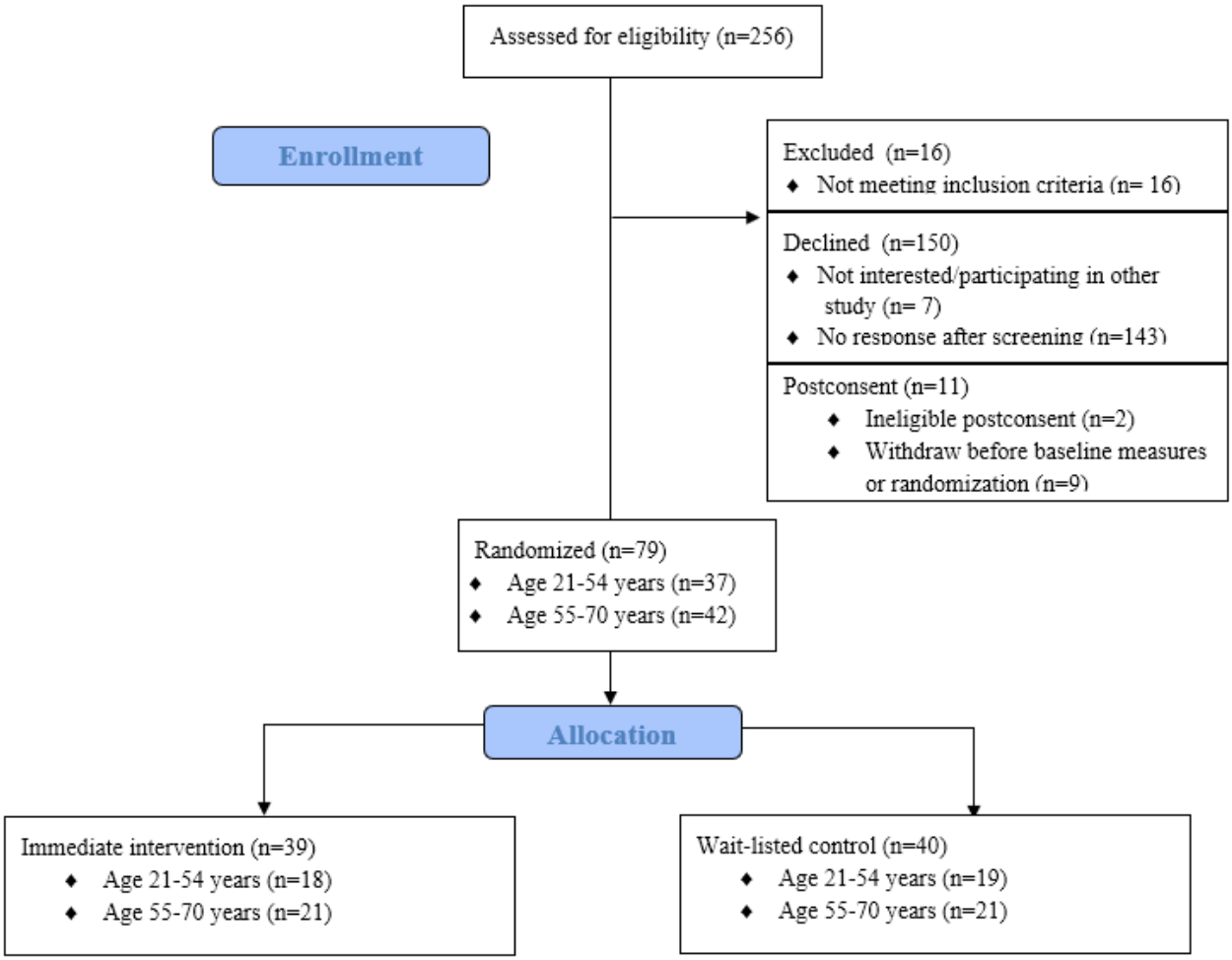
Data collection for this study has been completed. Processing data from the activity monitors is underway, after which analyses will begin. The main study results will be submitted for publication in 2021. No adverse events were reported.

A total of 256 individuals were screened for eligibility (Figure 5). Few were determined ineligible during phone screening (n=16). Reasons for ineligibility included self-report of meeting recommended activity levels, no desire to involve a physician, no dependable access to a computer, and inability to safely

perform moderate-intensity activity. Seven individuals declined to participate owing to one of the following reasons: considering participation in another study with physical activity goals and no interest in the program format. An additional 143 individuals did not contact study staff during the 5 months of active recruitment and could not be reached after three attempts.

Physician referrals and signed consent forms were received for 90 individuals (Figure 4). Two individuals signed the consent while participating in other lifestyle programs with problem solving and goal setting for physical activity, making them ineligible. Another nine individuals decided not to participate in the study shortly after consenting but before completing the baseline assessments or being randomized. Reasons for withdrawing after consent included new diagnosis requiring surgery, need to care for a family member, and no longer wanting to participate. A total of 79 individuals (37 aged 21-54 years and 42 aged 55-70 years) completed baseline assessments and were randomized for the study.

Figure 5. Recruitment flow chart.

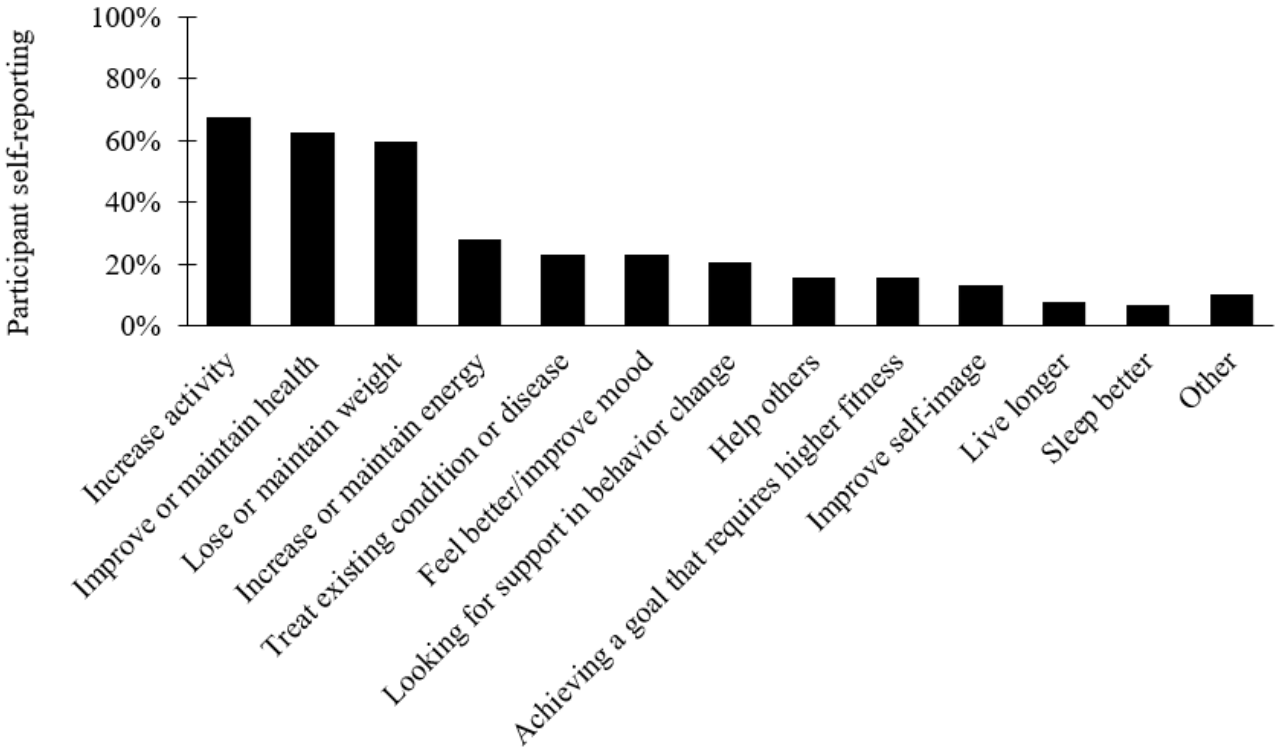


The mean age of the participants at baseline was 50.8 (SD 15.8) years. Overall, 77% (61/79) were female and 24% (19/79) reported a race/ethnicity other than white, non-Hispanic (approximately 15% African American, non-Hispanic). Our recruitment goal was to recruit a sample representative of the UPP-GIMO patient population, which is 68% female and 25% other than white, non-Hispanic.

Based on self-reported activity levels from the study screener, median physical activity levels were 15 (IQR 0-43) minutes/week of at least moderate-intensity physical activity. A total of 56 of 79 (71%) participants reported overweight or obese BMI (≥25 kg/m^2) at baseline. Additionally, most participants (58/79, 73%) reported attending “some college” or completing a degree, and 39% (n=31) reported working full time (≥40 hours/week), 17% (n=13) reported preretirement part-time work (<40 hours/week), 11% (n= 9) reported unemployment (preretirement), and 33% (n=26) reported partial or full retirement.

At the beginning of the program, all participants were prompted to “list your reasons for joining the program.” Participants were able to provide up to six reasons for wanting to take part in the ActiveGOALS Study intervention. The enrollment reasons were coded by two readers and summarized by percentage of participants reporting at least one reason pertaining to that category (Figure 6).

Figure 6. Self-reported reasons for taking part in the ActiveGOALS Study intervention (percentages based on 79 participants).



In general, participants wanted to be more physically active and hoped to see improvements in health toward preventing diseases, increasing longevity, and/or treating existing conditions. Specifically, participants most commonly reported wanting to increase activity (n=53, 67%), wanting to improve or maintain health (n=49, 62%), and wanting to lose or maintain weight (n=47, 60%). Not all reasons for participation were directly related to health. Close to 15% (n=12) of participants reported having specific life goals that required improving their fitness. Similarly, close to 15% (n=12) wanted to help others through their participation (most commonly reporting that they wanted to set a good example for others).

Discussion

Brief Summary

The ActiveGOALS Study was designed to determine the efficacy of an online physical activity intervention designed to coordinate with a patient's clinical care. The study was also designed to examine maintenance of physical activity changes for up to 3 months after program session completion and to determine patient attitudes and beliefs regarding maintenance of behavior changes related to physical activity. The results of this study will be utilized for the development of a referral program for physicians to refer primary care patients with low activity levels to a year-long intervention program for physical activity improvement.

Limitations

Currently, there are no guidelines suggesting a clinically relevant maximum level of sedentary behavior that should be observed by adults or a specific number of minutes to set as a goal for reducing sedentary behavior [10,50]. This study was powered for a sedentary reduction of 75 minutes/day, which was suggested to be feasible in a recent meta-analysis (although most studies set lower goals and achieved 30 to 60-minute reductions) [51]. Therefore, it is possible that this study could be underpowered for a smaller level of change that is later identified as a clinically relevant sedentary reduction goal.

The generalizability of this study to other populations may be limited by the fact that the study sample was recruited in Pittsburgh and the surrounding region. For example, our study sample predominantly involved white, non-Hispanic people, with African American, non-Hispanic people reported as the next largest racial/ethnic group. There were few individuals reporting other racial or ethnic groups.

Strengths

This study has a number of important strengths. First, health centers in Pittsburgh, Pennsylvania draw patients from a wide radius, and the online research format allowed us to recruit participants from within and beyond the Pittsburgh metro area. It also made it possible to retain participants who moved away from Pittsburgh and/or changed health providers during the study period.

The outcome measures for this study were collected with a validated waist-worn accelerometer. Most existing studies examining the effects of clinical prescription programs for physical activity improvement and lifestyle interventions with physical activity goals rely on self-report questionnaire data [13,25,32]. While questionnaires are useful for providing information on the types of activities performed, they can be subject to misreporting bias and are not as valid as accelerometers for providing precise estimates of *total time* spent performing physical activity or in sedentary behavior [52-54].

Additionally, existing studies for clinical physical activity referral are typically limited to clinical advice [25]. For the ActiveGOALS intervention program, we combined evidence-based strategies for behavioral change with input from important stakeholders toward developing materials that provide patients with support for behavior change in a way that is both feasible and acceptable for adult clinical patient populations. We contend that patient- and provider-centered approaches are needed to identify and address needs specific to clinical physical activity referral, which may not be as important to programs delivered in other settings. This study is also unique in reporting patient progress to referring physicians and collecting feedback from physicians regarding the utility of patient reports.

Finally, clinical physical activity referral programs currently lack strategies for long-term maintenance of behavior change. By collecting data on maintenance of behavior changes and participant attitudes and beliefs regarding long-term maintenance of physical activity, we will be able to develop better strategies for postintervention physical activity maintenance phase materials.

Conclusions

ActiveGOALS program materials were developed using existing evidence-based materials and inputs from important stakeholders. To our knowledge, there are few theory-based programs involving clinical referral to physical activity and none involving a full social-cognitive theory–based curriculum with problem solving and gradual goal setting [25,29-31]. Furthermore, owing to short follow-up periods and the lack of maintenance strategies in existing clinical programs for physical activity referral, little is known about behavior maintenance following participation in clinical referral programs [25].

The results will be used to inform the development of a 12-month theory-based behavioral change program for physical activity improvement that will be coordinated with a patient's clinical care. This program will include both behavior change and maintenance strategies, as well as clinically administered screening for low activity levels, electronic referral to the intervention, and meaningful feedback on participant progress to referring clinical teams.

Acknowledgments

We would like to acknowledge the Clinical Translational Science Institute at the University of Pittsburgh for making REDCap available for this project (NIH UL1-TR-001857). We would also like to acknowledge the PaTH Network and the Storybooth Project (Patient-Centered Outcomes Research Institute award: PCORI CDRN no. 130604912) for providing access to stakeholder engagement resources. This research was funded by the Agency for Healthcare Research and Quality through a K12 career development grant (K12 HS 022989-01 AHRQ) sponsored by the Clinical Translational Science Institute at the University of Pittsburgh. The funder and sponsor had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Only study investigators will have access to the final data set.

Authors' Contributions

BRW and KMM conceived of the presented idea. BRW, GSF, AMK, MBC, and DD helped to develop the study protocol. BRW and CR analyzed the baseline data. All authors discussed the results and contributed to the final manuscript.

Conflicts of Interest

KMM is an author on online adaptations of lifestyle lessons based on the Diabetes Prevention Program curriculum, which have been adapted for use in this intervention. The University of Pittsburgh has licensed the curriculum for commercial use and receives royalties. KMM has assigned copyright to the University and does not receive royalties, though the author directs a portion of the royalties focused on research and patient care. There are no other conflicts of interest to report.

Multimedia Appendix 1
K12 reviewer comments and author addendum with reported changes made per reviewer comments.
[PDF File (Adobe PDF File), 74 KB - resprot_v9i11e18891_app1.pdf]

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Abbreviations

DPP: Diabetes Prevention Program
EHR: electronic health record
EIM: Exercise is Medicine
GOALS: Guided Online Access to Lifestyle Support
RCT: randomized controlled trial
UPP-GIMO: University of Pittsburgh Physicians-General Internal Medicine Oakland

Edited by G Eysenbach; submitted 06.04.20; peer-reviewed by J Kariuki, B Bock; comments to author 09.07.20; revised version received 18.09.20; accepted 21.09.20; published 03.11.20.

Please cite as:
Rockette-Wagner B, Fischer GS, Kriska AM, Conroy MB, Dunstan D, Roumpz C, McTigue KM
Efficacy of an Online Physical Activity Intervention Coordinated With Routine Clinical Care: Protocol for a Pilot Randomized Controlled Trial
JMIR Res Protoc 2020;9(11):e18891
URL: https://www.researchprotocols.org/2020/11/e18891
doi:10.2196/18891
PMID:33141103

Protocol

Postdischarge Intervention for Stroke Caregivers: Protocol for a Randomized Controlled Trial

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Abstract

Background: The majority of stroke survivors return to their homes and need assistance from family caregivers to perform activities of daily living. These increased demands coupled with the lack of preparedness for their new roles lead to a high risk for caregivers developing depressive symptoms and other negative outcomes. Follow-up home support and problem-solving interventions with caregivers are crucial for maintaining stroke survivors in their homes. Problem-solving interventions are effective but are underused in practice because they require large amounts of staff time to implement and are difficult for caregivers logistically.

Objective: The aim of this study is to test a problem-solving intervention for stroke caregivers that can be delivered over the telephone during the patient's transitional care period (time when the stroke survivor is discharged to home) followed by 8 asynchronous online sessions.

Methods: The design is a two-arm parallel randomized clinical trial with repeated measures. We will enroll 240 caregivers from eight Veterans Affairs (VA) medical centers. Participants randomized into the intervention arm receive a modified problem-solving intervention that uses telephone and web-based support and training with interactive modules, fact sheets, and tools on the previously developed and nationally available Resources and Education for Stroke Caregivers' Understanding and Empowerment Caregiver website. In the usual care group, no changes are made in the information, discharge planning, or care the patients who have had a stroke normally receive, and caregivers have access to existing VA resources (eg, caregiver support line, self-help materials). The primary outcome is a change in caregiver depressive symptoms at 11 and 19 weeks after baseline data collection. Secondary outcomes include changes in stroke caregivers' burden, knowledge, positive aspects of caregiving, self-efficacy, perceived stress, health-related quality of life, and satisfaction with care and changes in stroke survivors' functional abilities and health care use. The team will also determine the budgetary impact, facilitators, barriers, and best practices for implementing the intervention. Throughout all phases of the study, we will collaborate with members of an advisory panel.

Results: Study enrollment began in June 2015 and is ongoing. The first results are expected to be submitted for publication in 2021.

Conclusions: This is the first known study to test a transitional care and messaging center intervention combined with technology to decrease caregiver depressive symptoms and to improve the recovery of stroke survivors. If successful, findings will support an evidence-based model that can be transported into clinical practice to improve the quality of caregiving post stroke.

Trial Registration: ClinicalTrials.gov NCT01600131; https://www.clinicaltrials.gov/ct2/show/NCT01600131

International Registered Report Identifier (IRRID): DERR1-10.2196/21799

(JMIR Res Protoc 2020;9(11):e21799) doi:10.2196/21799

KEYWORDS

COVID-19; stroke; caregivers; depression; burden; randomized controlled trial; web-based intervention; problem-solving

Introduction

Stroke is a leading cause of serious, long-term disability [1]. Most stroke survivors return to their homes and need family members to assist with daily activities such as bathing and toileting [2]. Evidence is accumulating that caregivers play a critically important role in helping survivors recover post stroke [3]. Researchers have found an association of family support with the improvements in the stroke survivors' physical, psychosocial, and overall functioning [4-6].

Because of the demands of caregiving, family members of stroke survivors are at high risk for developing depressive symptoms, burden, stress, and poor quality of life [7-9]. These negative caregiver outcomes are a major contributor to survivors' hospital readmission and institutionalization [10-14]. Strokes, unlike most other chronic diseases, occur without warning, and family caregivers need to quickly learn how to care for stroke survivors who have multiple impairments (eg, motor, speech, cognitive, behavioral) while simultaneously adjusting to changes in their own lives [11]. As a result, caregivers usually have feelings of inadequacy in their new roles and many unmet needs [15-18]. Thus, transitional care, follow-up support, and education with caregivers are crucial for maintaining stroke survivors in their homes.

Researchers have consistently found that interventions to help caregivers resolve problems are the most effective in supporting caregivers at home [19,20]. Unfortunately, these problem-solving interventions have been underused in practice because they require large amounts of staff time to implement and are difficult for caregivers who must travel for the intervention or be available for phone calls or visits in the home. To overcome these barriers, stroke caregiver programs are needed that involve low-cost, feasible interventions that are sustainable in routine clinical practice.

Individualized, tailored problem-solving and support programs are more likely to change health behaviors and improve self-efficacy than generic programs [19,21]. Bakas et al [22] conducted a randomized controlled trial (RCT) of an 8-week program using a telephone support approach and a task skill-building kit (TASK II), and found that the intervention improved depressive symptoms and other outcomes among caregivers with mild to severe depressive symptoms. King et al [23] conducted an RCT of a 10-session problem-solving intervention delivered in-person and by telephone. This study found improvements in caregiver depression, perception of life changes, and health at 3 months, though the improvements were not sustained at 6 months [23]. Although these interventions were effective in improving stroke caregiver outcomes, they were conducted in-person or by telephone and were, therefore, labor intensive and required scheduling to meet the convenience needs of the caregivers. For these reasons, these problem-solving interventions have been underused in practice.

Telehealth technologies offer promising approaches for overcoming traditional barriers to stroke caregiver interventions and improving outcomes. These approaches allow clinicians and researchers to provide health services through technologies such as the internet and online messaging, either alone or as supplements to enhance in-person or telephone caregiver support and training. The advantage of using internet-based interventions is that adults can receive up-to-date information in a place and time that is convenient for them. To our knowledge, only a few investigators have conducted technology-based interventions for caregivers [24].

One potentially effective technology-based delivery method that has not been well studied is online messaging between providers and patients and their caregivers. Previous researchers found that online messaging enhanced access to care [25], improved quality of care [26], and reduced the cost and use of care [27,28]. Other benefits include patients' comfort while asking questions and the ability to save messages [29]. Additionally, previous studies found that online messaging is acceptable to patients and improved a variety of patient outcomes [30-32].

To our knowledge, no previous studies have been conducted with online messaging for stroke caregivers. To address gaps in previous research, this study tests a tailored, problem-solving intervention for stroke caregivers that is delivered in one telephone session during the transitional care period (eg, time in which the stroke survivor is discharged home) followed by online messaging center sessions over a secure messaging system. The long-term goal is to develop a model for future caregivers that can be sustainable in routine clinical practice and is not overly burdensome for caregivers.

This study has five aims. The primary aim (aim 1) is to test the effect of the intervention on stroke caregivers' depressive symptoms at 11 and 19 weeks after baseline data collection. Aim 2 is to test the effect of the intervention on stroke

caregivers' burden, knowledge, positive aspects of caregiving, self-efficacy, perceived stress, health-related quality of life, and satisfaction with care at the posttest assessments. Aim 3 is to test the effect of the intervention on stroke survivors' outcomes: functional abilities and health care use (ie, unintended hospital stays, emergency room visits). Aim 4 is to determine the budgetary impact of implementing the intervention. Aim 5 is to determine the facilitators, barriers, and best practices for implementing the intervention. Our primary hypothesis is that stroke caregivers who receive the intervention will have fewer depressive symptoms compared to those in the usual care group. Our secondary hypotheses are that caregivers and stroke survivors in the intervention arm will have superior outcomes compared to the usual care arm.

Methods

Ethics Approvals and Monitoring

Approvals were obtained from the Veterans Affairs (VA) Central Institutional Review Board and the local VA Rehabilitation and Development committees at the three primary sites (Gainesville, Tampa, and Miami). The protocol is registered in ClinicalTrials.gov (NCT01600131). Informed consent is obtained from all caregivers participating in the study. Although stroke survivors do not directly participate in the study, we discuss their medical history with their caregiver. Therefore, we also obtain informed consent from the stroke survivors. The study is monitored through annual reports to the VA Health Services Research & Development Data Safety Monitoring Board [33]. No interim data analysis has or will be conducted.

Advisory Panel

We established an advisory panel consisting of clinicians and VA leadership at the national and local level. Initially, monthly conference calls were held to obtain members' input in the planning and development phases. Later, periodic meetings were held to obtain advice on conducting the study. After the data are collected, panel members will meet to help in the interpretation of the study findings and planning for the dissemination of results and strategies to sustain the intervention in practice if it is found to be successful.

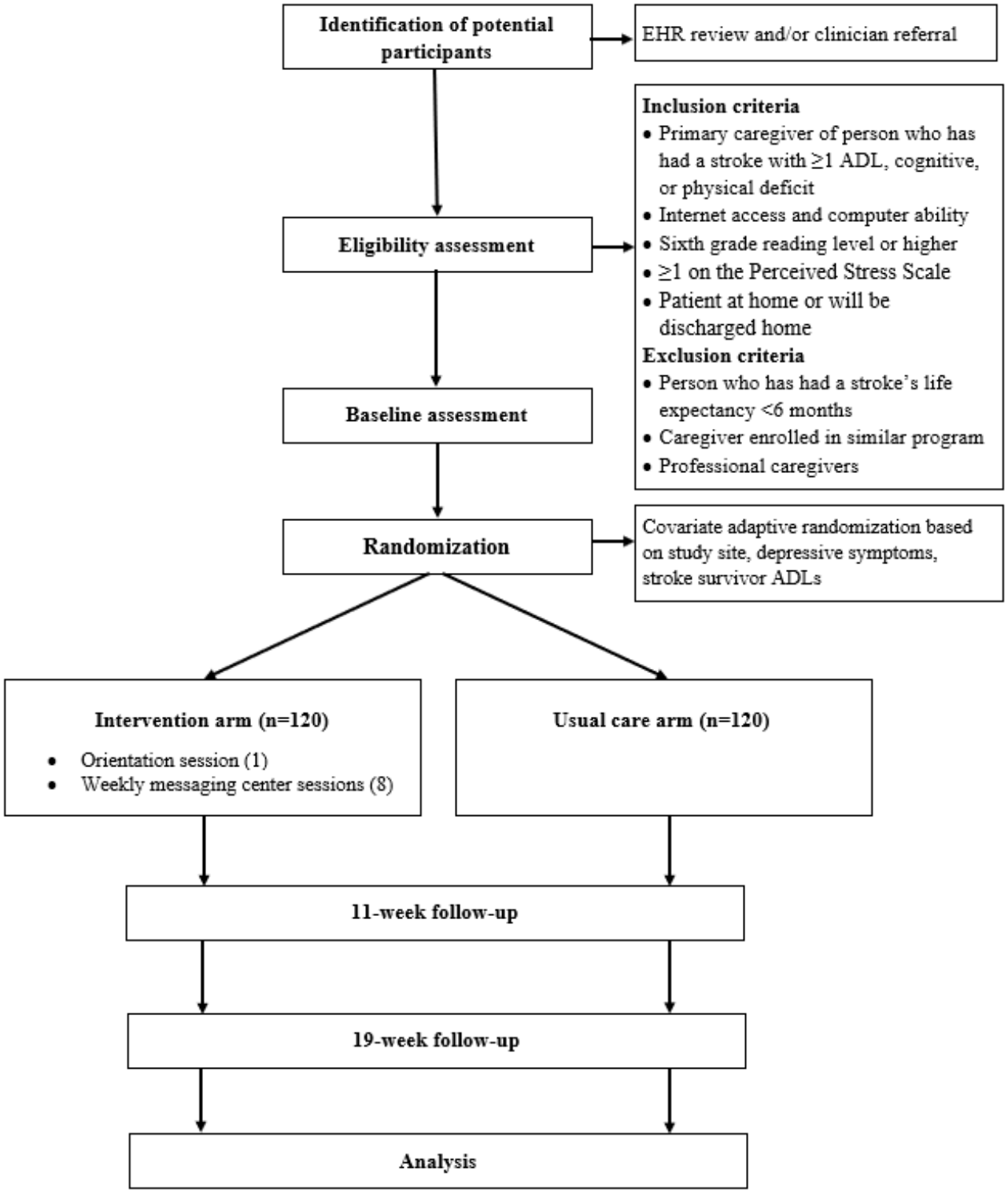
Study Setting

The original protocol was to conduct the study at three Florida VA medical centers (Gainesville, Tampa, and Miami). These three sites will be referred to as the main study sites. Due to lower than expected initial enrollment, we modified the protocol after initiating the trial to expand recruitment to five additional or remote VA sites: Houston, TX; Richmond, VA; Little Rock, AR; Nashville, TN; and Boston, MA. At the three main sites, staff assist with the management of the study, conduct the intervention, and recruit caregivers from all eight study sites.

Study Design and Eligibility Criteria

This study is a two-arm parallel randomized clinical trial with repeated measures. The study flowchart is presented in Figure 1. All caregivers of stroke survivors are eligible for participation if they meet the following criteria: are the primary caregiver and provide the majority of care for an individual who has a primary diagnosis of stroke (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD10] codes for stroke: 160.0-169.998), stroke survivor has ≥1 activity of daily living (ADL) deficit (≤95 on the Barthel Index [34]) or a new or worsening cognitive or physical functioning problem, caregiver has internet and email access and ability, caregiver reads English at the sixth-grade reading level or better (≥13 on the Behavior Rating Inventory of Executive Function Health Literacy Scale [35]), caregiver scores ≥1 on the Perceived Stress Scale [36], and stroke survivor was discharged home within the preceding 4 months or plans to be ultimately discharged home. Eligibility is determined by caregiver self-report and review of the stroke survivor's electronic health record (EHR).

Figure 1. Study flowchart. ADL: activity of daily living; EHR: electronic health record.



Caregivers are excluded if the stroke survivors they care for are terminally ill, have a life expectancy of 6 months or less, are prisoners, or are currently enrolled in or have completed similar caregiver interventions. Caregivers are also excluded if they are professional caregivers who have no pre-existing relationships with the stroke survivor. Life expectancy and service use are determined by reviewing the EHR and conferring with the in-patient staff and the investigators' clinical team members. If an enrolled caregiver no longer meets eligibility criteria (eg, no longer caring for the stroke survivor), they are withdrawn from the study. If an enrolled caregiver is unable to complete the intervention, we still attempt to collect follow-up data from them.

Recruitment and Enrollment

Recruitment is conducted through two strategies: clinician referral followed by face-to-face recruitment or EHR review followed by telephone recruitment. At the main study sites, clinicians caring for stroke survivors inform study staff of interested participants. Study staff then contact the caregiver

either in-person or by phone, explain the study, and screen the stroke survivor and caregiver for eligibility. A second strategy is to identify stroke survivors at all study sites who have a diagnosis of stroke based on ICD10 codes by reviewing the VA Patient Care Encounter Package Dataset and the VA's EHR. The team mails letters of invitation and self-addressed, stamped recruitment postcards with an opt-in or opt-out option to the stroke survivor or next of kin. A staff member telephones the stroke survivors or their next of kin (ie, those who returned the postcards with positive responses or those who did not return the postcards) and explains the study and determines eligibility.

Staff conduct the informed consent process with eligible participants in person or by telephone.

For patients who have had a stroke who have potentially diminished decision-making capacity, a study staff member asks the patient screening questions to assess their orientation (ie, "what is the month?" "what is the year?" "what state are we in?") and comprehension (ie, asking the patient to reiterate back their understanding of the study). If patients are unable to answer the screening questions or the clinical staff indicates the potential for diminished decision-making capacity, we obtain consent from the patient's legally authorized representative. We obtain assent of the patients who have had a stroke and respect any dissent of the patients. If patients have physical disabilities and are unable to sign the informed consent forms, the patients are asked to make marks with witnesses present. If patients who have had a stroke are aphasic or unable to speak clearly, we confer with the patient's clinical staff regarding their decision-making capacity.

Study staff at the main study sites are responsible for all recruitment and enrollment activities. Only caregivers participate in data collection and the intervention. Caregivers receive a US $20 incentive for each data collection session they participate in (US $60 total). Caregivers selected for qualitative interviews receive an additional US $20 incentive.

Randomization

After the baseline assessment, caregivers are randomly assigned to one of the two study groups (ie, intervention or usual care) using the Pocock-Simon covariate adaptive randomization procedure [37] that is overseen by the study statistician. This randomization procedure is used to allocate an approximately equal number of caregivers assigned to the two groups within each covariate level (ie, depressed or not, high or low ADL, and study site). The technique has demonstrated an ability to provide good marginal balance in covariates and is frequently used in clinical trials [38].

Intervention Arm

We are conducting a nurse-guided intervention. In the original study proposal, the first intervention session was planned to occur face-to-face in the in-patient setting shortly before the stroke survivor's discharge from the hospital. However, because many stroke survivors have a short inpatient stay or are discharged to rehabilitation facilities across a large geographic region, we modified the protocol to begin the intervention after the stroke survivor's discharge home. Thus, the original intervention manual was modified to include two parts: a telephone orientation component and online messaging center component. These changes were made prior to initiation of recruitment.

The intervention is theoretically based on D'Zurilla and Nezu's [39] relational and problem-solving model of stress, and incorporates constructs from Lazarus and Folkman's [40] stress appraisal and coping theory. The model was subsequently refined by Houts and colleagues [41,42] and summarized by Creativity, Optimism, Planning, and Expert Information (COPE). This model emphasizes creative thinking to view problems in new ways, maintaining an optimistic attitude, developing a plan to solve problems, and learning how to seek expert information. Throughout the intervention, the nurses use motivational interviewing techniques [43].

Resources and Education for Stroke Caregivers' Understanding and Empowerment Website

The Resources and Education for Stroke Caregivers' Understanding and Empowerment (RESCUE) website [44] serves as the foundation for the entire intervention. Consistent with the COPE model theory, the website uses the theme of RESCUE to illustrate how caregivers act as "lifeguards" and are responsible for the safety and well-being of those under their watchful care. Following this theme, the image of a life preserver is used as a branding image and integrated throughout the website. The website has been extensively pretested and evaluated [45]. The website is written in both English and Spanish languages, and includes the following sections: list of resources, a library of patient education newsletters, self-help tools, a glossary of medical terms with phonetic pronunciations, testimonials from stroke caregivers, links to other stroke and caregiver websites, more than 45 fact sheets, a problem-solving training module, and a problem-solving diary form.

A major part of the intervention is teaching from the comprehensive library of over 45 fact sheets. The fact sheets are organized by the COPE framework and include the following: basic information about the problem (eg, common signs and symptoms that caregivers should look for), information that the problem is common but that there are effective treatments, helpful tips for dealing with the problem, and information on when caregivers should seek emergency help or (if less severe symptoms exist) when to call their health care providers. A list of RESCUE website fact sheets is presented in Textbox 1.

Textbox 1. Resources and Education for Stroke Caregivers' Understanding and Empowerment fact sheet library topics.

General Stroke

- About Stroke, After Stroke, Stroke Rehabilitation

Obtaining Good Healthcare Information

- Communicating with your Loved One's Healthcare Team, Finding Health Information, My Health*e*Vet

Understanding How Caring for a Loved One Affects You

- Changes in Relationships, Caregivers who Work Outside of the Home, Caregiver Stress/Depression, Long-Distance Caregiving

Caring for Someone with Physical Needs

- Personal Care, Speech & Communication, Changes in Body Function, Pain, Spasticity, Swallowing, Fatigue, Sleep, Urinary Incontinence, Sex After Stroke

Caring for Someone with Emotional & Behavioral Needs

- Coping with Emotional Changes, Depression, Apathy, One-Side Neglect, Cognitive & Memory Problems, Personality Changes, Difficult Behaviors

Keeping Your Loved One Healthy

- Managing Medicines, Healthy Eating & Exercise, Spirituality

Helping Your Loved One Become More Independent

- Preventing Falls, Ways to Make Home Safer, Assistive Devices, Driving & Transportation

Finding Community Resources

- Community Services, Getting Help, Stroke Support Groups, Respite Care, Long-Term Care, End of Life Care

Managing Financial & Legal Issues

- Finances, Help with Legal Matters, Paying for Community Services

Helpful Tools

- Aphasia Card, Medication Card, Personal Health Record

Intervention Sessions

The first intervention component, the orientation session, is conducted in one session over the telephone the week following the baseline assessment. Before participating in this session, the caregiver receives in the mail a workbook that provides information about the study and how to access and navigate the website. The goal of this first session is to develop rapport and to orient the caregivers to the RESCUE website and intervention. The nurse provides a guided tour of the RESCUE website and asks the caregivers for a return demonstration of navigating and finding specific information on the website. Similar to how teachers use Powerpoint (Microsoft Corporation) presentations for classroom instruction, the nurse uses the module and diary on the RESCUE website to teach caregivers the steps of the problem-solving method. With coaching and feedback from the nurse, the caregiver develops their personalized problem-solving plans. Last, the nurse summarizes the training, answers questions, and orients the caregivers to the RESCUE messaging center and the follow-up messaging center sessions. Telephone orientation session goals and activities are presented in Textbox 2.

Textbox 2. Intervention session objectives and activities.

Telephone orientation session

- Rapport building and caregiver assessment
  - Discussion of changes in stroke survivor
  - Assessment of caregiver skills and needs
- Website orientation
  - Workbook review
  - Website tour
- Review problem-solving module on the Resources and Education for Stroke Caregivers' Understanding and Empowerment (RESCUE) website
  - Discussion of the basic concepts of the problem-solving approach (Creativity, Optimism, Planning, and Expert Information)
- Apply the problem-solving approach and the RESCUE website to address a common caregiver problem
  - Illustrative example on caregiver depression and stress
  - Nurse demonstrates application of problem-solving approach
- Development of a personalized problem-solving plan
  - Nurse guides caregiver in identifying and prioritizing problems
  - Review of fact sheet(s) tailored to the caregiver's problem
  - Caregiver works with nurse to develop problem-solving plan
- Summary of the problem-solving approach and messaging center
  - Nurse summarizes the session and answers questions
  - Nurse demonstrates how to use the RESCUE messaging center

Messaging center sessions

- Assess for changes
  - Nurse assesses caregiver and stroke survivor status and identifies any changes since previous session
- Review educational material
  - Nurse assesses comprehension of assigned fact sheets
- Review discharge plan
  - Nurse asks tailored questions pertaining to stroke survivor's discharge plan
- Apply problem-solving approach
  - Nurse providers feedback on caregiver's previous worksheet
  - Nurse asks tailored follow-up questions on caregiver's problem-solving plan
- Identify new problems (optional)
  - Caregiver identifies a new problem they would like to work on (if applicable)
  - Caregiver applies problem-solving approach to the new problem
- Prepare for next session
  - Nurse assigns fact sheet for next session

The second component, the messaging center component, consists of 8 asynchronous sessions that are conducted over the RESCUE messaging center. The sessions reinforce, sustain, and supplement what was learned during the orientation session component. The goals of the messaging center component are to refresh the caregiver's knowledge of the problem-solving method, motivate and empower the caregivers' abilities to access information on the RESCUE website to resolve their problems,

and provide additional skills training to facilitate caregivers' successful adjustment after the stroke survivors' return to home.

The messaging center sessions involve three parts: (1) education on the RESCUE website, (2) problem-solving planning, and (3) discharge plan review. For part one, caregivers read assigned fact sheets on the RESCUE website that focus on general caregiving skills needed by all caregivers as well as fact sheets that are directly targeted to the unique needs that are identified by the caregivers. The nurse will respond each week with targeted questions about the assigned fact sheets to ensure the caregiver is receiving and understanding the intended information. The nurse also answers any questions from the caregiver and assesses the health and well-being of the stroke survivor and caregiver. In the second part of each session, the caregivers apply their skills training to develop personalized problem-solving plans using the RESCUE messaging center. The role of the nurse is to empower the caregivers via the messaging center to solve their problems by helping them apply their problem-solving training. The third part of each session covers the stroke survivors' discharge plan. The nurse provides tailored questions pertaining to progress on discharge goals (ie, follow-up appointments, obtaining durable medical equipment). The messaging center session goals and activities are presented in Textbox 2.

The messaging center is a secure site that is located behind the VA firewall. The messaging center uses structured electronic worksheets with a free-text format that enables the caregivers and the nurse to asynchronously communicate online over an encrypted channel. The messaging center is designed to be simple and user-friendly. The caregiver-nurse communication reinforces information that the caregiver has learned and empowers caregivers to act on their behalf, by providing acceptance and integration of new knowledge and reinforcing positive problem-solving skills. For the messaging center sessions, the study team maintains records of "exact correspondence" of the caregiver-nurse communications on the messaging center. We collect data on the amount of time caregivers report spending on the intervention to monitor participant adherence.

The first messaging center session is arranged during the orientation session. Sessions are due weekly, which is communicated to the caregiver in the orientation session and in each messaging center worksheet. A reminder call is placed if the session is not complete the day before it is due. Up to three reminder calls are placed if the session is overdue. If we are unable to reach the caregiver after three attempts, they are withdrawn from the study. If a caregiver is unable or unwilling to continue with the intervention, they are offered the opportunity to discontinue the intervention but remain in the study for data collection phone calls. If a caregiver falls more than 2 weeks behind, the case is discussed at weekly study team meetings. The principal investigator makes the final determination of whether to continue or discontinue the intervention with the participant. Any deviations from the intervention schedule are documented.

Usual Care Arm

For caregivers in the usual care group, no changes are made in the information, discharge planning, and care the patients who have had a stroke normally receive. Similar to procedures in the intervention group, the staff document the discharge planning and care received by reviewing the stroke survivors' electronic records. Caregivers randomized to the usual care group participate in data collections at the same time points as the intervention arm (11 and 19 weeks after baseline). No information about the RESCUE website is provided to the usual care group participants during the study, but it is possible for these participants to access the website, as it is publicly available. To assess for contamination, we ask usual care participants if they have ever visited the RESCUE website during follow-up data collection. After completion of the study, usual care participants are mailed self-help materials along with the RESCUE website URL.

Fidelity Considerations

The team uses recommendations of Borrelli et al [46] and Burgio et al [47] to lessen problems with fidelity and increase the likelihood that the intervention is delivered consistently. The team uses a pretested, standardized study manual that includes data collection scripts and step-by-step directions for conducting the informed consent procedures and intervention. The team provides extensive training to team members that include role-playing activities and didactic instruction on topics such as motivational interviewing, stress reduction techniques, and caregiving issues.

To monitor the delivery of the intervention, a mental health counselor or mental health nurse practitioner listens to the research nurse's orientation sessions with their first two assigned caregivers to identify any fidelity issues at the beginning of the project. Following this initial monitoring, we periodically review the remaining sessions. We also ask the research nurses to track the number of minutes they spend with each caregiver and to keep detailed notes of any deviations from the study protocol that occur. We discuss the deliveries of the intervention and evaluate adherence to study protocols, noting all deviations on a form. Feedback is provided to the nurses and additional training is provided if needed.

Similarly, we monitor the messaging center sessions that are conducted via the RESCUE messaging center. The counselor or nurse practitioner reviews the first two "exact correspondences" of the caregiver and nurse to identify initial fidelity issues. After this assessment, the counselor or nurse practitioner periodically reviews the exact correspondences between the caregiver and nurses on the messaging center. The research nurses conducting the messaging center sessions also keep detailed notes of any deviations in the protocol that occur during the messaging center sessions. We review the fidelity check data and provide feedback and training, as needed, to the nurses.

We evaluate "enactment" using an adapted treatment acceptability and enactment tool [48,49]. The tool asks caregivers in the intervention group to rate the amount of information and contact they received during the orientation

and messaging center sessions, how much they used the skill-building strategies and the RESCUE website, how helpful the intervention was, and whether their problems were resolved. Each item is scored on a 5-point rating scale. We also ask caregivers in the usual care if they used the RESCUE website and whether their problems were resolved.

Data Collection

Quantitative

Staff members administer study instruments to caregivers via telephone at baseline and then caregivers are randomized to one of the two arms. Two posttests are conducted by blinded staff members at 11 and 19 weeks after baseline assessment. Data collection time points were chosen to assess immediate (ie, 1 week postintervention) outcomes and determine if the effect of the intervention is sustained at 2 months postintervention. The staff also supplement information provided by the caregiver about the stroke survivor (ie, demographics, discharge plans, health care use) by reviewing the stroke survivors' EHR.

Qualitative

Staff members conduct in-depth qualitative interviews with a subsample of 15 caregivers who have completed the intervention. A sample size of 15 was chosen due to the relatively narrow scope of our research question, specificity of our sample, and pilot trial experience [50-52]. To obtain a diversity of caregiver perceptions, we use a maximum variation sampling technique [53,54] to select caregivers with high (≥16) and low (<16) scores on the Center for Epidemiological Studies Depression depressive symptom scale [55]. Interviews are collected via telephone separately from quantitative data. In-depth information from the caregivers' perspectives of the value, acceptability, and facilitators and barriers of the intervention is obtained. The interviews are digitally recorded and transcribed verbatim.

Data Management and Quality Control

Trained team members use a standardized manual for data collection. Data collectors record participant responses on paper and then enter them into an online database. Quality checks of the data are collected and entered by staff. Within 2 business days, a study member who did not enter or collect the data checks paper data collection forms against database entries to assure that the information is accurate and no data are missing.

Blinding

The principal investigator and staff collecting outcome data are blinded in this study. Access to files containing group assignment is restricted to unblinded study team members. Prior to collecting outcome data, study staff remind caregivers that they are not to reveal their group assignment. After collecting outcome data, staff complete a blinding assessment. The blinding assessment will be compared to the actual group allocation to assess the effectiveness of blinding procedures.

Outcomes

The primary outcome is change in stroke caregivers' depressive symptoms at 11 and 19 weeks after baseline data collection. Secondary caregiver outcomes are changes in burden, stroke knowledge, positive aspects of caregiving, self-efficacy, perceived stress, health-related quality of life, and satisfaction with care at 11 and 19 weeks after baseline. Secondary stroke survivor outcomes are change in functional abilities at 11 and 19 weeks after baseline data collection and health care use.

Measures

We carefully chose measures that have good psychometric properties, are easy to administer, and are relatively short in length to reduce participant burden. An important consideration in our selection was including measures that had been used in our previous caregiver studies so that we could compare our results with existing literature. Two burden measures were used to capture the time and difficulty of specific caregiving tasks [56,57] in addition to caregivers' general feelings of burden [58]. The measures used are presented in Table 1.

Table 1. Outcome measures.

Concept; instrument	Description of instrument	Time (mins)
Stress; Perceived Stress Scale [36]	Changes in perceived stress will be measured by the PSS-4[a]. The 4-item measure assesses stress experienced in the last month on a 5-point Likert scale ranging from 0 (never) to 4 (very often). Scores range from 0-16, with higher scores indicating more stress.	<2
Stroke knowledge; National Institutes of Health Stroke Knowledge Tool [59]	The Stroke Knowledge Tool is adapted from the online quiz developed by the National Institutes of Health. The tool consists of 7-items that ask caregivers about their knowledge of the signs, symptoms, and risk factors of stroke. Items are true/false or multiple choice, with higher scores indicating better stroke knowledge. Scores range from 0 to 7.	<5
Depressive symptoms; CES-D[b] [55]	CES-D is a 20-item, 4-point Likert scale ranging from never (0) to most of the time (3). Possible scores range from 0 to 60, with higher scores indicating more symptoms. It has been used in numerous studies with caregivers and has good reliability and validity [55,60].	<5
Positive Aspects of Caregiving Scale 11-item [61]	The Positive Aspects of Caregiving Scale is an 11-item, 5-point Likert scale ranging from disagree a lot (1) to agree a lot (5) with a range of 11-55. The scale assesses perceptions of benefits within the caregiving context. The questionnaire has demonstrated good reliability and construct validity [62].	<5
Revised Scale for Caregiver Self-Efficacy [63]	This 15-item tool measures caregivers' judgments about their ability to perform caregiving tasks. We administer the Obtaining Respite (5 items) and Controlling Upsetting Thoughts About Caregiving (5 items) subscales. Respondents rate their level of confidence for each item from 0 to 100. The scale has shown adequate reliability and construct validity [63].	<5
Caregiver burden – Short Version of the Zarit Burden Interview [58]	Items in this 12-item instrument fall into five categories (health, well-being, finances, social life, and relationship with impaired person). This instrument is scored on a 5-point Likert scale ranging from 0 (never) to 4 (nearly always). Possible scores range from 0 to 48, with higher scores indicating higher burden. The instrument was originally developed to measure dementia caregiver burden but has been used in stroke caregiver studies and is appropriate for other caregiver populations [58,64].	<5
Health-related quality of life; VR-12[c] [65]	The VR-12 consists of 12-items that measure health-related quality of life. Items are scored on a 3-point or 5-point scale. It consists of physical and emotional scales. Scores for each scale are calculated by using an algorithm. Higher scores indicate better health-related quality of life. This is a widely used tool in stroke caregiver studies and has good psychometric properties [66].	<2
Patient satisfaction; General Satisfaction Subscale of the Patient Satisfaction Questionnaire [67]	The scale consists of 6 items on feelings about the recent medical care they have received. Responses to items range from 1 (strongly agree) to 5 (strongly disagree). Scores range from 6 to 30. The scale has demonstrated excellent reliability and good internal consistency [67].	<5
Oberst Caregiving Burden Scale [56,57]	This instrument uses a 5-point response scale to measure the perceived amount of time spent and the perceived level of difficulty of 15 tasks and activities that caregivers do to help stroke survivors. Each item is scored on a 1-5 scale for difficulty (1=not difficult, 5=extremely difficult) and time (1=no time, 5=a great deal of time). The scale has shown good reliability, construct validity, and content validity [57].	<8
Treatment Acceptability and Enactment Tool (adapted from McLennon et al [48] and Bakas et al [49])	This adapted 9-item tool measures caregivers' perceptions of the value, helpfulness, and enactment of the intervention using a 5-level Likert scale. The caregivers rate different components of the intervention and indicate how often they visited the Resources and Education for Stroke Caregivers' Understanding and Empowerment website, how often they used problem-solving strategies, and how many problems they resolved. Higher scores indicate a greater level of acceptability and enactment.	<2
Activity of daily living; Barthel Index [34] (completed by caregiver)	This 10-item tool measures patients' abilities to perform self-care tasks (eg, feeding, bathing). Response options are scored on 5-point increments (eg, 0=unable, 5=needs help, 10=independent). Total scores range from 0 to 100, with higher scores indicating greater functional abilities. The tool has been reported to have excellent reliability, validity, and adequate responsiveness to change in measuring neurologic physical disability [34,68,69].	<2

[a]PSS-4: Perceived Stress Scale.

[b]CES-D: Center for Epidemiologic Studies Depression.

[c]VR-12: RAND 12-Item Health Survey.

Data Analysis

Caregiver and Stroke Survivor Outcomes

For aims 1-3, the focus of the primary analysis is to examine the effect of the intervention based on "intention to treat." Data from all the participants will be part of the primary analyses regardless of the actual number of completed messaging center sessions. The effectiveness of the intervention will be examined taking into account real-world compliance factors. As an exploratory study element, the team will assess compliance and attempt to determine its effect on study results. The general linear mixed model for repeated measures will be used to model the follow-up depression and secondary outcome times (11 and 19 weeks after baseline data collection). Of primary interest is the estimated within-site intervention effects at 11 and 19 weeks after baseline data collection, controlling for baseline covariates, and stratifying by site. To control for possible chance sample imbalances resulting from randomization, the model will include

covariates for baseline prognostic factors (eg, discharge from hospital, community living center, or rehabilitation facility; caregivers' relationship to stroke survivor; number of previous strokes), deemed to have significant relationships with the response and groupwise imbalances. Thus, the analyses will be able to compare the groups on the measure of interest while controlling for these factors.

Budgetary Impact

We will determine the budgetary impact of the intervention. This analysis will consist of two parts: (1) the incremental cost of the intervention itself over and above usual care and (2) the impact of the intervention on health care use. Microcosting techniques [70] combined with average costing [71] will be used to determine the average staff time, wage, space, and equipment costs associated with the intervention. The microcost estimate for the orientation and messaging center sessions will use the average elapsed time of such sessions along with an estimate of the average national wage of the type of nurse most likely to deliver the intervention in the field. To determine the intervention's impact on the costs of health care use, the team will rely on the Professional Society for Health Economics and Outcomes Research 2014 budgetary impact analysis guidelines [72]. Data on VA-funded use costs will be obtained from Managerial Cost Accounting System and the Non-VA Medical Care files. The team will tabulate all costs from these sources for study enrollees throughout the study, calculate the difference between intervention and usual care average costs, and test for the statistical significance of this difference using the *z* score method proposed by Zhou et al [73]. The final step in determining the budgetary impact of the intervention will combine parts 1 and 2 to determine the complete impact of the intervention on the VA budget.

Qualitative Interviews

Qualitative data will be managed using NVIVO (QSR International). We will use template analysis for qualitative data [74,75]. Template analysis is a method of thematically organizing and analyzing qualitative data. We will develop a coding framework with a priori themes based on the qualitative interview guide. We will apply this framework to the first three interviews and add or revise themes as needed. We will use an iterative process in which team members will independently code each transcript and meet to compare coding and resolve discrepancies. Study team members will continue this process until no new themes are identified. The qualitative team members will interact regularly with the principal investigator and the entire team to discuss the findings and to search for alternative explanations in the data. An audit trail containing a log of all decisions and changes, along with the reason for the decision or change, will be kept to ensure methodological rigor.

Power Analysis and Rationale for Sample Size

The sample for aims 1-4 consists of 240 caregivers. Assuming a standard deviation of 8.2, 84 subjects per group will achieve 80% power to detect a mean intervention effect size of 3.5 on depression at a 5% significance level. The sample size of 120 per group (ie, intervention group, usual care group) was selected to account for the occurrence of a 30% dropout rate. The dropout rate, expected effect size, and variability were deemed reasonable based on previous literature [49,55,76]. For aim 5, we will select a purposive subsample of 15 caregivers who completed the intervention arm of the study. Typically, 8-12 participants are needed to reach theoretical saturation [53].

Safety Considerations

The study team includes a mental health counselor who will be involved in all cases where there may be concern about a caregiver's mental health. In the event that a study team member believes caregivers are experiencing unmanageable stress but not severe stress, the caregiver will be advised to call the stroke survivor's assigned VA primary care social worker or the primary care clinicians of the patient's care team. Study staff will also give the caregivers the phone number of the VA Caregiver Support Line and other referral sources as needed. If any study team member feels that a caregiver may be experiencing severe stress or crisis, or if the team member uncovers that the patient who has had a stroke has serious changes in their health, the team member will call a member of the stroke survivor's VA primary care team or the local emergency response system. In the event that any abuse or neglect is suspected, study personnel will follow established procedures by oversight agencies, including the VA, Institutional Review Board, and the state Abuse Hotline.

Results

Study enrollment began in June 2015 and is ongoing. As of May 2020, we have enrolled 141 caregivers and 104 caregivers have completed the study. The first results are expected to be submitted for publication in 2021.

Discussion

The RESCUE Intervention

It is well documented in the literature that strokes are disabling and require extensive involvement of family caregivers for successful rehabilitation of the stroke survivor [1,3]. Caregivers are often ill-prepared to manage their own problems as well as the multiple psychological, social, and physical disabilities of their stroke survivors. Thus, national organizations emphasize the importance of providing information and support interventions to facilitate the problem-solving skills of caregivers [2,3].

Although tailored support and problem-solving interventions have been effective in improving stroke caregiver outcomes, these interventions are often burdensome to caregivers and not feasible to implement in routine clinical care. The RESCUE intervention was planned to be pragmatic and, if found to be successful, easily implemented in the real-world setting. Use of the asynchronous messaging center minimizes caregiver burden and requires less health care system resources compared to in-person or telephone interventions. This intervention is especially relevant because over 70% of American caregivers use the internet to obtain health information [77]. Although we used a VA platform for this intervention, the RESCUE website is publicly available, and the program could be delivered in

other health care systems through patient portals and secure messaging systems.

This study has several strengths. Few stroke caregiving studies have included an aim to assess the budgetary impact of the intervention. Although the study is not powered to conduct a full cost-effectiveness study, our data will provide information on costs that can be used to guide future implementation efforts. The study uses implementation science strategies such as the development of partnerships with VA and community clinicians and leaders to collaborate throughout all the study phases and develop plans for dissemination of findings and strategies to transport the intervention to other sites. The qualitative interviews will additionally provide information for improving and refining the intervention to further increase the likelihood that it will be useful in clinical practice.

Limitations

Because the study is an RCT, threats to internal validity are less likely to be an issue [78]. However, even with this study design, there are internal threats to validity, such as diffusion of treatment and the Hawthorne effect. External validity threats may jeopardize the generalizability of the study findings. For example, the sample is restricted to caregivers who have a reading level above sixth grade and are capable of navigating the internet. It may be possible that only caregivers who already have problem-solving skills and are confident will choose to participate, thereby further restricting the sample to caregivers who already have self-efficacy and are less in need of the intervention.

Respondent burden is a potential limitation but is minimized by using instruments that are brief and understandable. Data collection sessions are arranged at convenient times and messaging center sessions are conducted asynchronously online whenever the caregivers choose to participate. Except for the budgetary impact, the data are self-reports from caregivers, and thus, there may be errors due to poor recall and caregivers providing socially desirable answers.

A challenge in this study is recruitment and retention. We have experienced lower than expected recruitment that is likely attributable to a variety of factors, including a general decline in admissions for stroke in recent years, VA patients receiving care at non-VA facilities, advancements in stroke care, a lower than expected number of patients who have had a stroke at VA facilities, and potential participants failing to meet eligibility criteria, such as lack of internet access. We sought to address these issues by expanding our recruitment sites; however, recruitment remains a challenge. Other strategies we employed to address recruitment issues include regular clinic visits by the research nurse, presentations about the study to clinicians and other stakeholders, and consultation with the advisory panel. To mitigate retention issues, staff carefully explain how much time and effort is required prior to enrollment and schedule study activities at times convenient to the caregiver. In addition, we mail postcards to enrolled caregivers who the team cannot contact after three attempts. Implementation of the program in routine practice may alleviate some of these issues by removing study-specific eligibility criteria, but the program may also have less reach than originally anticipated.

Conclusions

This is the first known study to test a transitional care and messaging center educational intervention combined with online training and application of the problem-solving approach to improve the quality of caregiving and the recovery of patients post stroke to enable them to remain at home. Other outcomes will be an updated stroke caregiver website and an evidence-based intervention (transitional care, online training, and messaging between providers and caregivers) that can be transportable to other sites and used as a model to improve caregiving of patients with other chronic diseases.

Acknowledgments

We would like to acknowledge the contributions of Karen Besterman-Dahan, Kimberly Findley, Tim Hogan, John Kairalla, Lindsay Hall, John Midolo, Tatiana Orozco, Kristen Wing, Jason Rogers, Sergio Romero, Xinping Wang, and Samuel Wu to this project.

This study was supported by funding from the US Department of VA Health Services Research & Development grant IIR 11-343. The funders had no role in the study design, data collection and analysis, interpretation of data, decision to publish, or preparation of the manuscript.

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of VA or the United States government.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from HSR-6 Post-acute and Long-term care.
[PDF File (Adobe PDF File), 1118 KB - resprot_v9i11e21799_app1.pdf]

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Abbreviations

ADL: activity of daily living
COPE: Creativity, Optimism, Planning, and Expert Information
EHR: electronic health record
ICD10: International Statistical Classification of Diseases and Related Health Problems, 10th revision
RCT: randomized controlled trial
RESCUE: Resources and Education for Stroke Caregivers' Understanding and Empowerment
VA: Veterans Affairs

Edited by G Eysenbach; submitted 02.07.20; peer-reviewed by T Bakas, S Douglas; comments to author 03.10.20; revised version received 08.10.20; accepted 09.10.20; published 11.11.20.

Please cite as:
LeLaurin JH, Lamba AH, Eliazar-Macke ND, Schmitzberger MK, Freytes IM, Dang S, Vogel WB, Levy CE, Klanchar SA, Beyth RJ, Shorr RI, Uphold CR
Postdischarge Intervention for Stroke Caregivers: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2020;9(11):e21799
URL: http://www.researchprotocols.org/2020/11/e21799/
doi:10.2196/21799
PMID:33174856

Protocol

The Active Brains Digital Intervention to Reduce Cognitive Decline in Older Adults: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Increasing physical activity, improving diet, and performing brain training exercises are associated with reduced cognitive decline in older adults.

Objective: In this paper, we describe a feasibility trial of the Active Brains intervention, a web-based digital intervention developed to support older adults to make these 3 healthy behavior changes associated with improved cognitive health. The Active

Brains trial is a randomized feasibility trial that will test how accessible, acceptable, and feasible the Active Brains intervention is and the effectiveness of the study procedures that we intend to use in the larger, main trial.

Methods: In the randomized controlled trial (RCT), we use a parallel design. We will be conducting the intervention with 2 populations recruited through GP practices (family practices) in England from 2018 to 2019: older adults with signs of cognitive decline and older adults without any cognitive decline. Trial participants were randomly allocated to 1 of 3 study groups: usual care, the Active Brains intervention, or the Active Brains website plus brief support from a trained coach (over the phone or by email). The main outcomes are performance on cognitive tasks, quality of life (using EuroQol-5D 5 level), Instrumental Activities of Daily Living, and diagnoses of dementia. Secondary outcomes (including depression, enablement, and health care costs) and process measures (including qualitative interviews with participants and supporters) will also be collected. The trial has been approved by the National Health Service Research Ethics Committee (reference 17/SC/0463).

Results: Results will be published in peer-reviewed journals, presented at conferences, and shared at public engagement events. Data collection was completed in May 2020, and the results will be reported in 2021.

Conclusions: The findings of this study will help us to identify and make important changes to the website, the support received, or the study procedures before we progress to our main randomized phase III trial.

Trial Registration: International Standard Randomized Controlled Trial Number 23758980; http://www.isrctn.com/ISRCTN23758980

International Registered Report Identifier (IRRID): DERR1-10.2196/18929

(JMIR Res Protoc 2020;9(11):e18929) doi:10.2196/18929

KEYWORDS

telemedicine; dementia; internet-based intervention; geriatrics; feasibility studies; randomized controlled trial

Introduction

Background and Rationale

The prevalence of dementia is estimated to be between 5% and 7% among those aged 65 years and above [1,2]. Although the rates have fallen slightly in the United Kingdom over the past 20 years [2], the absolute number of cases is likely to increase owing to longer life spans [3]. Over the next 30 years, 10-15 million cases are predicted in Europe [3], and 132 million in the world by 2050 [4], with approximately 43% of prevalent cases needing high-level care (equivalent to nursing home care) [3]. It has been estimated that if interventions could delay both disease onset and progression by one year, there would be nearly 9.2 million fewer cases of the disease worldwide by 2050, almost all attributable to a reduction in persons needing a high level of care [3].

Cognitive impairment in the absence of dementia is common, but prevalence estimates vary considerably depending on the definition [5]. Mild cognitive impairment (MCI) is the most commonly used definition, conventionally defined as a deterioration in at least one nonmemory cognitive domain in addition to memory impairment, without severe functional impairment or loss of independence in Instrumental Activities of Daily Living [3,6]. The incidence of MCI is high in those aged above 65 years [7-9], ranging from 51 to 76.8 per 1000 person-years. There is not enough evidence yet that screening for MCI is either effective or cost-effective [10], but a systematic review of cohort studies suggests that between 5% and 10% of MCI cases progress into dementia annually [11]. However, defining cognitive impairment solely in terms of MCI misses a large group of individuals who are at a similar risk of developing dementia [12-14]. An alternative way of characterizing cognitive impairment is age-associated cognitive decline (AACD). AACD is described as 1 SD below normal cognitive functioning in any cognitive domain, with some investigators considering an additional criterion (self-report of a gradual decline in memory present for at least 6 months) [5]. The estimated prevalence of AACD depends on the number of cognitive domains assessed and whether additional criteria are used, which may explain the variable prevalence estimates—in one population-based study, up to 20% of those aged above 60 years had AACD using the simple criteria described by Ritchie et al [14] and as low as 1.4% in the UK Cognitive Functioning and Ageing Studies, where detailed criteria were used [5]. Progression to dementia is common no matter which definition is used, with rates almost comparable with that of MCI: 9% per annum in a population-based study (additional criterion not used) [14] and 10% in Cognitive Functioning and Ageing Studies (additional criterion used) [12,13]. Importantly, there is currently no diagnostic or treatment pathway for people with AACD. Given the scale of the problem, there are clearly insufficient resources on offer to help prevent cognitive decline or dementia in those with cognitive impairment or to prevent the development of cognitive impairment.

There is mounting evidence that healthy behaviors (particularly physical activity) and cognitive exercises improve cognitive functioning and activities of daily living, and a recent trial from other settings has demonstrated the potential effectiveness of combining healthy behavior and cognitive interventions [15].

Healthy Behaviors: Physical Activity and Healthy Eating

Several large cohort studies and systematic reviews indicate that leisure time physical activity—even at moderate intensity levels—is protective, as is greater fish and fruit and vegetable consumption, with increased risks shown for obesity and high saturated fat intake [16-23]. The Caerphilly cohort is representative of the UK population and measures protective

factors (not smoking, BMI levels, fruit and vegetable intake, physical activity, and moderate alcohol intake [22]), and after 30 years, it demonstrated markedly reduced risks of cognitive impairment (odds ratio [OR] for having 4 to 5 protective risk factors=0.36 and dementia OR=0.36). A trial of the Mediterranean diet for over four years demonstrated beneficial effects on cognitive decline among those with no cognitive deficits at baseline: changes in cognitive z-scores were 0.04 (95% CI −0.09 to 0.18) for the Mediterranean diet plus olive oil, 0.09 (−0.05 to 0.23 vs controls) for the Mediterranean diet plus nuts, and −0.17 (−0.32 to −0.01) for the control diet [24]. Interventions to increase physical activity are protective in the shorter term [25] with effects even at 6 months to a year on both cognitive decline, gray matter volume, and atrophy [26-28]. The population attributable risk (PAR) has been estimated for diabetes, hypertension, obesity, physical inactivity, depression, smoking, and low educational attainment, with the highest PAR found for physical inactivity (PAR 21.8%, 95% CI 6.1-37.7) [29].

Cognitive Exercises

A systematic review of cognitive exercise trials [30] documented a strong effect size in cognitive performance (weighted mean difference=1.07; 95% CI 0.32 to 1.83; n=3194) with effects maintained after 2 years. A more recent systematic review of cognitive and memory training among those with MCI documented substantial heterogeneity of interventions [31] but a promising effect of cognitive exercises (effect sizes ranging from 0.10 to 1.21). The large Advanced Cognitive Training for Independent and Vital Elderly study investigated the effect of training in several cognitive domains (memory, reasoning, and processing speed) [32]; the change in reasoning (effect size=0.26) was particularly important, resulting in significantly less functional decline in activities of daily living, which was maintained over 5 years. Booster training produced additional improvement in reasoning performance (effect size=0.28) [33].

Feasibility of Online Delivery

Although there is evidence that suggests healthy behavior changes can be protective against cognitive decline, behavioral interventions are complex and resource intensive, if delivered by purely face-to-face methods. In contrast, the internet is now used extensively and successfully by older people for self-management of health [33,34]. Although many individuals may benefit from using an intervention independently, the additional impact of behavioral facilitation may be important in helping initiate and maintain behavior change [35,36], and the effectiveness and cost-effectiveness of a more intensive intervention may vary with the risk of developing dementia.

Internet Use Among Older Adults

Recent UK government statistics demonstrate that the proportion of older adults using the internet is rapidly increasing. Among those aged 55 to 64 years, 88.3% reported recent (in the past 3 months) internet use. Although this proportion declines across age groups, this age group has demonstrated the fastest growth. Over the past 7 years, the proportion of adults aged 75 years and above reporting recent internet use has nearly doubled from 20% in 2011 to 47% in 2019 [37].

The research team has extensive experience of ensuring intervention engagement and accessibility to encompass a range of user preferences [38] and has experience of successfully supporting older patients, for example, exercises for dizziness [39], rehabilitation for stroke [40], and fall prevention [41]. The team can also draw upon existing experiences of developing suitable interventions to ensure engagement and accessibility for people of all ages and computer abilities, including those with lower health literacy [38,42].

Internet-Delivered Interventions Among a Cognitively Impaired Population

A large trial (n=2912) led by one of the research team's coinvestigators (CB) [43] used a web-based cognitive training package in our target populations (Reasoning and problem-solving Cognitive Training [ReaCT] package) with improvements after 6 months in instrumental activities of daily living, reasoning, and verbal learning (standardized effect sizes of 0.15, 0.42, and 0.18, respectively). There were very similar effect sizes among those with cognitive impairment (AACD). This suggests that a web-based package is likely to be feasible and effective among those with cognitive decline. Although some people in our target population are currently not internet users, this proportion is rapidly declining [44]; therefore, the findings of this study will be relevant to the large majority of the older adult population in the future.

Intervening With Noncognitively Impaired Older Adults

Intervening with noncognitively impaired older adults may also prevent dementia. Although an intervention for noncognitively impaired older adults may be expected to have a smaller effect, data from the large ReaCT trial [43] suggest that this is not necessarily the case. Furthermore, the noncognitively impaired older adults are a substantially larger proportion of the population, so an intervention to target this group provides potential for helping many more of the older adult population. This population is also very concerned about developing dementia: 80% of those aged 50 years or above in a survey undertaken by Saga (n=9049) said they feared dementia, which was equivalent to the fear of cancer, and 84% feared dementia in their partners, which was more than they feared cancer in their partners [45]. Fear of dementia, the need to improve dementia knowledge, and having adequate support for behavioral change rather than simply being told what to do are likely to be major motivators toward changing health behaviors in an older adult general population group [46]. Thus, it is plausible that a well-designed and engaging behavioral intervention to help prevent cognitive decline and dementia will be both well-received and effective among an older adult general population sample and will be strongly supported by their partners.

Objectives

The primary aim of this study (*the Active Brains study—feasibility trial* ISRCTN 23758980) is to assess the feasibility and acceptability of our trial procedures and of a web-based digital intervention (Active Brains), which helps support people in making healthy changes (physical activity,

brain training, and diet) to maintain cognitive function and prevent cognitive decline.

Primary Research Objective

The primary outcome was to investigate the feasibility of collecting clinical outcomes and notes review data. This is built around our stop or go criteria for the proposed full RCT: the project will progress to a full RCT if 80% of the clinical outcome and notes review data from randomized participants are available for analysis. If the figures are 70%-80%, we will discuss our plans for appropriate mechanisms to increase the response rate with the trial steering committee. If less than 70% of the data are available, in negotiation with the funder, we will consider not proceeding to the main trial unless there is a clear and plausible plan to increase response rates or reduce missing data. The feasibility and resource requirements for recruitment will also affect the likelihood of progression to the main trial.

Secondary Research Objectives

The evaluation of feasibility and acceptability in terms of (1) suitability of recruitment screening methods; (2) acceptability of all trial procedures (eg, recruitment, randomization, study materials, follow-up); (3) recruitment and attrition rates; (4) acceptability of the digital intervention (uptake, usage, attrition, and qualitative process evaluation); (5) appropriateness of the human support module (uptake, adherence, number of sessions, and qualitative process evaluation); (6) suitability of all outcome measures; and (7) Health Economics analysis—the key resources to be collected—to inform the choice of quality of life instruments to be used in the full trial.

We will also explore the analysis of the characteristics of outcomes for power calculations to confirm the target sample size for the trial and preliminary estimates of change in relevant behaviors (based on automatically recorded intervention usage, eg, goals set and reviewed, scores on brain training games).

Study Design

The randomized controlled study will use a parallel design. Participants will be divided into *cognitively impaired* and *noncognitively impaired* subgroups based on existing cognitive impairment (each subgroup is treated as a separate trial for randomization and reporting). A total of 180 participants from each group will be randomly allocated to 1 of 3 study groups (totaling 360 participants):

1. Usual care (60 participants from each group).
2. Access to the Active Brains intervention (60 participants from each group).
3. Access to the Active Brains intervention with flexible human support from a central support facilitator (60 participants from each group).

It is anticipated that the noncognitively impaired group will recruit more quickly than the cognitive impairment group, due to the low prevalence of MCI and AACD within the age group. Participants exceeding the allocated group size of 180 will not be randomized but will be offered to access the intervention (no support) as part of a cohort group.

Methods

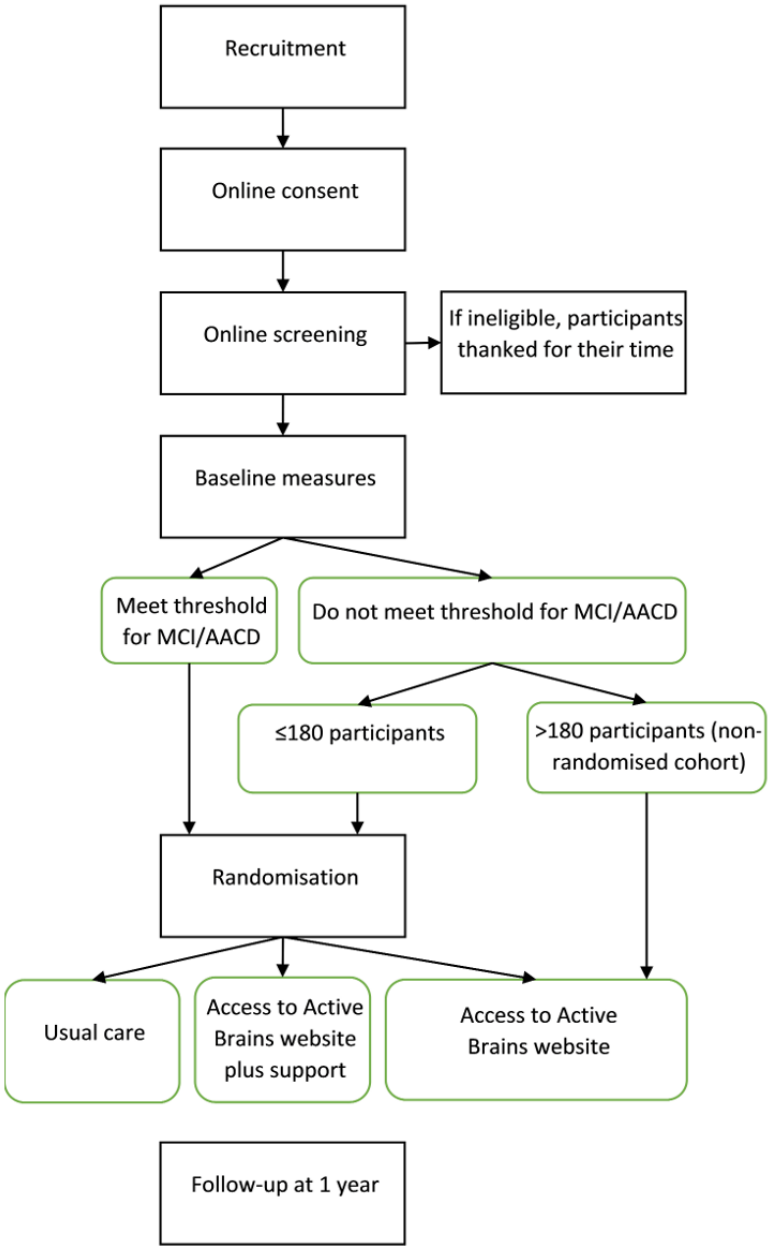
Study Setting

Primary care recruitment will involve practice staff inviting patients from searches of UK practice lists based in England (GPs [General Practitioners] will screen practice lists to avoid inviting those who have an existing diagnosis of dementia and who are terminally ill or seriously mentally ill) between October 2018 and January 2019. Participants will also be recruited opportunistically during consultations with practitioners. Invitation letters, participant information sheets, reply slips (for those not interested to inform us why), and a *getting started* card with instructions on how to log on to the website to start the study will be sent from GP practices. Participants can also contact the research team directly if they have any questions. Following informed consent, GP practices will be asked to provide demographic data (gender, age, and postcode to help us establish the level of deprivation) for all participants who are invited to the study. We will compare the demographics of those invited but who do not participate in the study with recruited participants to examine any differences between these 2 groups. This will help the assessment of the likely generalizability of our findings.

Eligibility Criteria

Figure 1 outlines the participant identification and screening procedures. Participants recruited through primary care will be screened to include only participants aged between 60 and 85 years and to exclude persons with a diagnosis of dementia, terminal illness, serious mental illness, or persons within the same household.

Figure 1. Randomized controlled trial and pilot study procedure flowchart. AACD: age-associated cognitive decline; MCI: mild cognitive impairment.



When participants first access the Active Brains study website, they will be asked to sign up with a username, password, and their unique ID code (provided on their study invitation letter). They are then presented with the information sheet and web-based consent form to complete. If they consent, they then answer a series of screening questions to ensure that they fit the study inclusion criteria (shown in Textbox 1). Age, dementia diagnosis, and the same household questions will be repeated in the web-based screening. Additionally, web-based screening will include willingness and ability to access the internet, the Godin Leisure Time Exercise Questionnaire (this questionnaire [47] will be used to screen highly physically active participants as it is a short and simple measure, collecting only sufficient data for screening participants and tailoring intervention content. The International Physical Activity Questionnaire [48] will be used to assess physical activity as an outcome measure as it has higher granularity and assesses sedentary behavior, which is targeted in the intervention), the Instrumental Activities of Daily Living Questionnaire (IADL) [49], and 4 cognitive tasks (short computer games that evaluate cognitive skills). If eligible, participants will be asked to complete baseline measures (Table 1).

Textbox 1. Inclusion and exclusion criteria for the Active Brains feasibility trial.

Step 1: General practitioner screening

Inclusion criteria

- Between 60 and 85 years of age

Exclusion criteria

- Diagnosis of dementia
- Terminal Illness
- Serious mental illness

Step 2: Web-based screening

Inclusion criteria

- Able and willing to access the internet
- Cognitive impairment group: ≥1 SD below the norm on the Baddeley Reasoning Test [44]
- No cognitive impairment group: <1 SD below the norm (or above norm) on the Baddeley Reasoning Test [44]

Exclusion criteria

- High levels of leisure time physical activity (score ≥30 on Godin Leisure Time Exercise Questionnaire [47] (moderate or vigorous physical activity only)
- Another member of the household already participating in the study

Table 1. Outcome measures and times presented to each group for the Active Brains feasibility trial.

Measure	Time		Group			
	Baseline	12-month follow-up	Usual care	Active Brains intervention	Active Brains intervention and support from central facilitator	Nonrandomized cohort study participants (receiving the Active Brains intervention)
Sociodemographic data	✓[a]	—[b]	✓	✓	✓	✓
Clinical and behavioral data	✓	✓	✓	✓	✓	✓
Clinical measures (from notes review)	—	✓	✓	✓	✓	—
Cognitive Performance Tasks [50-53]	✓	✓	✓	✓	✓	✓
Instrumental Activities of Daily Living [49]	✓	✓	✓	✓	✓	✓
The Patient Enablement Scale [48]	—	✓	✓	✓	✓	✓
International Physical Activity Questionnaire [54] plus strength and balance items[c]	✓	✓	✓	✓	✓	✓
EQ-5D-5L[d] [55]	✓	✓	✓	✓	✓	✓
EQ-5D-5L-proxy version 2 (for contact person completion if required) [55]	—	✓	✓	✓	✓	—
ICEpop CAPability measure [56]	✓	✓	✓	✓	✓	✓
Short-form Health Survey [57]	✓	✓	✓	✓	✓	✓
Dementia diagnosis (from notes review)	—	✓	✓	✓	✓	✓
Mortality	—	✓	✓	✓	✓	—
Health economic analysis of cost-effectiveness (from notes review)	—	✓	✓	✓	✓	—
Food Frequency Questionnaire [58]	✓	✓	✓	✓	✓	✓
Problematic Experiences of Therapy Scale [59]	—	✓	—	✓	✓	✓
Brief Geriatric Depression Scale [60,61]	✓	✓	✓	✓	✓	✓
Self-efficacy for exercise [62]	✓	✓	✓	✓	✓	✓
Medical Outcome social support Survey [63,64]	✓	—	✓	✓	✓	✓
Social Support for Exercise [65]	—	✓	✓	✓	✓	✓
Locus of Causation in Exercise [66]	✓	✓	✓	✓	✓	✓
Technology Acceptance Model Perceived Ease of Use scale [67-69]	—	✓	—	✓	✓	✓
Informant Questionnaire on Cognitive Decline in the Elderly–short form (if participants do not complete full measures) [70]	—	✓	—	✓	✓	—
Objective patient data						
Use of the Active Brains intervention	—	—	—	✓	✓	✓
Objective supporter data						
Supporters' use of Active Brains intervention (throughout the study)	—	—	—	✓	✓	—
Emails sent to participants throughout the study	—	—	—	✓	✓	—

Measure	Time		Group			
	Baseline	12-month follow-up	Usual care	Active Brains intervention	Active Brains intervention and support from central facilitator	Nonrandomized cohort study participants (receiving the Active Brains intervention)
Qualitative data						
Interviews with patients about their experiences of the study and/or intervention	—	—	✓	✓	✓	—
Interviews with Central Support Facilitators about their experiences of the study and intervention	—	—	✓	✓	✓	—

[a]✓: indicates yes.

[b]—: indicates no.

[c]"During the last 7 days, on how many days did you do activities or exercises to improve your strength and balance? Examples would be exercises such as standing on one leg, doing repeated sit to stands in a chair, lifting weights or heavy objects at home or at a gym or using resistance bands. Please only include time where you have purposefully decided to do these exercises for improving strength and balance." Response requested: Number of days and number of hours or minutes on an average day.

[d]EQ-5D-5L: EuroQol-5D 5 level.

Subgroups of cognitively impaired participants will be identified by combinations of impairment in the Baddeley reasoning cognitive task, IADL, and memory cognitive task. Key subgroups are MCI, which will be defined as 1.5 SD below the norm in a nonmemory cognitive domain plus memory impairment [5,12,13], and AACD will be defined as 1 SD below the norm for the Baddeley Reasoning Test [50] and IADL.

Assignment of Interventions

Simple randomization will be used to assign participants to intervention arms using the study software's computer-generated random numbers. Randomization occurs online after a participant completes baseline measures, ensuring blind randomization. They will have an equal chance of being in each of the 3 groups. Once randomized, participants will be informed of their group allocation (they will also be emailed this information). If participants are in one of the treatment arms, they will be taken directly to the Active Brains intervention. These participants can then use the Active Brains intervention as much as they would like to over the course of the study. The central facilitator will be notified by email when a participant is randomized to the support arm of the trial, so that they know to expect to provide support to the participant in the coming weeks. Research staff will not be blinded to the participant group but the statistician and health economists conducting the analyses will be.

Patient and Public Involvement

At the outset, the project recruited 2 older adult patient and public involvement (PPI) representatives to inform the development of the intervention and trial. They contributed to the development of the protocol and early intervention drafts. When intervention development began, it was determined that further PPI input would be essential to make the intervention and study materials engaging and easy to use. Three older adult representatives were recruited. Their input was invaluable in providing direction and feedback on the content and structure of the intervention (eg, the name, logo, content, order of pages) as well as the consent processes, interview topic guides, screening, and study measures (eg, feedback on unsuitable phrasing, resolving questionnaire burden).

During and after the trial, the PPI representatives will inform the discussion and interpretation of the trial outcomes and process evaluations and provide a patient perspective on resolving problems with recruitment, retention, participant support, and follow-up.

Active Brains Intervention

The Active Brains intervention was developed to provide interactive tailored support to older adults in initiating and maintaining evidence-based behaviors that support cognitive and physical health using appropriate behavior change techniques. All intervention content has been iteratively developed with extensive input from the target user group to ensure that it is highly accessible and engaging. The Active Brains study website (containing the consent material and the study measures) is accessible to all participants, with only the intervention arm participants having access to the Active Brains intervention content. For the first 7 months, the intervention groups will have access to the Active Brains "Starter Section," which provides support for users to initiate changes to their lifestyle in line with the intervention's recommendations.

Within the first section of the Active Brains intervention, 3 modules will become available to users, released sequentially. Within these modules, users will have access to information addressing common concerns, instructions about recommended activities, guided goal setting and reviewing, personalized motivational feedback about their progress, and motivational reminder emails. The modules are as follows:

- Active Lives: a physical activity module that provides guidance on general physical activity, strength and balance exercises, and decreasing sedentary behavior.
- Brain Training: access to online *Brain Training* games.
- Eat for Health: guidance on healthy eating and increasing intake of foods beneficial for cognitive health.

After 6 months, users will be given access to the Active Brain "Booster Section," providing further advice on habit formation and additional resources.

Textbox 2 summarizes the Active Brains intervention using the Template for Intervention Description and Replication (TIDieR) checklist [71]. For more details on the development of the Active Brains intervention, see the study by Essery et al (unpublished data, 2020).

Textbox 2. Description of the Active Brains intervention using the Template for Intervention Description and Replication checklist.

1. Brief name

- Active Brains Study

2. Why

- An aging population places strains on health services: particularly with the increase in dementia. Several lifestyle changes have been found to help protect against cognitive decline. The aim of this study is to develop and test a digital behavior change intervention to help older adults increase their physical activity, improve their diet and practice cognitive 'Brain Training' activities to reduce cognitive decline.

3. What material?

- Assessment: All participants will complete web-based questionnaires and complete the four cognitive assessment games at 0 and 12 months
- Intervention Group: Participants in this group receive access to the Active Brains digital intervention.
- Intervention with support group: Participants in this group will receive the Active Brains digital intervention and additionally will be offered up to eight 10 minute support phone calls with a trained supporter.
- Control Group: Participants in this group will receive usual care from their GP and brief web-based advice about getting more active, improving diet and staying mentally active.
- The Active Brains Digital Intervention contains 4 sections described below.
- Month 0: Active Brains Starter Section. Access to 'Active Lives', including 'Strength and Balance', 'Taking Breaks from Sitting' and 'Getting Active'. These modules contain: Information addressing common concerns; Provision to order a step counter and guidance on using it; User stories modeling overcoming barriers; Instructions about obtaining social support; Suggestions for environment restructuring; Instructions about recommended activities (including Strength and Balance videos); Facilities to set, plan and review goals about their chosen activities; Tailored motivational feedback about their progress; Reminder emails to motivate them to continue with their activities and to revisit intervention content as appropriate.
- Month 1: Access to Brain Training. This module provides: Brief information about the rationale and evidence base for Brain Training tasks and how they are intended to work; User stories modeling overcoming barriers; Access to six web-based brain training games (via the existing PROTECT website) which they are encouraged to play between three and five times per week; facilities to set, plan and review goals about their chosen activities; tailored motivational feedback about their progress; reminder emails to motivate them to continue with their activities; Six additional games are made available to users during months 1-6
- Month 2: Access to Eat for Health. This module contains: Information on the benefits of healthy eating for cognitive and physical health; Information and techniques to allow them to make healthy changes to their existing eating behaviors (eg, increasing fruit and vegetable consumption, cutting down on processed foods); Facilities to set, plan and review goals about their chosen activities; User stories modeling overcoming barriers; Tailored motivational feedback about their progress; Reminder emails to motivate them to continue with their activities; Recipes
- Month 6: Transition to Active Brains Booster Section. This module contains: Tailored summary of their progress and engagement with the Starter Section content; Links to additional resources for additional support and to extend their progress with the behavioral changes made.
- The content was developed to support self-efficacy and autonomy. It used simple and accessible language, using persuasive rather than directive phrasing (ie, “you can” rather than “do”), and promoting guided choice rather than direction (eg, offering a range of ideas for goals).

4. What procedure

- Screening and randomization: Participants will complete web-based screening to ensure eligibility. Participants will then complete cognitive tasks and the Instrumental activities of daily living (IADL) questionnaire to determine work stream (with or without cognitive impairment). If the assigned work stream is full (capped at n=180), participants will be given access to Active Brains (no support) as part of a cohort study. Participants in each work stream will be randomized to one of the three groups. They will be informed of their group allocation on the website immediately.
- Intervention Group: Participants will receive full access to the Active Brains intervention. They will receive regular emails to remind them to access the intervention. They will be sent reminder emails when follow-up measures are available to complete.
- Intervention with Support Group: Participants will receive full access to the Active Brains intervention. Participants in this group will additionally be sent emails from an assigned supporter. They will be invited to book phone call appointments to support them with their use of the intervention.
- Control Group: Participants will receive basic information online about getting more active, improving diet and staying mentally active. They will be sent reminder emails when follow-up measures are available to complete.

5. Who provided

- Assessment: Participants will be invited to take part using a letter from their GP practice. They will access the screening and measures online.
- Intervention Group: Participants will use the intervention online.
- Intervention with Support group: Participants will additionally be provided with support from trained supported from the university of Southampton. These are members of the research team who have completed brief web-based training in the CARE approach. The CARE (Congratulate, Ask, Reassure, Encourage) approach is intended provide support to patients based on Self-Determination Theory. Supporters will also offer technical support.

6. How

- Intervention delivered entirely online.
- Follow-up procedures may include telephone and post.

7. Where

Intervention delivered entirely online, intended to be used in the participant's home.

8. When and how much

- Intervention Group: The intervention is divided into a 'Starter Section', lasting 6 months and a 'Booster' section provided at 6 months. The starter section unlocks 'Active Lives' at month 0, 'Brain Training' at month 1 and 'Eat for Health' at month 2. Participants will be encouraged to set goals and plans for each section and return to review the goals after one week. After 'Brain Training' unlocks, participants will be encouraged to set a goal to play the games 3-5 times a week until month 6, and then play for 3-5 times a week for a month every 3 months. Initially 6 games will be available with new games unlocking every month until 12 games are available. Participants will be guided to form healthy habits so that after 6 months they will be less reliant on the intervention. For participants with a BMI>30, a weight loss tool 'POWER' will be offered at month 6.
- Intervention with support group: In addition to the intervention, these participants will be offered three support phone calls at weeks 2, 6 and 10. They may request up to 8 phone calls in total.

9. Tailoring

- The intervention will tailor physical activity recommendations to self-rated Strength and Balance and current physical activity. Participants may then choose any or all of the three physical activity modules.
- Strength and balance exercises are tailored to self-rated strength and balance.
- The weight loss tool will only be offered to participants with a BMI>30.
- Goal review feedback will be tailored to prior performance (the past two review ratings for that module).

10. Modification

- The intervention will not be modified during the trial.

11. How well

- The intervention was created using the Person-Based Approach (PBA). Experts in digital behavior change oversaw the development. End users were consulted at all points of development and the intervention was iteratively refined to overcome anticipated barriers. The intervention was thoroughly tested by the research team to ensure that there were minimal problems with the software.

Participants will be encouraged to set and review goals every week when using Active Brains. When they unlock “Brain Training,” they will be encouraged to play the games 3 to 5 times per week for the first 6 months. The intervention will be available to the participants for a year. However, the Active Brains intervention aims to help participants establish healthy habits (eg, regular walking) so that participants are not dependent on the intervention in the long term—we anticipate that participants will not need to use the website every week for 6 months to gain benefits from the intervention. The level of engagement that is effective in improving outcomes will be investigated in the main trial.

Central Facilitator Support

Patients in the group receiving support from a central facilitator (in addition to the website) will be offered a brief (10 min) telephone support call 2 weeks after they begin the study. In this support call, they will discuss the cognitive or lifestyle changes that they are planning to try. Patients will be offered 2 more support contacts by phone (up to 10 min) or email to support them in making behavioral changes.

Central facilitators will be people trained in the congratulate, ask, reassure, and encourage (CARE) approach to provide support to patients, which is based on Self-Determination Theory [72] and designed to promote autonomous motivation for making behavioral changes. This approach has been successful in previous trials [73].

Usual Care

The comparison group will receive usual care from their GP practice, in addition to brief web-based advice about becoming more physically active, improving the diet, and staying mentally active.

Outcome Measures

Table 1 presents a list of the measures and when they will be presented to participants. Participants will receive follow-up reminders by email, post, and telephone and by contacting a nominated contact person (optional). If no contact is successful, the contact person will be asked to help put the research team in touch with the participant or to complete 3 short questionnaires about the participant (EQ-5D-5L proxy version 2 [55], IADL [49], and Informant Questionnaire on Cognitive Decline in the Elderly [70]).

Participant Timeline

Participants will register, be randomized, and complete baseline measures. Participants in the intervention arm will then be given access to the intervention, which they can use for one year.

Participants in the support arms will be invited to have a support call at weeks 2, 6, and 10. A sample of participants will be invited to participate in a qualitative process interview at 6 months. All participants will be invited to complete outcome measures at 12 months.

Sample Size

This is a feasibility trial, so it was not powered to measure patient outcomes. A sample size of 180 for each of the 2 subgroups was chosen for several reasons. As Active Brains is a digital intervention with multiple possible pathways through it, a sufficiently large group would be required to observe different patterns of usage. Fully web-based interventions are easy to recruit and manage larger numbers of participants, making this possible. The proposed fully powered trial would need to recruit over 20,000 patients, so implementation issues and trial processes (eg, managing multiple supporters) needed to be tested at scale. A total of 360 participants would provide robust evidence for the feasibility of the trial.

Data Collection, Management, and Analysis

Outcome measures will be collected by using the software at registration and at one year. It will be held securely in a database accessible only by the data controller and members of the study team. Each participant will be assigned a unique study ID when they register with the website. Anonymous outcome data will be held in a separate write-only database to the personally identifiable data to ensure blinding and guard against modification.

Personally identifiable data will be held in accordance with the General Data Protection Regulation [74]. It will only be accessible to members of the study team throughout the study to monitor usage and provide support. The data will be analyzed by a statistician who has had no access to these data.

Statistical Analysis

The primary analysis will determine whether the feasibility trial has met the stop or go criteria and will therefore describe the completeness of the data in relation to the number of participants recruited.

Data for the secondary analyses will be explored descriptively and graphically for the other key feasibility outcomes, including intervention uptake, adherence, attrition, retention, and the number of participants recruited per practice. We will estimate the variability of proposed outcome measures and discuss any implications for the sample size for the full trial.

All participant data will be analyzed, including those who have withdrawn, unless the participant specifically requests for their data to be removed. All participants will be analyzed as randomized. The pattern and frequency of missing data will be explored descriptively in the feasibility context to determine whether there are whole instruments or items on instruments that participants opted not to complete and to inform the stop or go decision for the full trial.

The same outcomes will be assessed in a cohort study to explore whether it is feasible to recruit additional participants and collect data to inform future implementation in this way.

For the feasibility study, we will provide only descriptive estimates (ie, we will not be performing an inferential analysis to establish whether there are significant differences between groups).

Health Economic Analysis

At this feasibility stage, we aim to collect resource usage information associated with the intervention and explore and identify the likely changes in practice due to the intervention through questionnaires, case note review, and qualitative interviews. We plan to develop and refine the methods for collecting such information and to inform the choice of which instrument will be used to measure quality of life for the later planned, fully powered trial.

The study will explore both the National Health Service (NHS) and social service perspectives. All itemized resource usage will be costed using published information (eg, the Personal Social Services Research unit [75], the BNF [76]). Quality of life will be measured using EQ-5D [55], ICECAP [56], and SF-12 [57] at baseline and 12 months. We will apply the UK tariff to translate the questionnaire scores to utility scores. We aim to test the sensitivity and feasibility of these instruments in the study population, hence informing the choice of the instrument in the full trial.

The economic analyses of costs and quality of life will be mainly descriptive (with mean and standard deviation). We will correlate all utility scores with the planned primary outcome [50] to see the magnitude of sensitivities. The focus will be on the direction of correlation, spread, and confidence intervals.

Such information will allow us to investigate the most relevant resource use of information to be collected and inform choice of the quality of life instrument to be used in the definitive trial.

Qualitative Process Analysis

There will be 2 qualitative process studies, one with participants and one with central support facilitators. Interviews in both these studies may be carried out at any time between 2 and 12 months after participants begin the study. Both of these studies will allow assessment of the acceptability and feasibility of the intervention and highlight any modifications to the intervention or study procedures that might be required before embarking on the later planned, fully powered trial.

Qualitative Process Study With Participants

We will interview 12 to 18 participants from each of the intervention arms, employing purposive sampling to ensure a diverse range of participants in terms of demographic and clinical profiles as well as website usage. Participants will be invited to participate by the research team and asked if they would be willing to take part in a telephone interview. They will complete a separate consent form (online) before taking part in an interview. During the interview, open-ended questions will be used to explore participants' perceptions of the study, the website (if in one of the intervention groups), and the support they received from the central facilitator (if in the support group). Those in the control group will be asked about the brief advice they were given at baseline.

Qualitative Process Study With Central Support Facilitators

The second substudy will use face-to-face or telephone interviews to explore central support facilitators' views of the study procedures, the website, the training they were provided, and the support they provided to patients (including perceptions of the CARE approach).

Analysis

Data from both qualitative process studies will be analyzed using inductive thematic analysis with interrater agreement reached between team members. The findings will be discussed and interpretations agreed between the coinvestigators (including PPI representatives).

Monitoring Adverse Events

Serious adverse events (SAEs) will be reported by both participants, practice staff, and possibly by the central support facilitators who will have contact with participants during the study. It is not anticipated that SAEs will be related to this research. SAEs are defined as any untoward medical occurrence or effect that at any dose results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization (excluding hospitalization for pre-existing conditions or planned procedures), results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or results in other important medical events. Any SAE occurring to a research participant will be reported to the ethics committee where, based on the initial judgement made by the chief investigator or an agreed deputy, the event was related to the administration of any of the research procedures and was an unexpected occurrence. Nonserious adverse events will not be collected.

GP practices and the central support facilitation staff will inform the research team and/or the Clinical Trials Unit of any SAEs within 24 hours of them being aware of the event occurring. GP practices and central support facilitation staff will be provided with a standard operating procedure and a form for SAE reporting. Patients may also report SAEs. Reports of SAEs will be provided to the ethics committee within 15 days of the chief investigator becoming aware of the event. In addition to the chief investigator making the initial judgement about the SAE, all SAEs will also be sent to the trial steering committee for adjudication.

Ethics

Informed Consent

Participants will be fully informed of the risks and benefits of the study and their right to withdraw at any time for any reason. Consent will be collected digitally before data collection.

Ethical Approvals

Ethical approval for the Active Brains study was obtained from the NHS Research Ethics Committee (IRAS ID 239448, REC number 17/SC/0463). Research and development approvals were obtained from relevant clinical research networks.

Results

The results of this trial will be published in peer-reviewed journals and presented at conferences. Findings will be conveyed to the public through press releases and public engagement activities (eg, science fairs). Findings will be sent to all GP practices and participants who request them. Social media (eg, Twitter) will also be used to share publications and dissemination activities to the wider academic community and the general public. If found to be feasible, Active Brains will proceed to a full RCT.

Recruitment for this study was conducted from October 2018 to January 2019. All data were collected and the trial website was closed by May 2020. The analysis will be conducted in 2020, and results will be published in 2021. The prospective main trial will begin in late 2020.

Discussion

The Active Brains feasibility trial has several strengths. First, the design of the intervention can be easily implemented at scale—this will be useful for the planned larger RCT and, if found to be effective, future dissemination to the public. Second, the development of the intervention used a person-based approach (combining theory, evidence, and primary qualitative research)—this has improved its chance of being acceptable and effective. *Active Brains* is the first web-based digital intervention to test this combination of evidence-based behavioral components for reducing cognitive decline (targeted physical activity, healthy eating, and brain training). This study will provide evidence for the feasibility of conducting a trial of an intervention similar to *Active Brains* and help us to improve upon the delivery of a larger trial. Limitations of the study are that this trial does not look at the long-term impact of healthy behavior change on cognitive health. This will be examined in a subsequent RCT.

Acknowledgments

This work was supported by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research (Reference Number RP-PG-0615-20014). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

The Active Brains intervention was developed using Life Guide software, which was partly funded by the NIHR Southampton Biomedical Research Centre (BRC).

The research program of LY is partly supported by NIHR Applied Research Collaboration-West, NIHR Health Protection Research Unit for Behavioral Science and Evaluation, and the NIHR Southampton BRC.

The research program of MR is supported by the NIHR University College London Hospitals BRC.

Authors' Contributions

KS and KB drafted the paper. KS, KB, RE, SP, FB, MW, AF, AK, PL, and LY wrote the protocol. KS, RE, SP, FM, JS, JD, VH, JK, JS, EG, GY, PL, and LY conducted the trial. KS, RE, SP, FM, J Slodkowska-Barabasz, JD, VH, JZ, EG, MW, AF, AK, SR, BG, RP, TS, JN, PL, and LY developed the *Active Brains* intervention. BS, NM, GG, LR, MR, CB, JG, SG, TK, SR, PL, and LY led the research program. All coauthors contributed to the design, development, and optimization of the intervention or supported the preparation and implementation of the feasibility trial and have read and commented on the drafts.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer reviews of grant application.
[PDF File (Adobe PDF File), 320 KB - resprot_v9i11e18929_app1.pdf]

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Abbreviations

AACD: age-associated cognitive decline
BRC: Biomedical Research Centre
CARE: congratulate, ask, reassure, and encourage
IADL: instrumental activities of daily living
MCI: mild cognitive impairment
NHS: National Health Service
NIHR: National Institute for Health Research
OR: odds ratio
PAR: population attributable risk
PPI: patient and public involvement
RCT: randomized controlled trial
ReaCT: Reasoning and problem-solving Cognitive Training
SAE: serious adverse event

Edited by G Eysenbach; submitted 27.03.20; peer-reviewed by C Forbes, M Nomali, B Adusumilli; comments to author 12.06.20; revised version received 04.08.20; accepted 16.08.20; published 20.11.20.

Please cite as:
Smith KA, Bradbury K, Essery R, Pollet S, Mowbray F, Slodkowska-Barabasz J, Denison-Day J, Hayter V, Kelly J, Somerville J, Zhang J, Grey E, Western M, Ferrey AE, Krusche A, Stuart B, Mutrie N, Robinson S, Yao GL, Griffiths G, Robinson L, Rossor M, Gallacher J, Griffin S, Kendrick T, Rathod S, Gudgin B, Phillips R, Stokes T, Niven J, Little P, Yardley L
The Active Brains Digital Intervention to Reduce Cognitive Decline in Older Adults: Protocol for a Feasibility Randomized Controlled Trial
JMIR Res Protoc 2020;9(11):e18929
URL: https://www.researchprotocols.org/2020/11/e18929
doi:10.2196/18929
PMID:33216010

Protocol

Assessing the Effect of Training on the Cognition and Brain of Older Adults: Protocol for a Three-Arm Randomized Double-Blind Controlled Trial (ACTOP)

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Abstract

Background: To prevent age-related cognitive impairment, many intervention programs offer exercises targeting different central cognitive processes. However, the effects of different process-based training programs are rarely compared within equivalent experimental designs.

Objective: Using a randomized double-blind controlled trial, this project aims to examine and compare the impact of 2 process-based interventions, inhibition and updating, on the cognition and brain of older adults.

Methods: A total of 90 healthy older adults were randomly assigned to 1 of 3 training conditions: (1) inhibition (Stroop-like exercises), (2) updating (N-back-type exercises), and (3) control active (quiz game exercise). Training was provided in 12 half-hour sessions over 4 weeks. First, the performance gain observed will be measured on the trained tasks. We will then determine the extent of transfer of gain on (1) untrained tasks that rely on the same cognitive process, (2) complex working memory (WM) measurements hypothesized to involve 1 of the 2 trained processes, and (3) virtual reality tasks that were designed to mimic real-life situations that require WM. We will assess whether training increases cortical volume given that the volume of the cortex is determined by cortical area and thickness in regions known to be involved in WM or changes task-related brain activation patterns measured with functional magnetic resonance imaging. Dose effects will be examined by measuring outcomes at different time points during training. We will also determine whether individual characteristics moderate the effect of training on cognitive and cerebral outcomes. Finally, we will evaluate whether training reduces the age-related deficit on transfer and brain outcomes, by comparing study participants to a group of 30 younger adults.

Results: The project was funded in January 2017; enrollment began in October 2017 and data collection was completed in April 2019. Data analysis has begun in June 2020 and the first results should be published by the end of 2020 or early 2021.

Conclusions: The results of this study will help understand the relative efficacy of 2 attentional control interventions on the cognition and the brain of older adults, as well as the moderating role of individual characteristics on training efficiency and transfer.

Trial Registration: ClinicalTrials.gov NCT03532113; https://clinicaltrials.gov/ct2/show/NCT03532113

International Registered Report Identifier (IRRID): DERR1-10.2196/20430

(JMIR Res Protoc 2020;9(11):e20430) doi:10.2196/20430

KEYWORDS

cognitive training; working memory; brain plasticity; aging; cognitive reserve

Introduction

Background

Slowing age-related cognitive decline is a central concern for the prevention of pathological aging and loss of autonomy. Cognitive training has been identified as having significant potential in this context [1]. Many studies have identified working memory (WM) as a target for cognitive training because it is considered a foundational element of cognition. WM maintains and manipulates online information and supports many complex cognitive activities including language comprehension, reasoning, and mathematical abilities. Furthermore, aging and neurodegenerative diseases can impair WM, which has a negative impact on the ability to carry out high-level cognitive tasks. WM is a multicomponent system and relies on different attentional control processes (see [2] for a review), some of which have been the target of WM training programs. The goal of this study is to compare the effect of 2 attentional control training programs in older adults, each targeting major WM processes: inhibition and updating. A side-by-side comparison of inhibition and updating training programs will determine their respective and comparative impact.

We propose to measure the training program's effect on proximal measures, as well as on transfer tasks and brain outcomes. Moving from proximal to transfer tasks is critical. A large number of studies have used updating training in older adults and found improvements on proximal tasks, (eg, [3-5]), with some generalization to switching tasks (eg, [6]). A few studies reported that inhibition training was effective when measured with inhibition tasks that were similar to those done in training [7,8]. However, little evidence was found to support generalization to untrained tasks. Thus, inhibition and updating training improve tasks that are similar to the training, but little is known about their effect on more complex tasks or comparative efficacy. It is important to determine whether improving one attentional process improves another, which would suggest within-WM generalization. In addition, tasks typically used to measure transfer rely on laboratory-based cognitive tasks, designed to reflect fine cognitive functions or processes. They are therefore not representative of the complexity present in everyday life. Thus, in addition to traditional complex WM tasks, transfer will be assessed using virtual reality, which can be used to reproduce real-life situations [9,10].

Neuroimaging can also provide critical information regarding brain processes engaged by the 2 training programs. Updating has been consistently associated with activation of the frontal and parietal lobes, including the dorsolateral and ventrolateral prefrontal cortices, the inferior parietal lobules, insula, and the premotor and supplementary motor areas [11-13]. Inhibition processes have been associated with the anterior cingulate cortex, middle frontal gyrus, inferior frontal regions, and parietal areas [14-16]. Functional neuroimaging studies have shown that updating training increases activation in the striatum, while reducing activation in areas of the frontal and parietal lobe, as well as in the anterior cingulate and temporal cortices, which would reflect better neural efficiency following training [17-19]. Less is known about inhibition training, but it has been found to be associated with increased cortical thickness [7] and decreased activation in the inferior frontal gyrus [7,20]. Given that updating and inhibition are both part of the same WM system, it is important that we compare the effects of different process-based training programs within a single experimental design. Neuroimaging will also be used to assess whether differences in brain structure or function at baseline explain interindividual differences in training efficacy as proposed in prior studies [18,21,22].

In addition, effects of cognitive interventions may vary because of individual factors influencing the rate and magnitude of training gain [23-27]. Pathophysiological factors, such as the volume of white matter lesions, are known to impair brain plasticity and reserve in older adults [28] and may modulate the efficacy of cognitive interventions. Efficacy may also be moderated by sex [29], intracranial volume [30], and genetics, as these factors affect resilience to cognitive aging. For example, a common single-nucleotide polymorphism ($Val^{66}Met$) from the brain-derived neurotrophic factor (BDNF) tends to decrease BDNF and reduce neuroplasticity. However, very little is known about the influence of BDNF polymorphism on the efficacy of WM training for cognition and brain health. WM training could be more beneficial for the Met carriers because they show a reduced baseline performance for attentional control performance compared to the Val homozygotes. However, only the Val homozygotes show significant reduction in performance over a 10-year span [31], suggesting that they may also respond well to WM training. Catechol-O-methyltransferase (COMT) $Val^{158}Met$ is involved in dopamine degradation, which contributes to frontal modulation and cognition. For instance, carriers of the Val allele of the COMT polymorphism demonstrate reduced baseline performance [32,33], but may show larger performance gains from WM training than carriers of the Met allele [34]. Meanwhile, it was found that the brain activation decreases more in the prefrontal cortex of Met carriers after WM training [35]. Moreover, apolipoprotein ε4 (APOE-ε4) is known to increase the risk of Alzheimer disease.

Objectives

The general goal of the study is to compare 2 process-based interventions, inhibition and updating WM training, and assess their effect on the cognition and brain of cognitively healthy older adults relative to an active control condition. There are 6 objectives to the study: (1) measure the gains on the trained tasks; (2) determine transfer of gain on (i) proximal measures that are not trained directly but reflect the trained process, (ii) complex WM measures, and (iii) virtual reality tasks designed to reflect WM in real life; (3) identify the effect of WM training on cortical thickness and task-related brain activation in regions known to be involved in updating or inhibition or both; (4)

assess whether cognitive (eg, pretraining cognition), psychosocial (lifestyle, education, motivation), and biological markers (eg, white matter lesions, sex, genotype) moderate the effect of training on cognitive and brain outcomes; (5) examine dose effects by measuring training, transfer, and cerebral outcomes at different time points; and (6) assess if training reduces the age-related deficit on cognitive and cerebral measures.

Hypotheses

It is hypothesized that older participants enrolled in WM training will show larger cognitive gains than those in the active control condition, and that gains will be specific to the cognitive process trained. We expect brain changes to be observed in regions that are associated with the trained process, with an overall decrease in activation due to improved neural efficiency for both functional magnetic resonance imaging (fMRI) tasks. It is expected that both trainings improve brain and performance parameters in older adults, which will increase to the levels of younger adults. Finally, it should be possible to identify individual factors that moderate the magnitude of the effect. The intervention may especially benefit participants with less advantageous cognitive and genetic profiles. However, these participants may require additional training for the intervention to be effective [26].

Methods

Trial Registration and Reporting Guidelines

The Attentional Control Training in Older People (ACTOP) study is registered with the US National Institutes of Health clinical trials registry (ClinicalTrials.gov identifier NCT03532113). The methodology of the protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [36]. All the collected data are stored using an anonymized protocol.

Study Design

The study design presented in Table 1 is a randomized double-blind controlled trial where older participants are randomly assigned to 1 of 3 parallel groups: inhibition, updating, and active control. In line with prior empirical work from our team showing transfer effects following attentional control training in older adults [37], training was provided in 12 30-minute training sessions over 4 weeks. All transfer measurements were completed once by a group of younger adults who did not receive the training. This is used to assess whether training helps increase performance and brain status of older adults to the level of younger adults. Given the large number of appointments, participants were recruited and trained in 5-6 waves. The study was carried out at the Research Center of the Institut universitaire de gériatrie de Montréal (CRIUGM).

Table 1. Study design.

Schedule of events	Study period											
	Screening, baseline, and pretest		Intervention	Posttest 1	Intervention	Posttest 2		Intervention	Posttest 3	Intervention	Posttest 4	
Timepoint	V1	V2	V3–V5	V6	V6–V8	V9	V10	V11–V13	V14	V14–V16	V17	V18
Enrollment												
Eligibility screen	X											
Informed consent	X											
Confirmation of eligibility		X										
Randomization		X										
Interventions												
Updating			X		X			X		X		
Inhibition			X		X			X		X		
General knowledge			X		X			X		X		
Assessments												
Clinical Assessments												
Montreal Cognitive Assessment (MoCA)	X											
Logical Memory Test	X											
Geriatric Depression Scale (GDS)	X											
Ischemic Index	X											
Cognitive Reserve Proxy Questionnaire (CRQ)	X											
Training outcomes												
Inverse efficiency score												
Updating			X		X			X		X		
Inhibition			X		X			X		X		
Proximal outcomes												
Updating composite measure												
Keep track	X					X					X	
Running span	X					X					X	
Inhibition composite measure												
Stroop Victoria	X					X					X	
Anti-saccade	X					X					X	
Complex working memory outcome												
Working memory transfer												
Alpha span	X			X		X			X		X	
Reading span	X			X		X			X		X	
Virtual car ride task composite measure												
Verbal memory	X			X		X			X		X	
Visual detection	X			X		X			X		X	
Brain structure												
Regional gray matter volume		X					X					X
Cortical thickness		X					X					X

Schedule of events	Study period											
	Screening, baseline, and pretest		Intervention	Posttest 1	Intervention	Posttest 2		Intervention	Posttest 3	Intervention	Posttest 4	
Timepoint	V1	V2	V3–V5	V6	V6–V8	V9	V10	V11-V13	V14	V14-V16	V17	V18
Intracranial volume		X					X					X
White matter lesions		X					X					X
Brain activations												
Updating related		X					X					X
Inhibition related		X					X					X
Salivary sample							X					

Study Population and Eligibility Criteria

A total of 90 community-dwelling older adults (age 60-85) and 30 younger adults (age 20-35) were enrolled in the study. Older adults and younger adults were recruited in the Montreal area through advertisements in community centers, associations, local newspapers, and CRIUGM's participants registry (*Banque de participants duCRIUGM*). In addition, students, who were enrolled in an undergraduate laboratory course and wished to help with the study recruited younger adults among their acquaintances. Younger and older adults with similar educational levels were recruited in order to reduce the cohort effect on education.

Participants with the following criteria were included in the study: right-handed, fluent in French, and sufficient visual and auditory acuity to undergo neuropsychological testing. Participants were only included if they performed above the cut-offs on the delayed recall portion of the Logical Memory Test of the Wechsler Memory Scale for older adults. Performance on the Logical Memory Subtest was considered normal based on the following education-adjusted cut-off scores used in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study: 9 or more for 16+ years of education; 5 or more for 8-15 years of education; 3 or more for 0-7 years of education [38-40].

Participants were excluded from the study if they had received a diagnosis of a disease or injury of the central nervous system (ie, moderate to severe chronic static leukoencephalopathy [including previous traumatic injury], multiple sclerosis, neurodevelopmental disorders, subdural hematoma [past or current], subarachnoid hemorrhage, primary cerebral tumor or cerebral metastases, epilepsy, dementia or other neurodegenerative diseases, stroke, intracranial surgery or major surgery within the last 2 months), alcoholism or substance abuse, general anesthesia in the past 6 months, serious comorbid conditions, major depression or anxiety, schizophrenia, or other major psychiatric disorders (eg, bipolar disorder). Participants were also excluded if they were unable to undergo an MRI scan, due to medical contraindications, or tolerate the procedure. Older adult participants were excluded if they reported subjective cognitive decline [41], such as feeling their memory is worse than it used to be and that it worries them, or if they had previously participated in structured attentional control training. Despite the time required for the participants to carry out the study, no change in the habits of daily living was required, except to abstain from cognitive training during the intervention. The younger adults were only included in the study if they were no longer full-time students. This constraint was intended to increase the diversity of age and education in our sample of younger participants in order to better match the diversity of our sample of older subjects. Moreover, it was not possible to determine the final level of education of the students, many of whom were actively involved in training programs that have made them experts in metacognitive strategies.

Procedure

After a first telephone contact to assess global eligibility, potential participants were invited to the laboratory to consent to participate in the study, complete standardized clinical and neuropsychological assessments, and the outcome measurements for the baseline (V1; see list in Table 1). A brain imaging examination for the baseline was completed the following week (V2). Eligible participants were given CAD 50 (~US $38) at each brain imaging session, for a total of CAD 150 (~US $114) for older adults and CAD 50 (~US $38) for younger adults.

Data on proximal cognitive and brain outcomes were collected at 3 timepoints: no more than 2 weeks prior to training for the baseline (PRE), between training sessions 6 and 7 (POST2), and no more than 1 week following the end of training (POST4) for the postbaseline tests. Complex WM outcomes were measured at 5 time points: (1) at PRE; (2) after the third training session (POST1), (3) at POST2, (4) after the ninth training session (POST3), and at (5) POST4. The complex WM outcomes at POST1 and POST3 were completed on the same day as a training session to reduce travel and the number of visits to the laboratory. The standard duration of the study was 8 weeks and involved 18 appointments. Participants were informed that the study must be performed without discontinuity. A postponement of up to 1 week was exceptionally authorized in the event of unforeseen circumstances. To limit the influence of the circadian rhythm on performance, training sessions and assessments were performed at similar times of day (ie, morning or afternoon) for a given participant. In addition, at the end of the first appointment, a personalized calendar containing all dates and durations of appointments was given to each participant in paper format. A reminder email (or a phone call

made if no email address was available) was also sent the day before each MRI appointment.

Randomization and Blinding

Participants meeting eligibility criteria were randomly assigned to 1 of the 3 interventions. An independent project coordinator, who was not involved with the enrollment process, cognitive assessments, or interventions, generated blind randomized samples without replacement. Randomization allocated eligible participants individually to 1 of the 3 training conditions using a computer-based random digits program (ie, one participant at a time as they enter the study). In this double-blind study design, participants were blind and unaware of the experimental and control conditions, as they were instructed that different capacities were trained in different programs. Assessors were blind to the participants' intervention condition. If a participant accidentally shared information that may identify their intervention group to an assessor, the incident was recorded and a different assessor was assigned for this participant for the following assessments. Training supervisors were aware of the intervention assigned to the participants. All participants were assigned 2 anonymized identification numbers: one known by the training supervisors only and the other known by the assessors only. For simplicity, the counterbalancing for the tasks' versions of transfer outcomes was done upstream for each age group separately, using a replicated Latin square design, regardless of the older adults' intervention.

Interventions

The 2 experimental training conditions (inhibition and updating) were provided by the Neuropeak web platform (Lussier M et al, unpublished data) using a Samsung Galaxy Tab 2 (Android version 4.2.2).

The updating training involved 2 N-back-type exercises (1-2- and 3-back) with different sets of stimuli. Both sets were performed during each of the 12 training sessions. The first set comprised stimuli made from digits (1 to 9) and the second comprised symbols (moon, planet, star, dog, bird, snake). The stimuli were displayed on the center of the screen, one by one, at the rate of 4 seconds per item (Figure 1A). In both sets, participants were asked to indicate whether each item matches the one presented in the *n* position previously (eg, 3-6-3-9-9 wherein the second "3" is the only match in a 2-back block). Each round comprised 8 blocks grouped by N-back level and performed in the following order: 1-back (2 × 11 trials), 2-back (3 × 12 trials), and 3-back (3 × 13 trials). Each of the 8 blocks were set to include 40% "match" responses. Nonetheless, participants were able to reach the 3-back level only if their accuracy was equal or above 75% at the 2-back level. If they were below this percentage, they finished the round with a 1-back block instead. Participants were instructed to respond as fast as possible. "Match" and "Mismatch" buttons were permanently displayed on the right side of the screen and participants were required to answer with their right thumb.

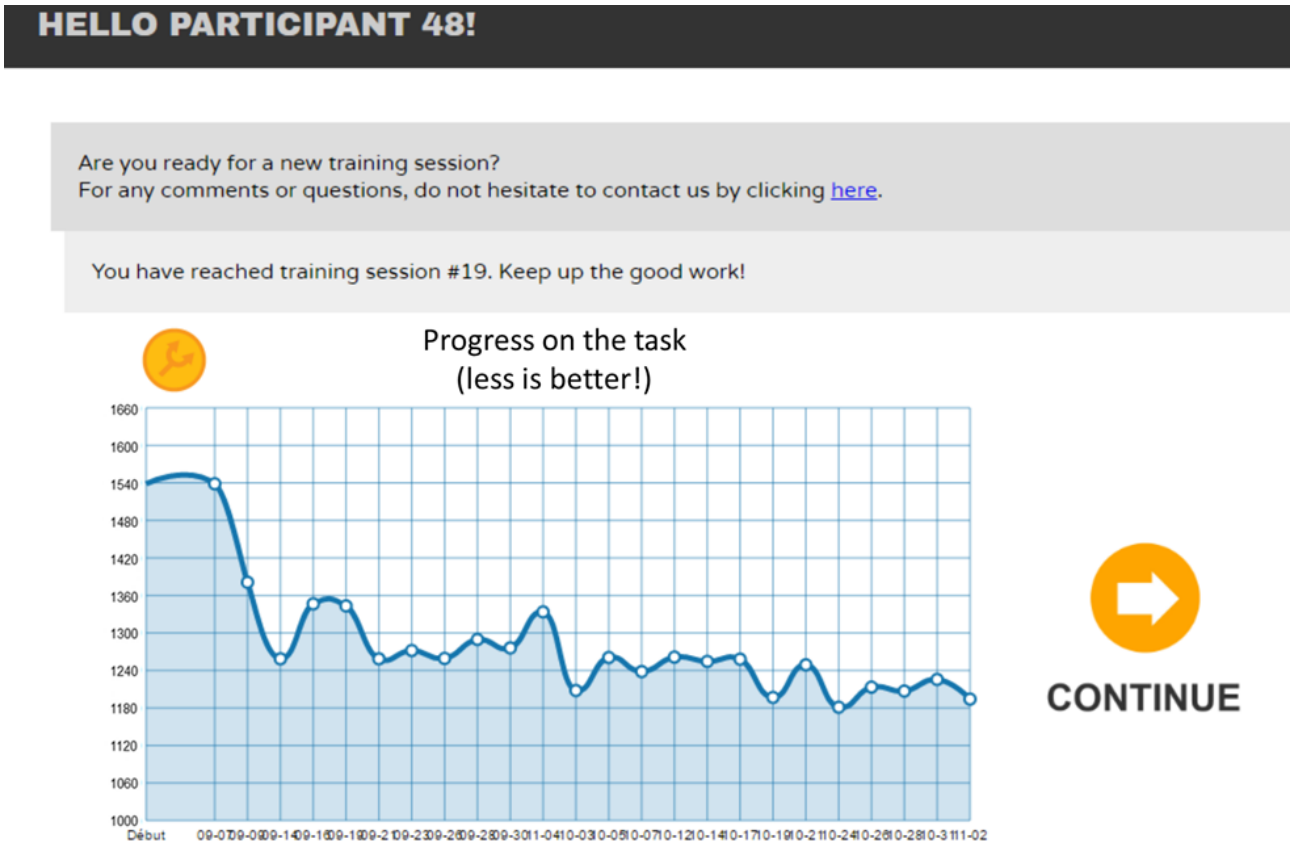
Figure 1. Illustration of the training exercises used to train attentional control: (A) in this Neuropeak updating exercise, the task consisted of indicating whether the current symbol (eg, a star) matches (or does not match) the previously displayed symbol in 1-, 2-, or 3-back position. (B) In this Neuropeak inhibition exercise (incongruent trials), the task consisted of indicating the number of copies (eg, 5) of the digit displayed in the center of the screen (eg, 2). (C) In this general knowledge quiz game, the task consisted of indicating the number of the correct answer (eg, 4) to the question displayed in the upper part of the screen.

Inhibition training also involved 2 Stroop-like exercises with different sets of compound stimuli. Both sets were performed during each of the 12 training sessions. The first set comprised compound stimuli made from digits (1 to 6) and the second included compound stimuli made from letters (D, F, H, L, S, T). The 2 different sets were used to reduce the stimulus–response dependency of the improvement in performance on tasks, and hence facilitate transfer. Stimuli was displayed in the center of the screen (Figure 1B). In the first set, participants were asked to count the number of items in each trial while in the second set, they were asked to identify the largest letter. In each set, they were presented 3 types of stimuli: congruent (eg, 5 copies of the digit "5" or a large "H" formed from smaller Hs), neutral (eg, five copies of the symbol "*" or a large "H" formed from smaller "*"), and incongruent (eg, 5 copies of the digit "3" or a large "L" formed from smaller Hs). Each of the 2 sets comprised 7 blocks. The first block contained 20 congruent compound stimuli, the second block contained 60 neutral stimuli, and the third 60 incongruent compound stimuli. Incongruent items require inhibiting the smaller stimuli to determine the larger one. The congruent and incongruent blocks were then repeated twice in alternance. Participants were instructed to respond as fast as possible while maintaining high accuracy. Response keys were displayed on both sides of the touchscreen, and participants responded with their thumbs. Participants were instructed that there was no time limit but responses taking longer than 4 seconds were not recorded to avoid the impact of outliers. A response immediately triggered the following target in order to reduce the contribution of task preparation to performance.

For both inhibition and updating training, visual feedback was provided for each response by changing the color of the response button to green when correct or red when incorrect. Moreover, successive correct answers were combined with positive visual

feedback (ie, good, great, amazing, unbelievable) and displayed in the center of the screen below the target. At the end of each training session, an individualized graphic representation depicted the participant's average daily performance (ie, the mean of reaction time divided by 1, minus the proportion of errors) and plot progression from the beginning of training (Figure 2).

Figure 2. Illustration of a graph showing the progress of a fictive participant from the inhibition training group through each session. The score is the IES (Inverse Efficiency Score).



The active control is a general knowledge quiz intervention run with E-Prime 3.0 software (Psychology Software Tools, Inc) on a laptop (Lenovo; Figure 1C). Previous studies have found that casual video games appear to be well suited as an active control condition [42,43], especially for computerized cognitive training where frequent responses are requested. Furthermore, a quiz game that does not require significant attentional control processes can appear to be a credible computerized cognitive training to the participants. An additional advantage of using a quiz game is that semantic knowledge and vocabulary are cognitive components that are unaffected by aging. As a result, semantic training was not expected to yield substantial cognitive benefits outside of the practiced task. Participants were presented with a series of 4-choice questions on 18 different topics (960 questions on food, science, geography, video games, history, sports, music, inventions, animals, movies and television series, art and literature, Canada, physics and space, monuments in the world, key historical dates, people and languages, herbs and spices, and fruit trees). The questions were adapted from OpenQuizzDB [44] or created by our research team. Each session included 2 blocks of 40 new questions. After an overall randomization of the entire pool of questions, they were displayed one by one in the same order for all participants, who had a maximum of 20 seconds to provide their response. Below each question, multiple answers (numbered 1, 2, 3, and 4) were displayed. Participants responded by pressing the corresponding number on a keypad. The selected questions were rated as medium difficulty on the OpenQuizzDB website. Positive feedback (ie, happy face emojis with the message "Bravo" or "Excellent, this is the right answer") and a short explanation was provided following correct answers. Informative feedback (ie, "this is not the right answer") and a short explanation was provided following incorrect answers, and displayed a second time at the end of the block.

To improve adherence, participants completed their training using individual tables, but in small groups of 6-10 individuals under the supervision of a trainer, who answered questions related to the task, helped manage technical issues, and encouraged completion of all exercises. All training sessions took place in the same room located at the CRIUGM. Five students were trained who rotated to ensure consistent supervision of training sessions.

Baseline Characterization

At baseline, participants provided demographic information (age, sex, education), completed a Cognitive Reserve Proxy Questionnaire (CRQ) [45], Ischemic Index [46], and depression questionnaires (short version of Geriatric Depression Scale [GDS] for older adults [47] and Beck Depression Inventory II (BDI-II) for young adults). Cognition was measured with the

Montreal Cognitive Assessment (MoCA) [48] and a French version of the Logical Memory Subtest from the Consortium for the Early Identification of Alzheimer's Disease (CIMA-Q) [41] adapted from Wechsler Memory Scale [39]. Participants provided a saliva sample with the Oragene OG-500 collection kit at POST2 (V10). The sample was used to determine the single-nucleotide polymorphism rs4680 (Val^{158}Met) of the *COMT* gene, the rs6265 (Val^{66}Met) of the *BDNF* gene, and the rs7412 and rs429358 of the *APOE* gene.

An MRI examination was used to measure brain structure and function at the Functional Neuroimaging Unit of CRIUGM, using a Siemens Magnetom Prisma Fit 3 Tesla scanner (32-channel head coil). This will provide measures of baseline brain status, some which will be used as moderators and others as outcomes (see below for sequences used as outcomes). Sequences will be used to determine baseline intracranial volume, regional volumes (repetition time [TR]/echo time [TE] 2300/2.98 ms, Fa 9°, field of view [FOV] = 256 × 256, matrix 256 × 256, voxels 1 mm^3, 192 slices), and volume of white matter lesions taken with the fluid attenuated inversion recovery sequence (TR/TE 9000/120 ms, Fa 90°, FOV 240 × 240, matrix 256 × 256, voxels 0.9 × 0.9 × 3 mm, 48 slices).

Effect on the Trained Tasks

The improvements on the trained tasks will be reported using inverse efficiency scores (IESs) for each participant, which corresponds to the mean of the reaction time per session divided by the proportion of error minus one. These scores will be calculated for the 1-, 2-, and 3-back blocks separately for the updating training and separately for congruent and incongruent blocks for the inhibition training.

Effect on Transfer Tasks

Transfer to Proximal Outcomes

An updating composite score and an inhibition composite score will be used as proximal and primary outcomes. The updating composite score will be computed by averaging the z-scores from the keep track task and the running span task, where the calculation of and "s" are based on the data from the PRE of each task. In the keep track task [49], participants were presented lists of 12 words from four different categories (eg, fruits, clothes, music, colors). The words were displayed one by one on a computer screen and participants were asked to report the last word belonging to each of the 4 categories. Participants updated their WM content each time they encountered a new word from the same category. The dependent variable is the proportion of words correctly recalled. In the running span task, participants were presented with lists of letters displayed one by one on a computer screen. The size of the lists varied randomly from n, where n is the participant's letter span minus 1, to n + 6. Participants reported the n last letters in their correct order but were not informed of list's length in advance. The dependent variable is the proportion of letters correctly recalled.

As described above for the updating composite score, the inhibition composite score will be computed by averaging z-scores from the antisaccade task and the Victoria Stroop Test. In the antisaccade task [50], participants were asked to indicate their response with a key controlling the pointing direction of an arrow (up or down) presented in the right or left portion of a computer screen. Prior to the arrow presentation, a flashed cue will appear on the opposite side of the screen. The dependent variable is the proportion of correctly identified target arrow directions, despite the distracting cue. In the Victoria Stroop Test [51], participants were first asked to name colors using dots printed in color, noncolor words printed in color, and finally, the names of colors printed in different colors than its name. The dependent variable is the reading time for the incongruent colored words divided by the reading time for the dots printed in color. The directionality of the z-scores will be turned in the same direction as the antisaccade task (ie, higher is better).

Transfer to Complex WM

Performance on complex WM tasks will be measured using the alpha-span [52] and reading-span [53] tasks. In the alpha-span task, participants were asked to orally recall 5 series of words in alphabetical order rather than in the order of presentation. The words were read aloud by the assessor at a rate of 1 item per second; the size of the series corresponded to n minus 1. Prior to the alpha-span task, an individual's n was determined as the longest sequence of words that could be repeated in the same order as presented. The dependent variable is the proportion of words recalled in the correct order. In the reading-span task, participants made yes/no semantic plausibility judgments on a series of 2-5 sentences. Following each series, participants were asked to recall orally the last word of each sentence. The dependent variables are the proportion of correct words recalled.

Transfer to Complex WM in Virtual Reality

An immersive virtual reality dual task was used to reflect transfer to situations that require closer to real-life cognition [10]. The task was presented with Virtools 5 (EDS Technologies) on a Dell Precision T3600 PC (Inter Xeon CPU ES-1620 0 3.60 GHz, 10-GB RAM processor, and NVIDIA GeForce GTX 600) using an HMD nVisor ST50 headset with stereoscopic vision (1280 × 1024 full color with 50° diagonal field-of-view). During this task, participants were sitting in a car as a passenger and asked to detect road signs (by pressing the left mouse button) to guide the driver to the cities "Chauminont" or "Montformeil." Forty road signs were presented, and half were targets. At the same time, participants memorized and recalled a series of 12 words aloud, which were presented orally by the driver. The dependent variable is a dual-task score computed by averaging z-scores on the memory and detection (accuracy and reaction time) tasks.

Brain Outcomes

Brain Structure

The structural sequence is a T1-weighted 3D MPRAGE sequence (TR/TE 2300/2.98 ms, Fa 9°, FOV = 256 × 256, matrix 256 × 256, voxels 1 mm^3, 192 slices). Regional gray matter volume was measured in the prefrontal and lateral temporal

cortices, basal ganglia, and hippocampi. Cortical thickness was measured in the parietal, prefrontal, and lateral temporal cortices.

Brain Activations

Task-related activations associated with performing updating and inhibition tasks were examined using an interleaved simultaneous multislice (accelerator factor = 6) and echo-planar imaging (TR/TE 785/30 ms, Fa 54°, FOV 192 × 192, matrix 64 × 64, voxels 3 mm^3, 39 slices). A letter N-back task was used to assess updating activations using a block design. Three conditions were presented pseudo-randomly for a total of 15 blocks: (1) a 0-back condition serving as a control, in which a "yes" response was required upon presentation of the letter X; (2) 1-back; and (3) 2-back conditions, in which a "yes" response was required if a given letter was identical to the one presented at the *n*-back position in the sequence; and in other cases, a "no" response was expected. A 3-color Stroop task was administered to assess activity relating to inhibition. The 3 conditions, presented across 15 blocks, were as follows: (1) neutral (a string of the letter X presented in blue, green, or red font), (2) congruent (the words "BLUE," "GREEN," and "RED" presented in blue, green, and red font, respectively), and (3) incongruent (these same words in a colored font that does not correspond to the significance of the word). Throughout all conditions, participants also indicated the color of the font.

Quality Control and Data Management

All assessors and supervisors received an 8-hour training session to ensure treatment adherence and harmonize data collection. They were provided with a manual that details the procedure or training. Furthermore, the first 2 participants were tested under supervision. Data were entered at the end of each wave by the assessors, who were blinded to treatment allocation. Double data entry was used for quality control for transfer cognitive tasks with manually entered scores (ie, running span, keep track, alpha span, reading span, and verbal recall in VR task). When the study was complete, the participants were contacted by phone to answer a Likert-scale questionnaire assessing their motivation associated with the intervention they received (Multimedia Appendix 1).

Statistical Analyses

Sample Size

Our aim is to recruit 90 participants in total. Given an attrition rate between 10% and 16% (see [54] for a review), there would be approximately 27 participants per condition. Assuming a significance level of α=.05, a power of 0.80, and a correlation of r=.50 between 3 repeated measures, the G*Power 3 software for mixed designs estimates that the sample size will provide sufficient power to detect a small to medium effect (f=0.15). Indeed, small to medium effect sizes correspond to those observed with similar training programs in the meta-analysis by Lampit et al [55].

Analysis of Behavioral and Brain Outcomes

We will use a modified intention-to-treat analysis of behavioral outcomes to minimize attrition-related bias, so that all participants who have completed at least one postbaseline assessment will be analyzed. The effect of training programs on the behavioral outcomes will be analyzed with linear mixed-effects models (LMMs) as this analysis makes it possible to compare performance growth between groups and is resistant to missing values. Training improvements will be tested using IES as the dependent variable with 2 separate analyses using *session* (12 levels: session 1 to session 12) × *condition* (3 levels: IES 1-back/IES 2-back/IES 3-back) for the updating training and *session* (12 levels: session 1 to session 12) × *condition* (2 levels: IES Congruent/IES Incongruent) for inhibition training. When significant interaction effects are found, pairwise comparisons will be computed within each training group (comparing performances at sessions 6 and 12 to session 1) and between training conditions at sessions 6 and 12.

Efficacy of training to improve proximal task performances will be tested at 2 separate *time* (three levels: PRE/POST2/POST4) × *training* (3 levels: inhibition/updating/general knowledge) LMMs, using inhibition and updating composite scores as dependent variables. When significant interaction effects are found, pairwise comparisons will be computed within each training group (comparing performances at POST2 and POST4 to PRE) and between training groups (comparing performances for the inhibition and updating condition to general knowledge condition) at POST2 and POST4. To reduce the statistical power cost due to multiple testing corrections and as we have a priori hypotheses, we will also conduct LMM analyses in the absence of interaction to make a direct comparison between the performances of the general knowledge training group (control active) and the updating or inhibition training groups separately.

Efficacy of training to improve complex WM will be tested in the same way with separate time-varying LMMs (5 levels: PRE/POST1/POST2/POST3/POST4) × *training* (3 levels: inhibition/updating/general knowledge) for each task (ie, reading span, alpha span, and VR composite score).

Finally, we will use a per-protocol analysis for the neuroimaging outcomes. Structural MRI images will be analyzed with FreeSurfer 6 [56] to calculate regional cortical gray matter thickness, area, and volume, in the prefrontal, parietal and temporal cortices. Subcortical volumes were segmented for basal ganglia and hippocampi. fMRI images will be preprocessed with SPM12 [57] (realignment, slice timing, coregistration, normalization, smoothing) and will be analyzed as a block design model at subject level with a fixed-effects general linear model (GLM). The GLM will use 1 regressor for each condition task convolved with a canonical hemodynamic response function. A high-pass filter of 128 seconds will be applied to remove low frequencies. Task-related activation will be analyzed using the following fMRI contrasts: [1-back > 0-back] and [2-back > 0-back] as a measure of updating at varying task loads; and [2-back > 1-back] as a measure of load-related activation for the N-back task; [congruent > neutral] as a measure of reading-related activation; and [incongruent > neutral] and [incongruent > congruent] as measures of inhibition for the Stroop task. Whole-brain analysis will help determine task-related activation and whether alternative regions are recruited throughout or after training. Mixed ANOVAs will be carried out in regions of interest using beta weights from the activation clusters and from well-documented task-related regions. We will also adopt a parametric approach analysis, in

which the first-level GLM included regressor for task block with parametric modulator for WM load.

Analysis of Moderators

Linear and logistic regression analyzes will evaluate the relationship between change scores (from behavioral and brain outcomes) and personal variables. As predictors, we will use: (1) education, (2) cognition at baseline; (3) scores on the CRQ; (4) motivation scale score; (5) sex; (6) genotypes (ie, BDNF, COMT, and APOE-ε4); (7) pretraining intracranial volume and white matter lesions; (8) regional gray matter volumes in the prefrontal and lateral temporal cortices; (9) basal ganglia and hippocampi; and (10) pretraining functional activations in the prefrontal and lateral temporal cortices, basal ganglia, and hippocampi. Linear multiple regression and dichotomous moderator analyzes will also be used to examine whether the CRQ's score and the genotypes moderate the relationship between the change scores and the other predictors.

Analysis of Dose Effects

Dose effect will be analyzed with unconditional and conditional growth models to estimate and model the changes in behavioral and brain outcomes as training progresses.

Analysis of Age Differences

After ensuring that the 3 training groups are equivalent, we will first assess the effect of age prior to intervention using ANOVAs, which will compare the performance in both age groups at baseline to assess whether the intervention reduces the effect of age on behavioral and brain outcomes. Separate analyses will be used for the different outcome variables. Using additional ANOVAs, we will then compare the performance of younger participants to the POST4 performance of older participants as a function of their training group and task conditions. Performance of each training group will be compared to the younger group using pairwise comparisons. Finally, whole-brain T-tests in SPM12 will compare age groups at PRE and POST4 to observe differences in activation patterns.

Ethics Approval and Consent to Participate

The study has been approved by the Ethics Committee for Aging-Neuroimaging Research of the Integrated University Center of Health And Social Services of South-Central-Island-of-Montreal (CIUSSS; application #CERVN17-18-02, approval May 8, 2017). Participants signed an informed consent form at their first evaluation visit.

Security, Storage, and Confidentiality

The data are deidentified. Participants are assigned a single alpha-numeric number based on their entry in the project. All data and information are identified with this number. Brain images are processed to remove any personal information or identifier. Personal information and the key with the assigned number are kept in locked filing cabinets and available just for the principal investigator (SB). If anonymized information has to be downloaded to computers, it is kept in secured files.

Access to Data

The data sets for this study will be made available after publication on request to the principal investigator.

Dissemination Policy

Data will be presented in international conferences and through publications in journals with peer-reviewed committees. Study results will also be presented to the public through lay-audience talks and press releases.

Results

The project was funded in January 2017; enrollment began in October 2017 and data collection was completed in April 2019. Data analysis has begun in June 2020 and the first results should be published by the end of 2020 or early 2021.

Discussion

This study is a randomized double-blind controlled trial designed to examine the impact of 2 attentional control interventions, inhibition and updating, on the cognition and brain of older adults. The effect will be examined on proximal measures of inhibition and updating, complex WM measures and brain status, which will be measured with structural MRI and fMRI. Updating and inhibition are linked to age-related decline in WM [58], and have been identified as the most critical attentional control processes supporting fluid cognition [59]. Some studies have found some cognitive improvements following attentional control training in older adults (see [54] for a review). However, no study has yet to compare the relative efficacy of 2 attentional control interventions in older adults.

One strength of this study is precisely the side-by-side comparison of updating and inhibition interventions, against an active control condition. Moreover, updating and inhibition rely on distinct brain regions (eg, frontostriatal regions and right inferior frontal gyrus, respectively), which simplifies the examination of the relationship between brain and cognitive changes. This study will also establish whether inhibition and updating training programs are useful cognitive interventions to improve performance beyond the training tasks and, ultimately, to improve complex WM functioning in aging. The inclusion of a group of younger adults will help determine whether the training programs increase the performance of older adults to the level of the younger participants. Comparing younger and older adults will also clarify whether cognitive gains result from the restoration of the specialized brain regions (eg, normalization of activations relative to younger adults) or from compensative processes (eg, increased activations in specialized or alternative regions).

This study is particularly innovative due to the use of VR, which will objectively measure performance in situations that approximate real life and examine transfer in everyday situations. Transfer to real life is usually measured using self-reported questionnaires, which may lack sensitivity to intraindividual changes, especially within the short period covered by this study (eg, [60]). Finally, another strength of this study is the analyses of genetic moderators to identify and characterize responders. There has been tremendous interest recently in the potential of plasticity-related genes. A better understanding of the moderating role of genetic polymorphisms

on training efficiency and transfer will help promote better adapted cognitive training programs.

The study requires many in-laboratory sessions, which may limit the recruitment of less mobile or less healthy older adults, hence reducing the generalizability of our findings. Another limitation is the absence of a no-contact control group because the cognitive gains from the active control intervention (a general knowledge quiz game) are unknown. As this training induces memory searching and potential reflexive abilities, WM could be moderately stimulated. Therefore, the differences in cognitive gains between the experimental groups and the active control group may not be as strong as expected, which would suggest a cautious interpretation of the impact of the interventions.

Acknowledgments

We warmly thank Nick Corriveau-Lecavalier for his help in starting the study, Maxime Bergevin for his contribution as the coordinator for cognitive training, Julie Legault, Adama Fanta Kaba, and Marie-Claude Veilleux for their contributions regarding enrollment and cognitive assessment. We also want to acknowledge the students who have been involved as trainers and in various aspects of the preparation of the study: Justine Fortin, Camille Hamelin, Barbara Lefranc, and Léo Mottron-Belleville. Finally, thanks to Annie Webb for English revision. This study is funded by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canada Research Chairs Program, the Montreal Geriatrics Institute Foundation (Sojecci), Lemaire Foundation and the Fonds de Recherche en Santé-Québec. AB is funded by the CRIUGM Postdoctoral Fellowship Program and by CIHR (Grant S. Belleville). The sponsors were not involved in the design, methods, recruitment, data collection, analysis, or preparation of the paper.

Authors' Contributions

Everyone that has significantly contributed to this work has been listed as coauthor. SB is the leader of the trial. She conceptualized the initial study and all authors provided feedback on the design. Final decisions are made by SB. AB is the project coordinator and oversees all aspects of the project with the exception of randomization done by SMe, and brain imaging done by SB, SMe, SMa, and LVV. AB and SB wrote the first version and the final revised version of the paper. All authors revised the paper and accepted the final submitted version.

Conflicts of Interest

SB has been a consultant for research development on the prevention of Alzheimer disease for the Fondation IUGM (2016) and for Sojecci (2017 to current), and for the development of a cognitive stimulation program for the Centre de promotion de la Santé AvantÂge (2015). She has intellectual property rights on the "Programme de Stimulation pour une santé cognitive, Memoria, Batterie d'évaluation de la mémoire Côte-des-Neiges" and "MEMO, Méthode d'Entrainement pour une Mémoire Optimale". She collaborates and receives funding from Mind Maze and Beam Me Up. The remaining authors declare that they have no competing interests.

Multimedia Appendix 1
Likert scale questionnaire assessing motivation and perceptions of improvement associated with the interventions.
[DOCX File , 16 KB - resprot_v9i11e20430_app1.docx]

Multimedia Appendix 2
Previous peer-review report.
[PDF File (Adobe PDF File), 1110 KB - resprot_v9i11e20430_app2.pdf]

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Abbreviations

ADNI: Alzheimer's Disease Neuroimaging Initiative
APOE-ε4: apolipoprotein ε4
BDI-II: Beck Depression Inventory II
BDNF: brain-derived neurotrophic factor
CIMA-Q: Consortium for the Early Identification of Alzheimer's Disease
COMT: Catechol-O-methyltransferase
CRIUGM: Research Center of the Institut universitaire de gériatrie de Montréal
CRQ: Cognitive Reserve Proxy Questionnaire
fMRI: functional magnetic resonance imaging
FOV: field of view
GDS: Geriatric Depression Scale
GLM: general linear model
IES: inverse efficiency score
LMM: linear mixed-effects models
MoCA: Montreal Cognitive Assessment
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TE: echo time
TR: repetition time
WM: working memory

Edited by G Eysenbach; submitted 19.05.20; peer-reviewed by S Heinzel, J Vermeir; comments to author 08.07.20; revised version received 16.10.20; accepted 20.10.20; published 24.11.20.

Please cite as:
Boujut A, Mellah S, Lussier M, Maltezos S, Verty LV, Bherer L, Belleville S
Assessing the Effect of Training on the Cognition and Brain of Older Adults: Protocol for a Three-Arm Randomized Double-Blind Controlled Trial (ACTOP)
JMIR Res Protoc 2020;9(11):e20430
URL: http://www.researchprotocols.org/2020/11/e20430/
doi:10.2196/20430
PMID:33231556

Protocol

Injectable Amoxicillin Versus Injectable Ampicillin Plus Gentamicin in the Treatment of Severe Pneumonia in Children Aged 2 to 59 Months: Protocol for an Open-Label Randomized Controlled Trial

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Abstract

Background: Pneumonia causes about 0.9 million deaths worldwide each year. The World Health Organization (WHO) guidelines for the standard management of severe pneumonia requires parenteral ampicillin every 6 hours and once-daily parenteral gentamicin for 5 to 7 days. Although this treatment has contributed to the reduction of mortality, it requires nursing interventions every 6 hours for 7 days. Further intervention trials should be conducted to search for alternate antibiotics with better adherence, reduced cost, and reduced hospital stay. Parenteral amoxicillin is an effective alternative to ampicillin, as it has a longer half-life and broader coverage.

Objective: The aim of this clinical trial is to compare the efficacy of a dose of injectable amoxicillin every 12 hours plus a once-daily dose of injectable gentamicin with a dose of injectable ampicillin every 6 hours plus a once-daily dose of injectable gentamicin in children hospitalized for severe pneumonia.

Methods: This randomized, controlled, open-label, noninferiority trial is being conducted in Dhaka Hospital of the International Centre for Diarrheal Disease Research, Bangladesh. A sample size of 308 children with severe pneumonia will give adequate power to this study. Children aged 2 to 59 months are randomized to either intravenous ampicillin or intravenous amoxicillin, plus intravenous gentamicin in both study arms. The monitoring of the patients is carried out according to the WHO protocol for the treatment of severe pneumonia. The primary objective is the rate of treatment failure, defined by the persistence of danger signs of severe pneumonia beyond 48 hours or deterioration within 24 hours of initiation of the therapy. The secondary objectives are (1) improvement in or the resolution of danger signs since enrollment, (2) length of hospital stay, (3) death during hospitalization, and (4) rate of nosocomial infections.

Results: Enrollment in the study started on January 1, 2018, and ended on October 31, 2019. Data entry and analysis are in progress. Findings from the study are expected to be disseminated in October 2020.

Conclusions: Our study's findings will improve compliance with the use of antibiotics that require less frequent doses for the treatment of severe pneumonia.

Trial Registration: ClinicalTrials.gov NCT03369093; https://clinicaltrials.gov/ct2/show/NCT03369093

International Registered Report Identifier (IRRID): DERR1-10.2196/17735

(JMIR Res Protoc 2020;9(11):e17735) doi:10.2196/17735

KEYWORDS

severe pneumonia; treatment failure; amoxicillin; children; randomized controlled trial, Bangladesh

Introduction

Even after remarkable progress in child survival from 1990 to 2015, pneumonia is still considered the leading cause of death globally in children younger than 5 years [1]. Every year, 150 million children contract pneumonia, and 11 million of them require hospitalization [2]. Pneumonia mortality was 0.9 million in 2015 [3,4], which indicates that despite global economic development, improved nutrition, and effective vaccination, more progress is required in case management [5,6]. Case management is one of the key interventions to reduce death in children with pneumonia [7]. Cost-effective interventions, including effective antibiotics, contribute to better outcomes and compliance [8]. Etiological analysis has shown that bacteria and viruses accounted for 33.7% and 54.5% of infection, respectively, in hospitalized patients with severe pneumonia [9,10].

Streptococcus pneumoniae were the most common bacteria (33.9%) in cases in which mortality occurred within 30 days of hospitalization [9]. The World Health Organization (WHO) recommends parenteral ampicillin and gentamicin for 5 to 7 days for the treatment of severe pneumonia in children aged 2 to 59 months [11]. As many developing countries, including Bangladesh, lack enough pediatric hospital beds to accommodate the demand for the 5- to 7-day hospitalization of all children with severe pneumonia, alternative treatment options, such as the day care approach, during recovery from danger signs have been investigated and shown to be effective [12,13]. According to local published data, the rate of treatment failure in parenteral ampicillin and gentamicin was 50% [14]; moreover, hospitalization for 5 to 7 days with nursing interventions every 6 hours incur treatment costs and reduce parental compliance with treatment [15]. To address this limitation, we may need to propose a more convenient antibiotic regimen to reduce the cost of treatment and the duration of hospital stay after the disappearance of danger signs. As an alternative drug to ampicillin, amoxicillin has been shown to have an antimicrobial spectrum and level of activity virtually the same as that of ampicillin, with the added advantages of a longer half-life and an equally potent oral formula [16,17]. A combination of amoxicillin and an aminoglycoside may have a synergistic effect against *Streptococcus* species, which are common pathogens for childhood pneumonia [18-20]. When comparing the local cost of these drugs, parenteral amoxicillin is a third of the price of parenteral ampicillin. With the reduced number of intravenous interventions, we also assume a lower incidence of nosocomial infection and a reduced hospital stay. Thus, this report describes the study design of a clinical trial to compare the efficacy of 2 doses of parenteral amoxicillin plus a single dose of gentamicin to 4 doses of parenteral ampicillin plus a single dose of gentamicin in treating children aged 2 to 59 months with WHO-classified severe pneumonia.

Methods

Ethics and Research Approval

This study was reviewed and approved by the institutional review board at the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) (approval No. PR-17061, version 4.0, dated July 4, 2018). The trial was registered at ClinicalTrials.gov (NCT03369093) on December 11, 2017. To monitor the overall activity of this trial, a data safety and monitoring board (DSMB) was constituted, comprising members of Bangabandhu Sheikh Mujib Medical University, Dhaka University, and the Ethical Review Committee of icddr,b. Results of this study will be disseminated by publication in a peer-reviewed scientific journal and presented at relevant academic conferences and to health policy makers. The study protocol follows the SPIRIT (Standard Protocol Items: Recommendation for Intervention Trials) guidance for protocol reporting (see Figure 1 and Multimedia Appendices 1 and 2).

The legal guardian of the study participants must personally sign and date the approved version of the informed consent form before any trial-specific procedures are performed (see Multimedia Appendix 3). Written and verbal versions of the participant information and informed consent are presented to the participants and their parent or legal guardian, detailing no less than the exact nature of the trial, what it involves for the participant, the implications and constraints of the protocol, the known side effects, and any risks involved in taking part. It is clearly stated that the participant's parent or legal guardian is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. A brief follow-up visit plan is also explained during the consent process.

Figure 1. Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) figure showing the schedule of enrollment, interventions, and assessments. IV: intravenous.

		Study period				
	Screening	Enrollment	Assessment & allocation	Intervention	Follow-up	
					1st follow-up	2nd follow-up
Time point	Day 0	Day 0 to 1	Day 0 to 1	Day 1 to 7	Day 7	Day 30
Enrollment						
Eligibility screen		✓				
Informed consent		✓				
Randomization and allocation			✓			
Interventions						
IV ampicillin or IV amoxicillin			✓	✓		
Assessments						
Demographics	✓					
Comorbidities	✓					
Physical examination	✓	✓	✓	✓	✓	✓
Primary outcome						
Rate of resolution of danger signs (by 48 hours)				✓		
Secondary outcomes						
Time of improvement or resolution of danger signs since enrollment				✓		
Length of hospital stay				✓		
Death				✓		
Rate of nosocomial infections				✓		

Study Design and Settings

This is a single-center, randomized, controlled, open-label, noninferiority trial. A noninferiority design was chosen to evaluate if there is any difference in treatment failure among ampicillin and amoxicillin. The primary objective is to compare the efficacy of 2 doses of injectable amoxicillin plus a single dose of injectable gentamicin to 4 doses of injectable ampicillin plus a single dose of injectable gentamicin in the management of children aged 2 to 59 months hospitalized with severe pneumonia. Efficacy of the 2 drugs will be measured by treatment failure in response to therapy, defined by persistence of any danger signs of severe pneumonia beyond 48 hours or deterioration within 24 hours of initiation of therapy (development of any new danger signs or clinical signs of respiratory failure, development of severe sepsis or meningitis, or radiological deterioration). The secondary objectives are (1) improvement or resolution of danger signs since enrollment, (2) length of hospital stay, (3) death during hospitalization, and (4) rate of nosocomial infections. To determine improvement, clinical signs, including hypoxemia (oxygen saturation by pulse oximetry [SpO_2] of <90% in room air) [21], grunting, convulsion, abnormal mentation, inability to feed or drink, very severe lower chest wall indrawing, and the normalization of fast breathing, will be monitored from enrollment to discharge.

This study is being conducted at the Dhaka Hospital of icddr,b, Dhaka, Bangladesh. This is the largest diarrheal disease hospital in the world, located in the capital of Bangladesh. In 2019, it provided treatment to over 166,000 diarrheal patients with or without associated complications, including pneumonia, sepsis, malnutrition, or complications related to diarrhea. Details of the settings are described elsewhere [22]. The vast majority of the patients come from lower socioeconomic backgrounds from urban and periurban localities, including slums. This hospital is well equipped, with a modernized critical care unit for critically sick children. All the essential laboratory investigations are available in the International Organization of Standardization (ISO)–accredited laboratory facility (ISO 15190:2003) situated on the same premises. All treatment and lodging in the hospital are provided free of cost.

Study Participants

Children aged 2 to 59 months are eligible for study enrollment upon meeting clinical criteria of severe pneumonia, as defined by the WHO classification updated in 2014 [6,20].

Those coughing or having difficulty breathing are screened by the study staff for eligibility. All screened patients are allotted a unique identification number and interviewed about contact information and demographics. Eligible children are enrolled in the study upon meeting the case definition of severe pneumonia, with cough or difficult breathing plus at least two of the following: (1) central cyanosis or SpO_2 of <90%, (2) severe respiratory distress (eg, grunting, very severe chest indrawing), or (3) signs of pneumonia with a general danger sign (eg, inability to breastfeed or drink, lethargy or unconsciousness, convulsion).

To tackle differential misclassification, the study enrollment process is witnessed by a nonstudy hospital care provider. Once eligibility is confirmed, the randomization envelope is opened in the presence of a nonresearch physician.

We exclude children who have been on antibiotic therapy at home or in the hospital for at least 48 hours before coming to the hospital or with a known congenital or chromosomal anomaly (eg, congenital heart disease, laryngomalacia, cleft lip, cleft palate, trisomy 21). We also do not recruit children who present with a life-threatening condition that requires immediate assisted ventilation or referral to a higher facility for critical serum creatinine values.

Randomization

The allocation ratio is 1:1 with a parallel-group enrollment. The permuted block randomization technique is applied. The sequence of randomization was prepared before the commencement of the study by an independent statistician at icddr,b unrelated to this clinical trial. Randomization is performed by computer-generated random numbers with a prefixed block number unknown to the researcher. For blinding of the treatment arms, randomization numbers are provided to the study investigators in sequentially numbered, sealed, opaque envelopes containing the name of the treatment on a card inside the envelope. The study physician opens the subsequent numbered envelope in the presence of another nonstudy physician of the intensive care unit (ICU) or general ward when a participant has formally entered into the trial after written informed consent from the parents or caregivers. After treatment allocation, the child is assigned the allocated antibiotics by the study physician or the study nurses. The enrolled patient is randomized in either the WHO-recommended ampicillin plus gentamicin arm or the amoxicillin plus gentamicin arm.

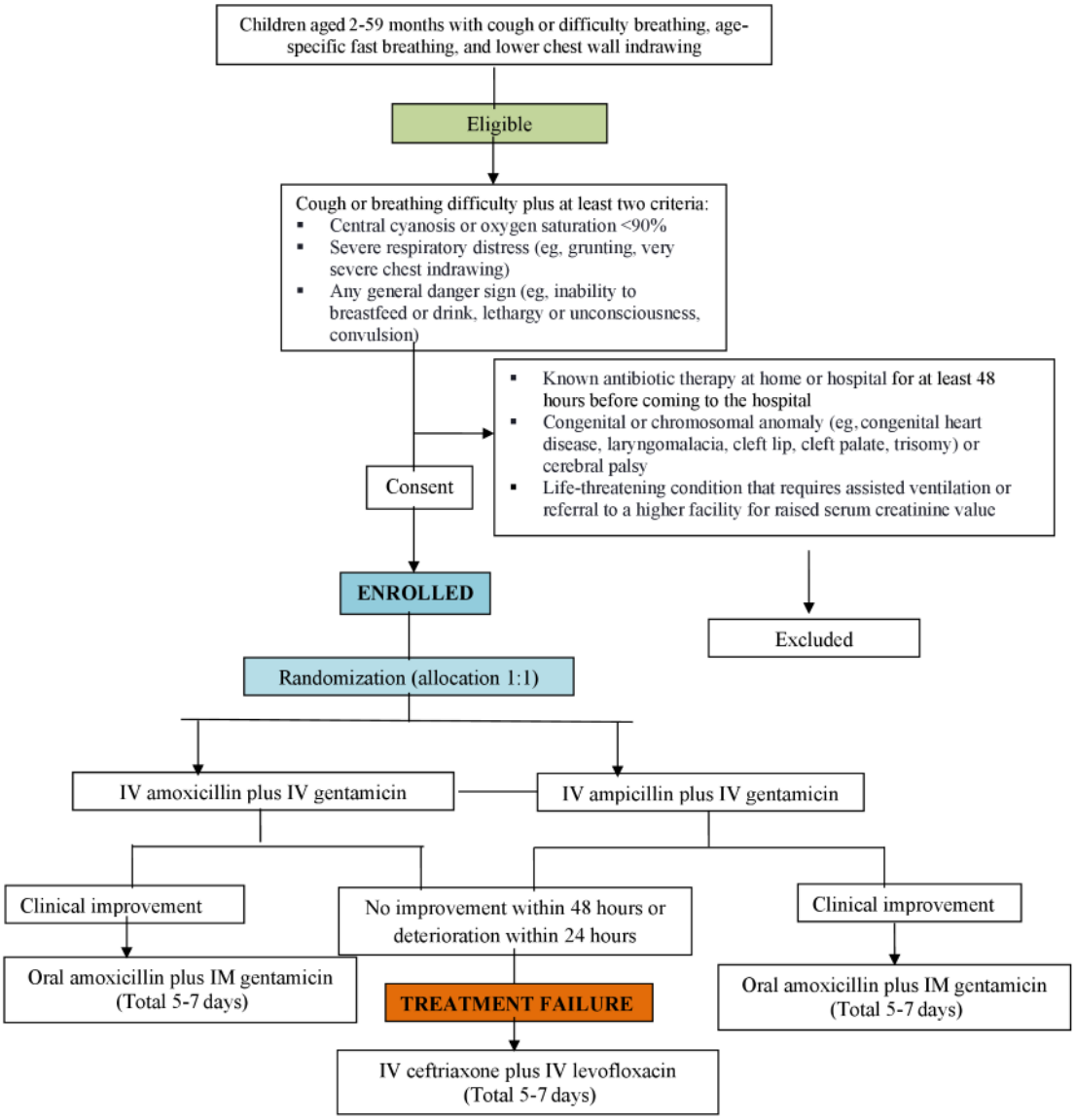
Treatment Procedures

Hospital standard-of-care management initiates as soon as a patient is admitted. However, the study-specific antibiotic therapy starts following enrollment. The flowchart for the study design is illustrated in Figure 2.

In the ampicillin arm, the patient receives a 50-mg/kg dose of intravenous (IV) ampicillin every 6 hours and a 7.5-mg/kg dose of IV gentamicin once daily for 5 to 7 days. In the intervention arm (amoxicillin arm), the patient receives a 40-mg/kg dose of IV amoxicillin every 12 hours and a 7.5-mg/kg dose of IV gentamicin once daily for 5 to 7 days. In both arms, duration of therapy depends on the patient's clinical improvement and the clinical judgement of the attending physicians. Children in both regimens require an IV cannula kept in place for the administration of the medication. It is expected that in the absence of complications, clinical improvement should be present [21]. After improvement or resolution of danger signs, when the children can take oral feeding, parenteral ampicillin or amoxicillin is switched to oral amoxicillin at a dose of 40 mg/kg every 12 hours with ongoing intramuscular gentamicin. Children showing subsequent improvement [21] with resolution of all danger signs are advised for discharge under ambulatory medical support, where they receive the remaining doses of intramuscular gentamicin to accomplish the 5- to 7-day course of antibiotic therapy. If any participants refuse the ambulatory medical support due to its far distance, they complete the treatment locally.

At enrollment, oxygen saturation is measured using a pulse oximeter (N-560; Nellcor Puritan Bennett Inc) with a probe on a finger or toe when the child breathes in room air. Oxygen saturation of <90% in room air is defined as hypoxemia, which indicates the need for oxygen therapy. Participants with grunting or hypoxemia are immediately put on bubble continuous positive airway pressure oxygen therapy, following the standard practice of the hospital [14], and kept in the ICU. Participants having feeding difficulty in the form of being unable to suck or swallow, experiencing frequent vomiting (>3 episodes in an hour), or having a respiratory rate of over 70 breaths per minute are started on nasogastric feeding until resolution of symptoms. The management of severe acute malnutrition and related complications is carried out according to standard hospital practice [23,24]. Likewise, the assessment of dehydration and the management of complications is carried out according to hospital protocol [25,26]. The study participants' care is provided by dedicated study physicians and study nurses by following standard operating procedures. To ensure the uniformity of care, regular training and surprise evaluations are carried out by the trial investigators.

Figure 2. Flowchart for the proposed randomized controlled trial. IM: intramuscular; IV: intravenous.



Data Collection

A structured case report form (CRF) was pretested on 5 pilot patients before formal enrollment began. The CRF is compliant with good clinical practice. Baseline data, demographic and social information (age, sex, religion, parental age, parental occupation, gestational age, weight, drinking water source and sanitation, fuel use, number of rooms in the house, etc), detailed clinical examination data, vital signs including pulse oximetry, and anthropometric measurements are collected and recorded in the CRF. Information is collected about a child's feeding practices, such as their history of breastfeeding, infant formula, or other complementary feeding practices, as well as immunization status, family history of tuberculosis, recent respiratory tract infections of any family members, and past history of the child's pneumonia.

After treatment is initiated, data on a participant's vital signs, calorie intake, progression of illness, new problems, and treatment are recorded every 4 hours in the CRF until discharge. A study physician performs standardized clinical examinations daily to assess clinical signs of treatment failure or clinical improvement.

Laboratory Tests

All laboratory investigations are carried out according to standard hospital care, and no additional test is advised for this study purpose. For patients with severe pneumonia and malnutrition, complete blood count, chest radiograph, and serum electrolyte tests are performed, according to hospital policy. A blood culture is performed for febrile children.

All laboratory investigation reports and x-ray films are kept covered in the study office under lock and key. Participants' medical record forms are preserved electronically as a source document. All the medical records are identified by coded numbers to maintain participants' confidentially and enable tracking throughout the study. Only authorized study staff have access to the files.

No biological products from patients are stored for future use.

Discontinuation Procedure

The criteria for discontinuing the allocated interventions, as per the study design (Figure 2), are (1) no improvement of danger signs after 48 hours of starting antibiotic therapy; (2) clinical deterioration of the patient in terms of appearance of hypoxemia, grunting, or respiratory failure requiring mechanical ventilation; (3) septic shock or severe sepsis; or (4) referral to other hospitals for conditions such as acute kidney injury (raised serum creatinine). In such instances, patients are declared treatment failures. The ongoing medications are discontinued and the patient is switched to second-line antibiotics (IV ceftriaxone, 80 mg/kg once daily, plus IV levofloxacin, 10 mg/kg once daily) and continued on these medications for 5 to 7 days based on clinical improvement. Once a patient is declared a treatment failure, a blood culture, chest radiogram, and other investigations are recommended, as per standard care. Regardless, the patient is followed by the study team until discharge.

Follow-up After Discharge

At discharge, patients are advised to return for follow-up visits at day 7 and day 30. During follow-up visits, although no compensation is provided, patients undergo anthropometric measurement and receive a physician's consultation, including the update on the previous condition. Nutritional follow-up is provided during this visit, along with a demonstration of the preparation of a healthy diet for the children. Clinical examination findings and history of any intercurrent illnesses are recorded in the CRF. If the participants do not return at their scheduled time, the study staff contact the patient's legal guardian over the phone. In the reachable cases, we ask about the patient's health status and the presence of any new illnesses after discharge from the hospital and record the answers accordingly. During discharge and follow-up, caregivers are assured that their children will be provided standard treatment in subsequent visits if they wish to bring their child to this hospital.

Reporting of Adverse Events

All serious adverse events after initiation of the study intervention are recorded and elaborated upon to the DSMB members within 24 hours of the event. The serious adverse event report includes a structured template of the patient's detailed medical history, the study intervention, the sequence of events, and management attempts until the outcome of the patient. For patients who are referred, the outcome is collected over the phone. The entire safety outcome is analyzed by intention-to-treat analysis.

Outcome Measures

Primary Outcome Variable

The primary outcome variable is the percentage of children with treatment failure, as determined either by the persistence of danger signs over 48 hours or by the appearance of new danger signs within 24 hours of the study intervention.

Secondary Outcome Variable

There are 4 secondary outcome variables: (1) time to resolution of danger signs of severe pneumonia, (2) length of hospital stay, (3) rate of nosocomial infections, and (4) death during or after discharge. The secondary outcome measurement variables are the time (in hours) of disappearance of danger signs, time (in days) to discharge from the acute phase, and rate of suspected nosocomial infections (a nosocomial infection will be diagnosed based on the appearance of new signs of infection, such as fever, cough or respiratory distress, diarrhea, or crying during urination, after 48 hours of admission or within 72 hours of discharge from the hospital).

Sample Size

This is a noninferiority trial. The main therapeutic effect of the intervention therapy (amoxicillin) is not expected to be unacceptably worse than that of the standard therapy (ampicillin) considering all parameters, such as cost, length of hospital stay, and chance of nosocomial infection. Here, the null hypothesis is $p_2 - p_1 \geq \delta$ (inferior), where we assume that the proportion cured in the standard arm will be 50% (denoted as π=0.50) [14]. Even if recovery in the intervention arm is 16% less (δ=0.16) than that of the standard arm (ie, up to 34%), we would consider the intervention therapy to be noninferior considering all possible effects. With 80% power and an α of .025 (1-sided), the estimated minimum sample size per group is 154, or 308 in total. Intention-to-treat analysis will be performed. No inflation was added for the consideration of dropout due to cost and time constraints. The sample size calculation was conducted using Stata 15 (StataCorp) using the Statistical Software Components archive package, also known as the Boston College archive.

Statistical Analysis

Data analyses will be performed using SPSS (version 20.0 for Windows; IBM Corp), Stata (Statistics and data version 13) and Epi Info (version 7.0; Centers for Disease Control and Prevention). Other statistical software packages may be used as required. Statistical analyses will include descriptive as well as analytical methods. Descriptive analysis will be performed between children enrolled in the amoxicillin arm and the ampicillin arm.

Categorical variables will be compared using the chi-square test, and the Fisher exact test will be applied if the expected frequency in any cell is 5 or less. Parametric continuous variables will be compared using 2-tailed Student *t* tests, and nonparametric data will be compared using the Mann-Whitney U test.

As the secondary outcome variables are time to resolution of danger signs and length of hospital stay, survival analysis will be performed to see the response in each group. For the final analysis, a Cox proportional hazard model will be performed.

Logistic regression analysis will be used for predicting the outcome of a categorical (yes or no) variable over one or more predictor variables. Death is a categorical variable (yes or no) and will be analyzed using bivariate analysis. Afterward, a logistic regression model will be prepared to identify the causative variables. A *P* value of <.05 will be considered statistically significant, and the strength of association will be determined by calculating relative risks and their 95% confidence intervals.

Statistical analysis will be performed on data from all randomized patients in the study on an intention-to-treat basis. No per-protocol analysis or imputation of missing data will be performed for this study. Data from children withdrawn because of failure to respond to the usual treatment of severe pneumonia and voluntary dropouts will be included in the analysis up to the time of withdrawal. A supplementary analysis excluding the children withdrawn may be performed.

Results

Enrollment into the study started on January 1, 2018, and ended on October 31, 2019. Data entry and analysis are in progress. Findings from the study are expected to be disseminated in October 2020.

Discussion

Summary

The purpose of this clinical trial is to determine if parenteral amoxicillin is superior to parenteral ampicillin for treating children with severe pneumonia. The WHO-recommended standard antibiotic treatment is successfully reducing child mortality [4,20], but it requires hospitalization for 5 to 7 days to receive antibiotics at 6-hour intervals [21]. Many developing countries, including Bangladesh, do not have enough pediatric hospital beds to accommodate the demand for admission of all children with severe pneumonia. In resource-limited settings, different treatment options, such as the day care approach, with other antibiotic options have been shown to be equally effective in the treatment of severe pneumonia [12]. Therefore, intervention trials should be conducted to search for alternate antibiotics with better adherence, reduced cost, and reduced hospital stay. Parenteral amoxicillin is an effective alternative to ampicillin, as it has a longer half-life and broader coverage. The main purpose of this randomized controlled trial is to assess whether it would be possible to treat severe pneumonia in a hospital with an antibiotic regimen that requires less frequent doses than the current standard. The data gathered from this study will hopefully be of great interest to health care professionals and researchers who seek to modify the management strategy for severe pneumonia in order to achieve a reduced hospital stay and improved treatment outcome.

According to the WHO, standard management of severe pneumonia requires hospitalization with parenteral antibiotics for at least 5 days, and in the absence of any complications, there should be signs of improvement after 48 hours of successful treatment. If the findings from this study show that there is no difference in treatment failure between the 2 arms, then after the improvement of danger signs and the establishment of oral feeding, parenteral amoxicillin can be switched to oral amoxicillin twice daily and intramuscular gentamicin once daily and continued for 5 to 7 days in an ambulatory setting under close monitoring. This will substantially reduce hospitalization costs, reduce parenteral drug usage, and improve patient compliance.

Our hospital has a dedicated respiratory ward with trained respiratory physicians, which allows us to conduct the research with high vigilance while minimizing biases. We expect that the findings of our clinical trial will improve compliance with the use of antibiotics that require less frequent doses in the treatment of severe pneumonia. In essence, the use of parenteral amoxicillin twice daily is cost-effective and requires less frequent parenteral intervention, which should contribute to reducing the incidence of nosocomial infections in our hospital.

Study Limitations

This study has three main limitations. First, as this is a single-center trial, study findings may not be generalizable to other settings. Second, this is an open-label trial, and the clinical staff could not be blinded due to the different frequencies of drug administration (eg, ampicillin every 6 hours and amoxicillin every 12 hours). We could have blinded the trial by introducing a placebo, but due to the secondary outcome of nosocomial infections, we omitted that. Third, due to cost constraints, we could not perform nasopharyngeal swab cultures to identify the etiology of the pneumonia and compare it with drug sensitivity.

Acknowledgments

We would like to acknowledge the physicians of Dhaka Hospital, who took time out of their busy schedules to discuss their opinions about patient enrollment, patient recovery, and deterioration with the research investigators. We are grateful to our patients for their active participation in this trial.

This study is funded by the Capacity Development Fund of the International Centre for Diarrhoeal Disease Research, Bangladesh. We acknowledge funding support to the International Centre for Diarrhoeal Disease Research, Bangladesh by core donors: the Government of Bangladesh, the Swedish International Development Coordination Agency, Global Affairs Canada, and the UK Department for International Development.

Authors' Contributions

TA originated the idea for the study and suggested the protocol design. LS and MJC led the protocol design. ASMSBS, ASMMHR, and MZI participated in the design of the study. TA, LS, MJC, FA, and SH were involved in the development of the study protocol. LS, ASMMHR, and FA were involved in the implementation of the study protocol. LS, MJC, and MZI were involved in the data analysis plan. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT Checklist.
[DOCX File , 24 KB - resprot_v9i11e17735_app1.docx]

Multimedia Appendix 2
Final Approved IRB protocol.
[PDF File (Adobe PDF File), 1374 KB - resprot_v9i11e17735_app2.pdf]

Multimedia Appendix 3
Informed consent form (local language Bengali).
[PDF File (Adobe PDF File), 1247 KB - resprot_v9i11e17735_app3.pdf]

Multimedia Appendix 4
External review of the Protocol.
[PDF File (Adobe PDF File), 2109 KB - resprot_v9i11e17735_app4.pdf]

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Abbreviations

CRF: case report form
DSMB: data safety and monitoring board
icddr,b: International Centre for Diarrhoeal Disease Research, Bangladesh
ICU: intensive care unit
ISO: International Organization of Standardization
IV: intravenous
SPIRIT: Standard Protocol Items: Recommendation for Intervention Trials
SpO_2: oxygen saturation by pulse oximetry
WHO: World Health Organization

Edited by G Eysenbach; submitted 09.01.20; peer-reviewed by EM Strehle, S Rhedin, K Baker, C King, T Lakiang; comments to author 11.08.20; revised version received 20.08.20; accepted 25.08.20; published 02.11.20.

Please cite as:
Shahrin L, Chisti MJ, Shahid ASMSB, Rahman ASMMH, Islam MZ, Afroze F, Huq S, Ahmed T
Injectable Amoxicillin Versus Injectable Ampicillin Plus Gentamicin in the Treatment of Severe Pneumonia in Children Aged 2 to 59 Months: Protocol for an Open-Label Randomized Controlled Trial
JMIR Res Protoc 2020;9(11):e17735
URL: https://www.researchprotocols.org/2020/11/e17735
doi:10.2196/17735
PMID:33136058

Protocol

Effect of Pain Education and Exercise on Pain and Function in Chronic Achilles Tendinopathy: Protocol for a Double-Blind, Placebo-Controlled Randomized Trial

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Abstract

Background: Achilles tendinopathy (AT) rehabilitation traditionally includes progressive tendon loading exercises. Recent evidence suggests a biopsychosocial approach that incorporates patient education on psychosocial factors and mechanisms of pain can reduce pain and disability in individuals with chronic pain. This is yet to be examined in individuals with AT.

Objective: This study aims to compare the effects on movement-evoked pain and self-reported function of pain education as part of a biopsychosocial approach with pathoanatomical education for people with AT when combined with a progressive tendon loading exercise program.

Methods: A single-site, randomized, double-blind, placebo-controlled clinical trial will be conducted in a university-based hospital in a laboratory setting and/or by telehealth. A total of 66 participants with chronic (>3 months) midportion or insertional AT will be randomized for the Tendinopathy Education of the Achilles (TEAch) study. All participants will complete progressive Achilles tendon loading exercises over 12 weeks and will be encouraged to continue with self-selected exercises as tolerated. All participants will complete 6-7 one-to-one sessions with a physical therapist to progress exercises in a standardized manner over 8 weeks. During the last 4 weeks of the intervention, participants will be encouraged to maintain their home exercise program. Participants will be randomized to 1 of 2 types of education (pain education or pathoanatomic), in addition to exercise. Pain education will focus on the biological and psychological mechanisms of pain within a biopsychosocial framing of AT. Pathoanatomic education will focus on biological processes within a more traditional biomedical framework of AT. Evaluation sessions will be completed at baseline and 8-week follow-up, and self-reported outcome measures will be completed at the 12-week follow-up. Both groups will complete progressive Achilles loading exercises in 4 phases throughout the 12 weeks and will be encouraged to continue with self-selected exercises as tolerated. Primary outcomes are movement-evoked pain during heel raises and self-reported function (patient-reported outcome measure information system—Physical Function). Secondary outcomes assess central nervous system nociceptive processing, psychological factors, motor function, and feasibility.

Results: Institutional review board approval was obtained on April 15, 2019, and study funding began in July 2019. As of March 2020, we randomized 23 out of 66 participants. In September 2020, we screened 267 individuals, consented 68 participants, and randomized 51 participants. We anticipate completing the primary data analysis by March 2022.

Conclusions: The TEAch study will evaluate the utility of pain education for those with AT and the effects of improved patient knowledge on pain, physical function, and clinical outcomes.

International Registered Report Identifier (IRRID): DERR1-10.2196/19111

(JMIR Res Protoc 2020;9(11):e19111) doi:10.2196/19111

KEYWORDS

Achilles tendon; tendinopathy; rehabilitation; pain; tendon; patient education

Introduction

Background

Achilles tendinopathy (AT) pain leads to decreased function and participation in work and recreation activities [1,2]. However, factors that contribute to the development and persistence of AT pain are not well understood. Recent evidence suggests that neurobiological pain processes in the peripheral and central nervous systems (CNS) contribute to chronic AT pain [3-7]. Factors that have been associated with AT include centrally mediated mechanisms such as elevated pain, psychological factors (fear of movement and pain catastrophizing) [5,8], and motor dysfunction (heel raise repetitions reduced by pain) [5]. However, this relationship is complex and bidirectional, as pain can also reduce function. In addition, there is mixed evidence for the presence of altered CNS regulation of nociceptive processing contributing to AT pain [4,5], with some studies indicating reduced conditioned pain modulation (CPM) and/or widespread decrease in pressure pain [6,7], whereas other studies indicate no difference compared with controls [4,5]. Peripheral mechanisms include nociceptive input, as evidenced by decreased pain pressure threshold (PPT) at the site of pain relative to multiple proximal and contralateral areas [4,5,7]. An improved understanding of how different physical therapy treatment approaches affect these mechanisms of AT pain could inform clinical practice.

Objectives

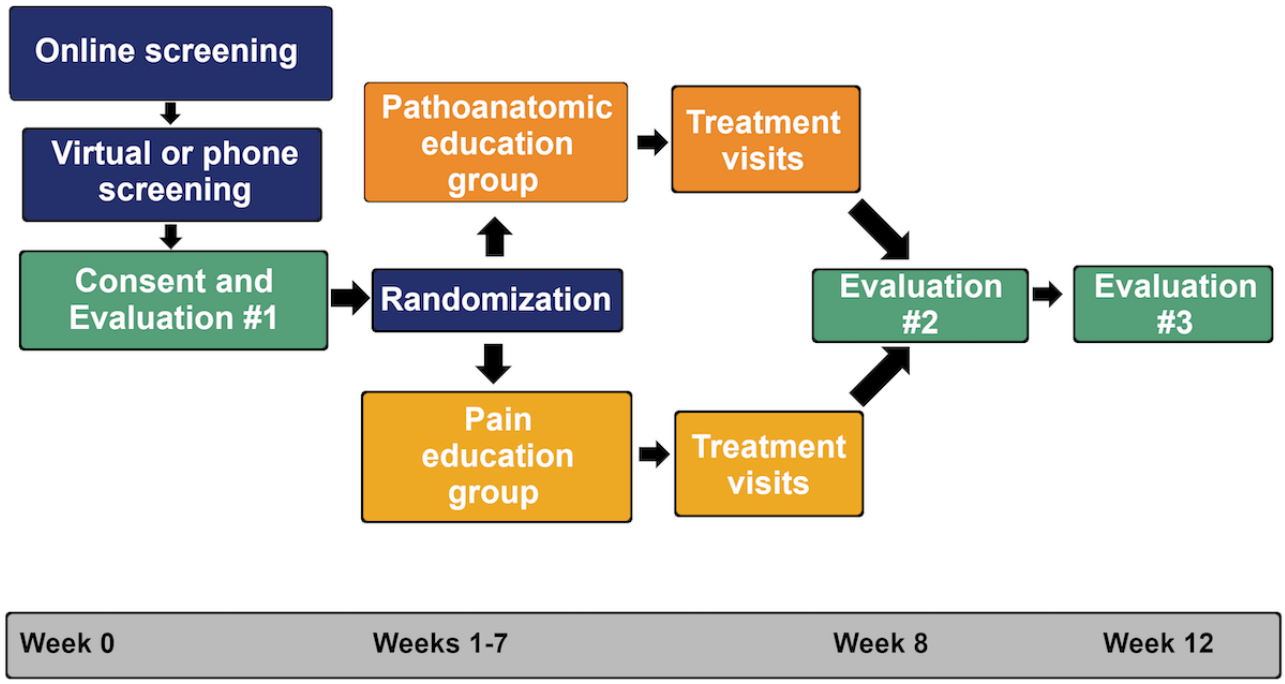
Chronic musculoskeletal pain conditions, such as AT, can be associated with elevated levels of kinesiophobia and catastrophizing [9]. Given the frequent chronic duration of AT symptoms, fear avoidance and negative beliefs about movement and exercise may negatively impact patient compliance and outcomes of tendon loading exercises [10]. Pain education as part of physical therapy, with a biopsychosocial approach, has recently emerged as a promising component of care for many chronic musculoskeletal pain conditions. Greater patient understanding of their condition facilitates improved self-efficacy and management of symptoms while decreasing kinesiophobia and pain catastrophizing [9]. The standard of care for AT includes progress in tendon loading exercises, based on a high level of evidence [8,10-13]. In contrast, no clinical trials have evaluated the effects of pain education on pain and function in patients with Achilles tendon pain [14]. We hypothesize that a biopsychosocial approach to patient education, which addresses pain-related psychological factors and provides accurate information on adaptation, biology, and central pain mechanisms, will decrease movement-evoked pain and improve self-reported function at 8 weeks more than standard care for patients with AT, which is usually based on a pathoanatomical educational approach.

Methods

Overview

Tendinopathy Education on the Achilles (TEAch; NCT *04059146*) is a randomized, double-blind, placebo-controlled trial for individuals with chronic AT. The primary outcomes of movement-evoked pain and self-reported function will be represented as a change from baseline to 8-week follow-up (Figure 1). All participants will receive a progressive tendon loading exercise program and be assigned to either a pain education program or a pathoanatomical education program on AT pathology. The TEAch study has 2 primary aims and 2 exploratory aims. The first aim is to determine if an 8-week progressive tendon loading exercise program combined with pain education on AT is more effective at reducing movement-evoked pain and self-reported function than pathoanatomical education on AT. The second aim is to identify processes (altered CNS regulation of nociceptive input, changes in fear or pain beliefs, and improved motor function) that change over time with the intervention, regardless of education type. Our first exploratory aim is to identify if improvements in pain mechanism knowledge related to AT are associated with an improvement in pain and function. The second exploratory aim will identify if improvements in pain processes (altered CNS regulation of nociceptive input, changes in fear or pain beliefs, and improved motor function) are associated with an improvement in pain and function. In addition, a feasibility aim will gather information (recruitment, treatment fidelity, outcome capture rate, and adverse events [AEs]) to inform future clinical trials through both in-person and telehealth delivery of interventions on the outcomes of pain and function.

Figure 1. After consent and baseline measures at Evaluation #1, participants who satisfy all eligibility criteria are randomized to education group. A physical therapist provides education along with exercise over 6-7 individual treatment sessions. At 8-weeks participants complete Evaluation #2 to repeat all baseline measures. At 12-weeks the participants complete Evaluation #3, which consists of online surveys.



Participants

Participants will be recruited through the University of Iowa and local community using mass emails, databases of participants previously enrolled in research studies, referrals from participants and collaborators in the Department of Orthopedics and Rehabilitation, and review of electronic medical records. All participants will be screened through a web-based survey and review of the medical records, if available, for inclusion and exclusion criteria (Textbox 1). Potential participants will be contacted via email and/or phone by the study coordinator. Participants will be consented at their first evaluation session, including a review of the purpose of the study, risks and benefits, procedures including confidentiality and interventions, and opportunity for participants' questions. After informed consent, an experienced physical therapist will confirm a diagnosis of AT by clinical exam and ensure that all inclusion criteria are met (Textbox 1). Participants who do not meet the eligibility criteria at evaluation session 1 will be excluded from randomization to the treatment group. Participants will be compensated for completion of evaluation sessions and travel and parking for evaluation and treatment visits. The protocol was reviewed and approved by the Institutional Review Board (IRB) at the University of Iowa.

Textbox 1. Study eligibility criteria are assessed during web-based screening and phone or virtual screening. A clinical exam by a physical therapist is used to verify eligibility criteria at evaluation session 1.

Inclusion criteria

- Primary source of pain localized to Achilles tendon insertion or midportion under load during clinical exam
- Localized pain 3/10 in the Achilles tendon (midportion, insertion, unilateral, or bilateral) during walking, heel raises, or hopping at evaluation session 1
- Pain that increases (>1 point on 11-point scale) with increasing load during evaluation session 1

Exclusion criteria

- Younger than 18 years of age
- Inability to read and write in English
- Achilles tendon pain for <3 months
- History of Achilles tendon rupture that was verified by surgical or conservative management
- History of invasive intervention (surgery and Tenex) for Achilles tendinopathy (AT) on more painful side
- Noninvasive treatment (physical therapy, nitroglycerine patch, iontophoresis, and injection) for AT in the past 3 months
- Diagnosed with systemic inflammatory conditions (eg, rheumatoid arthritis and ankylosing spondylitis), endocrine disorder with complications (eg, uncontrolled type 1 or 2 diabetes and diabetic peripheral neuropathy), and connective tissue disorder (eg, Marfan syndrome)
- Cardiovascular conditions that may be exacerbated by a 90-second submersion of hand in cold water (Raynaud's and cold contact urticaria)
- History of taking fluoroquinolones in the past 3 months
- Foot and ankle pain primarily owing to other causes, such as posterior impingement, bursitis, paratendonitis, sural nerve injury, ankle osteoarthritis, and radicular or referred symptoms (pain, altered sensation, weakness, and altered reflexes), from lumbar spine into lower extremities
- Four step square test >15 seconds (in-person fall risk assessment)
- Cardiovascular condition that prevents participation in an exercise program

Sample Size

The primary outcomes of this study were movement-evoked pain and self-reported function. The sample size is calculated to have sufficient statistical power for each primary outcome using a Bonferroni adjusted type I error rate of 0.025 (0.05/2 for 2 outcomes in aim 1). On the basis of findings by Moseley [15] for a randomized controlled trial (RCT) examining the effect of exercise and pain education for patients with chronic low back pain, we anticipate between-group differences with Cohen $d \geq 0.36$ for pain (between-group difference across 2 time points=0.75; 1.05 SD on the numeric pain rating scale; effect size of f=0.36; correlation between repeated measures=0.5) and self-reported function (between-group difference across 2 time points=1.95; 2.33 SD on low back pain–specific measure; effect size of f=0.42; correlation between repeated measures=0.5) [15]. Using these estimates, a sample size of 30 patients per group is needed to reach 80% power for the time-averaged difference between two group means in a repeated measures design with =.025 to detect a between-group effect size of 0.36. A final sample size of 60 is sufficient to detect estimated effect sizes for the outcome measures based on previously published differences or clinically meaningful minimal clinical difference/minimal clinically important difference and SD for the AT population (Table 1). We will consent 110 participants, estimating a 40% ineligibility rate after screening and 10% attrition rate between the first and second evaluation visits, to achieve a total of 66 participants consented and randomized.

Table 1. The primary outcome measures are movement-evoked pain during single limb heel raises and self-reported function on the patient-reported outcome measure information system computer adaptive testing for Physical Function 2.0. Secondary outcomes include conditioned pain modulation as an indicator of altered central nervous system nociceptive processing, Tampa Scale of Kinesiophobia as an indicator of pain-related psychology, and maximum number of single limb heel raises as an indicator of motor dysfunction.

Outcome	Published mean difference of MCD[a] or MCID[b] and SD	Estimated effect size
Specific aim 1, powered to detect between-group effect sizes of *d* ≥0.36, mean (SD)		
Movement-evoked pain (NPRS[c]) [16,17]	1.0 (1.9)	0.53
Function (PROMIS PF[d]) [18,19]	7.9 (9.0)	0.88
Specific aim 2, powered to detect within group effect sizes of *d* ≥0.43, mean (SD)		
Altered CNS[e] nociceptive processing (CPM[f]) [20]	84.0 (68.1)	1.23
Pain psychology (TSK[g]) [21]	5.6 (6.2)	0.90
Motor dysfunction (heel raises)	4.7 (10.0)	0.47

[a]MCD: minimal clinical difference.

[b]MCID: minimal clinically important difference.

[c]NPRS: numeric pain rating scale.

[d]PROMIS PF: patient-reported outcome measurement information system—physical function.

[e]CNS: central nervous system.

[f]CPM: conditioned pain modulation.

[g]TSK: Tampa Scale of Kinesiophobia.

Study Design

This is a randomized, double-blind, placebo-controlled trial with individuals who have chronic AT. Participants will be randomized to 1 of 2 groups: pain education or pathoanatomic education. All participants will receive the same progressive tendon loading exercise intervention. Each participant will complete 2 evaluation sessions where primary outcomes will be collected at baseline and 8-week follow-up, 6-7 treatment sessions with a physical therapist, and 1 evaluation session at 12-week follow-up with self-reported measures (Figure 1).

Randomization

Participants will be randomized using a permuted block design with variable block sizes. Randomization will be stratified by sex and AT location (insertional and midportion). Randomization codes will be stored electronically and printed by a lab assistant and placed into opaque envelopes and sealed. Each envelope will be numbered in sequential order and stored separately from the recruiter, outcome assessor, and treating physical therapist. Immediately before each participant's first treatment session, the treating physical therapist will either open an envelope or receive an email with the participant's group allocation. Thus, randomization will occur after baseline assessment and remain concealed from participants for the duration of the study. Following all outcome collections, participants' planned unmasking will be completed at 12 weeks, where participants will be informed of their group allocation by providing references and resources used for both education groups. Following completion of the study, participants will be offered the option of being sent a copy of the published findings, quarterly newsletters on study progress, and provided with any preliminary findings after study completion.

Interventions

The intervention will occur over 12 weeks. The educational component will take place over the first 8 weeks during individualized treatment visits. The last 4 weeks will include maintenance of a home exercise program (HEP) with a phone call and email follow-up, if not reached by phone, from the physical therapist at 10 weeks to address any questions regarding exercise progression. The education and exercise treatments will be provided to both groups by the same unblinded physical therapist. Although a single treatment provider minimizes confounding social effects between physical therapists, an unblinded provider does allow for the potential of a bias in exercise progression between groups. The education programs, including videos, handouts, and review questions, are similar in length, style, and presentation of content, including the use of a script by a physical therapist to maximize consistency. All educational materials including handouts, weekly exercise records, and questionnaires will be provided through email and completed electronically by participants through an electronic data management system (REDCap). The education programs address participant knowledge on the causes of their pain as well as the overall importance of exercise to address tendon pathology. The main differentiating component will be based on the proposed mechanisms of pain. The pain education group will receive information that addresses concerns about fear of movement and pain catastrophizing, relates these psychosocial factors to their own experience with AT pain, and provides information on how tendon pathology is a potential (but not necessary) contributor to AT pain and that there is evidence that progressive loading is safe (Textbox 2). Key resources used to develop this pain education content include Explain Pain, Retrain Pain Foundation, and Cognitive Therapy for Chronic Pain [22-26]. The pathoanatomic education group will use a pathoanatomical model where Achilles tendon pathology is

considered the primary contributor to pain (Textbox 3). Key resources used to develop this pathoanatomic education content include publicly available resources developed by the American Physical Therapy Association, the American Academy of Orthopaedics, and the FIFA Medical Network [14,27,28]. The fidelity of the intervention will be assessed by 2 steering committee members who will review a total of 10 recorded treatment visits and categorize them based on presumed participant group allocation and with a confidence rating of 0 (not confident at all) to 5 (completely confident) for the ability to determine participant group.

Textbox 2. Pain Educational Group treatment session themes and key messages related to Achilles tendinopathy. Homework assignments include an exercise log, multiple choice questions related to educational video content, and short-response questions to facilitate individualization of applying educational material.

Progressive loading exercises for tendinopathy (same for both groups):

- Defining the term load for tendon pain rehabilitation
- Types of loads placed onto the Achilles tendon during various activities
- Use of symptoms 24 hour after completion of exercises to inform exercise dosage

Rethinking the role of exercise for Achilles tendinopathy (AT):

- Achilles tendon load capacity and role of exercise to increase capacity
- Progressive increase in Achilles tendon exercise intensity and duration
- Difference between AT and Achilles tendon rupture

Common tendon adaptations to loading:

- Common tissue adaptations seen on imaging including bone spurs, tendon calcification, and Haglund deformity
- Lack of correlation between pathology viewed on imaging and clinical presentation of pain/stiffness with AT

Factors influencing pain:

- Pain neurobiological processing including nociceptor activity and signal interpretation by the brain to produce sense of pain to protect from harm or danger
- Impact of psychological factors such as stress and context of whole pain experience

Understanding pain:

- Hypersensitivity of the peripheral and central nervous system and persistent pain
- The role of descending facilitation and inhibition on chronic pain conditions
- Recognition that persistent pain is multifactorial

Benefits of exercise for chronic musculoskeletal pain:

- Neurotransmitters and inflammatory mediates present with persistent pain
- Roles of exercise on improving immune system and neurotransmitter function to decrease pain
- Physical activity guidelines from the Department of Health and Human Services

Textbox 3. Pathoanatomic Education Group treatment session themes and key messages related to Achilles tendinopathy. Homework assignments include an exercise log, multiple choice questions related to educational video content, and short-response questions to facilitate individualization of applying educational material.

Progressive loading exercises for tendinopathy (same for both groups):

- Defining the term *load* for tendon pain rehabilitation
- Types of loads placed onto the Achilles tendon during various activities
- Exercise progression and use of symptoms 24 hours after completion of exercises to inform exercise dosage

Effects of exercise on Achilles tendon pathology:

- Collagen tissue composition and common changes with tendinopathy
- Defining terminology of tendon pathology (tendinitis/tendinosis/tendinopathy)
- Role of exercise in addressing collagen tissue remodeling through progressive loading exercise

Soft-tissue and boney deformities associated with Achilles tendinopathy (AT):

- Prevalence and etiology of AT
- Presentation of radiographic images of common anatomical findings often associated with AT including Haglund deformity, bone spurs, and calcification within the Achilles tendon

Anatomical causes of AT pain:

- AT classification (midportion versus insertional)
- Continuum of mechanical tendon properties from healthy to tendon rupture
- Intrinsic and extrinsic factors which predispose tendon to dysfunction (age, activity level changes, foot mechanics, and repetitive trauma)

Understanding tendinopathy pathophysiology:

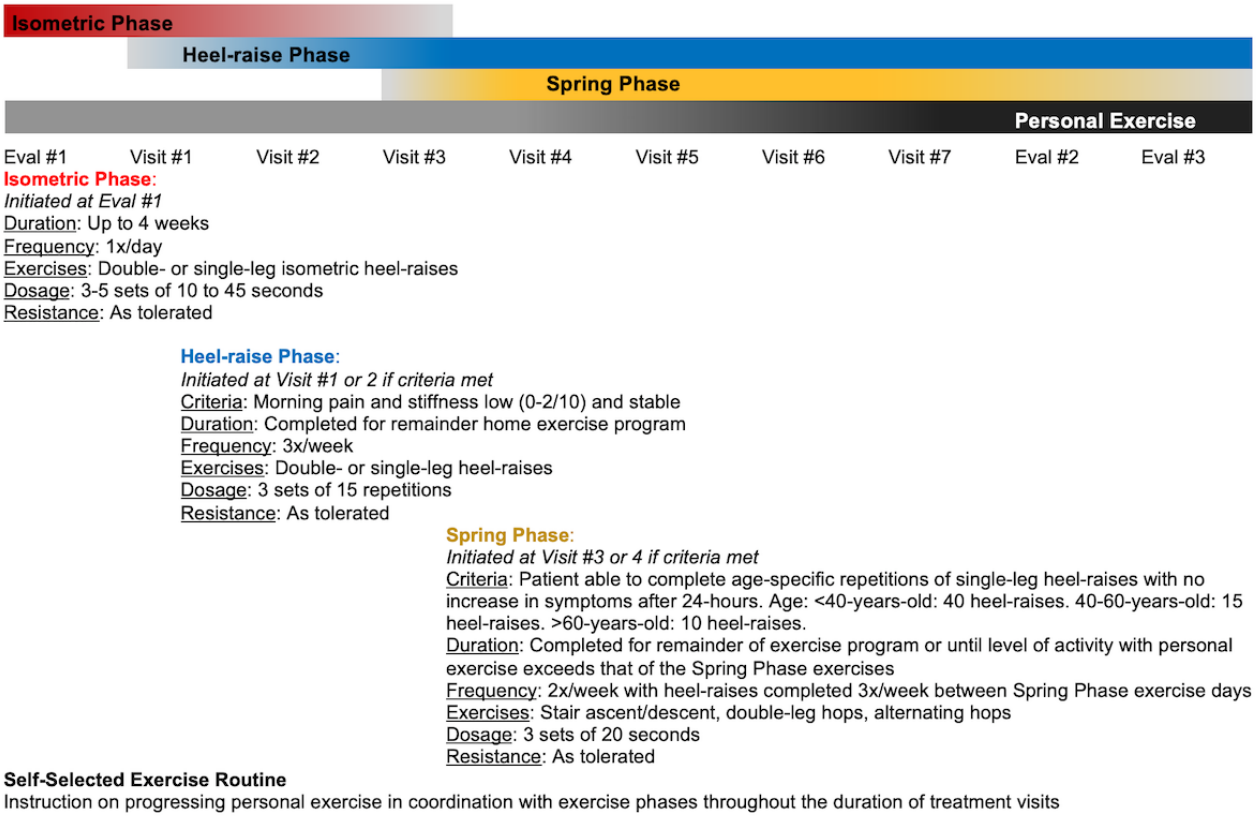
- Pathogenesis of AT
- Common imaging techniques used to identify pathology
- Components of clinical evaluation for AT diagnosis including patient history and physical examination

Whole body benefits of exercise:

- Impact of exercise on multiple systems throughout the body (immune system, cardiovascular system, and brain function)
- Physical activity guidelines from the Department of Health and Human Services
- Individualizing exercise goals

Each participant will receive the same standardized therapeutic exercise program where progression will be individualized to each participant based on pain levels, the physical therapist's clinical judgment, and predetermined physical function criteria (Multimedia Appendix 1). The exercise intervention is based on evidence supporting the use of isometric exercise as a safe starting point for tendon loading and for pain relief as well as progressive isotonic tendon loading and restoring the spring-like function of Achilles [14,29,30]. The exercise program will consist of 4 phases with a progressive increase in tendon loading beginning with isometrics, progressing to concentric/eccentric heel raises, a functional spring phase, and a self-selected exercise routine (Figure 2). Throughout study participation, we will monitor the pain level using the 11-point verbal numeric pain rating scale. If a participant has 4/10 pain, then we will offer them to take a break or modify the activity. Blood pressure will be assessed before and after initiating aerobic activity during the spring phase with in-person visits. Participants will not be eligible for telehealth visits if they report symptoms indicating the need for in-person blood pressure monitoring, including (1) inconsistent use of hypertension medications and/or (2) any recent/current associated symptoms with uncontrolled hypertension. Exercise will be stopped according to the American College of Sports Medicine guidelines [31]. Participants will be asked to refrain from other invasive and noninvasive interventions during enrollment, including surgery, injection at the Achilles, and other forms of rehabilitation. Participants will be offered the option of follow-up visits via a telehealth format. This option will be provided to participants who are unable to attend owing to illness, limited transportation, or any other circumstance that may restrict the participants' ability to complete in-person visits.

Figure 2. Progressive tendon-loading exercise program with 4 overlapping phases (isometric, heel raise, spring phase, and self-selected exercise). Participants are encouraged to maintain any ongoing personal exercise throughout the study, and then receive additional instruction on progression at final phase. Patient are instructed to monitor for symptom increase within 24-hour window after completion of exercises.



Outcomes

Outcomes are described by the specific aim and timeframe collected in Tables 2 and 3. Additional outcomes collected for exploratory aims and examining the feasibility of future clinical trials are provided in Table 4. At evaluation session 1 (0 weeks) and evaluation session 2 (8 weeks), participants will complete functional testing in the following order: walking at a self-selected pace, walking at a standardized pace (Froude 4) [32], heel raises, and hops. Participants will then complete the Tampa Scale of Kinesiophobia (TSK) and Pain Catastrophizing Scale with instruction to think about any pain or discomfort in their Achilles tendon during walking, heel raises, and hopping. Participants who complete in-person evaluation sessions will conclude the session with quantitative sensory testing.

Table 2. For specific aim 1, study outcomes will be assessed pretreatment (week 0 at evaluation session 1), after completion of education combined with exercise (week 8 at evaluation session 2), and after 4 weeks of continuing the home exercise program at home (week 12 at evaluation session 3).

Outcome	Description	Time (weeks)		
		0	8	12
Specific aim 1				
Pain				
Movement-evoked pain during heel raises[a]	Participants will rate the intensity and location of their Achilles tendon pain using the 11-point NPRS[b] during maximum number of single limb heel raises and 3 single limb hops [33,34]. Pain will be assessed during movement activities using the NPRS which consists of a 0-10 scale where 0 represent "no pain" and 10 represents "worst pain imaginable." Test-retest reliability: *r*=0.67-0.96. Convergent validity: *r*=0.79-0.95 [34]	X[c]	X	—[d]
Anticipated movement-evoked pain	Participants will rate the *anticipated* intensity of their Achilles tendon pain using a 101-point NPRS before heel raises and before hopping [33]	X	X	X
Tendon stiffness	Participants will rate the average duration of stiffness in the Achilles tendon in the morning from 0 to ≥100 min over the past week	X	X	X
Global rating of change	Anticipated and final change in the overall condition of the Achilles tendon on a 15-point scale. Test-retest reliability: ICC[e] 0.90. Face validity: *r*=0.72-0.90 [35]	X	X	X
Anticipated change in symptoms	Anticipated and final change in symptoms on a 15-point scale following physical therapy [35]	X	X	X
Function				
Global physical function[a]	Self-reported physical function will be assessed with the patient-reported outcomes measurement information system 2.0 and computer adaptive test physical function, which has been used in orthopedic and Achilles tendon populations [18,19]. Internal consistency reliability: *r*=0.96. Convergent validity: r=0.68-0.79 [36]	X	X	X
Achilles tendon function	Function will be assessed with the Victorian Institute of Sport Assessment-Achilles questionnaire as a symptom severity measure with activity that is specific to patients with AT[f]. Test-retest reliability: *r*=0.93. Construct validity: *r*=0.58 [37]	X	X	X
Activity log	Self-reported activity, including type (aerobic and strengthening) and duration per week on the home exercise log for first week compared with last week of exercise-education program	—	X	—
Activity level	International Physical Activity Questionnaire Short-Form and self-reported activity levels including number of days and time spend completing vigorous or moderate activity, walking or sitting over past 7 days. Test-retest reliability: *r*=0.32-0.88. Criterion validity: *r*=0.12-0.57 [38]	X	X	X
Patient-specific functional scale	Patient-reported ability to complete self-selected activities on an 11-point scale: 0=unable to perform activity and 10=able to perform activity at previous level. Test-retest: *r*=0.84 [39]. Concurrent validity: *r*=0.55-0.83 [40]	X	—	X

[a]Primary outcomes.

[b]NPRS: numeric pain rating scale.

[c]Outcome collected at timepoint.

[d]Outcome not collected at timepoint.

[e]ICC: intraclass correlation coefficient.

[f]AT: Achilles tendinopathy.

Table 3. For specific aim 2, study outcomes will be assessed pretreatment (week 0 at evaluation session 1), after completion of education combined with exercise (week 8 at evaluation session 2), and after 4 weeks of continuing the home exercise program at home (week 12 at evaluation session 3).

Outcome	Description	Time (weeks)		
		0	8	12
Specific Aim 2				
Altered CNS[a] nociceptive processing				
• Conditioned pain modulation at site of Achilles tendon pain • CPM[b] response on contralateral side at the hamstring • Widespread pain indicated by the Pain Pressure Threshold	PPTs[c] will be collected bilaterally at the Achilles (centered around the most painful region) and hamstring with a pressure algometer (Somedic Algometer Type II, Horby Sweden, probe 1 cm^2) at a rate of 50 kPa per sec. PPTs will be collected at the Achilles (painful side) and Hamstring (contralateral side) during the conditioning stimulus. The algometer will be positioned perpendicular to the skin with force applied in a posterior to anterior direction. The PPT value will be the average of a series of 3 repeated trails per site. The site for the Achilles on the painful side will be at the location reported to be most painful and the contralateral side will be at a similar distance from the tendon insertion on the contralateral side. The PPT for the hamstring will be on the semitendinosus/semimembranosus tendon located 3 cm from the crease along the back of the knee (test-retest reliability: ICC[d] 0.93-0.95) [5]. To minimize temporal summation, the interstimulus interval will be ≥10 seconds. PPTs are collected with hand in room temperature water and during the conditioning stimulus starting at 20 seconds. The allocation of the Achilles and hamstring as site 1 versus site 2 will be randomized as well as order of collecting PPT during room temperature water versus during the conditioning stimulus. Participants are instructed to press a trigger first when the pressure becomes painful (pain >0/10). For CPM testing, the participant's right hand is immersed up to the wrist in ice water (6 °C [SD 0.5]) for a total of 2 min as a conditioning stimulus. The intensity of the conditioning stimulus is maintained by visually monitoring temperature (brand of thermometer) throughout CPM testing and circulating the water with an aquarium air pump. Participants will also rate the pain in their hand at 5 seconds, 20 seconds, and 120 seconds (test-retest reliability: ICC 0.86-0.93) [5]	X[e]	X	—[f]
• Widespread pain indicated by Body Map	Participants will be asked to select the number of areas where they have experienced persistent or recurrent pain in the past 3 months using the Michigan Body Map [41]	X	X	—
Psychological factors				
• Fear of movement	Participants will be asked to complete the TSK[g] immediately following walking, heel raises, and hops completed during the evaluation and rate current level of fear about movement causing pain and injury during these activities. Test-retest reliability: r=0.64-0.89. Validity: r=0.70-0.81 [42,43]. Scored 17-68, a score of 37 indicates clinically meaningful levels of kinesiophobia [44]	X	X	—
• Pain catastrophizing	The pain catastrophizing scale (PCS) rates on a 5-point scale how often a participant has catastrophizing thoughts toward pain. Test-retest reliability: r=0.87. Validity: r=0.56 [45-48]. The PCS consists of 13 items and is scored 0 to 52 with a score >30 reported to demonstrate high catastrophizing [45]	X	X	—
• Self-efficacy • Anxiety • Depression	The PROMIS CAT[h] 1.0 to assess for pain management self-efficacy, anxiety, and depression [21,42,45,49-51]. Self-efficacy: Validity: r=0.56-0.75 [50]. Anxiety: Test-retest reliability: r=0.822. Validity: r=0.41 [51]. Depression: Test-retest reliability: r=0.859. Validity: r=0.41 [51]	X	X	—
Motor function				
• Single limb heel raises	We will use a 10-segment kinematic model of the body to quantify 3D motion. Participants will perform tasks over a force plate, flush with the floor, which provides 3D ground reaction forces. Plantar flexor endurance will be quantified with the maximum number of repetitions as well as the repeated heel raise work test [52], calculated using heel height (measured with a calcaneal marker) and force (measured with a force plate; test-retest reliability: ICC 0.83) [5]	X	X	—
• Counter movement jump	The vertical jump test will be used to quantify maximum jump height and peak ankle power [53]. Participants will be instructed to place their hands on their hips, bend their knee, and jump as high as possible on one leg. They will also try to take off and land in the same place (test-retest reliability: ICC 0.97) [5]	X	X	—

Outcome	Description	Time (weeks)		
		0	8	12
• Walking	Participants will walk at a self-selected (as if at home or work) and at a standardized speed (Froude 4) to capture use of the plantar flexors (peak ankle power) with this low-level daily activity. For in-person sessions, a minimum of 3 representative trials are collected per side for each gait speed. For virtual evaluation sessions, participants are asked to walk for 5 min in their home	X	X	—

[a]CNS: central nervous system.

[b]CPM: conditioned pain modulation.

[c]PPT: pain pressure threshold.

[d]ICC: interclass correlation coefficient.

[e]Outcome collected at timepoint.

[f]Outcome not collected at timepoint.

[g]TSK: Tampa Scale of Kinesiophobia.

[h]PROMIS CAT: patient-reported outcome measure information system computer adaptive test.

Table 4. For exploratory aim 1, the primary outcomes include primary outcomes for specific aim 1 and treatment fidelity. For exploratory aim 2, the primary outcomes include primary outcomes for specific aim 1 and specific aim 2.

Title and description	Time collected			
	Pre	During	Week 8	Week 12
Feasibility aim				
Recruitment				
Rate of recruitment (participants enrolled) per year	X[a]	X	X	X
Number of participants screened per month	X	X	X	X
Number of participants enrolled per month	X	X	X	X
Number of participants lost to follow-up per month	X	X	X	X
Rate of retention per year	X	X	X	X
Treatment fidelity				
Adequate knowledge of education program at 8-week follow-up	X	—[b]	X	—
Rating of audio recording by external reviewers for confidence of participant group allocation on 0-5 scale	—	X	—	—
Time participants spent in treatment sessions	—	X	—	—
Time participants spent doing education homework between sessions	—	—	X	—
Adequate blinding of participants to bias of research team • "At the beginning of the study, you were randomized to receive either Education A or Education B. We believe Education A is more helpful for recovery from Achilles tendinopathy than Education B. Which Education do you think that you received?" (A, B, I don't know)	—	—	X	—
Duration of each exercise phase	—	X	—	—
Highest loading level attained at each exercise phase	—	X	—	—
Therapeutic alliance • "What I was doing in physical therapy gave me new ways of looking at my problem." • "I was confident my physical therapist's ability to help me." • "My PA and I were working towards mutually agreed upon goals." (7-point scale from Never to Always)	—	—	X	—
Adherence to exercise program		X		
Outcome capture rate				
Percentage of missing data per outcome	X	X	X	X
Reasons for missing data	X	X	X	X
AEs[c]				
Frequency and type of AEs	X	X	X	X
Other prespecified outcomes				
Demographics				
Date of birth, sex, race/ethnicity, height/weight/BMI, description of AT[d] symptoms, goals for physical therapy, previous experience with conservative care, comorbidities	X	—	—	—
Four square step test				
Participants will perform a series of steps in a square formation. The duration of time needed to complete the step reflects dynamic balance and mobility	X	—	—	—
Ultrasound imaging of tendon pathology				
Ultrasound imaging will be used to quantify tendon thickness, echogenicity, presence of osteophytes/bone spur	X	—	X	—
Medication				
History, current use, and dose of all routine medications and specific questions about opioid use	X	—	X	X

Title and description	Time collected			
	Pre	During	Week 8	Week 12
Treatment history				
Treatments previously tried and if they were effective at reducing pain	X	—	—	—
Mode of participants' complete visits				
Percentage of participants who completed all visits (evaluation sessions 1 and 2 and follow-up visits) through in-person visits compared with those who completed a percentage of visits through telehealth format		—	—	X

[a]Outcome collected at timepoint.

[b]Outcome not collected at timepoint.

[c]AEs: adverse events.

[d]AT: Achilles tendinopathy.

Statistical Analysis

We will use a modified intention-to-treat analysis to examine the treatment effect for all outcome measures on participants based on group randomization. Characteristic comparisons will also be completed for those patients who remained in the study versus those who dropped out to determine if data at subsequent time points were consistent with missing at random data. For aim 1, we will compare differences between education groups for changes in movement-evoked pain and self-reported function from baseline to 8 weeks (primary endpoint) and 12 weeks using a linear mixed model for repeated measures. For aim 2, we will use a linear mixed model for repeated measures for intervention effect within groups on central pain mechanisms from baseline to 8 weeks. Secondary outcomes for pain, function, altered CNS nociceptive processing, psychological factors, motor control, pain, and function will be analyzed with a linear mixed model for repeated measures. Demographics, ultrasound imaging, and treatment history will be used to describe the sample and will be covariates in the analysis if different between groups. Secondary analyses of sex will examine for potential sex-based differences to inform sample size estimates for future clinical trials. Another secondary analysis of AT type (midportion vs insertional) will also be assessed to inform recruitment strategies for future clinical trials.

Exploratory aims 1 and 2 will examine whether changes in participant knowledge of pain education and central pain mechanisms, including altered CNS regulation of nociceptive input, changes in fear or pain beliefs, and improved motor function are associated with pain and function. For exploratory aim 1, we will use Pearson correlations between changes in knowledge from baseline to final evaluation (percentage of correct responses to pain education multiple choice questions) and changes in pain and function separately. For exploratory aim 2, we will examine Pearson correlations between changes in central pain mechanisms and changes in pain and function separately.

To evaluate the feasibility of future clinical trials, we will use descriptive statistics to assess patient retention, participant recruitment numbers, treatment fidelity, and patient adherence to their exercise program. To evaluate for potential confounders of treatment effect between groups, we will assess differences in duration of treatment sessions, time spent completing their HEP, time participants spent in each phase of their exercise program, percentage of participants who believed they were receiving the education program that the research team believed to be more effective, and the highest level reached within each exercise phase (half body weight, body weight, and machine weight) using two independent samples *t* tests, Wilcoxon rank-sum test for continuous variables, or Chi-square or Fisher exact test for categorical variables, as appropriate.

Alterations to Study After Initiation

From March 17 to July 15, 2020, in-person human subjects research was suspended in accordance with the University of Iowa policy related to COVID-19. We conferred with the Data Safety Monitoring Board (DSMB) and the safety officer on protocol changes to continue the clinical trial via telehealth. These protocol changes were approved by the IRB at University of Iowa on March 17, 2020. The intervention content and the primary outcomes of movement-evoked pain and self-reported function were not altered, yet the transition to a virtual format affected screening, evaluation, and mode of delivering treatment as outlined below. Participants who did not pass the additional virtual screening questions were categorized as *delayed owing to COVID* and rescreened once in-person human subjects research resumed.

Virtual Screening

Modifications to the screening process were included at initiation of intervention delivery via telehealth due to COVID-19 to ensure participant safety during completion of the exercise program:

- Fall risk was completed using the Stopping Elderly Accidents, Deaths, and Injuries (STEADI; score>4) [54] rather than in-person using the 4-square step test.
- Symptoms indicating the need for in-person blood pressure monitoring: (1) inconsistent use of hypertension medications and/or (2) any recent/current associated symptoms with uncontrolled hypertension.
- Unable to successfully complete virtual visits with a webcam and/or prefer only in-person visits.

Evaluation

Additional data collected via Zoom was completed to continue primary outcome collection during the telehealth format. The telehealth format did not permit imaging or QST data collection:

- Two-dimensional kinematics were collected via Zoom instead of 3D kinematics and kinetics.
- Ultrasound imaging and quantitative sensory testing were not completed.

Treatment

All treatment visits were completed on the web. There were no changes in the educational or exercise program content. The highest level of isometric and heel raise phases of the exercise program requires the use of an externally applied load via a Smith machine or weighted backpacks. Participants without access to a Smith machine in a gym, owing to lack of membership or COVID-19, were offered weighed backpacks.

Given that the educational materials (videos, handouts, and logs) had always been provided to participants via REDCap, the initial design of the intervention facilitated the transition of individualized discussion of materials from in-person to a virtual format. Since July 15, 2020, the option to complete virtual treatment visits remains available to participants who are unable to attend owing to illness, limited transportation, or any other circumstance that may restrict the participants' ability to complete in-person visits.

In addition, the pandemic has had negative effects on mental and physical health. Among adults in the United States, from June 24 to 30, 2020, 31% reported symptoms of anxiety disorder or depressive disorder [55]. A study including 906 health care workers at 5 major hospitals within the period of February 19 to April 20, 2020, reported that depression and anxiety were associated with the presence of physical symptoms, including musculoskeletal pain [56]. As a biopsychosocial approach addresses the interaction between mental and physical health, the pandemic may magnify the differential effects of pain education combined with exercise compared with a pathoanatomic education.

The psychosocial effects of this pandemic and study protocol changes motivated 2 additional exploratory analyses to (1) examine potential confounding effects of a pandemic and virtual participation on outcomes and (2) determine the feasibility of a clinical trial via telehealth. Our study sample can be divided into 3 groups of participants: all in-person visits (September 21, 2019, to March 16, 2020), all visits via telehealth (March 17 to July 15, 2020), and a mix of visits in-person and via telehealth during the pandemic (July 16 to study completion). To evaluate the potential interactions of the pandemic and virtual participation on the intervention, the changes in the primary outcomes (pain and disability) and psychological outcomes (fear of movement, pain catastrophizing, self-efficacy, depression, and anxiety) will be compared between the 3 pandemic groups within each treatment arm (pathoanatomic vs pain education). To examine the feasibility of future clinical trials using a virtual format, recruitment rates, retention, adherence to HEP, and AEs will be compared between the 3 pandemic groups (all in-person, all virtual, and mixed).

Ethics

All patient data will be stored in electronic records kept on a network drive of the Department of Physical Therapy and Rehabilitation Science at the University of Iowa and on REDCap. Access will be restricted to only the research team who will comply with the confidentiality of patient information consistent with the Health Insurance Portability and Accountability Act guidelines. An independent safety officer will review all AEs, serious AEs, unanticipated problems, and any protocol deviations affecting safety on a quarterly basis. The DSMB will meet yearly with the study team. The DSMB will convene annually to review the data, recruitment, and safety of subjects. This review will include a discussion of the allocation concealment process to ensure that concealment is done at the last minute and review of records to ensure that the proper random sequence was used. The review will also include reports of AEs, serious AEs, protocol deviations or violations, and unanticipated problems. Recruitment and retention will also be reviewed.

Role of Funding Source

Funding for this study was provided by the National Institute of Arthritis Musculoskeletal and Skin Disease research grant R00 AR071517 and the Collaborative Research Grant from the International Association for the Study of Pain (IASP). Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR002537. These funding sources had no role in the study design, collection, analysis/interpretation of data, or decision on submission for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Results

Overview

Institutional review board approval was obtained on March 15, 2019, and study funding began on July 1, 2019. The TEAch study began enrollment on September 17, 2019. As of March 2020, we randomized 23 out of 66 participants. In September 2020, we screened 267 individuals, consented 68 participants, and randomized 51 participants. We anticipate to complete the primary data analysis by March 2022 and will submit the results for primary outcomes no later than 1 year after the primary completion date on ClinicalTrials.gov (NCT: 04059146) and Open Science Framework (JF2XU).

Individual Participant Data Sharing Plan

In compliance with FAIR (findability, accessibility, interoperability, and reusability) data principles, data will be deposited at the University of Iowa open-access institutional repository, Iowa Research Online. The repository is open access and maintained by the Libraries at the University of Iowa for the preservation and sharing of intellectual work of faculty, students, and staff. The IPD will be available to other researchers for the primary outcomes. Data sets will be accompanied with appropriate descriptive, technical, and administrative metadata to facilitate discovery and scholarly reuse, and will be assigned unique digital object identifiers (DOIs) that can be incorporated into publications and cited in the literature. Metadata will be included in the data records in the repository through readme

files and structured information following the DataCite metadata schema.

Discussion

Improved understanding of pain mechanisms and reconceptualization of pain as protective through patient education is recommended for individuals with chronic musculoskeletal conditions [57-59]. Although psychological factors have been explored in patients with AT [5,8,60], no study has examined the effect of patient education on these factors in patients with chronic AT. Previous reviews indicate that pain education alone is not sufficient to reduce pain and disability by a clinically meaningful amount [9,59]. However, a recent meta-analysis indicated that pain education combined with exercise and provided over a longer time frame had a larger effect on pain and disability [61]. This clinical trial will compare the effect of pain education combined with exercise over an 8-week period on movement-evoked pain and self-reported function in patients with AT with pathoanatomical education. Moreover, this RCT will examine changes in altered CNS regulation of nociceptive input, changes in fear or pain beliefs, and improved motor function before and after physical therapy to determine how these pain mechanisms are affected by care. We aim to advance care for this patient population through improved understanding of how education combined with exercise affects clinical outcomes for patients with AT.

Acknowledgments

Research reported in the publication was supported by the National Institute of Arthritis Musculoskeletal and Skin Disease of the National Institutes of Health (NIH) under award number R00AR071517 and by the National Center for Advancing Translational Sciences of the NIH under award number UL1TR002537. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

The Steering Committee comprises Dr Sluka (University of Iowa), Dr Wilken (University of Iowa), Dr Bayman (University of Iowa), Dr Moseley (University of South Australia), and Dr Rio (La Trobe University).

The Data Safety Monitoring Board is comprised of Dr Benjamin Miller (Safety Officer), Dr Carol Vance, Dr Patrick Ten Eyck, and Dr Dana Dailey.

Authors' Contributions

All authors made substantial contributions to the study design. AP and RC wrote the first draft of the manuscript with KS, LM, EB, MH, CN, JW, and JD revising and approving the submitted version. CS is a paid consultant for Ossio, Paragon 28, and CurveBeam. CS has stock options for CurveBeam

Conflicts of Interest

LM receives royalties for key resources used for Explain Pain, Explain Pain Handbook: Protectometer, Explain Pain Supercharged, NOIgroup Publications, Adelaide, Australia; speaker fees for talks on contemporary pain education; and consults to various organizations on pain education and management. ER receives speaker fees for talks on tendinopathy and consults with various organizations on tendinopathy. ER is supported by the National Health and Medical Research Council of Australia (Early Career Fellowship). KS serves as a consultant for Pfizer Consumer Health and Novartis Consumer Healthcare/GSK Consumer Health care and receives royalties from IASP Press. GLM has received support from: ConnectHealth UK, Seqirus, Kaiser Permanente, Workers' Compensation Boards in Australia, Europe and North America, AIA Australia, the International Olympic Committee, Port Adelaide Football Club, Arsenal Football Club. Professional and scientific bodies have reimbursed him for travel costs related to presentation of research on pain at scientific conferences/symposia. He has received speaker fees for lectures on pain and rehabilitation. He receives book royalties from NOIgroup publications, Dancing Giraffe Press & OPTP for books on pain and rehabilitation. Other authors declare no conflicts of interest.

Multimedia Appendix 1
Exercise progression criteria.
[PDF File (Adobe PDF File), 82 KB - resprot_v9i11e19111_app1.pdf]

Multimedia Appendix 2
Peer-review report by AMS.
[PDF File (Adobe PDF File), 154 KB - resprot_v9i11e19111_app2.pdf]

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Abbreviations

AE: adverse event
AT: Achilles tendinopathy
CAT: computer adaptive test
CNS: central nervous system
CPM: conditioned pain modulation
DSMB: Data Safety Monitoring Board
HEP: home exercise program
IASP: International Association for the Study of Pain
ICC: interclass correlation coefficient
NIH: National Institutes of Health
PPT: pain pressure threshold
PROMIS: patient-reported outcome measure information system
TEAch: Tendinopathy Education of the Achilles

Edited by G Eysenbach; submitted 03.04.20; peer-reviewed by J Zellers, D Lipardo; comments to author 21.08.20; revised version received 15.09.20; accepted 15.09.20; published 03.11.20.

Please cite as:
Post AA, Rio EK, Sluka KA, Moseley GL, Bayman EO, Hall MM, de Cesar Netto C, Wilken JM, Danielson JF, Chimenti R
Effect of Pain Education and Exercise on Pain and Function in Chronic Achilles Tendinopathy: Protocol for a Double-Blind, Placebo-Controlled Randomized Trial
JMIR Res Protoc 2020;9(11):e19111
URL: https://www.researchprotocols.org/2020/11/e19111
doi:10.2196/19111
PMID:33141102

Protocol

Development of a Personalized Mobile Mental Health Intervention for Workplace Cyberbullying Among Health Practitioners: Protocol for a Mixed Methods Study

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Abstract

Background: Workplace cyberbullying harms the psychological and social functioning of professionals working in an organization and may decrease the productivity and efficiency of daily life tasks. A recent study on trainee doctors across 8 different United Kingdom National Health Service trusts found health issues and job dissatisfaction in people who have experienced workplace cyberbullying. This disabling effect is even more noticeable in low-socioeconomic communities within low-income countries. In Malaysia, there is a need to create a personalized mobile mental health intervention program for health care professionals. These programs should be directed to prevent and decrease psychosocial issues and enhance coordination among health care professionals to solve health issues in the community.

Objective: Our main objective is to study the pre-effects and posteffects of the Personalized Mobile Mental Health Intervention (PMMH-I) for workplace cyberbullying in public and private hospitals in Malaysia.

Methods: A hospital-based multimethod multi-analytic evidential approach is proposed, involving social and psychological health informatics. The project has been subdivided into 3 stages, starting with Phase 1, a prevalence study, followed by exploratory studies. Phase 2 consists of a quasi-experimental design, whereas the development of a prototype and their testing will be proposed in Phase 3. Each stage includes the use of quantitative and qualitative methods (mixed-method program), using SPSS (version 26.0; IBM Corp) and Stata (version 16.1; StataCorp) as tools for quantitative research, and NVivo (version 1.0; QSR International) and Atlas.ti (version 9.0.16; ATLAS.ti Scientific Software Development GmbH) for qualitative research.

Results: The results of this study will determine the pre- and posteffectiveness of an integrated PMMH-I for health care professionals. The prototype system platform will be developed and implemented in a public and private hospital. Results from Phase 1 will be published in 2021, followed by the implementation of Phase 2 in subsequent years.

Conclusions: This study will provide evidence and guidance regarding the implementation of a personalized mobile mental health intervention for health care professionals into routine public and private hospitals to enhance communication and resolve conflicts.

International Registered Report Identifier (IRRID): PRR1-10.2196/23112

(JMIR Res Protoc 2020;9(11):e23112) doi:10.2196/23112

KEYWORDS

workplace cyberbullying; mental health; personalized mobile mental health intervention; health informatics; Malaysia

Introduction

Background

Suicidal behavior, depression, loneliness, anxiety, and somatic symptoms are among the most common effects of cyberbullying experienced by students [1] and adolescents [2]. There is a huge psychological impact (ie, depression) on people who experience workplace bullying from coworkers, such as nurses [3-6], health care providers, and employers [7], especially among women. The prevalence of cyberbullying among first-year trainee doctors who reported experiencing it at least 1 time was 46.2% [8]. Another study found a high prevalence rate (28%) of cyberbullying among a diverse workforce sample in the United States [9].

Malaysia has a high mobile penetration rate due to thriving e-commerce [10]. The problematic use of smartphones can lead to addiction; increased use of mobile phones in India has led to an increase in technology addiction [11,12]. This addiction leads to depression, anxiety, stress, and self-esteem issues [13]. A school-based study identified a strong correlation between pathological internet use and cyberbullying in Greece [14]. However, there is a lack of evidence that pathological mobile use could lead to an increase in cyberbullying in the workplace. Most published studies, systematic reviews, and interventions are limited to cyberbullying at school, colleges, universities, or the young population.

Research Questions

We aim to explore the following 4 research questions in this study: (1) What is the current workplace cyberbullying status among Traditional Chinese Medicine practitioners (TCM) in Malaysia? (2) What is the pre- and postefficacy of the Personalized Mobile Mental Health Intervention (PMMH-I) on the prevalence of measurable factors (ie, depression, anxiety, and stress) in workforce cyberbullying on TCM practitioners? (3) What are the moderating and mediating factors of workplace cyberbullying on TCM practitioners? (4) What is the technological feasibility of implementing the integrated PMMH-I as a component of routine hospital-based systems?

Main Intention and Objective

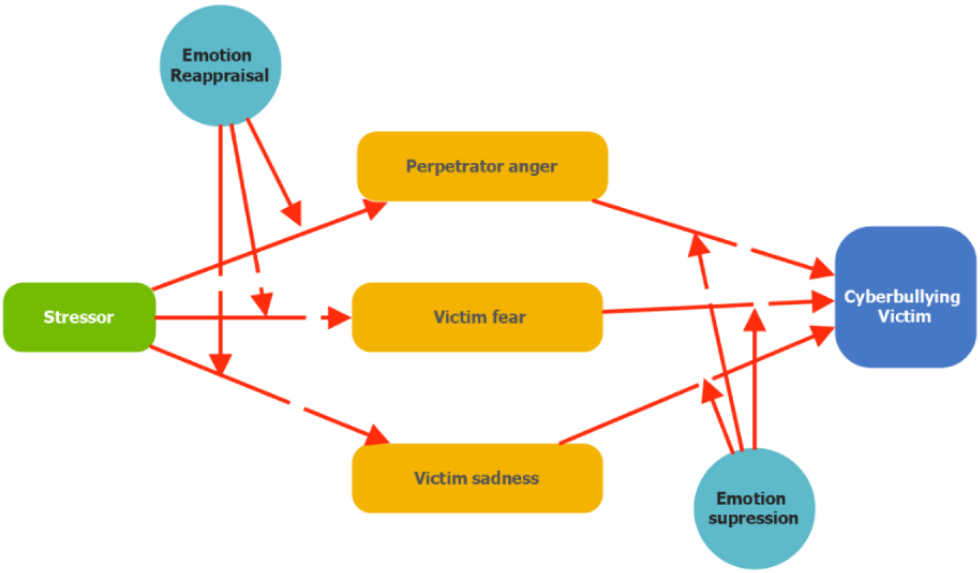
This study's main intention is to give awareness and authority to the community of health care professionals against cyberbullying by developing a Personalized Mobile Mental Health Intervention program (PMMH-I) in partnership with all health care providers. This partnership will seek to form alliances with public and private institutions to ensure the success and continuation of the program. The PMMH-I program will aim to reduce the psychometric properties of cyberbullying through awareness and adaptation of technology.

The main objective of this protocol is to develop and implement the PMMH-I program to decrease the psychometric properties of cyberbullying in the hospital-based setting in Malaysia. We hypothesize that the creation of PMMH-I programs will come about by executing a PMMH-I strategy that permits the fusion of global and local knowledge. PMMH-I promotes health care community development, thereby increasing social integration between different health care providers such as doctors, nurses, traditional and complementary medical practitioners, pharmacists, and other health care providers.

Theoretical Approach

We will adopt the emotion reaction model (ERM) [15] as our theoretical framework, which allows researchers to explore the relationships among concepts of stressor, emotions, emotion regulators, and people who experience cyberbullying in the hospital setting in Malaysia. The ERM elucidates how emotions may produce an impact on people who experience cyberbullying in the current technological era. The adaptation of ERM depicted in Figure 1 posits the relationship between stressor, emotions, and people who experience cyberbullying, which is mediated by emotion reappraisal and emotion suppression.

Figure 1. A proposed theoretical model of the emotion reaction model.



Methods

Ethics Approval

According to the local and national ethical instructions for research (the National Committee for Clinical Research) guidelines, this study did not require ethics approval.

Data Sharing Statement

No data are available. All data relevant to the study are included in the manuscript.

Study Plan

A hospital-based multimethod multi-analytic evidential approach is proposed, involving social and psychological health informatics. The project has been subdivided into 3 stages, starting with Phase 1, a prevalence study, followed by exploratory studies. Phase 2 consists of a quasi-experimental design, whereas the development of a prototype and their testing will be proposed in Phase 3. Flow diagrams for the research design are presented in Figures 2 and 3. A breakdown of our anticipated timeline for each phase of the study appears in Figure 4.

Each stage includes the use of quantitative and qualitative methods (mixed-method program), using SPSS (version 26.0; IBM Corp) and Stata (version 16.1; StataCorp) as tools for quantitative research, and NVivo (version 1.0; QSR International) and Atlas.ti (version 9.0.16; ATLAS.ti Scientific Software Development GmbH) for qualitative research.

Figure 2. Research flow diagram.

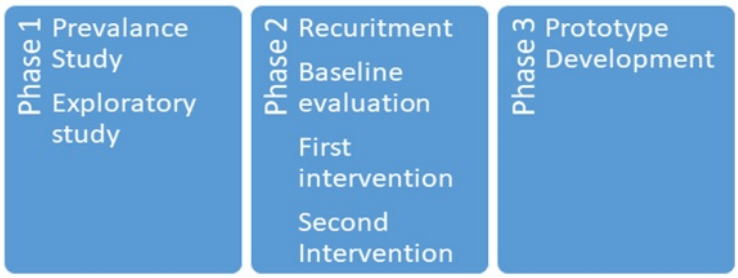


Figure 3. Flow diagram of the experimental design; PMMH-I: Personalized Mobile Mental Health Intervention.

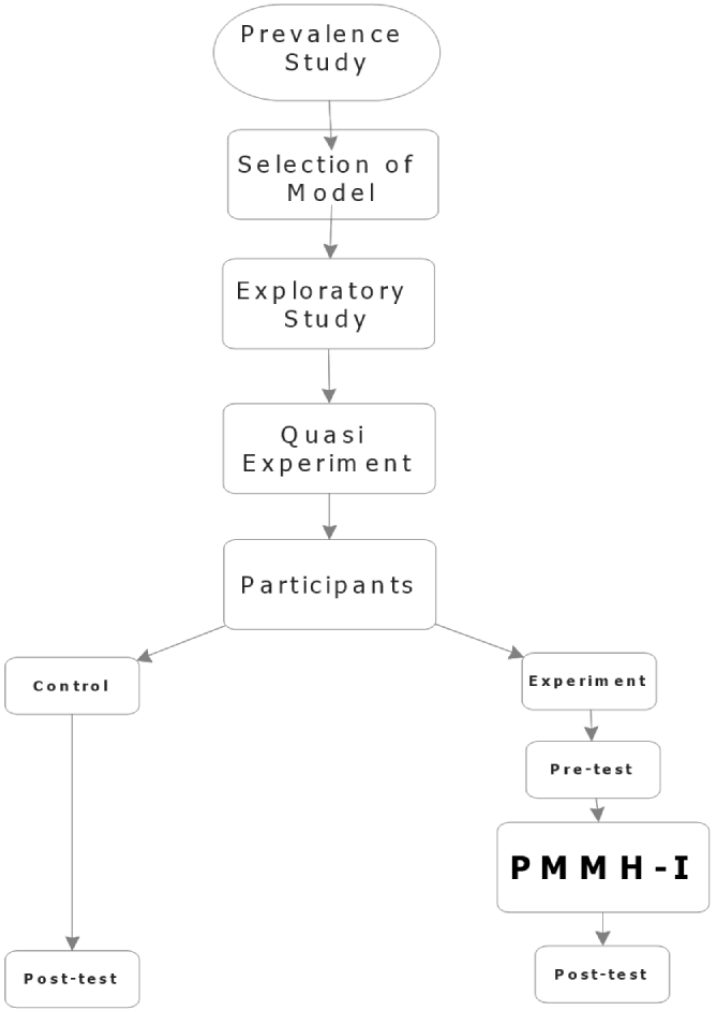
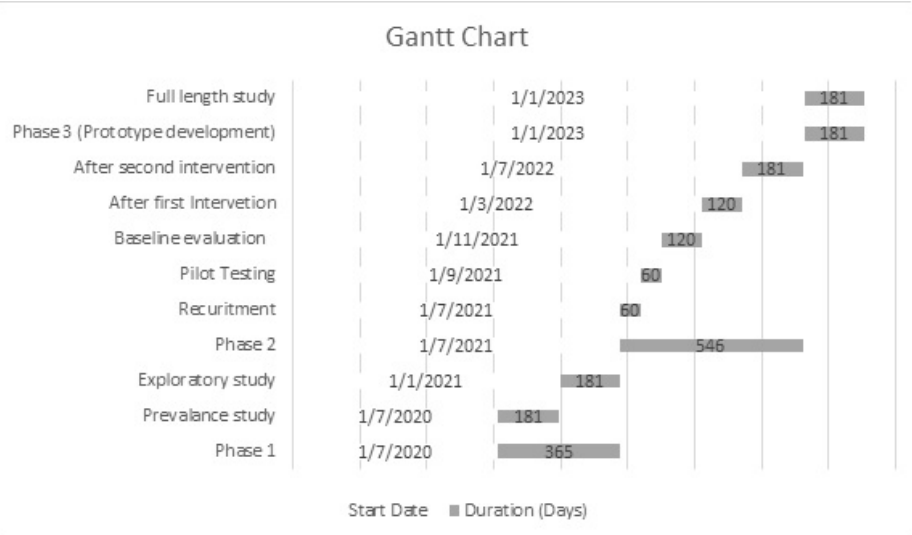


Figure 4. Gantt chart of study-related activities.



Phase 1: Multimethod Multi-Analytic Evidential Approach

Objectives

Phase 1 will consist of the identification and analysis of the problem. The duration of this phase will be 6 months and will include knowledge development about workplace cyberbullying among TCM practitioners.

Prevalence Study

The specific objectives of this study include (1) evaluating the overall prevalence rate of workplace cyberbullying and its

related psychological impacts (depression, anxiety, and stress) on TCM practitioner; (2) understanding the measures associated with various forms of workplace cyberbullying on age, gender, and frequency; and (3) understanding the measure associated with workplace cyberbullying on perpetrators responsible for workplace cyberbullying. The current research will be a survey-based online cross-sectional prevalence study. TCM practitioners are considered a hard-to-reach population; thus, we will conduct a nonprobability snowball sample of 1023 adults (3% precision, 95% confidence level) according to the number of TCM practitioners, which was approximately 15,000 in 2011 [16]. The Hamilton Depression Scale (HAM-D) [17], the Hamilton Anxiety Scale (HAM-A) [18], and the clinical anger scale [19] will be used to assess the psychological impact on TCM practitioners. The Cyberbullying Questionnaire (CBQ) and a short version of a cyberbullying behavior questionnaire (CBQ-S), adapted from Jönsson et al [20], will be used to identify the prevalence among TCM practitioners; these selected questionnaires were already validated in Sweden and the US adult population [20]. The prevalence will also investigate the association with moderating variables (age and gender). Perpetrators of cyberbullying will also be assessed in the specific identification of the prevalence of workplace cyberbullying using the CBQ and CBQ-S questionnaires. The sampling method to understand perpetrator effects in the prevalence will similarly be addressed. The survey will also include a socioeconomic assessment, including education, income, home characteristics, and commodities. The survey will be conducted online due to the current pandemic situation caused by COVID-19, following the CHERRIES guidelines given by Gunther Eysenbach [21].

Exploratory Study

The purpose of the exploratory study is to understand the moderating and mediating factors of workplace cyberbullying by using the ERM on TCM practitioners [15]. The specific questions of this study include the following: (1) What are the relationships between emotions, workplace stressors, cyberbullying perpetration, cyberbullying victimization, and control appraisal, reappraisal, and suppression? (2) What effects do demographic factors have on emotions, workplace stressors, cyberbullying perpetration, cyberbullying victimization, and control appraisal, reappraisal, and suppression? The survey will be conducted using a convenience method, with a sample size of 384 (5% precision, 95% confidence level). A structural equation model will be developed, and each construct will be discussed. A snowball sampling method will be used to approach the target population. There will be a lucky draw at the end of the exploratory study on the participants; the 10 winners of the draw will receive an electronic power bank.

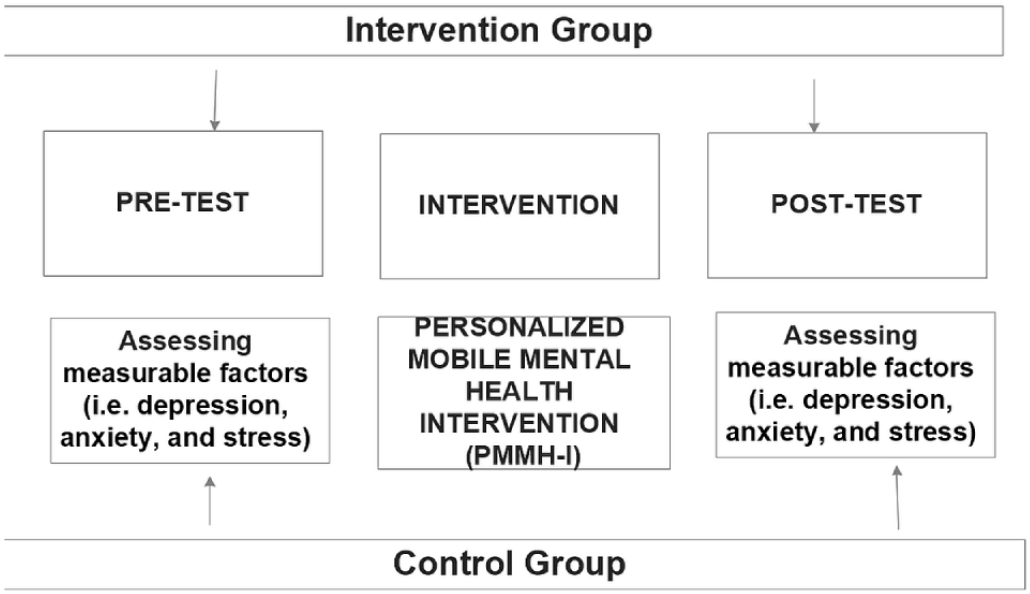
This procedure was selected due to a hard-to-reach study population and a study undertaken during the COVID-19 pandemic.

Phase 2: Program Development

Objectives

The aim of Stage 2 is to develop the anticyberbullying intervention program. Past approaches have been ineffective because of a lack of consistency within the community. To achieve this objective, a quasi-experiment with a nonequivalent pretest–post-test control group design will be conducted for a duration of 1-1.5 years (Figure 5).

Figure 5. Overview of the nonequivalent control-group pretest–post-test study.



Quasi-experiment with Nonequivalent Pretest–Post-test Control Group Design

The study design for this stage is quasi-experimental, in which the groups are nonrandomized into intervention and control groups and selected purposively. This study will be conducted in public hospitals and private hospitals located in Malaysia. All hospitals are eligible to participate. The selection of hospitals will be randomized for the implementation of the interventions. The randomization of hospitals will be performed by online statistical computing web programming to generate the randomization schedule [22]. The current methodology will help reduce selection bias in the study.

This intervention study will be conducted on TCM practitioners specifically. A baseline assessment will be done, in the intervention and control hospital, to measure the burden of bullying and its correlates using the CBQ and CBQ-S. This stage will begin after the investigation of prevalence and exploratory research. First, baseline information will be collected within 3 months, and then the intervention will be monitored twice after a regular period of 6 months in order to monitor the consistency of the intervention program.

The intervention program will be designed and finalized after (1) a systematic review of systematic reviews of previously published literature on bullying and the effectiveness of antibullying intervention programs; (2) the conducting of focus group discussions with TCM practitioners, patients, and other health care providers (to explore the perceptions, beliefs, and suggestions regarding bullying prevention programs); and (3) the conducting of a consultation workshop with all the stakeholders. The bullying intervention program (BIP) will pretest among 50 participants, which will include health care providers, TCM practitioners, and patients. The multicomponent hospital-based intervention strategy will be administered at 3 levels: (1) patients, (2) TCM practitioners, and (3) other health care providers. All the data of participants in this study will be password-protected and safe using Microsoft OneDrive. The recruitment of participants will follow the same procedure described for the exploratory study and prevalence study.

Phase 3: Electronic Anticyberbullying Monitoring System

Interface Design

An expert from each stakeholder group (TCM practitioners, other health care professionals, patients, and IT experts) will be involved in the interface design, information system design, and prototype testing. The system's overall performance and satisfaction will be acquired through questionnaires (questionnaires are available upon request). The CBQ and CBQ-S will be used to determine the effectiveness of an intervention program using a prototype (post-test). The compilation of this research will be used to design the Personalized Mobile Mental Health Intervention (PMMH-I). The duration for stage 3 will be 6 months.

Literature Review on Interventions for Workplace Cyberbullying

There is limited literature available on interventions for workplace cyberbullying among TCM practitioners. Most of the available literature is limited to the identification of exploratory factors, measurement factors, and increasing trends of workplace cyberbullying. Funded by the Massey University Research Fund, D'Souza et al [23] discussed the issue of workplace cyberbullying in New Zealand; the study sample size was limited to 20 participants, but they predict an increase of workplace cyberbullying [23,24]. Vranjes et al [25] developed the inventory of cyberbullying acts at the workplace (ICA-W); the available results are preliminary items and build upon existing knowledge.

Moreover, the results of available literature are often generalized, noncontextual, and lack practical implications [25]. Another online self-report survey on workplace cyberbullying in New Zealand reports an increasing trend in workplace cyberbullying [26]; however, self-reported answers may be exaggerated and lead to an increase in survey bias. The studies of Farley [27], who had worked on the workplace cyberbullying measurement scale, are limited to methodological improvement in the measurement scale; these studies call for further exploratory studies. Other studies on the exploratory factors of workplace cyberbullying [27-29] lack coordination between theoretical and practical applications. The subjects of cyberbullying literature in Malaysia are limited mostly to adolescents and undergraduate students, and the focus is primarily on prevalence, the determination of exploratory factors, and descriptive studies [30-33]. The available studies are limited to examining the exploratory factors of workplace bullying [34].

Our studies will adopt the ERM in hospitals, and will adapt personalized mobile-based IT consumerization of the ERM in workplace cyberbullying among health care professionals as the intervention. A recent study also supports mobile phone–and internet-based interventions for treating depression [35]. Our study will be the first to use a personalized mobile mental health intervention for workplace cyberbullying for TCM practitioners.

Data Collection and Analysis

The recruitment of participants will follow the same procedure as was described for the exploratory study and prevalence study. The participant will be invited to join through a webinar to complete the questionnaire. Only the participants who completed Phase 2 will be asked to continue. The prototype will be given to them, and a brief training will be provided through a 30-minute webinar. Stage 3 participants will be limited to the Stage 2 completers in order to gauge the effectiveness of the Step 2 intervention program and whether the prototype is capable of reporting cyberbullying effectively. Thematic analysis will be done on the data yielded from the control and intervention groups. All the data of participants in this study will be password-protected and safe using Microsoft OneDrive.

Results

The study was submitted for funding by an internal grant from Xiamen University Malaysia in May 2020. The prevalence study for Phase 1 began in July 2020, and it will be followed by exploratory research in January 2021. The duration for Phase 1 will be 12 months. For Phase 2, the recruitment of participants will begin in July 2021. The baseline study will be completed in 4 months. The intervention will be divided into two 4-month periods to measure the consistency of the intervention. The last phase will be the development and implementation of the prototype with pilot testing and post-testing, which will have a duration of 6 months (subject to the availability of funding).

Discussion

The impetus for this study is a need for technologically based interventions to decrease work-related cyberbullying identified by health professionals and academics. Workplace cyberbullying leads to counterproductive work behaviors [36] and may lead to violence due to conflicts or work-related stress. This study will also provide insight into how job-related stress (role conflicts), team-related stress (interpersonal conflicts), and organization-related stress (organizational change) can lead to unintentional cyberbullying communication. This causes cyberbullying victimization between doctors, traditional alternative practitioners, and other health care providers. There is a lack of evidence on knowledge generation indicators, such as prevalence studies. To reduce conflict and enhance work productivity, there is a need for exploratory studies to understand the ERM and the adaptation of technological interventions such as personalized mobile mental health in hospital-based settings.

Acknowledgments

This work was supported by the Research Management Center, Xiamen University Malaysia, grant number XMUMRF/2020-C6/ITCM/0005. The funding body had no role in the design and conduct of this study; the collection, management, analysis, and interpretation of the data; the preparation, review, and approval of the manuscript; or the decision to submit the manuscript for publication.

Special thanks to Aishah Rose Marie for her perseverance in proofreading the manuscript.

Authors' Contributions

MSA was involved in conceptualization, methodology design, data collection, data analysis, prototype development, and co-writing of the paper. YK was involved in methodology design, data collection from the hospitals, and co-writing of the paper. LQ was involved in methodology design, data collection from the hospitals, and co-writing of the paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer Review Report.
[PDF File (Adobe PDF File), 1474 KB - resprot_v9i11e23112_app1.pdf]

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Abbreviations

CBQ: Cyberbullying Questionnaire
CBQ-S: short version of a cyberbullying behavior questionnaire
ERM: emotion reaction model
ICA-W: inventory of cyberbullying acts in the workplace
PMMH-I: Personalized Mobile Mental Health Intervention program
TCM: Traditional Chinese Medicine

Edited by G Eysenbach; submitted 01.08.20; peer-reviewed by A Wahab, A van Kraaij; comments to author 03.09.20; revised version received 05.09.20; accepted 10.11.20; published 20.11.20.

Please cite as:
Kim YJ, Qian L, Aslam MS
Development of a Personalized Mobile Mental Health Intervention for Workplace Cyberbullying Among Health Practitioners: Protocol for a Mixed Methods Study
JMIR Res Protoc 2020;9(11):e23112
URL: http://www.researchprotocols.org/2020/11/e23112/
doi:10.2196/23112
PMID:33216000

Protocol

The Role of Demoralization and Meaning in Life (DEMIL) in Influencing Suicidal Ideation Among Patients Affected by Chronic Pain: Protocol of a Single-Center, Observational, Case-Control Study

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Abstract

Background: Chronic pain is a significant risk factor for suicidal ideation (SI) and suicidal behavior (SB), including a 20%-40% prevalence rate of SI, a prevalence between 5% and 14% of suicide attempts, and a doubled risk of death by suicide in patients with chronic pain compared to controls. In most studies, associations between chronic pain and suicidality are robust, even after adjusting for the effect of sociodemographics and psychiatric comorbidity, and particularly for depressive conditions. A number of specific conditions that can modulate suicidality risk in patients with chronic pain have been investigated, but there is a need for their more specific characterization. Numerous recent studies have shown that demoralization and meaning in life (MiL) constructs affect suicidality as risk and protective factors, respectively. These constructs have been mainly investigated in patients with somatic illness and in community-dwelling individuals who may present with SI or SB independently of a psychiatric diagnosis of depression. However, a paucity of studies investigated them in suicidal patients affected by chronic pain.

Objective: The primary objective of this project is to investigate the relationship between demoralization and MiL on SI risk in patients with chronic pain. The secondary objectives are (1) to test whether demoralization can occur independently of depression in patients with chronic pain and SI, (2) to examine whether the expected association between demoralization and SI may be explained by a sole dimension of demoralization: hopelessness, (3) to examine whether the presence of MiL, but not the search for MiL, is associated with less SI, and (4) to explore whether previously described MiL profiles (ie, high presence-high search, high presence-low search, moderate presence-moderate search, low presence-low search, and low presence-high search) emerge in our cohort.

Methods: This project is a single-center, observational, case-control study—the Demoralization and Meaning in Life (DEMiL) study—conducted by the Division of Clinical Pharmacology and Toxicology, the Multidisciplinary Pain Centre, and the Service of Liaison Psychiatry and Crisis Intervention at the Geneva University Hospitals. Self- and hetero-administered questionnaires were conducted among patients and controls, matched by age and gender. The Ethics Committee of the Canton of Geneva approved the scientific utilization of collected data (project No. 2017-02138; decision dated January 25, 2018). Data have been analyzed with SPSS, version 23.0, software (IBM Corp).

Results: From March 1, 2018, to November 30, 2019, 70 patients and 70 controls were enrolled. Statistical analyses are still in progress and are expected to be finalized in November 2020. To date, we did not observe any unfavorable event for which a causal relationship with the collection of health-related personal data could be ruled out. Results of this study are expected to form the basis for possible prevention and psychotherapeutic interventions oriented toward demoralization and MiL constructs for suicidal patients with chronic pain.

Conclusions: The interest in exploring demoralization and MiL in chronic pain patients with SI arises from the common clinical observation that experiencing chronic pain often requires a revision of one's life goals and expectations. Hence, the impact of chronic pain is not limited to patients' biopsychosocial functioning, but it affects the existential domain as well. The major clinical implications in suicidal patients with chronic pain consist in trying to (1) delineate a more precise and individualized suicide risk profile, (2) improve detection and prevention strategies by investigating SI also in individuals who do not present with a clinically diagnosed depression, and (3) enhance the panel of interventions by broadening supportive or psychotherapeutic actions, taking into consideration the existential condition of a person who suffers and strives to deal with his or her suffering.

International Registered Report Identifier (IRRID): DERR1-10.2196/24882

(JMIR Res Protoc 2020;9(11):e24882) doi:10.2196/24882

KEYWORDS

suicide; suicide behavior; suicide attempt; suicidal ideation; chronic pain; demoralization; meaning in life; study protocol

Introduction

Background

Chronic pain conditions are associated with an elevated risk of suicidal ideation (SI) and suicidal behavior (SB). Literature reviews indicate a 20%-40% prevalence rate of SI, a lifetime prevalence between 5% and 14% of suicide attempts, and a 2-fold higher risk of death by suicide in patients with chronic pain as compared to controls [1-7]. Most studies show that associations between chronic pain, SI, and SB are robust even after adjusting for the effect of sociodemographic factors and psychiatric comorbidity, particularly for depressive conditions [8-14]. A number of specific conditions that can modulate SI and SB risk in patients with chronic pain have been investigated, including pain characteristics, functional interference, illness beliefs, and access to opioids [2,3,15,16]. However, to improve SI and SB risk characterization in these patients, there is a need for the exploration of other potential risk and protection factors, in analogy to other chronic diseases [2,17]. To this end, the main goal of this project is to explore the role of two constructs, demoralization and meaning in life (MiL), in modulating SI among patients with chronic pain.

In an analogous study conducted in our institution, the same constructs [18-20], together with other psychological models [21-25], were investigated in a cohort of patients attending an emergency department. Demoralization and MiL concepts are theoretically and clinically connected, because meaninglessness is one of the five components of the definition of demoralization. Precisely, this link could be the key to utilize demoralization and MiL in supportive and psychotherapeutic interventions, that is, exploring with the patients the subconstructs of demoralization and the sense that the patient attributes to them, in order to restructure and reinforce an MiL that allows them to mitigate their suffering. The clinical interest in chronic pain patients with SI arises from the common clinical observation that experiencing chronic pain often requires a revision of one's life goals and expectations [26]; hence, the impact of chronic pain is not limited to the patients' biopsychosocial functioning but it affects the existential domain as well [16,27-30].

The Demoralization Construct and Pain

The constitutive components of the demoralization construct, according Kissane and Clarke's model, are loss of MiL, hopelessness or disheartenment, helplessness, sense of failure, and dysphoria [31,32] (see Costanza et al [18] for a detailed discussion on the demoralization construct). Various studies have indicated a possible relationship between demoralization and pain. For example, demoralization has been found to be associated with chronic facial pain [33], phantom tooth pain [34], and myofascial pain [35]. Greater pain intensity was found to be associated with the presence of demoralization in consultation-liaison psychiatry patients [36]. Another facet of painful illness, namely functional disability, was found to be correlated with demoralization in a sample of inpatients, independently of illness severity [37]. Loss of sense of dignity may also partially account for the association between physical problems and demoralization in advanced cancer patients [38]. Demoralization was found to be associated with lower pain reduction, reduced functional improvement, and decreased satisfaction among spine surgery patients [39].

Demoralization and Suicidality

Two issues represent the impetus for investigating demoralization in individuals presenting with SB: (1) the relationship between demoralization and depression and (2) the role of one of the components of the demoralization definition (ie, hopelessness) in influencing SI and SB. By focusing on their phenomenological differentiation, most studies have suggested that demoralization is an independent condition distinguishable from depression [30,31,40]. In patients with cancer [41-45] and other medical diseases [46], there may be frequent overlaps between demoralization and depression, but demoralization can occur independently of depression and the two conditions are not necessarily linked by a hierarchical connection. By contrast, the relationship between demoralization and hopelessness is still being debated in the literature. Hopelessness is a dimension of the construct of demoralization rather than a synonym of demoralization [30,31,42,47-49]. However, for some authors it is still not clear whether definitions

of demoralization containing hopelessness have predictive value over the construct of hopelessness alone [50]. This is particularly relevant for the evaluation of the role of demoralization in suicidality. Indeed, Beck first showed that hopelessness was an independent and more powerful predictor of suicidality than depression [51]. Therefore, more research is needed to better understand the relationship between demoralization and hopelessness, which has been found to be an independent mediator of SI and SB [31,52].

The MiL Construct and Pain

A consensus in recent psychological research in defining MiL can be centered on two dimensions: coherence, or a sense of comprehensibility and one's life making sense, and purpose, or a sense of core goals, aims, and direction in life. A third facet, significance, which focuses on values, worth, and importance of one's life, is gaining increasing attention [53] (see Costanza et al [19,54] for an in-depth discussion on MiL). According to the largely utilized conceptualization of Steger, MiL is "the web of connections, understandings, and interpretations that help us comprehend our experience and formulate plans directing our energies to the achievement of our desired future" [55]. This theoretical model divides MiL into two subconstructs, specifically the *presence of* and *search for* MiL [53,56], which are not mutually exclusive [57]. Presence of MiL is rather uniformly thought to be beneficial [20,58]. In contrast, search for MiL appears more controversial, with some authors considering it the essence of human motivation [59], while others consider it a sign that one has lost meaning [60] or feels like one's life has somewhat less meaning [58,61]. Different MiL profiles have been recently characterized in patients with chronic pain, resulting from the combination between low and high levels of presence of and search for MiL, which were associated with a unique adjustment outcome: patients having profiles with high scores of presence showed fewer depressive symptoms and greater life satisfaction [62]. Both MiL subconstructs have been found to be highly stable over time, suggesting that MiL may reflect a trait rather than a state aspect of individual functioning [63]. Among the psychotherapeutic interventions based on MiL, the *narrative* model, inspired by *logotherapy* described by Frankl [59], is the model for which clinical efficacy has been demonstrated both for patients with somatic conditions, such as palliative care patients [64], terminally ill cancer patients [65], and older adults with frailty [66], and also for individuals without an explicit somatic condition, such as older [67-69] and young adult patients [70], with or without depressive symptomatology.

MiL and Suicidality

A number of studies have investigated MiL in individuals presenting SI and SB. A negative correlation between MiL—without distinction between presence of and search for MiL—and SI and SB has been found in undergraduate students [71-78], older adults [79-81], veterans [82], and patients affected by psychiatric disorders [77,81,83-85]. Overall, these studies suggested a protective role of MiL toward SI and SB.

To our knowledge, the constructs of presence of and search for MiL in individuals presenting SI and SB have only been explored in two studies that used the Meaning in Life Questionnaire (MLQ) [61], which was conducted in undergraduate students [86] and in soldiers returning from deployments [87]. In both, presence of MiL was correlated with a lower risk of SI and SB over time [86,87]. In contrast, the search for MiL subconstructs predicted a lower SI in one study [78] but a higher risk of suicide in another [87]. Notably, psychotherapeutic interventions targeting MiL were found to be effective in reducing suicide risk [88] and represent a promising therapeutic opportunity [82,85,87,89].

Objectives

The primary objective of this project is to investigate the relationship between demoralization and MiL on SI risk in patients with chronic pain. The secondary objectives are (1) to verify if demoralization can occur independently of depression in patients with chronic pain and SI, (2) to examine if the expected association between demoralization and SI may be explained by a sole dimension of demoralization: hopelessness, (3) to examine whether the presence of MiL, but not the search for MiL, is associated with a lower SI, and (4) to explore if previously described MiL profiles [62,63] (ie, high presence-high search, high presence-low search, moderate presence-moderate search, low presence-low search, and low presence-high search) emerge in our cohort.

In summary, the demoralization and MiL constructs have been mainly investigated in patients with somatic illness and in community-dwelling individuals who may present with SI or SB independently of a psychiatric diagnosis of depression. Only a very small number of studies investigated them in patients affected by chronic pain presenting with SI. This population can provide the opportunity to analyze relationships between demoralization, depression, and hopelessness as well the role of the presence of MiL and search for MiL subconstructs in influencing SI and SB [26].

Methods

Participant Confidentiality and Data Handling

Participants' dignity, privacy, and health were preserved and respected, guaranteeing participants full anonymity if study data are to be presented at scientific meetings or published in scientific journals. Individual participant medical information remains confidential and will not be disclosed to third parties. Participant data were anonymized with coded identification numbers that correspond to the participants' medical records using a progressive numbering system (ie, 001, 002, 003, etc). All participant-related documents were stored in a secure and locked location. Electronic data were protected using strong password encryption. Data generation, transmission, storage, and analysis of health-related personal data followed the current Swiss legal requirements for data protection and were performed according to Human Research Ordinance Article 5.

General Project Design and Procedures

This project is an observational study—the Demoralization and Meaning in Life (DEMiL) study—conducted by the Division of Clinical Pharmacology and Toxicology and the Service of Liaison Psychiatry and Crisis Intervention at the

Multidisciplinary Pain Centre (MPC) of the Geneva University Hospitals (see Tables 1 and 2 [45,61,90-93]).

Table 1. Methodological tools to assess primary outcomes.

Variable and instrument	Main characteristics of the instrument
Suicidal ideation (SI)	
Item No. 9 of the Beck Depression Inventory-II [91], French-validated version	▪Self-report multiple-choice inventory ▪Indicator of the severity of depression ▪Standard cutoff scores: 0-13 (minimal depression), 14-19 (mild depression), 20-28 (moderate depression), and 29-63 (severe depression) ▪21 items, each one rated on a 4-point scale, ranging from 0 to 3, based on severity of the item ▪About 5-10 minutes to complete
Scale for Suicidal Ideation [92], French-validated version	▪Scale based on a semistructured interview with the patient ▪Indicator of characteristics and severity of an individual's plans and wishes to commit suicide ▪19 items, each one rated on a 3-point scale, ranging from 0 to 3 (except for item 13, which is rated on a 4-point scale), based on severity of the item ▪Total score for the 19 items: minimum score 0 and maximum score 38 (higher scores indicate greater SI) ▪About 5-10 minutes to complete
Demoralization	
Demoralization Scale [45]	▪Self-reported multiple-choice inventory ▪Indicator of the presence and severity of demoralization; standard cutoff score of >30 indicative of severe demoralization ▪24 items, each with a 5-point response scale describing the frequency of occurrence for each item: 0 (never), 1 (seldom), 2 (sometimes), 3 (often), and 4 (all the time) ▪5-factor structure (subscales): loss of meaning and purpose (5 items), dysphoria (5 items), disheartenment (6 items), helplessness (4 items), and sense of failure (4 items) ▪About 5-10 minutes to complete
Meaning in life	
Meaning in Life Questionnaire (MLQ) [61], French-validated version	▪Self-reported multiple-choice inventory ▪Measure of the *presence of* (5 items) and the *search for* (5 items) meaning in life; the MLQ does not have cutoff scores, because it is intended to measure meaning in life across the complete range of human functioning ▪10 items, each rated on a 7-point response scale, from *absolutely true* to *absolutely untrue* ▪About 3-5 minutes to complete

Table 2. Schedule of assessments (flow of research project).

Assessments	Occurrence of assessment[a] at each project period		
	Before initial routine visit	Initial routine visit: around 15 days after having received MPC[b] routine screening self-administered questionnaires	Second visit: 1-7 days after initial MPC routine visit
MPC routine screening and postscreening self-administered questionnaires (completed at home)			
Demographic data: gender, age, marital status, language, education, professional activity, and insurance claims	x		
Pain data: localization (pain drawings), intensity (Visual Analog Scale), duration, characteristics (McGill Pain Questionnaire), and aggravating and alleviating factors	x		
Severity disability (*Oswestry Disability Index*)	x		
Quality of life (36-Item Short Form Survey) [93]	x		
Patient expectations about MPC	x		
Illness beliefs (Brief Illness Perception Questionnaire–Revised)	x		
Demoralization (Demoralization Scale) [45]	x		
Severity of depression (Beck Depression Inventory-II [BDI-II]) [91]	x		
Suicidal ideation (item No. 9 of the BDI-II) [91]	x		
MPC routine visit + study information to patient (written communication)		x	
Study visit (required time 1 hour)			
Informed consent and inclusion			x
Clinical evaluation of suicidal ideation[c]			x
Characteristics and severity of suicidal ideation (Scale for Suicidal Ideation)[c] [92]			x
Meaning in life (Meaning in Life Questionnaire) [61]			x
Clinical diagnostic and exclusion of major depressive disorder and/or other psychiatric comorbidities (clinical interview and structured interview by French 5.0.0 version of the Mini-International Neuropsychiatric Interview [90])			x

[a]x indicates that the assessment was performed, while a blank cell indicates that it was not.

[b]MPC: Multidisciplinary Pain Centre.

[c]This assessment was only performed in patients with suicidal ideation: those with a score between 1 and 3 in question 9 of the BDI-II.

The research project was carried out in accordance with the research plan and Swiss legal and regulatory requirements, in agreement with the principles stated in the current version of the Declaration of Helsinki, the Essentials of Good Clinical Practice, issued by Public Health Switzerland. Self-administered questionnaires were sent out to each participant before their first routine MPC visit. The utilization for scientific purposes of data collected with these questionnaires was approved by the Ethics Committee (EC) of the Canton of Geneva (project No. 2017-02138, decision dated January 25, 2018). During their routine MPC visit, about 15 days after receiving the questionnaires, all participants received a written communication informing them about the research project and were able to pose questions or raise concerns with the project sponsor. Each participant was given at least 24 hours to review the written communication before being asked to sign the informed consent document, which took place during a subsequent study visit. A qualified team member reviewed the questionnaires for presence of SI and communicated relevant information about this study to the participants. Appropriate measures were taken for cases where severe SI was identified, including, if necessary, accompanying the patient to the psychiatric emergency ward. About 1-7 days after the routine MPC visit, patients who had agreed to be included in the study had a second study visit where they signed the informed consent form. All patients underwent completion of the MLQ [61].

The desire and possibility of being included in the study did not influence in any way the patients' overall evaluation or treatment. All patients received the appropriate treatment for their clinical situation as recommended by the MPC, which included pharmacological modifications, individual or group psychiatric treatment, and/or physical treatment.

They also underwent a clinical interview and a structured diagnostic interview to screen for psychiatric diagnoses, including major depressive disorder, according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) and the French version 5.0.0 of the Mini-International Neuropsychiatric Interview (MINI) [90]. Patients with SI—as identified by their positive response to question 9 in the Beck Depression Inventory-II (BDI-II) [91]—whose scores ranged from 1 to 3, additionally underwent a clinical evaluation of SI by a qualified team member using the Scale for Suicidal Ideation (SSI) to assess characteristics and severity of SI [92]. The study visit took approximately 1 hour to complete.

Recruitment and Screening

Participants were enlisted by ongoing recruitment through a project anchored in daily clinical practice at the MPC. To control for potential confounding individual differences, we screened for quality of life, assessed using the 36-Item Short Form Survey [93]; illness beliefs, assessed using the Brief Illness Perception Questionnaire–Revised [94]; pain characteristics; and drug therapy.

Inclusion criteria consisted of patients affected by chronic pain referred to the MPC and presenting with SI and control subjects not presenting with SI; groups were matched for age and gender. As the MPC is a third-line ambulatory referral center, most of the patients referred to the center by their treating physicians suffer from chronic neuropathic or nociceptive pain. Over the course of a typical year, about 40%-50% of incoming patients suffer from neuropathic pain; about 40% have osteoarticular pain, mostly lower back pain, fibromyalgia, and joint pain; while the remaining 10%-20% suffer from chronic visceral pain or from single-fraction radiotherapy cancer-related pain. Participants had to provide informed written consent and be 18 years of age or older. Exclusion criteria included patients with an insufficient comprehension of the French language and those affected by dementia, psychotic disorder, or borderline personality disorder. In cases of withdrawal of informed consent or noncompliance, participants were excluded from the study. If participants withdrew due to personal reasons, they were asked to inform the project leader about their withdrawal. Additional participants were recruited to replace those who had withdrawn.

Assessment of Primary and Secondary Outcomes

Regarding primary endpoints, we expected to observe a higher score on the Demoralization Scale (DS) [45] and a lower score on the MLQ [68] for patients with SI (presence and severity) as measured by question 9 of the BDI-II [91] and the SSI [92]. The DS and BDI-II were administered as part of routine questionnaires. In order to assess our primary endpoints, we utilized the instruments outlined in Table 1.

Regarding secondary endpoints, we expected that patients with SI (presence and severity) would have (1) a higher DS score but not necessarily a higher BDI-II score, (2) a higher score for search for MiL and a lower score for presence of MiL, and (3) an MiL profile of combined presence and search, with higher scores for search for MiL and lower scores for presence of MiL.

The following tools were used to assess secondary endpoints:

1. The BDI-II was utilized to assess depression severity [91]. The presence or absence of depression was determined during a clinical interview using a structured diagnostic interview to screen psychiatric diagnoses, according the French version 5.0.0 of the MINI [90] for DSM-IV disorders.
2. The MLQ [68] was used to define MiL profiles and categorize them as high presence-high search, high presence-low search, moderate presence-moderate search, low presence-low search, or low presence-high search.
3. The sense of hopelessness was determined with the helplessness
subscale of the DS [45], which comprises four items to which responses are given using a 5-point Likert scale; subscale scores range from 0 to16, and high scores indicate a strong sense of helplessness. It has been theorized that helplessness is a subdivision of hopelessness [21] and, from a dimensional perspective, leaving helplessness untreated may lead to hopelessness, which is in turn strongly associated with suicidal intent [31,32].

Definition, Assessment, and Reporting of Serious Events

A serious event (SE) is defined as any unfavorable event for which a causal relationship with the collection of health-related personal data cannot be ruled out and which (1) requires hospitalization or prolongation of hospitalization, (2) results in persistent or significant disability or incapacity, or (3) is life-threatening or results in death. When an SE occurs, the research project is put on hold and the EC is informed.

This would be followed by an assessment by the project leader with regard to the project-specific measure relationship according to the following definitions:

1. Unrelated: the occurrence of the event has no temporal relationship to the project-specific measures applied and can be explained by the underlying disease or other factors.
2. Related: there is a plausible temporal relationship between the occurrence of the event and the project-specific, applied measures and cannot be explained by the underlying disease or other factors.

SEs are documented in each participant's case report form and source document and reported to the EC within 7 days. A report would be submitted to evaluate the relationship between our study and the event, explaining how the event affected the project and, if applicable, outline further protective measures to prevent reoccurrence.

Statistical Methodology

Assuming a 5% margin of error; a confidence level of 95%; a target population size of 400, as around 400 new patients are evaluated annually at the MPC; and a response distribution of 50%, then the minimum sample size required for this study is approximately 200: 100 presenting SI and 100 nonpresenting SI participants matched by age and gender. Questionnaire data were manually entered into an SPSS, version 23.0, database (IBM Corp) [95] using double data entry to minimize errors. Each participant was assigned a unique code that was recorded on their questionnaire. Questionnaires and demographic data

were analyzed with SPSS, version 23.0, software (IBM Corp) [95].

Descriptive statistical analyses were conducted to compute means and SDs for numerical variables and frequencies (%) for categorical variables. The chi-square test or Fisher exact test was used for categorical variables and checked for matching between groups regarding age, gender, and years of education. To test our main hypothesis, repeated-measures analyses of variance were conducted to test for significant interaction between DS and MLQ variables and group factors (SI vs non-SI). The post hoc Tukey multiple-comparison test was used to find significant differences between means. In addition, hierarchical multiple regressions were used to test for predictive effects of MLQ and DS scores. Multivariate linear and logistic regression models were employed to explore the associations between MLQ score, DS score, and suicidal risk. Covariates were introduced into our model using a stepwise backward procedure to attain a parsimonious model to test effect modifications related to sociodemographic (ie, gender, education, drug therapy, etc) and pain characteristics. All results are reported with a significance threshold of 2-sided *P* values of less than .05 and effect size. Missing value analysis was performed for all questionnaire scores to check for significant patterns. Where no patterns could be identified, the random missing values were replaced by the mean.

Results

From March 1, 2018, to November 30, 2019, 70 patients and 70 control participants were enrolled. Statistical analyses are still in progress and are expected to be finalized in December 2020. We did not observe any unfavorable event for which a causal relationship with the collection of health-related personal data could be ruled out. The results of this study will be used to develop new proposals for prevention and psychotherapeutic interventions oriented toward demoralization and MiL in patients with chronic pain, which will be based on the model of already-existing psychotherapeutic interventions for patients with other somatic conditions.

Discussion

The interest in exploring demoralization and MiL in chronic pain patients with SI arises from the common clinical observation that experiencing chronic pain often requires a revision of one's life goals and expectations. Different coping mechanisms have been proposed for chronic pain [96,97]. However, the impact of chronic pain is not limited to patients' biopsychosocial functioning, but it affects the existential domain as well. The major clinical implications in suicidal patients with chronic pain consist in trying to (1) delineate a more precise and individualized suicide risk profile, (2) improve detection and prevention strategies by investigating SI also in individuals who do not present with a clinically diagnosed depression, and (3) enhance the panel of interventions by broadening supportive or psychotherapeutic actions. The two constructs of MiL and demoralization are intimately and opposingly linked because meaninglessness is one of the subconstructs underlying the construct of demoralization [31,32]. In the specific context of chronic pain, this link precisely could be key to utilize these theoretical models in psychotherapeutic interventions based on the *narrative* model [58,59,66-70], that is, to explore with patients the subconstructs of demoralization and the sense that they attribute to them in order to restructure and reinforce an MiL that allows them to mitigate their suffering, taking into consideration the existential condition of a person who suffers and strives to deal with their suffering.

Acknowledgments

The costs for the staff involved in this study were covered by the MPC Division of Clinical Pharmacology and Toxicology and by the Service of Liaison Psychiatry and Crisis Intervention of the Geneva University Hospitals.

Authors' Contributions

AC and VC wrote the primary draft of the text. AC, VC, VM, VP, and CC conceived and designed the study. JD, GB, and CC critically reviewed the text and supervised all the steps of the work. All authors approved of the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BDI-II: Beck Depression Inventory-II
DEMiL: Demoralization and Meaning in Life
DS: Demoralization Scale
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition
EC: Ethics Committee

MiL: meaning in life
MINI: Mini-International Neuropsychiatric Interview
MLQ: Meaning in Life Questionnaire
MPC: Multidisciplinary Pain Centre
SB: suicidal behavior
SE: serious event
SI: suicidal ideation
SSI: Scale for Suicidal Ideation

Edited by G Eysenbach; submitted 08.10.20; peer-reviewed by L Costantini, R Lee; comments to author 30.10.20; revised version received 03.11.20; accepted 03.11.20; published 26.11.20.

Please cite as:
Costanza A, Chytas V, Mazzola V, Piguet V, Desmeules J, Bondolfi G, Cedraschi C
The Role of Demoralization and Meaning in Life (DEMIL) in Influencing Suicidal Ideation Among Patients Affected by Chronic Pain: Protocol of a Single-Center, Observational, Case-Control Study
JMIR Res Protoc 2020;9(11):e24882
URL: https://www.researchprotocols.org/2020/11/e24882
doi:10.2196/24882
PMID:33144275

Protocol

The Precision Health and Everyday Democracy (PHED) Project: Protocol for a Transdisciplinary Collaboration on Health Equity and the Role of Health in Society

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Abstract

Background: The project “Precision Health and Everyday Democracy” (PHED) is a transdisciplinary partnership that combines a diverse range of perspectives necessary for understanding the increasingly complex societal role played by modern health care and medical research. The term “precision health” is being increasingly used to express the need for greater awareness of environmental and genomic characteristics that may lead to divergent health outcomes between different groups within a population. Enhancing awareness of diversity has parallels with calls for “health democracy” and greater patient-public participation within health care and medical research. Approaching health care in this way goes beyond a narrow focus on the societal determinants of health, since it requires considering health as a deliberative space, which occurs often at the banal or everyday level. As an initial empirical focus, PHED is directed toward the health needs of marginalized migrants (including refugees and asylum seekers, as well as migrants with temporary residency, often involving a legally or economically precarious situation) as vulnerable groups that are often overlooked by health care. Developing new transdisciplinary knowledge on these groups provides the potential to enhance their wellbeing and benefit the wider society through challenging the exclusions of these groups that create pockets of extreme ill-health, which, as we see with COVID-19, should be better understood as “acts of self-harm” for the wider negative impact on humanity.

Objective: We aim to establish and identify precision health strategies, as well as promote equal access to quality health care, drawing upon knowledge gained from studying the health care of marginalized migrants.

Methods: The project is based in Sweden at Malmö and Lund Universities. At the outset, the network activities do not require ethical approval where they will not involve data collection, since the purpose of PHED is to strengthen international research contacts, establish new research within precision strategies, and construct educational research activities for junior colleagues within academia. However, whenever new research is funded and started, ethical approval for that specific data collection will be sought.

Results: The PHED project has been funded from January 1, 2019. Results of the transdisciplinary collaboration will be disseminated via a series of international conferences, workshops, and web-based materials. To ensure the network project advances toward applied research, a major goal of dissemination is to produce tools for applied research, including information to enhance health accessibility for vulnerable communities, such as marginalized migrant populations in Sweden.

Conclusions: There is a need to identify tools to enable the prevention and treatment of a wide spectrum of health-related outcomes and their link to social as well as environmental issues. There is also a need to identify and investigate barriers to precision health based on democratic principles.

International Registered Report Identifier (IRRID): DERR1-10.2196/17324

(JMIR Res Protoc 2020;9(11):e17324) doi:10.2196/17324

KEYWORDS

precision health; health care access; health literacy; everyday democracy

Introduction

Advances in medical research have led to an awareness that different populations respond differently to the same forms of treatment and are host to distinct pathogens [1]. In understanding how best to respond to these differences and the relative role played by genomic characteristics or environmental and lifestyle variables, there have been calls for so-called "precision health care" and "precision medicine." The term "precision" denotes a sensitivity to these intergroup variables, pointing to the need to better model how environmental and genomic factors impact individuals unequally along socially and economically structured lines and with consequences for their health and receptivity to treatment. In this project, we refer to the health care, public health, and medical research aspects collectively as "precision health."

According to Oh et al [1], the impact of precision health is of great importance because it is well known that generalizing results from research on one racial/ethnic group to another can work but may have fatal consequences when relevant differences, such as societal and genomic factors, are ignored.

The lack of diversity in large-scale biomedical studies hinders our understanding of human disease and severely limits our ability to develop optimal therapeutic interventions and treatments [1]. The basis of precision health is grounded in knowledge and effective communication between patients and health care professionals, including both those directly engaged in patient care and practitioners active in medical research. Communication within precision health care is important since social, environmental, and genetic factors have their roles as causes and explanations in order to be able to provide the right diagnoses and treatments at the right time [2]. Therefore, it is important to communicate with patients in order to identify those social and environmental factors that could be explanations.

Medical personnel need to make treatment decisions and predict efficacy of treatments to ensure health care is better suited to the diverse needs of different populations, as well as minimize negative side effects. Precision health requires the ability to identify subpopulations with susceptibilities to specific diseases, whether due to genetic or social determinants, and to understand how negative health care outcomes can develop through the complex environmental interactions that need to be understood through the social sciences. For example, environmental and lifestyle factors, such as housing challenges, economic stress, physical inactivity, and smoking, are quite frequently observed among marginalized migrants in Sweden [3,4], and this points to high public health inequality.

The position of being a migrant, unless well resourced, creates particular health consequences for individuals. Migration, particularly that which is involuntary or forced, is known to cause mental stress, and the circumstances surrounding the migration while escaping the native country are important [3]. The exodus from the country of origin may have been sudden, and if the reasons are war, disaster, and political persecution, there could be long stays in refugee camps. After arrival in the recipient country, there is usually a time of uncertainty during the asylum process, which might increase the risk of mental illness [5,6]. Furthermore, migrants have higher risks of depression, psychosis, and suicidal thoughts [5]. According to a study by Hjern [7], migrants of non-European background in Sweden are three to four times more likely to experience poor or very poor health when compared with Swedish-born individuals.

When it comes to cultural competence within health care, health care provision could be defined as a continuing process with the goal of effectively caring for people with culturally diverse backgrounds [8]. Having specific knowledge of health care professionals' own cultural backgrounds, as well as patients' cultural needs ensures holistic and competent care [8]. It is important to acknowledge where practitioners and patients have expertise in knowledge of different cultural practices, cultural assessments, and communication skills [8]. If patients and health care professionals do not fully understand each other, the relationship becomes undermined, leading to insufficient emotional support [9] and unmet health care needs, as they are not able to make themselves understood [10].

The need to improve the relationship between health care professionals and patients [1], as well as include more data that could help measure diverse needs within national populations [11], has parallels to debates over the applicability of democratic theories to the development of new participatory models for "good" health care systems [12-14], with more recent interest in bringing those same insights to medical research by, for example, involving patients in the stratification of research priorities [15-17].

Methods

Conceptual Background

The application of concepts first developed in the social sciences is fraught with difficulties given that the central term "democracy" is highly ambiguous and may lead to quite

divergent outcomes, with mixed relevance to precision health. Enabling the patient's ability to select from a menu of choices, such as the hospital or key aspects of their treatment, has been criticized by some for unfairly passing responsibility for complicated decisions to those lacking sufficient training, supporting a neoliberal marketization of health services [18,19]. Stark disparities in health literacy (ie, patients' understanding of their health care needs and medical treatment) and access to medical services (eg, due to geographical proximity) are structural constraints not only limiting but also potentially opposing patients' ability to choose. Such inequality, where particularly vulnerable groups are most often negatively affected, means the "patient-choice" model is easily co-opted by new public management models in which health care is a matter of private consumption rather than public good.

Nevertheless, the juxtaposition of "health" and "democracy" has introduced an important intervention by applying both normative and analytical categories developed around democratic theories within the social sciences to health care, a field with a very different ontology and series of practices. Doctor-patient relations have been traditionally hierarchical, and indeed good health care and medical research arguably rely upon a clear distinction between those roles with one party positioned as authoritative, as patients and medical practitioners rarely have equal access to medical expertise and practitioners' authority has traditionally been a cornerstone of their professional legitimacy [20,21]. To speak of that relationship as "democratic" is potentially counter-intuitive. Despite this, several journals have emerged to focus on the application of democratic concepts to health care, and in several notable cases, such as the United Kingdom's National Health Service [22], "democracy" has been adopted as the central principle of best practice in relations between health care practitioners and patients. "Health democracy" fosters both a fertile academic debate and policy developments.

Much of the policy discussion can, at least at first, be understood within a broader neoliberalization of health care based around the notion of new public management with patients as the "users" or "customers," around which the economics of hospitals and medical research should orbit [23]. That connection may explain some of the initial drive for linking "democracy" to health care, by fostering a market model, and certainly much of the skepticism from those opposed to such a model [24]. That said, it is important to deconstruct the debate in order to identify those approaches that are of value. Since the late 1990s, there has been a paradigm shift within many Western countries, in which the authority of health care practitioners has been challenged by a series of "patient-centered" approaches [25-28]. There has been greater focus on designing health care provision as a series of choices from which the patient should choose, mirroring similar developments seen in the public sector within many Western states since the 1990s. Patient choice provided an important part of the mechanism through which this new form of accountancy was made possible, ensuring that there would be "consumers" able to redistribute finance along market principles. Choice-driven health care is based upon a simple (and not unproblematic) representative model of democracy, and the ability of patients to choose between multiple options of treatment is analogous to electoral rights [29].

However, where health democracy goes further than electoral democracy is its focus on the importance of informed consent, in which patients must be made aware with accessible information on their condition and the available options and likely outcomes [30]. Discussion has moved beyond analogies with electoral democracy to more substantive forms of democracy that acknowledge the need to not only ask the "public" but also facilitate dialogue that creates a subject able to act democratically, with awareness of their political being [31]. As such, in a critical response to the market-based approach, there has been growing attention to what can be learnt from deliberative models of democracy in the Habermasian tradition [30]. If "health democracy" is understood as following a deliberative model, a "good" health care system is one that incorporates whatever is needed to facilitate a dialogue in which patients and health care practitioners (eg, doctors) discuss openly such that each may understand the other's perspective toward reaching a position where each feels having been heard [32].

The key intervention of a deliberative approach to democratic thought is that the individual who is to vote, for example, is treated not as someone already able to act democratically, but, rather, as someone who has to be made as such via a process that goes beyond the vote itself. For democracy to function effectively, there is a requirement of access to open media, as well as education, and other institutions necessary for maintaining the minimum engagement required for effective deliberation. For health democracy, this can be read in the same way, with a good health care system requiring not only that the patient's views be heard, but also that the system be designed so as to ensure the patient can fulfill that role. This requires education and support for patients and their relatives to be "democratically" active, which are sensitive to the wider societal issues structuring their existing understanding of and access to health care. In recent years, this has included a new focus on posttreatment care to assist emotional and physical support, and counselling, as well as a better understand of the role of a patient's family and social network in recovery [33,34]. Consequently, health democracy leads to a much more pervasive, complex, and richer model of health care in terms of practice, but with implications for medical research and public health reform [35].

Given, however, that health democracy requires a rethinking of how to not only design but also evaluate health care systems, what are the drivers behind its development? As mentioned earlier, a simple choice-based model of democracy fits health care after 1980, as new public management market-based models spread across the public sector. The rhetoric around patient choice, as well as closer direct involvement of patients in their health care, has featured prominently within political speeches and printed materials, suggesting that health democracy has a legitimating function within many contemporary societies [36]. Where patient groups have responded in turn by calling for enhanced patient choice, there is also a belief (whether true or not) that health democracy improves the quality of health care. It can be speculated that listening to patients' diverse needs opens the health care system to a wider set of opinions and

experiences among the studied group, making it easier to design optimal policies. Recent research on patient-public involvement within medical research indicates that there is much to be gained for all parties concerned if, for example, cancer patients and their families are able to meet with medical researchers and health policy makers to deliberate priorities [17,37]. These types of engagements are sometimes described as "coproduction," a term developed within design studies and found increasingly in the social sciences [38]. In brief, coproduction requires engagement among private individuals, community associations, public service providers, and potentially private businesses for collaboratively deciding over funding priorities for usually public good. It is seen as a way to re-engage different actors within a broader maintenance of democratic society that counters a decline in public support for electoral democracy. Yet, beyond that normative goal, the project to combine a multiplicity of perspectives is driven also by a desire to promote environmental sustainability, viewing ecological damage as a product of exclusion where communities negatively affected by, for example, pollution are not able to influence decisions. Inclusion of those marginalized voices has the potential to not only aid those individuals [39], but also enhance the overall society by creating a check on unsustainable practices.

Consequently, health democracy places health care in its societal context, opening up the question of health care's role in society. In addition to curing illness and enhancing health well-being, health care is one of the main ways in which individuals experience being part of an organized society. This is most acute in the case of marginalized communities whom may otherwise feel disenfranchised from the wider community. The "democratic" element of health care draws attention to the "everyday" experience of being in a society. First, health care and medical research are shaped by basic questions around inclusion and exclusion. There are several questions. Who is given what level of health care and which genomes and populations, as well as conditions, are considered within medical research? Moreover, how does population health vary across groups? Furthermore, who is given access to the resources necessary to be an informed patient? Second, a key challenge for deliberative debates is whether they can ever escape the power relations that structure how humans interact, whether understood along the lines of gender, race, and wealth, or other lines. Health care and medical research take place within power structures. Health democracy requires identifying those power relations. Finally, health democracy also points to the role of health care, public health, and medical research in empowering individuals to engage in society. It is well-established that in addiction and other lifestyle disorders, such as morbid obesity, patient self-empowerment greatly enhances the efficacy of treatment [40]. Democratic models that help better operationalize empowerment and how it might be best achieved have great potential to enhance health care.

Political science has traditionally studied democracy with respect to the decision-making institutions governing nation states, primarily focusing on electoral systems and the maintenance of civil rights. Health democracy's turn toward questions of participation and deliberation, particularly in medical research, challenge an institutionalist model. For that reason, the project draws upon postinstitutionalist models that emphasize the importance of so-called "everyday" practices in which politics takes place. "Everyday" here is meant to mark out the banal largely ignored spheres of social life in which individuals interact and yet, as in the work of scholars like Davina Cooper [41], provide a microcosm in which the foundations of society are both maintained and contested on a frequent basis. Everyday practices matter not only in producing particular public goals but also as a means to socialize and engage individuals within democratic society. We developed the term "everyday democracy," drawing upon that perspective as well as others [42], in the context of precision health as a means to put health care and medical research in their social context. This enables us to better understand not just how health care and medical research impact society, but also how the role of health care and medical research in society may be used to enable precision health through everyday forms of democracy within health practices. There is also growing evidence that equity within the provision of social services, more generally, is essential to maintain a stable democracy [43].

Results

Health Inequity for Marginalized Migrants and Democratic Weaknesses

The Precision Health and Everyday Democracy (PHED) project has been funded from January 1, 2019, for 3 years, but with a 1-year extension owing to COVID-19 travel restrictions (it will run until December 2022). It has so far included a workshop at the University of Texas Medical Branch (Galveston) in April 2019, an international conference cohosted by Lund and Malmö Universities in October 2019, a large 14,3 MEUR application to the EU Horizon 2020 for a project on migrant health care during Spring 2020, and a commission in fall/autumn 2020 with oral and written submissions on the future of health care after COVID-19.

The project is grounded in an empirical focus initially developed through prior study of how marginalized groups are often excluded from health care, specifically, marginalized migrants living in the Skåne region of Sweden.

Earlier research through a research platform, in which several of our network participants are involved (MILSA), has already shown several results regarding the health and well-being of marginalized migrants. A research project within the MILSA platform studied marginalized migrants during 2015 and 2016, who were participating in the establishment process. The investigation showed that migrants self-reported good health, as well as a strong belief that they were able to influence their own health and low use of medications. The most common health problems were mental ill health, allergies, high blood pressure, asthma, diabetes, headaches, stomach pain, muscle pain, and deficient eyesight [3]. The lifestyle factors that could be seen as risk factors for this group of migrants were overweight, obesity, smoking, and physical inactivity. Almost 60% of the respondents have experienced serious threats of violence during the last 12 months preceding their arrival in Sweden, and one-fifth had been exposed to physical violence. The migrants had low confidence in the health care system and

the interpreters in Sweden [3]. We have also seen that crowded living increased the odds for recently arrived migrants having mental ill health, but after adjustments were made for stability of housing conditions, the odds decreased [4]. We have also investigated migrants' experiences of health care services after arrival in Sweden, and both qualitative and quantitative data revealed that migrants had difficulty obtaining the care they sought and experienced dissatisfaction regarding health care [10]. The reasons mentioned for not being able to get health care when needed were cost, long wait times, and language difficulties. Some mentioned having been denied care owing to asylum status and being lost within the referral system and care among different health care settings regarding, for example, diabetes [10]. As mentioned, recently arrived migrants had health and social challenges, and it could be discussed what kind of support and help health professionals need concerning this work within the health care system. Dzur lifts the importance of democratic professionalism and mentions that task sharing within different sites of professional authority could have a core element of democracy [44]. Task sharing could encourage capabilities, interests, and norms of behavior needed for a functioning democracy [44]. This could be a relevant way of introducing democratic perspectives within health care and therefore could support and help health professionals in their engagement for recently arrived migrants.

Scoping Review

A scoping review was conducted by Mangrio and Sjögren Forss [45] with the aim to compile research about the experiences that refugees worldwide have with the health care system in their respective host countries. The scoping review concluded that communication and information are important factors regarding the experiences that refugees have with health care. For example, in a Canadian study by Chen et al [46], some participants felt insufficient or impersonal communication. In a study by Shannon et al from the United States [47], many participants did not feel comfortable starting a conversation about their war trauma, but would most likely have responded if the doctor initiated the discussion. Two-thirds of the participants were never asked by a doctor about the political conflict in their country or how this may have affected them. In addition, more information needs to be provided about the participants' health care rights as asylum seekers [48], about their disease [49], and about the delivery room experience, for example, pain medication, why prenatal visits are important, use of interpretation services at the hospital, and what they can expect from the hospital staff [50].

In a Scottish study by O`Donnell et al [51], the results showed that asylum seekers were supposed to receive written information from the health board telling them how to register with a general practitioner, but some did not get this information. Redman et al [52] showed that only nine out of the 30 informants had received information about the free National Health Service and that they wished for even more information about this service. In the Swedish study by Wångdahl et al [53], the results showed that a considerable portion of the informants felt that they received little health care information during the examination and that the quality of communication was low. At least 30% of the informants did not understand what they were being told. Refugees with inadequate health literacy had felt to a lower extent that they received enough health care information and more commonly experienced not receiving any help with health problems.

Regarding the understanding of language during health care visits, Asgary et al [54] mentioned that informants pointed out that there was a lack of interpretation and that they experienced difficulties finding interpreters and were having problems communicating with health professionals. The findings from the report by Bhatia et al [55] confirm those from the report by Asgary et al [54], as the informants in this study also experienced language barrier difficulties and difficulties in obtaining a translator. It was also mentioned that sometimes appointments with doctors had to be rescheduled because no translator showed up. Only those refugees who were accompanied by a relative, friend, or refugee agency staff member could undergo a trouble-free registration process. Cheng et al [56] found that it was difficult for refugees to make appointments because of low proficiency in the English language and that because of the language problem, they preferred verbal reminders over written reminders.

Regarding satisfaction with the health care service among migrants, a Canadian study by Donnelly et al [57] mentioned that many of the participants believed that their health care provider did not spend enough time with them. Consequently, they felt disappointed, and there was distrust in the health care system. In an American study by Asgary et al [54], the authors could see that experiences varied among the participants regarding health care in the United States and that asylum seekers had fear of deportation, detention, and loss of legal status.

Discussion

Approach

Marginalized migrants represent an extreme case by which to illustrate health inequity and its wider social and economic consequences. The social exclusions identified in the MILSA project go beyond a concern for the affected individuals since they evidence a degree of segregation in Swedish society, where a high portion of the population, as well as information on their health, risks falling outside the national model for health promotion in the country. The enhancement of precision health requires that such exclusions are ameliorated, meaning increasing access, as well as participation and engagement from a diverse society within Swedish health care and medical research. There is a need to better understand the environmental and genomics data from the full population, including marginalized migrants. Calls for coproduction in health policy and medical research mean not only engaging otherwise often excluded populations, but also considering where they require a focus on sustainability. The ill health of marginalized migrants concerns not just those vulnerable individuals, but has to be seen as a threat to the health security of the broader society. That point has, of course, been well demonstrated during the COVID-19 pandemic, where societies unable to protect their most vulnerable residents, whether granted legal status or not, have had great challenges in controlling the spread of the virus.

Drawing on coproduction, PHED's transdisciplinary approach means building links across not only academic disciplines, but also professional fields. PHED is engaged therefore with both health care practitioners, such as health clinics, as well as civil society groups (eg, refugee rights organizations) and pharmaceutical firms. While such partners are likely to sometimes have conflicting interests, we consider identifying and working through these tensions as essential to the success of the project as they are part of the structure including and excluding different populations. Pharmaceutical firms that are for profit are easily vilified, and while it is important not to be naïve of their interests, it is necessary to first compare diverse positions and highlight tensions so we can move closer to producing shared knowledge that benefits all sides.

Our consortium therefore seeks to address an urgent challenge to society, namely the requirement to better understand how health practitioners and policy makers can better interact with an increasingly diverse population, as well as to remedy long-standing health inequalities that follow wider societal cleavages and forms of marginalization. To achieve that goal, the proposed multinational and transdisciplinary consortium is intended to internationalize the development of (1) precision health care tools that are sensitive to the needs of a varied population; (2) political science research to identify the social exclusions that undermine precision health care and explore the options for ensuring medical practitioners are better equipped to listen and acknowledge variation among the individuals they treat, using democratic theories; and (3) educational modules (including policy guidance) associated with these research topics. In the long-term perspective, our innovative program is likely to increase the equality of precision health care in Sweden, as well as promote the integration and education of new citizens, followed by an improvement in health equity with additional benefits for Sweden and other regions.

Time Span and Consortium

The project spans 3 years (2019 through 2021) and brings together scholar scientists and students from five different institutions, the pharmaceutical industry, nonprofit agencies, and three nations. To meet important societal challenges, Lund (coordinator) and Malmö Universities in Sweden will establish an international research and educational consortium characterized by collaborations across the borders of medical, social, political, and biological disciplines. Seed finance has been provided by the Swedish Foundation for International Cooperation in Research and Higher Education (STINT–Stiftelsen för internationalisering av högre utbildning och forskning) to establish the international consortium's research and education. Within the existing finance, we will not collect new data, and all data collection thus far has been via prior projects that have received ethical approval. Within the consortium, we are targeting a series of core and applied research funds in Sweden and internationally to develop a range of projects that fit within the broad remit of PHED and engage health care and medical research practitioners.

Planned Activities

We are planning to collaborate with researchers from Brazil and the United States through research, workshops, and conferences, and through this collaboration, we plan to strengthen existing relationships and establish new relations that can benefit Sweden's internationalization of education, research, and outreach. Brazil and the United States were chosen because of earlier collaborations between Lund University and researchers in these locations. The project is intended to be an open-ended partnership, seeking new collaborators across disciplinary divides to support the transdisciplinary approach essential to the project. We also aim to establish and identify precision health strategies as well as anchor equal access to quality health care for migrants. We will also strive to create educational models for students in methods relevant for precision health care as well as within everyday democracy. The whole project aims to provide junior colleagues (doctoral students, postdoctoral researchers, and junior faculty members) with a dynamic international environment that offers knowledge, new contacts and cultural experiences, leadership training, and career growth. The highly interdisciplinary consortium is held together by its central focus on "precision health." The concept of "everyday democracy" allows us collectively to enhance ongoing discussions over patient and public participation in health care and medical research, and to develop new insights into the banal practices through which participation can be enabled in a broader societal context.

Work in Progress

We have work currently ongoing and already completed in this research project. During autumn 2019, we arranged a workshop with the theme precision health and everyday democracy. We invited junior and senior research colleagues from the United States, Canada, India, and Europe and had different topics on the theme. We finalized the whole workshop with presentations from the health care sector and identified relevant challenges for us as researchers to focus our upcoming research on. We ended the whole consortium with a brainstorming meeting around future applications and cowriting of scientific papers. Collaboration between researchers in India, France, and Denmark and the PHED team started from this workshop and ended with an application for Horizon 2020 called PRePARe, which stands for PRogramme for marginalized migrants to Prevent Antimicrobial Resistant infections. It is an innovative and transdisciplinary project for enhanced clinical management and prevention of resistant bacterial infections. This application includes development of an app, which we suggest could enhance the health care access and information that needs to be between asylum seekers and health care professionals. Through this app development, we suggest that the contact and communication between asylum seekers and health care professionals could be improved. We as a research group took the lead in this app, and a total of eight countries were a part of this app. During the last 2 years, we have also been writing scientific papers on the management and prevention of resistant bacterial infection, on COVID-19 regarding the migrant situation health wise [58] and socially, and on migrants and the need for data security when increasing information and health care tasks are being conducted online. During fall 2020, we are having a commission online, which will be for an international audience, and the focus will be on health care access for marginalized migrants, with some focus on the recent pandemic and how this

vulnerable group was and is affected. This commission will result in an open-access published report. This and other events within PHED always provide an opportunity for new junior or senior scholars to join the network.

Conclusions

We are aware of the diversity among worldwide populations, as well as in our collaborating countries Brazil, the United States, and Sweden. We are confident that we can meet the challenges associated with different racial/ethnic groups physically, mentally, and socially. However, we need to identify tools to enable us to both prevent and treat a wide spectrum of health-related outcomes, and better understand how they are linked to social as well as environmental issues. We also need to identify and investigate health care barriers in order for the issues to be dealt with. Our international research team aims and strives toward finding tools and educational models that work to improve these mentioned areas of research. In political science, recent studies have established that democracy promotion can greatly benefit population health and well-being [59-61]. The PHED project goes further by approaching this relationship from the other way round, understanding health equity as not only a normative good but also a contributing factor to a stable and democratic society.

Acknowledgments

This article forms part of the Precision Health and Everyday Democracy (PHED) project based primarily at Lund and Malmö Universities, with support from the Malmö Institute for Studies of Migration, Diversity and Welfare. A presentation on this project was given within a series of workshops at the University of Texas Medical Branch at Galveston. We would like to thank all those who were present. This research was financed by the Swedish Foundation for International Cooperation in Research and Higher Education (STINT–Stiftelsen för internationalisering av högre utbildning och forskning).

Authors' Contributions

EM and MS had joint leading roles in writing the manuscript. CN and SZ offered methodological and scientific suggestions. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Reviewers' comments confirming approval of the project funding.
[PDF File (Adobe PDF File), 509 KB - resprot_v9i11e17324_app1.pdf]

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Abbreviations

PHED: Precision Health and Everyday Democracy

Edited by G Eysenbach; submitted 19.12.19; peer-reviewed by S Balsari, T Wang, M McKeown; comments to author 21.08.20; revised version received 15.10.20; accepted 03.11.20; published 30.11.20.

Please cite as:
Strange M, Nilsson C, Zdravkovic S, Mangrio E
The Precision Health and Everyday Democracy (PHED) Project: Protocol for a Transdisciplinary Collaboration on Health Equity and the Role of Health in Society
JMIR Res Protoc 2020;9(11):e17324
URL: http://www.researchprotocols.org/2020/11/e17324/
doi:10.2196/17324
PMID:33252352

Protocol

Long-Term Follow-Up of a Randomized Controlled Trial to Reduce Excessive Weight Gain in Infancy: Protocol for the Prevention of Overweight in Infancy (POI) Follow-Up Study at 11 Years

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Abstract

Background: The Prevention of Overweight in Infancy (POI) randomized controlled trial assessed the effect of a more conventional food, physical activity, and breastfeeding intervention, with a more novel sleep intervention on weight outcomes at 2 years of age. The trial had 58% uptake at recruitment, and retention was 86% at age 2 years, 77% at age 3.5 years, and 69% at age 5 years. Children who received the brief sleep intervention in infancy had just half the risk of obesity at 2 years of age compared to those who did not receive the sleep intervention. Importantly, this substantially reduced risk was still apparent at our follow-up at 5 years of age.

Objective: The primary aim of this follow-up at age 11 years is to determine whether differences in BMI z-score and obesity risk remain apparent now that it is at least 9 years since cessation of the sleep intervention. Several secondary outcomes of interest will also be examined including 24-hour movement patterns, mental health and wellbeing, and use of electronic media, particularly prior to sleep.

Methods: We will seek renewed consent from all 734 of the original 802 POI families who expressed interest in further involvement. Children and parent(s) will attend 2 clinics and 1 home appointment to obtain measures of anthropometry and body composition (dual-energy x-ray absorptiometry scan), 24-hour movement patterns (sleep, sedentary time, and physical activity measured using an AX3 accelerometer), mental health and wellbeing (validated questionnaires), family functioning (validated questionnaires), use of electronic media (wearable and stationary cameras, questionnaires), and diet and eating behaviors (24-hour recall, questionnaires).

Results: This follow-up study has full ethical approval from the University of Otago Human Ethics Committee (H19/109) and was funded in May 2019 by the Health Research Council of New Zealand (grant 19/346). Data collection commenced in June 2020, and first results are expected to be submitted for publication in 2022.

Conclusions: Long-term outcomes of early obesity intervention are rare. Despite the growing body of evidence linking insufficient sleep with an increased risk of obesity in children, interventions targeting improvements in sleep have been insufficiently explored. Our initial follow-up at 5 years of age suggested that an early sleep intervention may have long-term benefits for effective weight management in children. Further analysis in our now preteen population will provide much-needed evidence regarding the long-term effectiveness of sleep interventions in infancy as an obesity prevention approach.

Trial Registration: ClinicalTrials.gov NCT00892983; https://tinyurl.com/y3xepvxf

International Registered Report Identifier (IRRID): DERR1-10.2196/24968

(JMIR Res Protoc 2020;9(11):e24968) doi:10.2196/24968

KEYWORDS

infant; child; obesity; prevention; sleep; physical activity; mental wellbeing; screen time; diet

Introduction

Childhood obesity remains a serious global health challenge [1], with an estimated 38.2 million children under the age of 5 years [2] and over 340 million children and adolescents aged 5-19 years considered overweight or obese [1]. New Zealand is no exception; more than 33% of those aged 2-14 years are overweight or obese [3], with Māori (the indigenous population of New Zealand) and Pasifika children and those living in areas of greater socioeconomic need being disproportionately affected [3-5]. Obesity in childhood persists into adulthood, with risks to immediate and future health and wellbeing [6-8]. The costs of childhood obesity, including drug therapy, are high and rising yearly [9-11]. Drug therapy for obesity at any time, either in childhood or adulthood, is fraught with difficulties and often results in failure [12,13]. While genetic factors play a role in overweight and obesity, they are unlikely to explain the rapid rise in global obesity rates [14-17]. Unhealthy lifestyles, within the larger context of environmental, social, and economic forces, play a crucial role in the childhood obesity epidemic [17,18].

Despite evidence suggesting that the foundations for good health are laid down in the early years of life [19-21], until recently, relatively little attention has been paid to investigating the potential for obesity prevention in infants and toddlers [22-24]. To date, preventive approaches have largely focused on dietary intake [25-27] and physical activity [25-28]. For all their promise [29,30], initial findings from studies targeting nutrition, eating behaviors, physical activity, or sedentary behavior have been somewhat disappointing, perhaps due in part to many being underpowered or short-term [22,24,26,31-33]. However, a growing number of large randomized controlled trials (RCTs) aimed at promoting healthy eating behaviors, improving physical activity, and reducing sedentary time in infants and toddlers have also had somewhat mixed success in reducing excessive weight gain during the early years [27,34-36]. The Healthy Beginnings trial, undertaken in socioeconomically disadvantaged areas of Sydney, Australia, reported important group differences in mean BMI at the end of the intervention at 2 years of age [35]. However, these benefits had disappeared when the children were followed up at 5 years of age [37]. The Insight study, based in the United States, reported a modest reduction in BMI *z*-scores in children at the end of the 3-year intervention [36], but planned follow-up data have not been published to date. Other interventions aiming to improve infant feeding and parental feeding behaviors or physical activity and sedentary behavior have not produced significant benefits in terms of BMI, although they do report some important and relevant effects on obesity-related behaviors [34,38]. It seems that the prevention of overweight and obesity in childhood through changing dietary intake or physical activity levels at a young age is more challenging than initially anticipated [29,39-41].

Thus, other approaches require consideration [31]. One behavior receiving considerable attention more recently is the importance of good sleep for effective weight management in children. Multiple meta-analyses of observational studies have demonstrated a strong and consistent association between shorter sleep duration and increased obesity risk in children, including in the early years [42-44]. However, very few intervention trials have determined the impact of influencing sleep behavior in the first 1000 days (conception to 2 years of age) on weight outcomes in young children. The Insight intervention focused on responsive feeding and healthy dietary choices from infancy through to 3 years of age but also included messages relating to sleep [36]. Overall, the intervention was effective at reducing mean BMI z-score, but as the study involved a multicomponent intervention, the relative contribution of the sleep intervention cannot be isolated.

In 2009, we commenced the Prevention of Overweight in Infancy (POI) study, a 4-group RCT in 802 families that aimed to reduce the number of children with excessive weight gain in the first 2 years of life [45]. Women in the latter stages of pregnancy were randomized and stratified by parity and socioeconomic status, with equal probabilities to receive the following from late pregnancy through infancy: (1) Control (usual care); (2) conventional food, physical activity, and breastfeeding intervention (FAB); (3) more novel Sleep intervention; (4) Combination group (received both FAB and Sleep interventions). All participants received standard Maternity and Well Childcare [45]. Further details are available in the original study protocol and outcome papers [45-47]. No significant effect on BMI z-score was observed between intervention and usual care groups at the end of the intervention when children were 2 years of age. However, an exploratory analysis showed that children who had received the sleep intervention (including those from both the Sleep and Combination groups) had half the odds of obesity as children who did not receive the sleep intervention [47]. Given this promising effect of sleep, a follow-up study was undertaken with the cohort at 3.5 years of age and 5 years of age (just prior

to starting school). Interestingly, the benefit of the sleep intervention remained apparent at 5 years of age, despite no intervention having occurred for at least 3 years. Importantly, statistically significant differences were observed both in terms of mean BMI z-score (–0.23, 95% CI –0.38 to –0.07) and in the number of children classified as obese (relative risk 0.49, 95% CI 0.28 to 0.84) [46-48]. The reduction in both mean BMI *and* the number of children at the higher end of the BMI distribution as a result of our sleep intervention is a very important outcome from a public health perspective.

Our finding of a clinically important difference in obesity rates at 5 years of age following a brief intervention that finished many years previously clearly warrants further follow-up given the public health implications of this finding, particularly given the dearth of long-term follow-up of obesity prevention trials in children [49]. The POI children are now 11 years of age, providing an invaluable opportunity to assess the long-term effects of the initial intervention. Other variables of interest including sleep, dietary, and activity behaviors; body composition; physical and mental health and wellbeing; family functioning; and use of electronic media will also be examined, as outlined in our methods.

The primary aim of this follow-up study is to determine whether differences in BMI z-score and obesity risk remain apparent between those who did and those who did not receive early sleep intervention at least 9 years after completion of the intervention.

Secondary objectives relating to the RCT are to determine whether early sleep intervention has long-term effects on sleep, physical activity, and dietary intake; influences body composition in pre-adolescents; and impacts pre-adolescent physical and mental health and wellbeing.

Secondary objectives relating to cross-sectional and cohort analyses include associations between early 24-hour movement behaviors (sleep, sedentary time, physical activity) and subsequent body composition and bone health, whether 24-hour movement behaviors (sleep, sedentary time, physical activity) are associated with physical and mental health and wellbeing in children, and how preteens use electronic media before bed and associations with sleep and mental health and wellbeing.

Methods

Study Design and Participants

The original 4-arm POI RCT determined the impact of sleep and more conventional food and activity interventions (individually and in combination) on weight gain from birth until 2 years of age. Eligible participants were pregnant women aged 16 years or older; able to communicate in English or Te Reo Māori (the indigenous language of New Zealand); resided in Dunedin, with no plan of leaving the local area before the child's second birthday; and were booked into the Queen Mary Maternity Unit, Dunedin Hospital at 28-30 weeks' gestation, or their Lead Maternity Carer had notified the POI team of their expected home birth before 34-week gestation. Queen Mary is the main birthing unit where most births (≥97%) occur in Dunedin (the remaining 3% are home births). After birth, children born before 36.5 weeks' gestation and children with any form of congenital abnormality that could potentially affect feeding and growth were excluded from the study. Based on the inclusion and exclusion criteria, a total of 802 pregnant women took part in the original RCT [46]. Retention rates were 86% at 2 years, 77% at 3.5 years, and 69% at 5 years of age [46,47].

All participants from the original RCT, except for 68 families who had requested no further contact, will be invited for this follow-up at 11 years of age. Full ethical approval for the 11-year-old measures has been obtained from the University of Otago Human Ethics Committee (H19/109), and written informed consent will be obtained from both child and parent participants before this follow-up study commences.

Sample Size

Given the 734 families who have indicated an interest in future follow-up and the high retention rates at baseline and first follow-up measurement when the children turned 3.5 years old and 5 years old [47], we estimate that at least 500 (62%) of the original cohort will be retained in this follow-up. This number of participants will provide 80% power to detect differences in BMI z-scores of 0.23 between 2 approximately equally-sized groups of those who did and those who did not receive early sleep intervention (observed differences at 3.5 years of age and 5 years of age were 0.24 and 0.23, respectively) assuming an SD of 0.90 (estimated from data at 3.5 years of age and 5 years of age) using two-sided $P<.05$.

Data Collection

All outcome data will be collected at 3 scheduled appointments: 2 visits to our University research clinic rooms (60-90 minutes each) and 1 (15-45 minutes) home visit. At the first visit, children will be weighed and measured and undergo a dual-energy x-ray absorptiometry (iDXA) scan to assess body composition. Both the child and their parent will complete questionnaires as detailed in the following sections, and children will be fitted with an accelerometer to be worn over the following week. At the second clinic visit, a 24-hour recall will be conducted, and additional questionnaires will be completed. Researchers will visit each home during the experimental week to set up the wearable and stationary cameras and to collect a second 24-hour recall in a random subsample of children. At the end of the study, children will be given a NZ $100 gift voucher for their participation.

Outcome Measures

Overview

Outcome measures for the 11-year-old follow-up are presented in Table 1. The methods used for each measure are also highlighted [50-62]. All follow-up measurements will be carried out, as per standard protocols, by research staff who are trained and blinded to the original group allocation [50]. As our interest is in real-world effects from offering the intervention, the main analyses will be performed on a modified intention-to-treat basis (using all available data, with multiple imputation used for the primary outcome as described in later sections). The primary outcomes are BMI z-score and relative risk of obesity at 11

years of age [45,48]. Other measures described herein are related to the secondary objectives at the 11-year-old follow-up.

Table 1. Outcome measures at 11 years.

Category, method	Measure	Child (11 years old)	Parent
Anthropometry			
International Growth Reference [50]	Height, weight, BMI-for-age z score	√	N/A[a]
International Growth Reference [50]	BMI	√	N/A
Calculated BMI z-score ≥85th but ≤95th percentile	Prevalence of overweight	√	N/A
BMI z-score ≥95th percentile [50]	Prevalence of obesity	√	N/A
Blood pressure (BP)			
Automated BP Monitor (Omron)	Systolic and diastolic BP	√	N/A
Body composition and bone health			
DXA[b] scan	Body fat (g)	√	N/A
DXA scan	Lean mass (g)	√	N/A
DXA scan	Bone mass (g)	√	N/A
DXA scan	Bone mineral content (g/cm^2)	√	N/A
Mental health and wellbeing			
Strengths and Difficulties Questionnaire (SDQ) [51]	Emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, prosocial, behavior problems	√	√
Child Health Utility 9D instrument [52,53]	Health-related quality of life	√	N/A
The WHO[c]-5 Well-Being Index [54]	Current mental wellbeing	√	N/A
Family functioning			
McMaster Family Assessment Device (FAD) 12-item General Functioning Scale [55]	General functioning	N/A	√
Sleep			
AX3 accelerometer	Sleep timing, duration, and awakenings	√	N/A
Adolescent Sleep Hygiene Scale [61]	Sleep hygiene	√	N/A
PROMIS[d] Pediatric Sleep Disturbance [62]	Sleep disturbances	√	√
PROMIS Pediatric Sleep Impairment [62]	Sleep problems	√	√
Physical activity and sedentary behavior			
AX3 accelerometer	Physical activity and sedentary behavior	√	N/A
Dietary intake			
24-hour dietary recall [56]	Food and nutrient intake	√	N/A
Camera (food images)	Food and nutrient intake	N/A	√
Child Eating Behavior Questionnaire [57]	Eating behaviors	N/A	√
Screen time			
Bedtime and electronic devices recall	Pre-bed and in-bed screen use	√	N/A
Wearable and bedroom camera	Pre-bed and in-bed screen use	√	N/A
Youth Activity Profile [58]	Total daily screen use	N/A	√
Economic analyses			
BMI z-score at 2, 3.5, 5, and 11 years of age	Retrospective cost-effectiveness analysis	N/A	N/A
BMI z-score at 2, 3.5, 5, and 11 years of age	Incremental cost-effectiveness ratios	N/A	N/A
Child Health Utility 9D instrument [52,53]	Numbers and percentages	N/A	N/A

[a]N/A: not applicable.

[b]DXA: dual-energy x-ray absorptiometry.

[c]WHO: World Health Organization.

[d]PROMIS: Patient-Reported Outcomes Measurement Information System.

Anthropometry

All anthropometric measurements will be conducted following standard protocols by trained measurers [50]. Weight in kilograms will be obtained with children wearing light clothing using regularly calibrated electronic weight scales (Wedderburn WM206). Height (cm) will be measured using a wall-mounted Harpenden Stadiometer (Holtain Ltd, Crymych, United Kingdom). Both measurements will be obtained in duplicate, with a third measurement undertaken if duplicate measures are not within 0.1 kg for weight and 0.5 cm for height [45]. Where 3 measurements are recorded, the mean of the 2 closest values will be used; if all 3 measurements are equally spaced, the overall mean (or, equivalent, the median) will be used. BMI z-scores will be calculated using the World Health Organization growth reference for 5-19 years, with overweight defined as a BMI z-score ≥85th percentile but <95th percentile and obesity defined as ≥95th percentile [50].

Sleep, Physical Activity, and Sedentary Time

A single AX3 accelerometer (Axivity, Newcastle, UK) [59] will be used to measure 24-hour movement patterns (sleep, physical activity, sedentary time) [60] over 1 week. The accelerometer will be worn on the nondominant wrist (flexible wrist strap) 24 hours a day for 7 days including during showering, bathing, swimming, and other water-based activities. Children will complete the Adolescent Sleep Hygiene Scale [61] and the pediatric version of the 8-item Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Sleep Disturbance and 8-item Sleep-Related Impairment questionnaires [62]. The Adolescent Sleep Hygiene Scale has good reliability with high internal consistency (Cronbach α of .84 in children of a similar age group as our study) [63]. Parents will also complete the proxy versions of the PROMIS questionnaires. These questionnaires provide a subjective assessment of difficulties with falling asleep and staying asleep, as well as daytime sleepiness in children, and the impact on functioning [62]. The PROMIS Pediatric Sleep Disturbance and Sleep-Related Impairment questionnaires have reliabilities of 0.91 and 0.88 respectively in children aged 8-17 years [64]. Children will self-complete 6 questions from the Youth Activity Profile [58], a self-report tool designed to assess physical activity and sedentary behavior in youth.

Dietary Intake and Eating Behavior

Dietary intake will be assessed using a multiple-pass 24-hour recall similar to the National Health and Nutrition Examination Survey multiple-pass method [56] but administered in person and supplemented with digital camera images of food taken before each eating occasion. The multiple-pass method entails a structured interview with the child to recall all food and drink consumed over the previous day (from midnight to midnight). A quick list of all foods and beverages consumed in the previous day is obtained (first pass). Additional information on the time and place of eating, along with camera images of food taken before meals, will be used to help aid recall (second pass). Comprehensive information regarding each food and drink item is collected including brand name; recipe, if known; and portion size (third pass). To assist this process, a variety of aids will be used to help participants report portion size including measuring cups, spoons, portion charts, and images of common food and beverage brands on an online shopping website from a major supermarket chain [65]. In addition, a list of typically forgotten foods will be presented. Finally, the 24-hour dietary recall will be reviewed with the child, and any additional food item(s) recalled will be added to the recall list (fourth pass). Recall data will be collected across all days of the week in the total sample, aiming for an approximately equal number of participants for each day of the week. A second recall will be collected on a different day of the week in a random sample of 50 participants in order to estimate "usual" intake using the Multiple Source Method, which enables estimates of usual dietary intake using data from multiple 24-hour recalls. The parent-report 35-item Child Eating Behavior Questionnaire [57] will be used as a subjective measure of eating style in children. The Child Eating Behavior Questionnaire has good internal consistency and reliability for food responsiveness (α=.83), emotional overeating (α=.70), and satiety responsiveness (α=.84). The questionnaire assesses eating style across 8 scales, namely food responsiveness, enjoyment of food, emotional overeating, desire to drink, satiety responsiveness, slowness in eating, emotional undereating, and food fussiness.

Body Composition, Bone Health, and Blood Pressure

Body composition and bone health will be assessed by DXA (Lunar iDXA; GE Healthcare, Madison, WI), performed and analyzed by one experienced operator with Lunar enCORE software version 18.0. This is the most advanced DXA system with a high degree of clarity, precision, and image resolution. The Lunar iDXA will determine the total body fat mass (kg) and the fat content of specific anatomical regions including trunk and extremity fat (these are automatic default regions) and central and peripheral fat (manual regions of interest) [66,67]. The percent coefficient of variation (%CV) for repeated in vivo scans on 10 adults from our laboratory is 1.3% for fat mass, 0.9% for lean mass, 1.8% for fat percentage, and 1% for total body bone mineral density. Blood pressure (BP) will be assessed using OMRON HEM-7211 upper arm BP monitors (Omron Healthcare Inc, Kyoto, Japan). These monitors are clinically proven to be accurate and validated within ±3 mm Hg for both systolic and diastolic BP readings in children (3-12 years old) and the adult population. Three readings will be obtained, with a fourth measurement taken if there is a difference of more than 10 mm Hg between the second and third systolic measurements. The mean of the second and third or 2 closest BP readings will be used. Following clinical practice guidelines for the screening of high BP in children and adolescents, readings higher than 100-119 mm Hg for systolic and 65-76 mm Hg for diastolic will be categorized as high [68,69].

Wellbeing and Family Functioning

Mental health, wellbeing, and family functioning will be assessed using several validated questionnaires. To assess wellbeing, both the child and parent will complete the 25-item

Strength and Difficulties Questionnaire [51]. This is a standardized measure of overall emotional and behavioral wellbeing in children and young people with subscales of emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior [51]. The internal consistency and reliability of the Strength and Difficulties Questionnaire in adolescents aged 11-17 years and their parents is 0.70 [70]. Children will also complete the Child Health Utility 9D instrument [52,53], a pediatric generic preference-based measure of health-related quality of life, consisting of 9 dimensions with 5 levels in each [52,53]. In youth aged 8-12 years and 13-17 years, the Child Health Utility 9D instrument has a Cronbach α score of .77 and an intraclass correlation coefficient of .65 [71]. The World Health Organization WHO-5 Well-Being Index [53], a brief 5-item measure of current mental wellbeing for children aged 9 years and older, will also be completed by the child. Parents will complete the 12-item General Functioning Subscale of the McMaster Family Assessment Device [55] to assess family functioning. This is a validated single-index measure of the overall level of family functioning in areas of problem solving, behavior control, communication, roles, affective responsiveness, affective involvement, and general family functioning [55], giving insight into the relationships between parental efficacy, warmth, family rules, and the outcomes of interest (both obesity and mental health) [55]. The 12-item General Functioning Subscale has a good Cronbach α score of .86 with parents of children aged 4-16 years old.

Screen Time

Total daily screen use will be assessed using 6 questions from the Youth Activity Profile [58] completed by the children. We are also interested in the impact of electronic media before sleep — both in the hours before bed and once in bed. Due to the inherent difficulties in obtaining an accurate assessment of screen use in children, we will use an objective-driven approach to measure both pre-bed and in-bed screen use using wearable and stationary video cameras (PatrolEyes SC-DV7 Ultra 1296p Body Camera with Night Vision). One camera will be worn by the child via a chest harness (facing outwards so directly observes screen use) from 5 pm until bedtime in the home environment on a single night. The second infrared camera will be placed on a tripod in the room where the child sleeps and will capture screen use from 30 minutes before bedtime until the child gets out of bed in the morning. Objective data from the PatrolEyes camera with Night Vision will be used to measure screen device use throughout the night. Extensive guidelines are discussed with families to ensure that ethical obligations are met, including those that center around privacy issues [72]. We have also developed a new brief Bedtime and Electronic Devices recall to assess screen use both before bed and once in bed. Children will complete this recall about screen-based activities on the night before, on 2 days, including the day after the cameras. We will use data from a similar population of Dunedin children collected as part of a separate but associated study (Bedtime and Electronic Devices study, n=85 children aged 10.0-14.9 years with 4 days of camera data and 7 days of recall data) to determine whether reactivity to the camera (change in behavior from knowing the camera is present) has occurred.

Economic Analyses

Cost-effectiveness analysis will be conducted at the child level and based on intention-to-treat. The incremental cost per BMI z-score reduction for the Sleep intervention and the Combination (FAB and Sleep) groups will be compared to usual care (Control group). Costs will include the cost of delivering the Sleep and Combination interventions (eg, training of nurses, antenatal sessions, home visits, additional support, and written resources) and health care costs (eg, hospital, pharmaceutical, and general practitioner costs). Bootstrapping will be used to generate cost-effectiveness acceptability curves that estimate the probability the Sleep and Combination interventions are cost-effective for a range of willingness-to-pay thresholds. A health funder perspective will be reported for the analysis.

Statistical Analyses

Based on results from earlier phases [46,47], the primary analysis will compare BMI z-scores between those receiving the Sleep intervention and those not (after checking for evidence of interaction between the Sleep and FAB interventions, these interactions were $P \geq .261$ for 3.5 years and 5 years). In the absence of such interactions, as with ages 3.5 years and 5 years [47], multiple imputation using chained equations will be used and BMI z-score compared between the 2 groups using linear regression adjusting for stratification variables and the FAB intervention. Models will also examine secondary outcomes including overweight and obesity, estimating relative risks using Poisson regression with robust standard errors. Internal consistency will be assessed for all scales using Cronbach α with values ≥.80 considered to be at least good and values .70-.79 considered acceptable. For continuous outcomes where the assumptions required for linear regression cannot be satisfied, even after investigating natural logarithmic transformations, we will use quantile regression to model medians. If evidence of an interaction between the 2 interventions (Sleep and FAB) is present at this age, the interaction term will be retained, and otherwise identical 4-group comparisons will be presented instead. Standard model diagnostics will be used. Analyses will be conducted using Stata 16.1 and/or R 4.0.2 (or later versions), and 2-sided $P<.05$ will be considered statistically significant. As noted earlier, multiple imputation with chained equations will be used to accommodate missing-at-random data for BMI using the same auxiliary variables and parameters as previously [47]. While it is possible that informative missing data mechanisms exist, for example less enthusiasm to participate for children with very high BMIs, it would be surprising if such effects differed by their intervention group 9 years later. As was the case with our age 3.5 years and 5 years analyses [47], we will impute separately by intervention group and consider informative missingness mechanisms through exploring plausible scenarios adjusting imputed values in order to assess the robustness of our findings.

Results

This follow-up study has full ethical approval from the University of Otago Human Ethics Committee (H19/109) and

was funded in May 2019 by the Health Research Council of New Zealand (grant 19/346). Data collection commenced in June 2020, and first results are expected to be submitted for publication in 2022. Data collection will only take place while New Zealand is in Alert Levels 1 or 2 (physical distancing and appropriate hygiene recommendations) during the COVID-19 pandemic. The Otago region in New Zealand, where all data collection will take place, has been in Level 1 for all but 7 weeks of 2020 as overall case numbers in New Zealand remain extremely low (<2000 in a population of more than 5 million). As daily life is essentially normal in Level 1 with the exception of closed international borders, we feel confident that the pandemic will have relatively little effect on our data.

Discussion

Although long-term follow-up of early life interventions for preventing childhood overweight and obesity is crucial in order to understand the health and economic benefits of differing approaches [49,73-75], few such analyses exist [49]. Most follow-ups to date are relatively short-term, all less than 5 years in duration (and many considerably less than this) [22,31,37], making it necessary to infer longer-term outcomes. Given the earlier promising results of our sleep intervention [46] and the paucity of obesity interventions reporting long-term outcomes [49], it is timely to undertake this follow-up, which is at least 9 years post-intervention. Our POI study also provides the opportunity to examine multiple influences on sleep and weight that are important during childhood, utilizing objective measures (7-day accelerometry and time-stamped cameras) to assess 24-hour movement patterns. Combined with the use of other novel measures to assess the use of electronic media prior to sleep, our analyses should also provide much-needed objective information about screen and sleep behaviors that can be difficult to measure accurately in children. Previous studies have shown that children's sleep is particularly vulnerable to screen use [76,77], yet there is a dearth of objective data in this area (both screens and sleep), especially the critical information concerning pre-bedtime screen use. There is a clear need for a longer-term follow-up of early life obesity prevention approaches to inform effective risk reduction models [49,74,75]. This study aims to provide insight into the potential benefits of early sleep intervention for health and wellbeing in pre-adolescent children, providing a prevention strategy that could contribute to a new narrative about childhood obesity prevention.

Acknowledgments

This study is supported by the Health Research Council of New Zealand (19/346). RT is supported by a Fellowship from the Karitane Products Society. TA is supported by the Lady King PhD Scholarship from the University of Otago, and BB is supported by a Department of Medicine PhD Scholarship from the University of Otago. The Health Research Council and other funding sources (Karitane Products Society, Lady King PhD Scholarship, and Department of Medicine PhD Scholarship) had no role in study design, writing of the protocol manuscript, and in the decision to submit the manuscript for publication.

Authors' Contributions

RT and BT are the co-principal investigators of the POI study. RT, BT, AG, BG, A-LH, SF, KM-J, and TS designed the follow-up project and applied for funding. TA and RT produced the first and subsequent drafts of the manuscript. AG advised on study design, sample size analysis, and statistical design. DM is the project coordinator. DM and TA developed the study data collection protocols, and BB developed the bedtime camera protocols. KM-J planned all accelerometry and DXA analyses. All authors made an important intellectual contribution to the manuscript, and all have read and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from Health Research Council New Zealand.
[PDF File (Adobe PDF File), 485 KB - resprot_v9i11e24968_app1.pdf]

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Abbreviations

BP: blood pressure
DXA: dual-energy x-ray absorptiometry
FAB: food, physical activity, and breastfeeding
FAD: McMaster Family Assessment Device
POI: Prevention of Overweight in Infancy
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial
SDQ: Strength and Difficulties Questionnaire
WHO: World Health Organization

Edited by F Drozd; submitted 14.10.20; peer-reviewed by B Falkner; comments to author 16.10.20; revised version received 20.10.20; accepted 03.11.20; published 30.11.20.

Please cite as:
Adebowale TO, Taylor BJ, Gray AR, Galland BC, Heath ALM, Fortune S, Meredith-Jones KA, Sullivan T, McIntosh D, Brosnan B, Taylor RW
Long-Term Follow-Up of a Randomized Controlled Trial to Reduce Excessive Weight Gain in Infancy: Protocol for the Prevention of Overweight in Infancy (POI) Follow-Up Study at 11 Years
JMIR Res Protoc 2020;9(11):e24968
URL: http://www.researchprotocols.org/2020/11/e24968/
doi:10.2196/24968
PMID:33252344

Protocol

Sedentariness and Back Health in Western Cape Primary School Students: Protocol for a Pragmatic Stepped-Wedge Feasibility Randomized Controlled Trial

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Abstract

Background: Despite growing evidence of deleterious health outcomes associated with sedentary behavior, prolonged static sitting in classrooms remains ubiquitous in primary schools. Sedentary behavior is associated with the development of cardio-metabolic conditions and poor back health. Preventative strategies to reduce sedentary behavior and its negative health effects may be required in a resource-constrained environment such as South Africa.

Objective: The primary objective of this study is to assess the feasibility of conducting a full trial to evaluate the effects of a multifaceted intervention comprising novel multifunctional classroom furniture and a video-based curriculum versus usual care on sedentary behavior among students aged 10-11 years in primary schools. The secondary objective is to assess the preliminary effects of the intervention on sedentary behavior and postural dynamism.

Methods: Eighty grade 5 or 6 students, aged 10 and 11 years, in mixed-gender schools within the Western Cape metropolitan urban area in Cape Town, South Africa are eligible to participate in this pilot cluster stepped-wedge trial design with classroom as the unit of randomization. Data will be collected at the schools. The intervention will comprise multifunctional classroom furniture that allows for sitting and standing as well as a video-based curriculum on sedentary behavior. Usual practice is the absence of the intervention. The primary outcomes assessed will be (1) adherence to the intervention and (2) project pragmatics. The secondary outcomes will be (1) sedentariness measured using activPAL3 microsensors and (2) postural dynamism measured using Noraxon Myomotion inertial measurement units. We randomized the school to the first or second start of the intervention. This is an open-label trial and therefore blinding will not be possible for any group. Descriptive analysis of the feasibility and physiological outcomes will be presented. We will report the preliminary estimates of the effects of the intervention on sedentariness and postural dynamism using the mean difference and 95% CI.

Results: At the time of submission, two classrooms have been recruited into the study. Baseline physical activity and postural dynamism data have been collected from 10 participants from each class.

Conclusions: The results of this feasibility stepped-wedge cluster randomized controlled trial will be useful in informing the design of the main trial to assess whether this multifaceted intervention of multifunctional classroom furniture that allows for

sitting and standing as well as a video-based curriculum versus usual care has any effect on sedentary behavior in low-resource-setting primary schools.

Trial Registration: Pan African Trials Registry PACTR201811799476016; https://tinyurl.com/y4upoys8

International Registered Report Identifier (IRRID): RR1-10.2196/18522

(JMIR Res Protoc 2020;9(11):e18522) doi:10.2196/18522

KEYWORDS

sitting; standing; postural dynamism; sit-stand desks; classroom; school; sedentary; children

Introduction

Background

A lifestyle of sedentary behavior may result in the development of noncommunicable conditions such as metabolic syndrome [1] and poor back health [2]. Metabolic syndrome represents a range of interrelated disorders comprising abdominal obesity, raised blood pressure, dyslipidemia, and hyperglycemia [1]. Even when the guidelines for physical activity are met, sedentariness remains an independent risk factor for the development of noncommunicable diseases (NCDs) [3].

The school environment typically requires students to remain seated for prolonged periods of time, thus encouraging sedentary behavior [4]. Prolonged periods of sitting with accentuated thoracic kyphosis reduces and even reverses the natural, protective spinal curvature [5]. Although the etiology of back pain is multifactorial, poor postural alignment and reduced postural dynamism (number and extent of body movements while sitting) are common risk factors of back pain [6-9]. Static sitting may place an excessive physiological load on the spinal structures, leading to accumulative microdamage and consequent pain [10]. Dynamic posture reduces the accumulated damage from prolonged periods of sitting by breaking up the sitting periods into smaller epochs, which may help to reduce back pain [11] owing to a reduction in accumulated intervertebral disc compression [12]. Therefore, modifying the design of school furniture to optimize postural alignment and dynamism during sitting and increasing sit-stand transitions may address the potential health risks caused by prolonged sitting in the school environment. However, most of the research aimed at testing the efficacy of dynamic classroom furniture to increase classroom physical activity has been conducted in high-income settings [11,13-24]. Moreover, there is a paucity of studies regarding the effectiveness of classroom furniture in reducing classroom sedentariness and promoting back health, especially for low-to-middle income countries (LMICs). Currently, no back health intervention studies have examined an association with sedentary behavior, despite its recognition as an important risk factor. Furthermore, the majority of studies have implemented unimodal interventions to address either back pain or NCDs separately. Designing health programs that address more than one health problem is preferable in LMICs where health budgets are constrained. To our knowledge, no studies have addressed sedentariness by assessing the effect of a multimodal approach aimed at reducing sedentariness and promoting back health.

Prior to embarking on a large, definitive trial to assess a multimodal intervention aimed at reducing classroom sedentariness, an imperative first step is conducting a feasibility study [25]. Feasibility studies provide information on whether an intervention is contextually viable [26]. Therefore, the primary aim of this project is to assess the feasibility of conducting a multimodal, contextualized classroom-based intervention aimed at reducing sedentariness in primary school students. The secondary project aim is to yield preliminary data on the effect of the intervention on physiological outcomes of interest, namely physical activity and postural dynamism.

Study Aims and Objectives

Primary Objectives

Adherence and project pragmatics are the two primary feasibility outcomes of interest in this study. Adherence to the intervention refers to the extent to which students and teachers comply with the novel furniture and utilize the health education video curriculum. The pragmatics refer to effectively capturing physical activity and postural dynamism data with activPAL microsensors (PAL Technologies, Glasgow, UK) and Noraxon Myomotion (Noraxon, Scottsdale, USA) inertial measurement units (IMUs), respectively. Several pragmatic factors have been identified that could threaten data loss, such as electromagnetic interference from classroom furniture and building infrastructure, Wi-Fi frequency traffic from wireless-enabled devices in close proximity, and IMU sensor battery performance during multiple days of capturing prolonged trials in excess of 1 hour. To our knowledge, activPAL sensors have not previously been used to measure physical activity in this population in South Africa. This study therefore provides the first opportunity to appraise acceptability of using this technology.

Secondary Objectives

The secondary study objectives are (1) to determine the preliminary effects of the intervention on sedentariness, and (2) to develop a novel method of analysis of postural data collected using IMUs in a real-life context.

Methods

Study Design

This study protocol, designed according to the CONSORT (Consolidated Standards of Reporting Trials) statement for feasibility trials [25], has a stratified, closed cohort, two-cluster stepped-wedge design with a pragmatic approach. The stepped-wedge design offers an ideal structure that allows for a robust evaluation of an intervention within the bounds of

logistical constraints [27]. In addition, this study design allows both clusters to be exposed to the intervention with consideration of the unique context of each cluster.

Participants

Two primary schools were recruited for participation in the study. Participant classrooms (children aged 10-11 years) will be the unit of randomization and both classrooms (clusters) will be exposed to the intervention but will serve as their own control. All participants in each cluster will be exposed to the intervention from which a sample will be selected to provide baseline and follow-up measurements, and qualitative interviewing. Measurements for each selected participant will be taken at baseline, prior to the onset of intervention implementation, and followed up at the end of the trial period. Baseline measurements and implementation of the intervention in classroom 2 will follow those of classroom 1. This study was granted ethical approval by Stellenbosch University Health Research Ethics Committee (reference number: S17/08/130).

Study Intervention

The proposed intervention has two components: (1) novel height-adjustable sit-stand desks (KUZE desks; patent reference: A2017/01821), and (2) a series of health educational videos that encourage reduced classroom sedentariness and promote classroom physical activity. Usual classroom furniture will be replaced with KUZE desks after baseline measurements are performed. Prior to the implementation of the intervention, the researcher will train the students and teachers on how to safely and effectively use the KUZE desks. The training will include how to select and adjust the seat and desk height for sitting and standing. When used as a standing desk, the KUZE desk is placed on the existing desk and adjusted to the appropriate height.

During a teacher consultation prior to the onset of the project, the teacher will be shown the playlist of short health education videos provided on a mobile external hard drive. The videos are voiceover animations about the importance of reducing classroom sedentariness, awareness of good sitting posture, and increasing physical activity beyond the classroom. All videos contain an interactive segment of physical activity linked with simple mathematics tasks that the students are encouraged to engage with. The frequency at which the videos should be played will not be prescribed to the teacher. Strategies based on findings from a prior qualitative process that explored the potential barriers and facilitators to implementing a classroom-based intervention in primary school classes will be discussed.

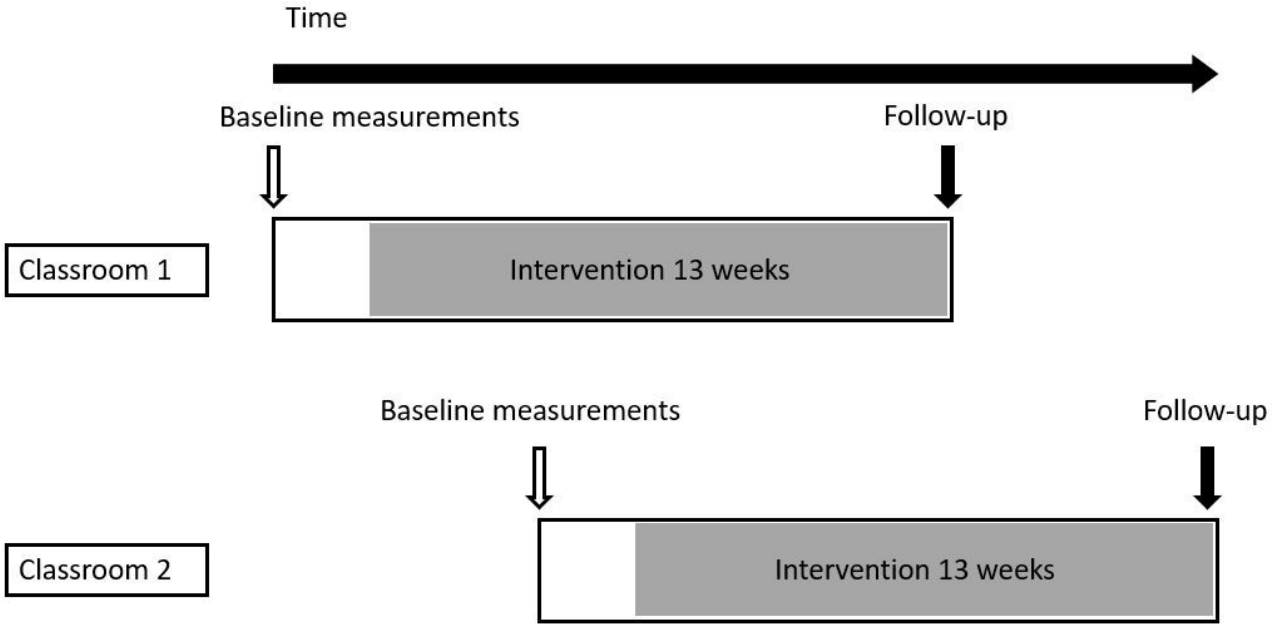
Setting

This study will be conducted in two primary school classrooms in the Western Cape region of Cape Town, South Africa. The Western Cape is characterized by broad socioeconomic, language, and cultural diversity, which will allow for the feasibility of the intervention to be tested in a resource-constrained environment as well as in an adequately resourced school environment. If the study is deemed to be feasible in a challenging resourced-strained environment, we consider that it will also be feasible in a range of less challenging scenarios.

Trial Design

This is a school-based, pilot cluster stepped-wedge feasibility trial. Individual students in grade 5 or 6 (10-11 years old) will be the unit of analysis with the classroom as the unit of randomization. Quintiles are socioeconomic categorizations of schools in South Africa that determine the state funding of the school, which is based on income levels, dependency ratios, and literacy rates in the area [28]. Although there will be no need to stratify the randomization of the clusters in this trial as there are only two participant classrooms, it is proposed that stratification by school quintile should be carried out during a future full trial. Baseline physiological data will be measured prior to the start of the intervention. Interviews with teachers and focus group discussions will be conducted after the intervention to assess the feasibility of the study. Figure 1 shows the proposed study design, and Multimedia Appendix 1 provides a SPIRIT diagram [29] for the design and timescales of the feasibility study.

Figure 1. Study design.



Feasibility Outcomes

Two broad feasibility criteria categories are to be considered: adherence and project pragmatics. The detailed success criteria and indicators are outlined in Table 1.

Table 1. Feasibility criteria.

Feasibility criteria	Success indicator	Measurement method
Delivery of the health education videos	The teacher develops a suitable routine of playing the videos and adheres to it	Qualitative feedback at exit interview (at 13weeks)
Acceptance of KUZE as a sit-stand desk	Students and teachers accepted the KUZE as the classroom furniture for the entire study period	Qualitative feedback at exit interview (at 13 weeks)
Compliance with wearing activPAL and IMU[a] sensors	100% of the subsample selected to be monitored agreed and complied to wearing the sensors during the data collection sessions	Researcher monitoring dropout rate
Usage of the KUZE desk	15% reduction in sitting time, reduction in episodes of prolonged sitting, increase in standing time, increase in sit-to-stand transitions	activPAL
Classroom retention to the study	All classrooms initially recruited remain in the study	Researcher monitoring
Integrity of physical activity and postural dynamism data	The integrity (degree of corrupt data due to technical or human factors) of 80% of all data captured with objective tools	Researcher monitoring

[a]IMU: inertial measurement unit.

Interpretation of Feasibility Success Criteria

Following the conclusion of the project, the success criteria will be interpreted as follows: (i) continue with large pilot/feasibility trial if all 6 success criteria are met, (ii) make minor modifications to the protocol if 3 or more criteria are met before continuing with a pilot/trial, and (iii) make significant protocol modifications if only 1 criterion is met [25].

Physiological Measures

Classroom sitting will be measured with activPAL3 microsensors attached to the anterior right thigh as prescribed by the user manual. The outcomes of interest will include total classroom sitting time, standing time, and sit-to-stand transitions. The activPAL3 microsensor will be placed on the participants prior to the start of the school day and removed at the end of the school day before they are dismissed home. The data captured during recess times will be excluded from the data analysis. The activPAL3 microsensor has been increasingly

used to objectively measure physical activity in recent years owing to its user-friendliness, practicality, and validity [30].

Postural dynamism will be measured using Noraxon Myomotion IMUs, which combine triaxial gyroscopes, accelerometers, and magnetometers. IMUs placed on the head, neck, thorax, and sacrum will be able to produce 3D kinematic and temporal outcomes, which can then be processed to produce a postural dynamism outcome.

Sample Size

A sample size calculation was not performed as per the CONSORT extension statement for feasibility studies [25]. A classroom from a fee-paying and a nonfee-paying school will be recruited. The diversity within the sample is expected to provide a sufficiently broad spectrum of considerations to assess the feasibility of the intervention and the pragmatics of data collection. To limit the impact on the classroom environment, no more than 10 morning data collection sessions per cluster are planned. The availability of only 2 Noraxon systems and 10 activPAL sensors presents a logistical constraint that will only allow for the collection of postural dynamism data and classroom physical activity data from 20 students from each cluster respectively. The sample selected for measuring physiological outcomes will be randomly chosen from the class list. An equal number of males and females of 10 to 11-year-old students will be sampled. The participants in the qualitative study will include students who took part in physiological data collection and those who were only exposed to the intervention but did not provide physiological data.

School Recruitment and Inclusion Criteria

Publicly funded schools will be stratified by socioeconomic categorization and then randomly contacted from a list of schools provided by the Western Cape Education Department. Only schools that have the requisite infrastructure to conduct the intervention will be considered for inclusion. This infrastructure includes technology for broadcasting the videos during normal teaching time and noninclined classroom desks. Schools that are conducting programs aimed at reducing classroom sedentariness or promoting spinal health will be excluded. At least one school from a predominantly black community will be recruited. A single class from the participant school that has students aged 10 to 11 years will be recruited into the study (Multimedia Appendix 1). Informed, written child assent and parent consent will be sought from the class teacher.

Participant Recruitment and Inclusion Criteria

All students in the class (regardless of age) will be provided with a project information document, along with assent and parent/guardian consent forms, which will explain the methods and intervention as well as the researchers' details. All students who return the completed assent and consent forms will be exposed to the intervention, but measurements will only be obtained from a sample of students.

Process Evaluation

The process will be evaluated through deductive content analysis of transcribed interview data collected during qualitative in-depth interviews with the two school principals and two class teachers as well as focus group discussions with the students from each participant class. Topics related to the process of negotiating access to the classroom, impact of the experimental setup for the collection of data, acceptability of and fidelity to the intervention, impact of the intervention in the classroom, and monitoring of the implementation of the intervention will be discussed.

Physiological Outcomes

Measurements will be taken from the study sample from each classroom at baseline and after implementation of the intervention to assess its effect. Classroom sitting will be measured for 10 consecutive school days using the activPAL3 microsensor. The sensor will be wrapped in a waterproof nitrile sleeve and attached to the proximal anterior right thigh of the participant with Hydrofilm. Participants will be required to wear the sensor from the beginning of the school day and it will be removed and collected by the researcher by the end of the school day.

School and Participation Appreciation

As an expression of appreciation to participating schools, they will be offered up to five KUZE desks as well as the video series for ongoing use. The staff, students, and their parent/guardians will also be invited to a presentation of the relevant findings of the study.

Data Analysis

Statistical Analysis

As per the CONSORT statement [25], feasibility outcomes will be described descriptively and narratively. Descriptive statistics will be used to report the clinical endpoints related to the feasibility outcomes. The number of participant classrooms and students, the number of children that remain in the study, and how many children use the school furniture throughout the study will be summarized. Owing to the small sample size, inferential statistics will most likely not be applicable. Study acceptability data will be presented per cluster as well as for the whole sample.

Qualitative Analysis

Thematic content analysis will be performed using Atlas.ti computer software by identifying and coding main themes and subthemes from the transcripts. A coding template will be compiled from the emerging themes and topics of interest relevant to the study objectives. An analytical diary will be kept alongside this coding template for justification of emerging themes. The coding template will be refined as more transcripts are coded. Encoded themes will be placed in context for analysis to recognize the significance and to understand the meaning thereof. Data will be analyzed per target group and by themes in cases of overlapping data between groups.

Results

At the time of submission, two classrooms have been recruited into the study. Baseline physical activity and postural dynamism data have been collected from 10 participants from each class.

Discussion

Projected Outcomes

Sedentary behavior, typified by prolonged periods of sitting, is not only increasingly associated with the development of cardio-metabolic disorders [31,32] but is also associated with adverse spinal changes [5]. Considering that the lifetime prevalence of back pain among adolescents in Africa is 36% [33] and that back pain experienced during adolescence often progresses to chronic pain during adulthood [34], there is significant potential to improve the health of many South Africans and reduce the health burden by effective health promotion. In a country with a significant health burden as a result of infectious diseases such as HIV/AIDS and tuberculosis, health promotion should be prioritized to avoid preventable health costs.

Preventative programs aimed at reducing adverse health outcomes are well-aligned with the South African Department of Health's agenda [35]. Its current policy to reintegrate and strengthen health care in schools attempts to improve access to early interventions and screening to a large proportion of the population with poor access to health care. It goes without saying that the efficacy of health programs must be rigorously tested through well-designed and efficiently conducted trials. A near essential preliminary step before conducting a full-scale trial is ensuring its feasibility [26].

Sit-stand classroom furniture has been shown to be effective in reducing classroom sedentary behavior [36] in several studies in well-resourced settings. However, no studies to test the effects of sit-stand classroom furniture on health outcomes have been previously conducted in South Africa. The resource-constrained South African context necessitates conducting a feasibility study ahead of a large, expensive trial. This feasibility trial will provide invaluable design and roll-out information for a future full-scale efficacy study.

Conclusion

This study protocol will provide methodological detail and contextual insights of the proposed feasibility trial findings. Researchers planning on conducting a stepped-wedge trial of the effectiveness of novel multifunctional classroom furniture and video sedentariness curriculum on student sedentary behavior in South African primary schools will find helpful guidance from this protocol.

Acknowledgments

This project is funded by the National Research Foundation (CPRR150720128324).

Authors' Contributions

All authors have made substantial contributions to the concept and design of the study. The study was conceived by DF and QL. LT contributed to the design of the study as a trial specialist. The first draft of the manuscript was written by DF. All authors have edited and critically reviewed the paper for intellectual content and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PNG File , 90 KB - resprot_v9i11e18522_app1.png]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
IMU: inertial measurement unit
LMIC: low-to-middle income country
NCD: noncommunicable disease

Edited by G Eysenbach; submitted 03.03.20; peer-reviewed by E Da Silva, K Stroetmann; comments to author 21.08.20; revised version received 24.08.20; accepted 08.09.20; published 30.11.20.

Please cite as:
Fisher D, Louw Q, Thabane L
Sedentariness and Back Health in Western Cape Primary School Students: Protocol for a Pragmatic Stepped-Wedge Feasibility Randomized Controlled Trial
JMIR Res Protoc 2020;9(11):e18522
URL: http://www.researchprotocols.org/2020/11/e18522/
doi:10.2196/18522
PMID:33089783

Protocol

Development and Validation of a Scale to Measure Intimate Partner Violence Among Transgender and Gender Diverse Populations: Protocol for a Linear Three-Phase Study (Project Empower)

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Abstract

Background: Intimate partner violence (IPV) is approximately twice as prevalent among transgender and gender diverse individuals (those whose current gender identity does not match their sex assigned at birth) than among cisgender individuals (those whose gender aligns with their sex assigned at birth). However, most existing scales measuring IPV are not validated among transgender and gender diverse populations and do not consider the unique forms of IPV experienced by transgender and gender diverse individuals.

Objective: This paper describes the protocol for Project Empower, a study that seeks to develop and validate a new scale to measure IPV as experienced by transgender and gender diverse adults. A new scale is necessary to improve the accuracy of IPV measurement among transgender and gender diverse populations and may inform the current tools used to screen and link to services for transgender and gender diverse adults who experience or perpetrate IPV.

Methods: The proposed new scale will be developed by a linear three-phase process. In Phase I, we will recruit a maximum of 110 transgender and gender diverse participants to participate in in-depth interviews and focus groups. Phase I will collect qualitative data on the experiences of IPV among transgender and gender individuals. After generating scale items from the qualitative data in Phase I, Phase II will conduct up to 10 cognitive interviews to examine understanding of scale items and refine wording. Phase III will then conduct a survey with an online recruited sample of 700 transgender and gender diverse individuals to validate the scale using factor analysis and examine the prevalence, antecedents, and linked health outcomes of IPV. This study will generate the first comprehensive IPV scale including trans-specific IPV tactics that has undergone robust mixed-methods validation for use in transgender and gender diverse populations, regardless of sex assigned at birth.

Results: Project Empower launched in August 2019, with Phases I and II expected to be complete by late 2020. Phase III (survey of 700 transgender individuals) is expected to be launched in January 2021.

Conclusions: A scale that more accurately captures the forms of IPV experienced by transgender and gender diverse people not only has the potential to lead to more accurate measurements of prevalence but also can identify unique forms of violence that may form the basis of IPV prevention interventions. Additionally, identifying the forms of IPV experienced by transgender and gender diverse people has the potential to lead to the refinement of clinical screening tools used to identify and refer those who experience and perpetrate violence in clinical settings.

International Registered Report Identifier (IRRID): DERR1-10.2196/23819

(JMIR Res Protoc 2020;9(11):e23819) doi:10.2196/23819

KEYWORDS

intimate partner violence; transgender; scale

Introduction

Background

Transgender and gender diverse individuals (individuals who identify as a gender different than the sex assigned to them at birth) are at 2.2 times the risk of physical intimate partner violence (IPV) and 2.5 times the risk of sexual IPV as compared with cisgender individuals [1]. Of the 27,715 transgender adults sampled in the 2016 US Transgender Survey (USTS) [2], 54% reported some form of lifetime IPV (35% reported physical IPV, 24% reported severe physical IPV, and 16% reported sexual IPV in their lifetime), and all rates were comparable to or greater than those documented in the general US population [2,3]. The few existing studies of IPV in transgender and gender diverse populations have shown links between IPV and a range of negative health outcomes, including posttraumatic stress disorder (PTSD) [4], avoidant coping behaviors, depressive symptoms [5,6], and HIV/sexually transmitted infection transmission risk behaviors, including transactional sex [7].

The experience or perpetration of IPV is commonly measured through scales that include lists of actions considered to constitute violence (ie, physical acts such as kicking or punching, sexual acts such as forced sex, and emotional acts such as verbal insults). However, many of the scales commonly used to measure IPV, for example, the Revised Conflicts Tactics Scale (CTS), were developed and validated with heterosexual cisgender populations and sometimes even only cisgender women [8]. Recent evidence demonstrates that there are acts of violence that are specific to the IPV experiences of transgender and gender diverse individuals, yet these acts are absent from commonly used IPV scales developed in cisgender populations. Omission of these transgender-specific acts from scales is problematic when measuring IPV in transgender and gender diverse populations, as these acts are common hallmarks of abuse for transgender and gender diverse individuals. In the 2016 USTS, 27% of participants reported experiencing some form of transgender-specific IPV in their lifetime, including their partner preventing them from accessing hormones (3%), telling them that they were not a "real" woman or man (25%), and threatening to "out" them as a transgender as a form of blackmail (11%) [2]. Perpetrators may undermine their partner's gender identity and expression by intentionally misgendering them or hiding/damaging items (eg, chest binders, wigs, makeup, clothing, and prosthetics) [9]. These acts can lower self-esteem and confidence, rendering transgender and gender diverse individuals more vulnerable to abuse and less confident to go out in public and increasing their sense of isolation and dependency [1,10]. Existing IPV measures do not screen for these trans-specific abuse tactics; thus, they are likely insufficiently sensitive as IPV screening tools in transgender and gender diverse populations. Accurate measurements of IPV are essential for effective intervention development and evaluation of the impacts of interventions on behavioral change.

Several recent attempts have been made to create measurement tools that more accurately reflect IPV as experienced by transgender individuals. While not a transgender-specific scale, Woulfe and Goodman developed a seven-item scale of "identity abuse" with lesbian, gay, bisexual, transgender, and queer (LGBTQ)-specific items, such as "The person told me I deserve what I get because of my sexual orientation or gender identity" (8.2%) and "The person questioned whether my sexual orientation or gender identity was real" (28.3%) [11]. Transgender participants were more likely (49.3%) than sexual minority cisgender women (42.8%) or men (28.4%) to experience identity abuse in adulthood. Peitzmeier et al created the first transgender-specific IPV (T-IPV) scale and piloted it in a sample of 150 transmasculine individuals (ie, individuals assigned a female sex at birth who identify their gender on a spectrum of masculinity) [12]. The scale was then expanded to 10 potential items and tested again in two independent samples of transfeminine adults (ie, assigned a male sex at birth and identify with femininity), with factor analyses yielding an eight-item unidimensional scale with moderate to good fit [13]. Scale content represented a variety of domains of trans-specific abuse, including partner sabotaging gender transition (10% lifetime report), policing gender expression (21%), and emphasizing the undesirability of transpartners (22%). Additionally, Dyar et al [14] used data from a sample of 352 sexual and gender minority individuals assigned female at birth (SGM-AFAB) to adapt versions of the Conflict Tactics Scale–Revised, a measure of coercive control, and to test the newly developed SGM-Specific IPV Tactics Measure, with results providing initial evidence of the reliability and validity of each measure. This five-item method was designed for use with LGBTQ populations broadly and focused on outing and social isolation as domains. While these recent studies have attempted to create transgender- or LGBTQ-specific measurements of IPV, they are not without limitations. Items from these scales were developed through expert and community consultation and review of existing qualitative literature, but none were grounded in an in-depth qualitative study whose specific purpose was to elicit acts of IPV specific to transgender and gender diverse individuals by transgender and gender diverse survivors themselves, which may have restricted the content validity of the scale or impacted how the items were worded. These studies also relied solely on psychometric validation, usually in a restricted sample of either transfeminine or transmasculine individuals but not both, and did not include cognitive interviewing of the proposed scale items and other validation methods to ensure that they accurately captured the experiences of transgender individuals.

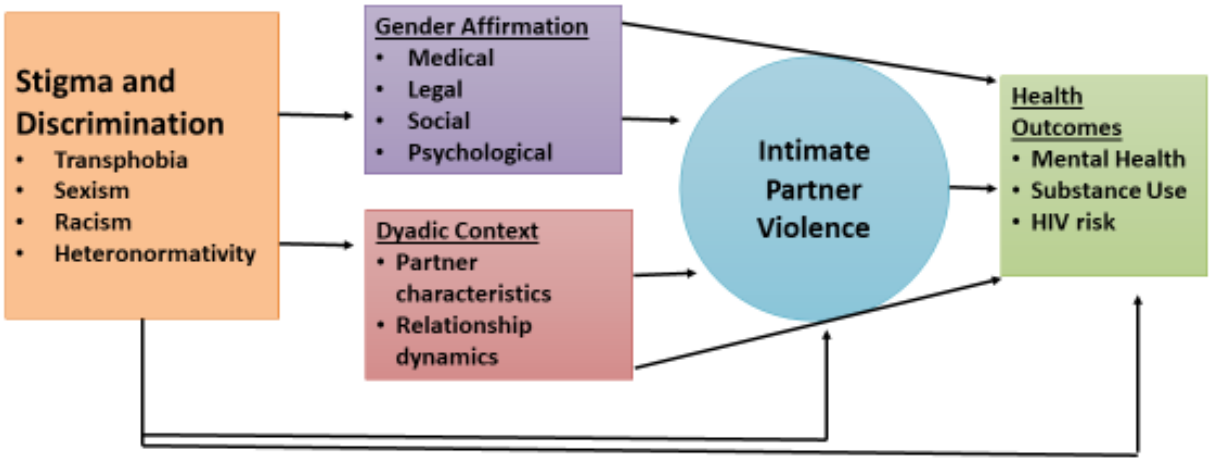
This study seeks to fill this gap through the development and validation of a scale that comprehensively accounts for both forms of IPV that may be experienced by individuals of all gender identities (ie, forced sex) and forms of IPV that are unique to transgender and gender diverse individuals. This paper describes the protocol for *Project Empower*, a project to develop

and validate a new scale to measure IPV as experienced by transgender and gender diverse populations aged over 15 years in the United States. A new scale is necessary to improve the accuracy of IPV measurement among transgender and gender diverse populations, and may inform the current tools used to screen and link to services for transgender and gender diverse adults who experience or perpetrate IPV. This scale will be grounded in *de novo* qualitative data collection specifically designed to elicit the types of abuse experienced by transgender and gender diverse survivors of IPV, and be comprehensively validated through qualitative focus groups, cognitive interviews, and finally quantitative psychometric validation.

Theoretical Framework for Scale Development

The conceptual model of IPV among transindividuals is presented in Figure 1. Our conceptual framework is guided by adaptions of the gender minority stress model and gender affirmation framework. According to the gender minority stress model, individuals who do not conform to societal norms regarding gender roles, expression, and identities are vulnerable to discrimination and stigma, which can affect emotions, cognitions, and health behaviors [15]. In accordance with the gender affirmation framework, gender minority stressors may increase the need for gender affirmation (eg, feeling safe, recognized, and supported in gender identity and expression [16,17]), particularly in intimate relationships. Gamarel et al developed and validated a measure of relationship stigma with transgender women, which measures enacted stigma and anticipated stigma experienced by transgender women in their intimate relationships [18]. Transgender-specific discrimination and relationship stigma have been associated with reduced relationship quality, as well as increased substance use behaviors and psychological distress for transgender women and their cisgender male partners [18,19]. Thus, IPV may be a result of societal oppression, transgender-specific discrimination, and relationship stigma, whereby partners of transgender individuals may withhold gender affirmation as a power and control tactic. The conceptual framework for our study draws upon these frameworks and hypothesizes IPV to be a function of multiple interlocking forms of stigma and discrimination (ie, antitransgender stigma), gender affirmation, and dyadic and individual factors. We hypothesize that the presence of any of these factors may influence IPV in one of the following two ways: (1) the creation of stress leading to an increased propensity for violence and (2) lowered access to and greater need for gender affirmation from a partner leading to greater vulnerability to or acceptance of violence. The model will be used to guide the collection of qualitative and quantitative data to understand the unique forms and antecedents of IPV among transgender and gender diverse individuals.

Figure 1. Conceptual model of intimate partner violence among transindividuals.



Methods

Trial Registration, Ethics, Consent, and Institutional Board Approval

This study has been reviewed and approved by the University of Michigan Institutional Review Board (IRB# HUM00171509). A certificate of confidentiality has been obtained from the National Institute of Child Health and Human Development, and a waiver of parental consent/assent will be obtained for participants who are 15 to 17 years old.

Study Design

Overview of Study Design

The proposed new scale will be developed by a linear three-phase process. Phase I consists of collecting qualitative data (ie, in-depth interviews and focus group discussions) with up to 110 transgender and gender diverse individuals aged over 18 years (for the in-depth interviews) and aged over 15 years (for the focus group discussions) to better understand the experiences of IPV, and it will provide content items for the proposed new scale. After extracting scale items from the qualitative data in Phase I, Phase II will consist of a maximum of 10 cognitive interviews to examine construct and content validity of scale items. Phase III will be a survey with an anonymous online sample of 700 transgender and gender diverse individuals aged over 15 years to examine the prevalence,

antecedents, and linked health outcomes of IPV and psychometrically validate a comprehensive IPV scale validated for use in transgender and gender diverse populations. Participation in the in-depth interviews is restricted to participants over the age of 18 years, as the interviews potentially involve disclosures of personal experiences of violence, and restricting participation to adults prevents the disclosure of child/minor abuse. Phase I and II data collection began in March 2020 and has continued throughout the COVID-19 pandemic that began in the United States in March 2020. The study has not experienced problems in recruiting participants for either Phase I or II. To recognize the potential for the additional stress of the pandemic to create contexts or triggers for IPV, we will add the measure of COVID-related stressors (ie, employment loss) to the Phase III survey.

Participants

For all phases, participants must be (1) transgender or gender diverse (ie, defined as a difference in the sex assigned at birth and current gender identity), (2) over the age of 15 years, (3) currently residing in the United States, (4) having access to a computer, tablet, or smartphone, (5) having at least one intimate partner in the past 5 years, and (6) able to participate in the study in English. For the in-depth interviews, additional eligibility criteria are having experienced IPV in the previous 5 years, using the IPV screener from the USTS, and being over 18 years of age [2].

Recruitment

The same recruitment process will be used for Phases I to III. We will recruit participants using racially and ethnically diverse banner advertising on mobile dating apps (eg, Fet-Life) and social networking websites (eg, Facebook and Instagram). Online advertising will be supplemented with placing advertisements on the webpages of leading transgender health and rights websites, tweeting links to study information with transgender-specific hashtags, and working with transgender activists and organizations to tweet and promote the study on their social media profiles. Recruitment will be limited to those residing in the United States. Individuals who click on the banner advertisements will be taken to the study website for more information. Interested individuals will complete an online consent form and eligibility screener. Eligible participants will then enroll by providing their name and email. Participants who do not consent, do not meet the eligibility criteria, or do not provide valid contact information will be excluded from the study.

Protection of Human Subjects

Throughout the phases of the study, we will take several important steps to ensure the safety and privacy of the participants. The synchronous focus group discussions, in-depth interviews, and cognitive interviews will be conducted using Health Insurance Portability and Accountability Act (HIPAA)-compliant video-based teleconferencing software (Zoom). Focus group discussions carry the risk of disclosure of personal information by other study participants. Participants will be informed that no personal information should be shared and will be asked to respect the confidentiality of other participants and not repeat discussions outside of the online chat room. They will also be instructed to sit in a private place when participating in the focus group discussion so that other people are not able to see images, hear audio, or view text contributed by the other participants in the focus group discussion. All study staff will follow a robust set of safety procedures to make sure that participants receive a high level of monitoring. Because there is potential for psychological discomfort owing to the research topic, participants will be reminded often that they may refuse to answer any question and that they may end their participation at any point. Participants experiencing mild distress during the interviews will be offered a small break prior to completing the interview and reminded that they can take breaks during the self-administered online survey. In the unlikely event that a participant experiences considerable distress, they will be offered a voluntary clinical assessment and/or counseling by the study clinical psychologist. If any person is judged by project investigators to be a danger to self or others, or judged to be in grave danger owing to medical or other conditions, the decision will be made to break confidentiality in order to inform authorities to intervene in preventing an adverse event. During the Phase III survey, participants will self-administer surveys. Reporting by participants that they have experienced recent suicidal ideation, self-harm, or IPV will trigger an automatic message asking if they would like study staff to follow-up with them the following business day. All staff will receive training for identifying suicide/homicide risk and/or dangerous intoxication and de-escalation of agitated or angry persons, and will be trained to appropriately evaluate and respond to these circumstances.

Phase I Study Procedures

The first phase of the project will include 20 to 30 semistructured in-depth interviews and eight focus group discussions. All qualitative data collection will involve a diverse sample of transfeminine, transmasculine, and nonbinary individuals. We will use purposive sampling to increase the racial and sexual orientation diversity of the participants [20]. Upon initial saturation, theoretical sampling and additional interviews (up to 30) may be conducted to expand upon or confirm findings from initial interviews if necessary [21]. In order to account for different types of data, we will use a two-pronged approach for conducting the focus group discussions. There will be asynchronous and synchronous focus group designs, with the aim of conducting four of each type of focus group discussion. The in-depth interview and four synchronous focus group discussions will be conducted using HIPAA-compliant video-based teleconferencing software. The four asynchronous focus group discussions will be conducted via FocusGroupIt for text-based focus group discussions, a format that works well for maximal anonymity on sensitive topics, and to allow participation from geographically dispersed participants across multiple time zones. Each focus group discussion will contain between 5 and 10 participants. Synchronous focus group discussions and in-depth interviews will be conducted virtually, using the HIPAA-compliant secure Zoom platform. After screening and enrolling, study staff will call participants to schedule the focus group discussion or in-depth interview.

The in-depth interview and focus group discussion will serve unique purposes. The in-depth interview will focus on collecting IPV narratives from survivors of IPV and understanding the specific abusive behaviors that took place, the perceived triggers of violent events, and how violence behaviors evolved over the course of the relationship and over the course of the individual's gender transition. After the in-depth interviews are transcribed, we will extract behaviors considered abusive by survivor participants and craft potential screening items to screen for these behaviors, using in vivo language as provided by survivors to the extent possible. The focus group discussion will enroll both individuals who have and who have not experienced IPV, and explore group norms and perceptions of IPV. The moderator will ask the participants if each of the potential screening items identified in the in-depth interview is considered violent, and will ask participants to name other actions that may be considered violent in a relationship, probing around actions specific to the transgender experience. We will also ask participants about items from commonly used scales, such as the CTS, and from other trans-specific IPV scales that have been developed in the past [2,13,14]. We will then ask focus group discussion participants to talk about what other behaviors they would consider abuse that we have not yet asked about. This process will ensure that the full range of IPV as experienced by transgender and gender diverse individuals will be captured by the scale based on qualitative data collection capturing the lived experiences of transgender and gender diverse participants. The qualitative data collection will be conducted by a transgender moderator. Participants will receive US $50 compensation sent via a Mastercard gift card for participation in the in-depth interview and US $30 for participation in the focus group. Participants who participate in the in-depth interview will not be eligible for the focus group discussion.

Phase II Study Procedures

The first task in Phase II will be to finalize the items for the new scale to measure IPV among transgender individuals. Focus group discussion and in-depth interview transcripts will be reviewed by three researchers in order to ensure that all unique forms of IPV mentioned by the participants were extracted to inform survey instrument development. The number of unique IPV items generated is expected to be several dozen. After generating the survey items, a maximum of 10 cognitive interviews will be conducted to explore item comprehension of the potential scale items. The aim of the cognitive interviews is to refine the language used in each of the scale items and ensure that participants understand the items in the manner intended. Participants for the cognitive interviews will be recruited in the same manner as participants in Phase I. Cognitive interviews will be conducted virtually, using the HIPAA-compliant Zoom platform. Participants will be asked to read the scale items and then repeat the meaning back in their own words. If there is a discrepancy in meaning, the interviewer will explain the intended meaning to the participant and ask the participant to rephrase the scale item to achieve the desired meaning [22]. We will also ask participants to "talk aloud" their thought process in how they respond to the questions and test assumptions inherent to the scale, such as understanding of an "intimate partner." Cognitive interview participants will receive US $30. Participants in the in-depth interview and focus group discussion will not be eligible to participate in the cognitive interviews.

Phase III

Phase III Study Procedures

After completing this process of generating potential IPV scale items and other variables of interest grounded in the Phase I qualitative data, we will conduct an online survey of 700 transgender and gender diverse individuals. Eligibility criteria, recruitment, and enrollment strategies are the same as those in Phases I and II, and the survey will sample those aged over 15 years. Once eligible and enrolled, participants will be emailed a link to a secure survey. The survey can only be taken once to prevent duplicates. Participants will receive US $40.

Sample Size for Phase III

We will enroll 700 transgender individuals aged over 15 years. Previous studies of IPV among transgender individuals have shown the prevalence of physical IPV to be in the range of 18% to 47%. Each of these studies has relied upon measures of IPV that are not transgender-specific, and we expect our prevalence estimates to be higher. A sample size of 700 is sufficient to detect a roughly 20% difference in IPV prevalence (ie, odds ratio 1.5-1.9) between two subgroups in our sample (eg, transfeminine, transmasculine, and nonbinary) with >80% power.

Survey Instruments

IPV

With regard to *experience and perpetration of IPV and scale development*, participants will view a list of acts that may constitute IPV and respond to the question, "Which of the following items would you consider to be violent or abusive if a sexual/romantic partner perpetrated them against you without your consent?" For each behavior, they will report if they have experienced or perpetrated it in the past 12 months and lifetime, and will report the number of times they have experienced each item in the past 12 months. With regard to *partnership-level experience of IPV*, for each intimate partner reported in the past 3 years (up to three partners), we will assess IPV victimization and perpetration. For partnerships in which victimization or perpetration is reported, respondents will complete the Controlling Behaviors Scale to assess IPV typology (eg, intimate terrorism versus common couples' violence [23]) and the injury scale of the CTS2 to measure the severity of physical violence [8]. With regard to *help seeking*, participants who experienced IPV will be asked in which ways they sought help or assistance from a variety of sources, including friends, family, physicians/medical workers, counselors/psychiatrists, social workers, and law enforcement.

Stigma and Discrimination

Gender minority specific stigma will be assessed using validated subscales from the Gender Minority Stress and Resilience Scale (GMSRS) [24]. Sexual minority stigma will be assessed with the Intersectional Discrimination Index [25] and the Everyday Experiences of Discrimination (Sexual Orientation) Scale [26-28]. Racial/ethnic stigma will be captured with the Brief

Perceived Ethnic Discrimination Questionnaire (Community Version) [29], the Everyday Experiences of Discrimination (Race/Ethnicity) Scale [26-28], and the Group Membership Questionnaire [30]. Experiences of sexism will be assessed with the Daily Sexist Events Scale [31] and the Internalized Misogyny Scale [32,33].

Gender Affirmation

Participants will also complete a gender affirmation scale that assesses domains, including need for, access to, and satisfaction with legal affirmation (eg, name changes), medical affirmation (eg, hormones and surgery), social affirmation (ie, correct pronouns), and psychological affirmation (eg, level of femininity/masculinity) [34]. We will also assess satisfaction with gender transition and gender comfort [17,35].

Dyadic Context

Participants will be asked to list their most recent intimate partners (defined as someone the participant felt emotionally, romantically, or sexually close to) in the past 3 years (up to three partners). For each partner, we will ask the gender, age, race, sexual orientation, education, and outness. Participants will complete measures of relationship functioning, which include the Dyadic Adjustment scale [18,36] Commitment scale [37], and Power and Attitudes in Relationships scale [38]. We will assess stigma experienced at the dyadic level with a validated measure of relationship stigma [18].

Demographics

Age, education, race, ethnicity, sexual orientation, employment, health insurance, health care access, and state of residence will be measured. Both sex assigned at birth and current gender identity will be collected. Current gender identity will include options for male, female, transmasculine, and transfeminine, as well as categories for genderqueer/gender nonconforming, nonbinary, agender/gender fluid, and participant-driven response.

Health Outcomes

The AIDS Risk-Behavior Assessment (ARBA) adapted to be relevant to transgender bodies and relationships [39] will be used to collect information on sexual behaviors with the three most recent partners in the past 3 years to enable partner-by-partner analyses. Participants will also be asked if they felt able to negotiate for condom use and/or contraceptive use with each partner. In addition to partner-level information on sexual behavior, participants will also be asked about their sexual behavior in the past 12 months with any partner. *History of HIV testing* will include measures of frequency, method of testing, and linkage to care (if HIV positive). Impact of *substance use* will be measured using the 10-item Drug Abuse Screening Test (DAST) [40], and harmful alcohol use will be assessed with the Alcohol Use Disorders Identification Test (AUDIT) [41]. We will measure nonprescribed and prescribed *hormone use*, age of starting hormones, types of hormones, dosage/regimen, and adherence to prescribed hormones. We will use the Brief Symptom Inventory [42] to measure current depressive symptomology and anxious symptomology. PTSD symptoms will be assessed with a scale [43,44] used in studies with transgender communities [4]. *Suicidal ideation* will be assessed with the Suicidal Ideation Scale (SIS) [45], and *nonsuicidal self-injury* will be assessed with the Inventory Statements about Self-Injury (ISAS) [46]. *General physical health* will be measured using the Patient-Reported Outcomes Measurement Information System (PROMIS) measure [46].

COVID-19 Stressors

To recognize the potential for the COVID-19 pandemic to create additional stress, the survey will assess the following COVID-19-related stressors: loss of employment or income, loss or changes in housing, changes in access to health care, increased participation in child or elder care, participation in social distancing, and feelings of anxiety, loneliness, and isolation specifically linked to COVID-19.

Phase III Data Analysis

We will reduce scale items by dropping items not considered to be violent by the majority (>60%) of respondents. To validate the scale and identify factors/subscales, we will conduct exploratory factor analysis (EFA) using victimization data for the past 12 months [47] from a randomly selected sample of half of the participants. We will not a priori propose a factor structure for the scale, but we will compare the resultant factor structure with those of commonly used IPV scales. We will examine whether the data are suitable for factor analysis with the Kaiser-Meyer-Olkin test and Bartlett test of sphericity [48,49]. Factor retention will be decided by examining eigenvalues, scree plots, and interpretability of factors [48]. Oblique and orthogonal rotations will be examined to determine the best solution. The reliability of each factor/subscale will be assessed by calculating Cronbach alpha, with adequate reliability indicated if Cronbach alpha is >.70 in the overall sample and among subgroups (ie, transmasculine, transfeminine, and nonbinary participants) [50]. Items may be reduced based on statistical (items should increase subscale alpha, have high item-total correlations, and load highly onto a single factor), theoretical (maintaining items for content validity), and practical (scale length) criteria [8,47,51]. As an additional exploratory analysis, we will conduct EFA separately for different subgroups of respondents (eg, transmasculine and transfeminine) to identify potential variations in scale content. We will compare the factor structures of the EFA conducted for subgroups of the sample, although the intent remains to create a single scale that represents the IPV experiences of all transgender and gender diverse individuals. We will then conduct a confirmatory factor analysis of the retained items with the participants not in the EFA sample. Model fit will be evaluated by looking for a root mean square error of approximation <0.06, confirmatory factor index >0.90, and standardized root mean squared error close to 0.08 [52,53]. Convergent validity will be assessed by measuring the correlation with existing IPV measures, use of domestic violence services, and relationship functioning. Analyses will produce a validated IPV scale with subscales corresponding to different forms (eg, physical, sexual, etc) that comprehensively measure IPV in transgender populations.

Quantifying Individual-Level Factors Associated With IPV Experience and Perpetration

We will define the following outcomes for the past 12 months and lifetime referent periods: (1) experiencing any form of IPV,

(2) experiencing each domain of IPV identified during scale development (eg, physical IPV and sexual IPV), (3) perpetrating any form of IPV, and (4) perpetrating each domain of IPV. Key covariates will be stigma and discrimination, gender affirmation, and demographic variables. Bivariate associations between each of the outcomes and covariates will be examined. The goal of this stage of the analysis will be to identify the prevalence of forms of IPV in different subgroups, including differences in the IPV by different subgroups (eg, transmasculine, transfeminine, and/or nonbinary identity), to assess IPV disparities within transgender and gender diverse communities. Additionally, multivariate logistic regression models will be fit to determine the independent risk of IPV associated with each individual-level characteristic.

Quantifying Partner-Level and Dyadic Factors Associated With IPV Experience and Perpetration

This analysis will use data reported for each recent partnership (up to three per participant). The outcomes will be the experience and perpetration of any IPV and of each form of IPV during each partnership. Covariates will include individual-level characteristics as above in the individual-level models, partner characteristics (eg, partner gender), and dyadic characteristics (eg, dyadic adjustment and relationship stigma). Multilevel logistic regression models with random effects will be fitted with partners clustered under individuals [54].

Quantifying Associations Between Experience and Perpetration of IPV and Health Outcomes

This analysis will use individual-level models to assess associations between IPV and health outcome measures enumerated above, including sexual health, mental health, substance use, and physical health outcomes. Logistic, multinomial, or linear models will be employed depending on the outcome. The key covariates in each model will be the experience or perpetration of IPV in the past 12 months and lifetime, adjusting for individual-level covariates. Then, partner-level multilevel models will be fit to quantify associations between IPV experience or perpetration within a given partnership and sexual behaviors for that partnership (eg, condom use).

Results

Project Empower launched in September 2019, with Phases I and II expected to be complete by late 2020. Phase III (survey of 700 transgender individuals) is expected to be launched in January 2021.

Discussion

Transgender and gender diverse people in the United States face adverse physical and mental health outcomes compared with cisgender populations [5,55-66]. There is a wealth of literature illustrating the epidemic rates of psychological distress [2], depression [67-73], and suicidal ideation [72,74-77], as well as poor self-rated physical health [2], high rates of HIV and other sexually transmitted infections [59,78-81], and elevated risk for chronic disease [82-84] among transgender and gender diverse individuals. These disparities may be driven in part by disproportionate rates of violence, including IPV, making sensitive and accurate screening, prevention, and response for IPV in transgender and gender diverse populations critical.

Central to the ability to develop efficacious interventions for the primary or secondary prevention of IPV is our ability to correctly define IPV as it is experienced by transgender and gender diverse individuals. Current commonly used IPV scales were developed primarily for use in heterosexual cisgender populations and do not necessarily capture the lived experiences of transgender and gender diverse individuals and the forms of IPV that they may uniquely experience. Prior work has developed and validated scales to measure IPV as experienced by gay and bisexual men [85] and developed and validated an IPV scale specifically for sexual and gender communities [14], and preliminary work has been performed to create an IPV scale specific to the unique experiences of transgender and gender diverse individuals [12]. Our current work extends this previous work by considering the experiences of transgender and gender diverse individuals as it relates to the experience of IPV. A scale that more accurately captures the forms of IPV experienced by transgender and gender diverse people not only has the potential to lead to more accurate measurements of prevalence, but also can identify unique forms of violence that may form the basis of violence prevention interventions. Additionally, identifying the forms of IPV experienced by transgender and gender diverse individuals has the potential to lead to the refinement of clinical screening tools that are used to identity and refer those who experience and perpetrate violence in clinical settings.

Conflicts of Interest

None declared.

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Abbreviations

CTS: Conflicts Tactics Scale
EFA: exploratory factor analysis
HIPAA: Health Insurance Portability and Accountability Act
IPV: intimate partner violence
LGBTQ: lesbian, gay, bisexual, transgender, and queer
PTSD: posttraumatic stress disorder
SGM: sexual and gender minority
USTS: US Transgender Survey

Edited by G Eysenbach; submitted 24.08.20; peer-reviewed by L Schwab-Reese, A Leddy; comments to author 22.09.20; revised version received 29.10.20; accepted 30.10.20; published 26.11.20.

Please cite as:
Stephenson R, Todd K, Gamarel KE, Peitzmeier S
Development and Validation of a Scale to Measure Intimate Partner Violence Among Transgender and Gender Diverse Populations: Protocol for a Linear Three-Phase Study (Project Empower)
JMIR Res Protoc 2020;9(11):e23819
URL: http://www.researchprotocols.org/2020/11/e23819/
doi:10.2196/23819
PMID:33242022

Protocol

Effectiveness of Educational Interventions to Increase Knowledge of Evidence-Based Practice Among Nurses and Physiotherapists in Primary Health Care: Protocol for a Systematic Review

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This is a corrected version. See correction statement: http://www.researchprotocols.org/2021/1/e27092/

Abstract

Background: The implementation of evidence-based practice (EBP) in daily health care practice is strongly encouraged; it is widely recognized as a means to improve the quality and safety of health care for patients and reduce avoidable costs. Primary care nurses and physiotherapists face numerous challenges in trying to ensure that they deliver effective daily care. Broadly promoted educational interventions aim to increase the integration and implementation of EBP in their daily practice.

Objective: This systematic review will retrieve and evaluate publications examining the effectiveness of educational interventions to increase the integration and implementation of EBP among nurses, nurse practitioners, and physiotherapists active in primary care.

Methods: We will conduct a systematic review of published articles in relevant professional, scientific journals (from their start dates) and in the following electronic databases, from inception until October 31, 2020: Medline Ovid SP (from 1946), PubMed (NOT Medline[sb]; from 1996), Embase.com (from 1947), CINAHL Ebesco (from 1937), the Cochrane Central Register of Controlled Trials Wiley (from 1992), PsycINFO Ovid SP (from 1806), Web of Science Core collection (from 1900), PEDro (from 1999), the JBI Database of Systematic Reviews and Implementation Reports (from 1998), and the Trip Database (from 1997). We will use the predefined search terms of “evidence-based practice,” “nurses,” or “physiotherapists” and combinations with other terms, such as “educational interventions.” We will also conduct a hand search of the bibliographies of all the relevant articles and a search for unpublished studies using Google Scholar, the ProQuest Dissertations and Theses dissemination, Mednar, WorldCat, OpenGrey, and Grey Literature Report. We will consider publications in English, French, German, and Portuguese.

Results: The electronic database searches were completed in October 2020. Retrieved articles are currently being screened, and the entire study is expected to be completed by March 2021.

Conclusions: This systematic review will provide specific knowledge about the effectiveness of educational interventions to increase the implementation and integration of EBP in the daily practice of nurses and physiotherapists providing primary care services. Its findings will inform us about the types and frequencies of the most successful educational interventions.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42017077309; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=77309

International Registered Report Identifier (IRRID): DERR1-10.2196/17621

(JMIR Res Protoc 2020;9(11):e17621) doi:10.2196/17621

KEYWORDS

evidence-based practice; primary healthcare; beliefs; knowledge; implementation; nurses; nurse practitioners; physiotherapists; interventions; education

Introduction

Evidence-based practice (EBP) is an emerging, breakthrough approach among health care providers (HCPs) [1,2]. It has its origins in evidence-based medicine, which has been defined as "the conscientious and judicious use of current best evidence in making decisions about the care of individual patients" [3]. Many evidence-based models were born of the evidence-based medicine model and helped understand how this concept could be applied to other health professions [4]. One of the ways in which EBP was first conceptualized in nursing was through its use in research. Although EBP includes a patient-centered approach, in research it is simply the rigorous use of research steps to critically appraise research evidence and implement that evidence in practice [5,6].

HCPs are expected to use EBP as a standard approach to daily practice [7-9], integrating research, patient preferences, clinical expertise, and innovative technologies [10,11]. However, the implementation of EBP remains a controversial process [12,13], and not all HCPs are convinced that it improves the quality of care [14,15]. Implementing EBP is challenging, especially in primary health care settings [16,17]. The Swiss Federal Law on Healthcare Professionals will change in 2020 [18]. All health care professionals active in Swiss health care settings will be expected to implement evidence-based care and treatments in their daily practice. Bearing in mind that not all health care professionals received training about EBP during their career trajectory, this raises questions about which educational interventions are most effective at increasing EBP skills among nurses and physiotherapists (PTs) in daily practice. Numerous studies have investigated perceptions about EBP among a variety of health care professionals [9,19,20]. Overall, most of them had positive attitudes towards EBP but lacked the knowledge and skills to implement it. A number of personal and organizational barriers impede EBP implementation [21].

This systematic review will support this reflection and examine those educational strategies. We expect this project to inspire other university hospitals and training centers for allied health care professionals to integrate creative and effective educational strategies to increase EBP skills.

Primary health care is defined as the entry level into a health care services system [22], providing the first point of contact for all new needs and problems. It involves patient-focused care over time, care for all but the most uncommon or unusual conditions, and coordination or integration of that care, regardless of where or by whom it is delivered. It is the primary means by which to approach the main goal of any health care services system: optimization of health status [23]. Health care provided by primary HCPs includes health promotion, prevention and diagnosis, detection, intervention, treatment, and case and care management [24,25]. Furthermore, primary HCPs, especially community health care nurses and PTs, are highly involved in frontline health care services to home-dwelling adult patients and long-term nursing home patients [26,27].

Nevertheless, in some acute health situations, home-dwelling individuals will need to be referred to medical specialists or acute hospital services for additional health care advice. Because of their close relationships with health care users during their daily practice, community health care nurses and PTs play important decision-making roles, strengthening communication and collaboration between the community and specialized HCPs in order to provide the best available overall health care to community-dwelling individuals [28]. Although it is generally considered that community health care nurses and PTs, just like all other HCPs, are accountable for providing the best available evidence-based health care [29,30], recent research has concluded that only a small percentage of them consistently do so [8]. EBP implementation rates among nurses and PTs in hospital institutions have been extensively documented [31-33], and multiple barriers to implementation have been reported [34,35]. These include time constraints, negative attitudes and a lack of personal motivation, professional resistance to research, and inadequate knowledge of and skills for EBP among clinicians [8,36,37].

Additionally, several authors have documented administrative and organizational problems in the workplace, a lack of mentors for EBP, inadequate resources at the point of care, gaps between theory and practice, the lack of any meaningful transition between training courses on EBP and the clinical reality, and an absence or lack of basic education on the subject [38-40]. Finally, different authors have highlighted that HCPs' beliefs about EBP are associated with their capacity to implement it [31,41,42]. Over the last 2 decades, the use of EBP in health care has been documented in exploratory and observational studies in different settings. Scurlock-Evans et al [8] summarized attitudes, barriers, enablers, and EBP interventions among PTs, although without specifying employment settings or assessing educational interventions. Melender et al [43] summarized the educational interventions used to train nursing students to improve outcomes in the implementation of EBP. Nevertheless, to the best of our knowledge, there has been no systematic review examining the effectiveness of educational interventions aimed at increasing the use of EBP in daily practice among nurses, nurse practitioners (NPs), and PTs active in primary health care.

Our research question is: How effective are educational interventions to increase the implementation of EBP in the daily practice of nurses and PTs delivering primary care among community-dwelling adults?

Methods

This review will be conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) recommendations [44], Meta-analysis Of Observational Studies in Epidemiology (MOOSE) reporting proposals [45], and methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions [46].

Inclusion Criteria

Types of Studies

This review will include randomized controlled trials, cluster randomized controlled trials, and nonrandomized studies (NRS). NRS have been defined as quantitative studies estimating the effectiveness of an intervention (harm or benefit) that does not use randomization to allocate units to comparison groups [47]. We will include prospective cohort studies, case-control studies, controlled before-and-after studies, interrupted-time-series studies, and controlled trials with inappropriate randomization (quasiexperimental studies) [48-50]. We will consider publications in English, French, German, and Portuguese.

Types of Participants

This review will consider studies involving registered HCPs, including those with bachelor's, master's, or doctoral degrees in physiotherapy (PTs) and nursing (registered nurses [RNs], NPs) and who are delivering primary health care, including nursing and physiotherapy students. Physical therapists and PTs will be considered synonymous.

Types of Primary Health Care

We will include all types of primary health care settings such as private practices, community and health maintenance organization practices, community and private primary health care settings, hospital outpatient departments, practices in hospital settings, and hybrid primary health care practices including community and private practices, health maintenance organizations, and outpatient departments.

Types of Interventions

We will examine all types of educational interventions aimed at improving the EBP delivered by RNs, NPs, and PTs to adults living at home as part of active primary health care.

Based on the Cochrane Effective Practice and Organization of Care taxonomy of interventions [51], we will consider educational interventions targeting health care organizations and health care professionals (Textbox 1). We will exclude interventions targeting the regulatory, economic, or financial aspects of EBP.

Textbox 1. Types of educational interventions targeted at health care organizations and health care professionals.

Health care organizations

- Ex-cathedra, interactive, online, or individual educational sessions on the steps and components of evidence-based practice (EBP) for registered nurses (RNs), nurse practitioners (NPs), and physiotherapists (PTs), such as reflexive practice, PICOT (population/patient problem; intervention; comparison; outcome; time)/PEO (population, patient, or problem; exposure; outcomes or themes) questions, critical appraisal of literature, and systematic reviews
- Organized journal clubs
- Systematic reviews organized within health care institutions

Health care providers

- Educational meetings aimed at RNs, NPs, and PTs alone or in collaboration with other health care professionals
- Distribution of educational materials (distribution of published or printed recommendations for clinical care, including clinical practice guidelines, audiovisual materials, and electronic publications)
- Web seminars and other individual-oriented educational activities, case studies, grand rounds, and mentoring
- Educational meetings (health care providers [HCPs] who have participated in conferences, lectures, workshops, or traineeships)
- Educational outreach visits (use of a trained person who has met with HCPs in their practice settings to give them information with the intent of changing their practice; information given may have included feedback on the HCP's performance
- Patient-mediated interventions (new clinical information, not previously available, collected directly from patients and given to the HCP [eg, depression scores from an instrument])
- Educational games as an educational strategy to improve standards of care
- Interprofessional education meetings
- Audit and feedback (any summary of the clinical performance of health care over a specified period; it may also have included recommendations for clinical action; information may have been obtained from medical records, computerized databases, or the observation of patients)

Types of Outcome Measures

The review's primary outcome measures will be increased or decreased beliefs, knowledge, implementation, and integration of EBP among RNs, NPs, and PTs active in primary health care settings (measured using methods [52,53] such as questionnaires, interviews, chart analysis, and self-reporting by RNs, NPs and PTs [53]), with a focus on dichotomous (yes/no), ordinal or continuous beliefs, and implementation or integration rates or scores.

The review's secondary outcome measures will be the production of systematic reviews; numbers of journal clubs organized; numbers of grand rounds organized; development of EBP guidelines or practice guidelines for care or case management; and the implementation of EBP programs, mentor coaching, or tutorial programs.

Search Methods for the Identification of Studies

In collaboration with the medical librarians (MS and PM) and using predefined search terms, we will conduct a systematic literature search for published articles in the following electronic databases, from inception until October 31, 2020: Medline Ovid SP (from 1946), PubMed (NOT Medline[sb]; from 1996), Embase.com (from 1947), CINAHL Ebesco (from 1937), the Cochrane Central Register of Controlled Trials Wiley (from 1992), PsycINFO Ovid SP (from 1806), Web of Science Core collection (from 1900), PEDro (from 1999), the JBI Database of Systematic Reviews and Implementation Reports (from 1998), and the Trip Database (from 1997). We will also conduct a hand search of the bibliographies of all the relevant articles and a search for unpublished studies using Google Scholar, ProQuest Dissertations and Theses dissemination, Mednar, and WorldCat. The search will be completed by exploring the grey literature in OpenGrey and the Grey Literature Report from inception until October 31, 2020.

The search syntax of the included databases will serve as the basis for all search strategies, using descriptors (EMTREE and Medical Subject Headings [MeSH]) and text terms with Boolean operators "AND" and "OR." The syntax consists of 4 search themes intersected by the Boolean terms "AND" and "OR." The descriptor terms included in the health occupations of RNs, NPs, and the allied health occupations of PTs are described in Textbox 2, and descriptor terms and keywords included in the search strategy for educational interventions on EBP are described in Textbox 3.

Textbox 2. The 4 search themes in the search for evidence-based practice (EBP) for health occupations of registered nurses (RNs), nurse practitioners (NPs), and the allied health occupations of physiotherapists (PTs).

Terms for nurses (RNs and NPs) active in primary care

- "Advanced Practice Nursing"
- "Nurse Practitioner"
- "Family Nurse Practitioner"
- "Community Health Nursing"
- "Home Health Nursing"
- "Parish Nursing"
- "Family Nursing"
- "Geriatric Nursing"
- "Hospice and Palliative Care Nursing"
- "Occupational Health Nursing"
- "Psychiatric Nursing"
- "Public Health Nursing"
- "Radiology and Imaging Nursing"
- "Rehabilitation Nursing"
- "Rural Nursing"
- "School Nursing"

Terms related to evidence-based practice

- "Evidence-based Healthcare"
- "Evidence-based Health Care"
- "Evidence-based Medicine"
- "Evidence-based Emergency Medicine"
- "Evidence-based Nursing"
- "Evidence-based Physical Therapy"
- "Evidence-based Physiotherapy"

Terms for physiotherapy or physical therapy

- "Physical Therapist"
- "Physiotherapists"
- "Evidence-based Physiotherapy"
- "Evidence-based Physical Therapy"

Terms related to evidence-based practice for physiotherapy or physical therapy

- "Physical Therapy Specialty"
- "Physiotherapy Specialty"

Textbox 3. Descriptor terms and keywords included in the search strategy for educational interventions on EBP.

Education intervention–related descriptor terms

- "Education, Nursing, Continuing"
- "Education, Nursing, Diploma Programmes"
- "Education, Nursing, Graduate"

Education intervention–related keywords

- "Mentoring"
- "Coaching"
- "Training Programme"
- "Workshops"

In addition to searching electronic databases, we will conduct a hand search of the bibliographies of all relevant articles and search for unpublished studies. We will consider publications in English, French, German, and Portuguese. Multimedia Appendix 1 presents the syntax used in all selected databases.

Data Collection and Analysis

Study Selection

Two pairs of reviewers (HV and PM, RH and MS) will independently screen the titles and abstracts identified in searches in order to assess which studies meet the inclusion criteria. Disagreements will be resolved through discussion, or, if needed, a consensus will be reached after discussion with the co-authors (AGM and FP).

Two pairs of reviewers (HV and PM, RH and MS) will independently assess the full-text articles to ensure that they meet the inclusion criteria. Disagreements will be discussed and resolved with the co-authors (AGM and FP). A flowchart of the trial selection process has been drawn in accordance with the PRISMA-P statement [44] (Multimedia Appendix 2).

Data Extraction

Data extraction will be conducted independently by 2 pairs of authors (HV, RH, FP) using a specially designed, standardized data extraction form (Multimedia Appendix 3). Discrepancies will be resolved through discussion and consultation with the co-authors (FP, RH, FP).

The following information will be extracted from each included study: (1) study authors, year of publication, and country where the study was conducted; (2) study characteristics (including setting and design, duration of follow-up, and sample size); (3) participants' characteristics (eg, profession, employment [% vs hours/week], employer, sex, age); (4) characteristics of interventions (eg, description and frequency of educational interventions, health care professionals involved); (5) characteristics of usual care group; and (6) types of outcome measures (Multimedia Appendix 3).

Assessment of the Risks of Bias in Included Studies

Two reviewers (HV and RH) will independently assess the risks of bias in all the randomized and nonrandomized studies of interventions (NRSIs) included. Disagreements will be resolved through discussion and consultation with the co-authors (HV, RH, FP).

We will use the validated Cochrane Risk of Bias Tool, version 2.0 [54], to assess the risk of bias in randomized trials and nonrandomized studies. This is based on 5 domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in the measurement of the outcome, and (5) bias in the selection of the reported result. Each of these 5 domains will be rated as one of the following: (1) low risk of bias, (2) some concerns, or (3) high risk of bias. Declaring that a study has a particular level of risk of bias in any individual domain will mean that the study as a whole has a risk of bias.

We will use the validated Robins-I tool for assessing the risk of bias in NRSIs [55]. This tool covers 2 dimensions and 7 domains through which bias might be introduced into an NRSI: (1) pre-intervention and at intervention (bias due to confounding, bias in the selection of study participants, and bias in the classification of the intervention) and (2) post-intervention (bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in selection of the reported result) [55]. Any disagreements in quality assessments will be resolved through discussion.

Statistical Analyses

Statistical analyses will be conducted following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [46] and the PRISMA and MOOSE statements [56].

For dichotomous outcomes, average intervention effects will be calculated as relative risks with 95% CIs using a random-effects model [57]. For continuous data, a random-effects model will be used to calculate weighted mean differences with 95% CIs. If required, we will calculate standard deviations from the standard errors or 95% CIs presented in the articles. Heterogeneity will be quantified using the I^2 and chi-squared tests. Funnel plots will be drawn, and Egger tests will be computed to explore the possibility of publication bias [58].

Reasons for heterogeneity in effect estimates will be sought in meta-analyses [59,60]. To explore the possible determinants of heterogeneity, we will conduct subgroup analyses according to

selected study characteristics (eg, participants' ages, country where the study was conducted, types of professions, types of interventions). Furthermore, sensitivity analyses will be conducted by (1) excluding relatively small studies (with fewer than 20 participants per randomization group) and (2) restricting the analyses to studies of good quality. Data will be analyzed using SPSS software (version 25.0) and Review Manager 5.3.

Results

The search strategy retrieved a total of 18,299 references (16,795 from databases and 1504 from other sources), and after removing duplicates, we included 12,948 references (11,469 from databases and 1479 from other sources) that will be analyzed on the titles and abstracts by 2 independent researchers (Table 1). In the second phase, full-text papers will be retrieved from the references and analyzed based on the inclusion and exclusion criteria. Finally, all included full-text articles meeting the criteria will be analyzed and reported in a structured paper. The final results are expected in March 2021.

Table 1. Number of references retrieved with the search strategy.

Sources	Date of search	Number of references	
		Found in total	After removing duplicates
Databases			
Medline OVID SP	October 31, 2020	3364	3356
Embase.com	October 31, 2020	4688	2718
PubMed	October 31, 2020	1749	1423
CINAHL EBSCO	October 31, 2020	3121	2120
PsycINFO OVID SP	October 31, 2020	1006	656
Cochrane Library Wiley	October 31, 2020	659	344
Web of Science – Core collection	October 31, 2020	2195	839
JBI OVID SP	October 31, 2020	13	13
Other Sources			
DART-Europe.eu	October 31, 2020	94	87
ProQuest Dissertations and Theses	October 31, 2020	377	359
SantéPsy	October 31, 2020	123	123
Lissa.fr	October 31, 2020	18	18
Opengrey.eu	October 31, 2020	93	93
PEDro.org	October 31, 2020	767	767
TRIP database.com	October 31, 2020	32	32

Discussion

Providing the best available, safe, high-quality health care is the gold standard objective in all health care settings. To the best of our knowledge, there exists no review of the effectiveness of educational interventions to increase the implementation of EBP among nurses and PTs working in primary health care. This systematic review research project will assess educational interventions aimed at both health care organizations and professional health care providers (RNs, NPs, and PTs). It will provide valuable information to HCPs, policymakers, and other stakeholders involved in primary health care.

Acknowledgments

This systematic review is funded by the Health Institute of the University of Applied Sciences and Arts Western Switzerland (funding reference number: Sagex 65137). This funding will support data collection and analysis. The funder was not involved in protocol design or the plan of analyses, nor will it be involved in the interpretation or publication of the scoping review's results.

Authors' Contributions

HV is the guarantor, and all the authors contributed to drafting the protocol. All authors will contribute to the development of the selection criteria, data extraction and analysis, and the search strategy (PM). RH, FP, and HV provided expertise in EPB. All the authors approved the final protocol manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Syntax of the systematic review.
[DOCX File , 204 KB - resprot_v9i11e17621_app1.docx]

Multimedia Appendix 2
PRISMA-P flowchart.
[DOCX File , 59 KB - resprot_v9i11e17621_app2.docx]

Multimedia Appendix 3
Data extraction sheet.
[DOCX File , 63 KB - resprot_v9i11e17621_app3.docx]

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Abbreviations

EBP: evidence-based practice
HCP: health care provider
MeSH: medical subject heading

NP: nurse practitioner
NRS: nonrandomized study
NRSI: nonrandomized studies of intervention
PICOT: population/patient problem; intervention; comparison; outcome; time
PEO: population, patient or problem; exposure; outcomes or themes
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols
PT: physiotherapist
RN: registered nurse

Edited by G Eysenbach; submitted 27.12.19; peer-reviewed by M Barwick, M Bestek; comments to author 21.08.20; revised version received 14.10.20; accepted 20.10.20; published 02.11.20.

Please cite as:
Verloo H, Melly P, Hilfiker R, Pereira F
Effectiveness of Educational Interventions to Increase Knowledge of Evidence-Based Practice Among Nurses and Physiotherapists in Primary Health Care: Protocol for a Systematic Review
JMIR Res Protoc 2020;9(11):e17621
URL: https://www.researchprotocols.org/2020/11/e17621
doi:10.2196/17621
PMID:33136056

Protocol

Effectiveness of Telemedicine Solutions for the Management of Patients With Diabetes: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Telemedicine is often suggested as a promising approach to support patients with diabetes. However, the effectiveness of diabetes-related telemedicine interventions in regard to patient-related outcomes requires further evaluation. Previous systematic reviews describing the effectiveness of telemedicine in diabetes management focus on a specific type of telemedicine, a specific type of diabetes, specific comparators, or specific outcomes. Moreover, the rapid development within telemedicine emphasizes the need for a new review.

Objective: The present review has a broad scope with an eye to performing an updated and exhaustive review within the field. The review aims to evaluate the effectiveness of existing telemedicine solutions versus any comparator without the use of telemedicine on diabetes-related outcomes among adult patients with diabetes.

Methods: The review will consider studies that include adult subjects with a diagnosis of diabetes (type 1, 2, or gestational), studies that evaluate various types of telemedicine interventions, and randomized controlled trials comparing a telemedicine intervention to any control that does not include telemedicine. Peer-reviewed full-text papers in English, Norwegian, Danish, and Swedish will be considered. A thorough search will be performed in the PubMed, CINAHL, EMBASE, and Cochrane Library Central Register of Controlled Trials (CENTRAL) databases. Data extraction will include details about the populations, study methods, interventions, and outcomes of significance based on the review objective.

Results: The results of the review are expected to provide an estimate of the treatment effect. The studies will be pooled via statistical meta-analysis and supplemented with narrative comparisons when necessary.

Conclusions: The review is important as it will inform clinicians and investigators about the effect of various telemedicine solutions within the field of diabetes.

International Registered Report Identifier (IRRID): DERR1-10.2196/22062

(JMIR Res Protoc 2020;9(11):e22062) doi:10.2196/22062

KEYWORDS

diabetes mellitus; glycemic control; HbA1c; telehealth

Introduction

Diabetes poses a major health care problem worldwide. In 2017, an estimated 8.4% of the adult world population had diabetes, and this number is predicted to increase to approximately 9.9% (425 million) in 2045 due to an increase in unhealthy dietary habits, overweight, physical inactivity, and other risk factors [1,2]. Type 1 diabetes (T1D) and type 2 diabetes (T2D) represent approximately 5%-8% and 90%-95% of diabetes cases, respectively, and preexisting T1D, T2D, or gestational diabetes mellitus (GDM) occur in approximately 1 of 6 pregnancies [1,3-5].

T1D and T2D are associated with premature death and several complications such as cardiovascular disease, nephropathy, neuropathy, and retinopathy [6]. Preexisting diabetes during pregnancy and GDM is associated with both maternal and neonatal complications such as preeclampsia, miscarriages, stillbirth, birth complications, and congenital abnormalities [5,7]. Furthermore, women with GDM and their babies have a considerably higher risk of developing T2D later in life [7]. Optimal glycemic control is crucial for the prevention and control of diabetes-related complications [5,6]. However, sustaining optimal glycemic control in the context of diabetes is challenging given that diabetes is a demanding chronic disease that requires numerous daily self-management decisions and the performance of complex care activities. One example is the challenge in estimating the appropriate diabetes medication dosage to avoid hypo- and hyperglycemic events, which requires consideration of various influencing factors. Another example is adherence obstacles with regard to following the recommended guidelines [6,8].

Self-management support in the management of diabetes is a recognized approach to help people with diabetes navigate unavoidable decisions and activities related to the disease, and is known to be associated with improvements in health-related outcomes [8]. The American Association of Diabetes refers to diabetes self-management support as activities that provide educational, behavioral, psychological, or clinical assistance in "implementing and sustaining the behaviors needed to manage his or her condition on an ongoing basis" [9]. Hence, self-management support should be highly prioritized in the management of diabetes.

Telemedicine has been suggested as a promising but unproven approach to support people with diabetes in the control of their disease [10]. Telemedicine includes the use of telecommunication and information technology to deliver health care services, including monitoring, education, consultative services, and counseling tasks, at a distance. Telemedicine interventions embrace various constellations such as simple reminders via text messaging, video consultation, and transmission of patient data (eg, blood glucose, blood pressure, dietary and medication intake) with feedback from health care professionals via web portal interfaces or the telephone. As diabetes mainly needs to be managed outside health care facilities, telemedicine could be an obvious solution to provide self-management support to people with diabetes. Moreover, telemedicine could be relevant to those who have difficulties traveling to health care facilities due to disabilities or large distances [11,12]. A recent systematic review and meta-analysis concluded that the use of telehealth solutions among people with diabetes is a safe option for the delivery of self-management support [13]. However, the approach still needs to be sufficiently evaluated in regard to its effectiveness in terms of patient-related outcomes (eg, clinical, behavioral, and psychological) within the diabetes context. Given this situation, a comparison and review of the effectiveness of different types of telemedicine interventions is highly relevant.

Previous systematic reviews describing the effectiveness of telemedicine for the management of diabetes exist [10,14-24]. However, these reviews are limited to specific types of telemedicine (eg, telemonitoring) [14,17-22], a specific diabetes type [15,23,24], specific outcomes (eg, hemoglobin A1c) [10,16], or specific comparators (typically usual care) [10,22]. In T2D, a previous systematic review observed heterogeneity among the included telemedicine studies, which may partly be explained by the variations in the types of telemedicine used [8]. This observation underlines the need for a review including a specific analysis considering the different types of telemedicine. The call for a new systematic review and meta-analysis of telemedicine solutions among people living with diabetes is further indicated due to the rapid development in the field of telemedicine. Hence, the expectation is that a large number of additional studies have been published since the performance of the previous reviews. Moreover, the possibility of integrating more telemedicine solutions increases in relevance owing to the increasing focus on the efficiency of health care resources [25].

The above-mentioned considerations suggest the value of a new and extensive review in the field. Therefore, the objective of this systematic review and meta-analysis will be to evaluate the effectiveness of existing telemedicine solutions versus any comparator without the use of telemedicine on diabetes-related outcomes among adult patients with diabetes. Telemedicine is defined as telecommunication and information technology that delivers health care services at a distance [11,12].

Methods

Study Design

The review will be conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [26], and a search protocol registered April 21, 2020 on PROSPERO (CRD42020123565) will form the basis of the review process.

Review Question

The question of this systematic review and meta-analysis is as follows: How effective are telemedicine solutions versus any comparator without the use of telemedicine in regard to diabetes-related outcomes among adult patients with diabetes?

As the question indicates, the review has a very broad scope. Hence, the review considers (1) studies related to T1D, T2D, and GDM; (2) all patient-related outcomes (physiological/clinical, psychological, and behavioral); and (3) any comparator that does not include telemedicine.

Inclusion Criteria

Participants

This systematic review and meta-analysis will consider studies that included adults ≥18 years of age who were diagnosed with T1D, T2D, or GDM. Studies that focused on pregnant women with preexisting T1D or T2D will also be considered. Studies reporting mixed disease populations (eg, diabetes and heart disease), mixed diabetes types, or mixed age groups (children and adults) will be included if the data for the population with diabetes or adult age group are reported separately in a transparent subgroup analysis. Studies will be excluded if they only include subjects at risk of diabetes or individuals with prediabetes.

Interventions

This systematic review and meta-analysis will consider studies that evaluate telemedicine interventions as a substitute or alternative to usual practice (ie, interventions with remote feedback/communication between either the patient and health care professional[s] or between the patient and trained peer[s]). Furthermore, wholly automatic telemedicine interventions will be considered. The telemedicine interventions may include various technologies such as telephone, smartphone, mobile phone, fax, text messaging, tablet, personal digital assistant, computer, and monitoring equipment (eg, glucometer, weight scale, pedometer, or sphygmomanometer) [11,12].

Comparators

This systematic review and meta-analysis will consider studies that compare the intervention to usual care or an alternative intervention without telemedicine. Both parallel and crossover designs will be considered.

Outcomes

This systematic review and meta-analysis will consider studies that report on any patient diabetes-related outcome(s) (ie, any physiological, psychological, or behavioral outcome). The primary outcome for T1D and T2D will be glycemic control, measured as a change in glycated hemoglobin (%). The primary outcome for pregnancy-related diabetes will be birth weight.

Study Types

This systematic review and meta-analysis will only consider randomized clinical trials (RCTs) with both a parallel and crossover design. Furthermore, studies will be included if the researchers consider the study to have adopted an RCT design based on the methodological approach of the individual study even if is the paper states that it used another design (eg, a quasiexperimental study design). Studies published in English, Danish, Norwegian, and Swedish as peer-reviewed full-text papers will be included. All studies published before the submission of the paper will be included, as both older and newer interventions are considered to bring value to the study (an updated search will be performed prior to submission).

Search Strategy

The search strategy aims to locate both published and unpublished studies. An initial limited search of the PubMed and CINAHL databases will be undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles will be used to perform a full search using PubMed, EMBASE, CINAHL, and the Cochrane Library Central Register of Controlled Trials (CENTRAL) databases. The full search history in PubMed is provided in Multimedia Appendix 1. The search strategy, including all identified keywords and index terms, will be adapted for each included information source. Search terms will include different synonyms, near-synonyms, spellings, and acronyms for each identified keyword and index term. Moreover, different search functions such as thesaurus, Boolean operators, truncation, abstract/title/keywords, phrase, free text, and advanced search will be applied to focus and structure the search.

To prevent selection bias, a follow-up search will be performed in each of the four databases prior to manuscript submission.

Citation searches and manual searches of the reference lists of relevant systematic reviews and of all studies selected for critical appraisal will be performed to identify additional studies.

Information Sources

The databases to be searched are PubMed (no limitation of search years), EMBASE (no limitation of search years), CENTRAL (no limitation of search years), and CINAHL (no limitation of search years). Two review authors will perform the database searches in collaboration with a research librarian.

Citation searches will be performed in SCOPUS, Web of Science, and through Google Scholar. ClinicalTrials will be searched to identify unpublished studies.

Authors of identified articles will be contacted if an article is not possible to access or if any question occurs during the selection or extraction processes.

Study Selection

Following the search, all identified citations will be collated and uploaded into RefWorks (Refworks, RefWorks-COS, ProQuest RefWorks 2.0, 2010), where the functions *Exact duplicates* and *Close duplicates* will be used for duplicate removal. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria of the review. Potentially relevant studies will be retrieved in full and assessed in detail by two independent reviewers against the inclusion criteria. Records on which the reviewers agree will be included in the systematic review. Any disagreement that arises between the reviewers at each stage of the study selection process will be resolved through discussion between the two reviewers or by including other reviewers in the decision-making process.

Reasons for exclusion of full-text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review and meta-analysis. The results of the search will be reported in full in the final systematic review and meta-analysis, and presented in a PRISMA flow chart as shown in Multimedia Appendix 2 [26].

Assessment of Methodological Quality

The risk of bias assessment of eligible studies will be performed by two or more independent reviewers using the revised Cochrane risk-of-bias tool [27].

Authors of papers will be contacted to request missing or additional data for clarification when required. Any disagreements that arise between the reviewers will be resolved through discussion or with a third or additional reviewer(s). The results of the risk-of-bias assessment of the eligible studies will be reported in a risk-of-bias chart using the revised Cochrane risk-of-bias tool [27].

All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible).

Data Extraction

Data will be extracted from the studies included in the review by three independent reviewers using tables in Microsoft Excel 2016. The data extracted will include specific details about the populations, study methods, interventions, and outcomes of significance based on the review objective. More specifically, three categories are considered relevant: (1) baseline characteristics of the study populations, (2) trial characteristics and key results, and (3) characteristics of the telemedicine interventions.

Any disagreements that arise between the reviewers will be resolved through discussion or with a third or additional reviewer(s).

Data Synthesis

All included studies will be pooled via a statistical meta-analysis to provide an overall estimate of the treatment effect. Meta-analyses will be performed with the RevMan VX.X (Copenhagen: The Nordic Cochrane Centre, Cochrane) software tool for T1D and GDM, and with Stata 14 software (StataCorp 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) for T2D. Effect sizes will be expressed as relative risks for dichotomous data. For continuous outcomes, effect sizes will be expressed as the mean (SD) change in outcomes from baseline to follow up for both groups, and, if not available, the absolute mean (SD) at follow up for both groups will be used. From this, the mean difference between the intervention and control group (or standardized mean difference) and confidence intervals can be calculated for each study. Heterogeneity will be assessed qualitatively by comparing the characteristics of the studies and statistically using I^2 tests. Statistical analyses will be performed using a fixed-effects model except if heterogeneity is deemed as being present (I^2>50%), in which case a random-effects model will be used. Subgroup analyses on types of telemedicine will be conducted when appropriate. Where statistical pooling is not possible, the findings will be presented in narrative form, including tables and figures to aid in data presentation when appropriate. A funnel plot will be generated to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed when appropriate.

Data Reporting

Three systematic reviews and meta-analyses will be conducted to obtain the results: one report on studies related to diabetes during pregnancy, one report on T1D studies (not related to pregnancy), and one report on T2D studies (not related to pregnancy). This subdivision is considered relevant to ensure a clear and easily accessible report of the results. The flowchart of the search will be reported in each of the reviews as it appears in Multimedia Appendix 2.

Assessing Certainty in the Findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be used, and a Summary of Findings (SoF) will be created using GRADEPro GDT 2015 (McMaster University, ON, Canada; developed by Evidence Prime, Inc) [28]. The SoF will present the following information where appropriate: absolute risks for the treatment and control groups; estimates of relative risk; and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision, and risk of publication bias of the review results. The outcomes reported in the SoF will be hemoglobin A1c (%) for T1D and T2D and birth weight for pregnancy-related diabetes.

Results

The systematic review is ongoing. A preliminary search in PubMed resulted in retrieval of 4813 records (Multimedia Appendix 1). The results of the review are expected to provide an estimate of the treatment effect. The studies will be pooled via statistical meta-analysis and supplemented with narrative comparisons when necessary. The results will be submitted for publication and peer review.

Discussion

The review is expected to have strengths as well as limitations. On the one hand, the search of literature will be very inclusive and exhaustive, which is a strength. On the other hand, the review is expected to be limited by the lack of homogeneity between the included telemedicine studies, as telemedicine studies tend to differ in intervention type, inclusion criteria, technology, and other aspects. The comparison of studies is expected to be complicated due to this divergence.

Acknowledgments

The authors acknowledge the research librarian Conni Skrubbeltrang for providing competent assistance during the search for articles.

Authors' Contributions

All authors contributed to the conception, design, analysis, and interpretation of data. SL drafted the article, and the remaining authors revised it critically for important intellectual content. All authors approved the final version of this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 15 KB - resprot_v9i11e22062_app1.docx]

Multimedia Appendix 2
Study selection flowchart.
[DOCX File , 66 KB - resprot_v9i11e22062_app2.docx]

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Abbreviations

CENTRAL: Central Register of Controlled Trials
GDM: gestational diabetes mellitus
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-analyses
RCT: randomized clinical trial
SoF: Summary of Findings
T1D: type 1 diabetes
T2D: type 2 diabetes

Edited by G Eysenbach; submitted 02.07.20; peer-reviewed by S Sarbadhikari, T Aslanidis; comments to author 16.09.20; revised version received 29.09.20; accepted 29.09.20; published 03.11.20.

Please cite as:
Laursen S, Hangaard S, Udsen F, Vestergaard P, Hejlesen O
Effectiveness of Telemedicine Solutions for the Management of Patients With Diabetes: Protocol for a Systematic Review and Meta-Analysis
JMIR Res Protoc 2020;9(11):e22062
URL: http://www.researchprotocols.org/2020/11/e22062/
doi:10.2196/22062
PMID:33141100

Protocol

Sella Turcica Morphology in Patients With Genetic Syndromes: Protocol for a Systematic Review

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Abstract

Background: The sella turcica is an important anatomical reference used in orthodontics and the evaluation of craniofacial growth. Studies have found an association between variations in sella turcica morphology in patients with certain syndromes affecting the craniofacial complex. It is hypothesized that each related syndrome or pathological condition is associated with a specific pattern of malformation of the sella turcica.

Objective: This study outlines the protocol for a systematic review that aims to determine if genetic syndromes involving the craniofacial complex are associated with abnormal radiographic sella turcica morphology and if there is a pattern of malformation that is consistent with each syndrome.

Methods: An electronic database search was conducted using a planned search strategy to identify relevant studies. We included primary studies evaluating the morphology of the sella turcica based on imaging from a lateral view. Specifically, only studies with postnatal human participants with genetic syndromes involving the craniofacial complex were included in this review. We placed no restrictions on the language or time frame of these studies. Based on the search findings, studies were further screened for relevance and eligibility by two independent reviewers. Data were extracted from the selected studies. We assessed the selected studies for risk of bias and quality by using risk of bias tools from the Joanna Briggs Institute. We will provide a narrative synthesis of our findings and a structured summary based on prespecified themes.

Results: The protocol is registered with PROSPERO (#CRD42019148060) and approved by the University of Western Cape Biomedical Science Research Ethics Committee (BM205/3). The literature search was conducted in September 2019 and updated in July 2020. The study was completed in August 2020, and the findings will be published in an open-access journal.

Conclusions: The results of this systematic review are expected to provide a comprehensive list of morphological variations of the sella turcica, which will aid in the identification of syndromes associated with the craniofacial complex. We also expect to identify patterns of sella turcica morphology that highlight genotype-phenotype correlations, thus adding to the body of evidence relating to genetics and craniofacial malformations.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42019148060; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=148060

International Registered Report Identifier (IRRID): RR1-10.2196/16633

(JMIR Res Protoc 2020;9(11):e16633) doi:10.2196/16633

KEYWORDS

sella turcica; craniofacial syndrome; craniofacial malformations; cephalometrics; systematic review

Introduction

The sella turcica is an important anatomical reference used in orthodontics and the evaluation of craniofacial growth [1]. It is easily determinable on the lateral profile and cephalometric radiographs and is useful in analyzing the relationship of the maxilla and mandible to the cranium, and to each other [2]. The sella turcica has several morphological variations that can be examined radiographically. Studies have found an association between variations in the sella turcica morphology in patients with dental anomalies [3-5] and those with certain syndromes affecting the craniofacial complex [6-9].

The sella turcica is an important region for the migration of neural crest cells to the frontonasal and maxillary developmental fields during embryological development [10,11]. The pituitary gland is located within the pituitary fossa, which is situated in the body of the sphenoid bone, within the cranium [10,12]. The pituitary gland is particularly important for endocrine function, and the development of the sella turcica is closely associated with that of the pituitary gland [13,14]. Thus, anomalies in the pituitary gland often present as abnormalities in the sella turcica [2,15]. Pathology of the pituitary gland often presents as aberrations in the size of the sella turcica. Pathological conditions such as adenomas, Rathke cleft cysts, and aneurysms are associated with enlargement of the sella turcica [14]. In contrast, hypopituitarism, growth hormone deficiency, and necrosis of the pituitary gland may result in a smaller sella turcica [14]. Moreover, numerous studies have found an association between conditions and syndromes affecting the craniofacial complex and morphological deviations of the sella turcica. These include Williams syndrome [8], Down syndrome [6], osteogenesis imperfecta [16], Axenfeld-Rieger syndrome [9], cleft-lip and palate [7], trisomy 18, Fragile X syndrome, and Cri-du-chat syndrome [1].

Several classifications describe the morphological variations of the sella turcica based on radiographic findings. Its morphology is often described subjectively and qualitatively, and it is classified into shapes such as circular, oval, flat, shallow, and J-shaped [17]. Several studies have examined the prevalence and distribution of different morphological presentations of the sella turcica in “normal” individuals to produce reference standards [2,15,17-19]. These reference standards assist in detecting deviations from the norm and pathology in the sella turcica [2].

According to Kjaer et al [1], each syndrome or pathological condition has a specific pattern of malformation of the sella turcica, which varies in severity depending on the phenotype. Therefore, this systematic review aimed to determine whether genetic syndromes involving the craniofacial complex are associated with abnormal sella turcica morphology and to identify patterns of malformations if they exist. The study also aimed to explore the clinical relevance of these findings.

Methods

Study and Ethics Approvals

This protocol has been compiled using the PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols) guidelines [20] and is registered with PROSPERO (#CRD42019148060). The systematic review conformed to the PRISMA guidelines [21].

Ethics approval and consent for participation were not required for this study. This study was approved by the University of Western Cape Biomedical Science Research Ethics Committee (BM205/3).

Study Eligibility Criteria

The literature search included primary studies evaluating the morphology of the sella turcica based on lateral radiographs or via digital imaging from a lateral view, such as cone-beam computed tomography (CBCT). Only studies on postnatal human participants with genetic syndromes primarily involving the craniofacial complex were included in the review. Reviews and letters to the editor were excluded. No restriction was placed on grey literature, language, and time frame. The inclusion criteria were deliberately left broad to attempt to find as many relevant papers that relate to the primary and secondary objectives of this study as possible, as the morphology of the sella turcica may be noted as an incidental finding in some published studies.

Anatomic Structure of Interest

The sella turcica is a saddle-like bony structure on the upper surface of the sphenoid bone. The most posterior part of the sella turcica is known as the hypophyseal or pituitary fossa that houses the pituitary gland [22]. It has an anterior and a posterior border, known as the tuberculum sellae and the dorsum sellae, respectively [14]. The dorsum sellae is continuous with the clivus and the posterior clinoid process. The two anterior and posterior clinoid processes project over the pituitary fossa [10,14].

As noted in the introduction, the morphology of the sella turcica is often described subjectively and qualitatively as shapes that broadly describe the shape of the sella turcica itself and its relation to the tuberculum and dorsum sellae [17]. Axelsson et al [18] created a detailed classification consisting of six morphological types of the sella turcica: (a) “normal,” (b) oblique anterior wall, (c) double contour of the floor, (d) sella turcica bridge, (e) irregularity (notching) in the posterior wall, and (f) pyramidal shape of the dorsum sellae. Andredaki et al [17] established the need for more quantitative methods to measure the size and shape of the sella turcica by using specialized software. In the review, we considered any method used to describe the morphology of the sella turcica.

Population of Interest

A syndrome is defined as a set of symptoms occurring together or a pattern of multiple malformations thought to be pathogenetically related and not known to represent a single sequence or polytopic field defect [23]. According to Kjaer [24], a craniofacial syndrome is characterized by morphological and

developmental deviations in the cranial tissue components, including the teeth. Humans with genetic syndromes primarily involving the craniofacial bony complex were included in this study. However, primary endocrine syndromes or syndromes caused by neoplasia as well as empty sella syndrome were excluded.

Imaging of the Sella Turcica

Imaging of the sella turcica for orthodontic and craniofacial growth assessment purposes is conventionally performed using either digital or nondigital lateral cephalometric radiographs. For this review, we also included studies involving lateral skull radiography and CBCT providing a lateral view of the sella turcica region [25]. Moreover, we also included studies providing an adequate description of the lateral view of the sella turcica with novel forms of imaging, given that measurements are correlated to a standard cephalometric radiograph.

Study Outcomes

The primary objective was to determine if genetic syndromes involving the craniofacial complex are associated with an abnormal morphology of the sella turcica based on radiographic analysis. Thus, we needed to first establish what is considered a "normal" morphology of the sella turcica. Axelsson et al [18] described the U-shaped morphology of the sella turcica as normal based on a subjective, visual assessment. Andredaki et al [17] used a software program to determine normative reference standards of the sella turcica. Therefore, we allowed flexibility in the definition of "normal" morphology as there is no accepted standard at present. If an adequate description of the "normal" reference morphology were provided in the included studies, it would be reported. Deviation from the "normal" was defined as "abnormal."

The secondary outcome measures relate to the findings of morphological aberrations of the sella turcica in individuals with the same syndrome as well as between them and individuals with no genetic syndromes if a comparator was used in the given study. This was done in the same manner as determining the primary outcome measure and then observing whether trends exist within and between studies.

Information Source and Search Strategy

An electronic search of several databases and journals was conducted using a planned search strategy (Table 1). SCOPUS, PubMed/MEDLINE, Web of Science, ProQuest, and WorldCat, as well as all databases within EBSCOhost, were searched. Each electronic database was searched using a tailored keyword or MeSH term. The results of the search were documented, reported, and compared between databases. Where papers were found to be relevant, the reference lists were manually searched for additional relevant papers. Additional searches were conducted using the search term "sella turcica genetic syndrome" with Google Scholar, ISI Citation Indices, and Web of Science ISI proceedings (conference proceedings).

Unpublished and ongoing studies were also sought from online registries, including the NIH Health Services Research Projects in Progress, the ISRCTN registry, the UK Clinical Trials Gateway, and the WHO International Clinical Trials Platform. In cases wherein studies were found to be potentially relevant and full-text papers could not be found, the authors were contacted to gain more information and determine whether the study should be included.

Table 1. Example of search strategy used in this review (Database: PubMed; Date: Sep 24, 2019; Limits: none).

No.	Search terms	Result
1	SELLA[ALL FIELDS]	8384
2	SELLA TURCICA OR HYPOPHYSEAL FOSSA OR PITUITARY FOSSA[ALL FIELDS]	8384
3	#1 OR #2	8384
4	SYNDROME[Title/Abstract]	8,65,737
5	GENETIC SYNDROME[ALL FIELDS]	1,08,333
6	#4 AND #5	8,92,138
7	#3 AND #6	1202

Study Selection

Papers were screened in two stages—initially by title and abstract screening and then by full-text screening. Two reviewers conducted the screening and data extraction independently, and any failure of consensus was resolved by a senior third party. Reasons for exclusion of studies will be provided in the report. Interrater agreement was calculated and reported.

Data Extraction and Management

Each reviewer independently performed data extraction. An electronic data extraction form was custom-made, piloted, and amended as required for this review. The data collection form included the fields enlisted in Textbox 1.

Textbox 1. Data extraction fields used in this study.

Study Information

- Authors, title, year of publication, journal
- Study designs
- County of study

Study Participants

- Recruitment procedures
- Baseline characteristics, demographics
- Type of syndrome
- Genetic information
- Any additional abnormalities or medical conditions
- Any therapies that the patients might have received (eg, bisphosphonates)

Methods

- Study design, study duration
- Allocation sequence concealment, blinding, other concerns about bias

Imaging Techniques

- Type of imaging used (cone-beam computed tomography, digital cephalogram, or other)
- Additional information regarding standardization of images

Outcomes

- Morphology of the sella turcica
- Method of measurement
- Method of classification
- Method of bias elimination in the determination of morphology

Results

- Determining the “normal” sella turcica within populations
- Prevalence of sella turcica abnormalities in patients with syndromes affecting the craniofacial complex
- Patterns of sella turcica morphology amongst the population
- Description of findings regarding sella turcica morphology

Availability of Data and Materials

All data generated or analyzed during this study will be included in the published study.

Study Quality and Risk of Bias Assessment

Each reviewer independently conducted an assessment of the study quality and risk of bias by using the risk of bias tools recommended by the Joanna Briggs Institute, for each included case study, case series, case-control study, and cohort study. Interrater agreement was then calculated. These assessments will be summarized and included in the report.

Analysis of Study Findings

We will provide a narrative synthesis of the findings from the included studies. The narrative synthesis will be structured according to themes in the following manner, to provide a coherent summary of findings: characteristics of included studies; baseline characteristics of the population (eg, age and sex); nature of the syndrome (a brief overview of the syndromes included with a summary of craniofacial manifestations); any genetic information considered pertinent; imaging techniques used; techniques used to describe sella turcica morphology; methods of classification of sella turcica morphology; prevalence of sella turcica anomalies; patterns of sella turcica abnormalities within and between syndromes; and any additional findings. Limitations and gaps in the reporting and methodologies will be noted and discussed.

Results

No patients were involved in the development of this study. This protocol was completed in September 2019 and registered with PROSPERO (#CRD42019148060) in December 2019. The electronic literature search was conducted in September 2019 and updated in July 2020. The original search yielded

11,844 titles. This study was completed in August 2020 and will be published soon. We intend to publish this study in an open-access journal to allow for the wide dissemination of findings and promote ease of access to the public.

Discussion

Principal Findings

This study aimed to determine if genetic syndromes involving the craniofacial complex are associated with abnormal sella turcica morphology and to identify patterns of malformations if they exist. Current evidence suggests that there is an association between morphological abnormalities of the sella turcica and abnormalities in craniofacial development and that these abnormalities appear to be patterned among patients with particular syndromes [1]. However, no systematic review has been conducted to confirm this.

The sella turcica is considered a borderline area between developmental fields [26]. The anterior part of the sella turcica is derived from the neural crest cells, whereas most of its posterior wall and floor is derived from the notochord mesoderm [27]. Thus, abnormalities in the anterior part of the sella turcica may be associated with malformations in the facial bones, and abnormalities in the posterior wall and floor may be associated with abnormalities in the spine [27]. The sella turcica bridge between the anterior and posterior walls is also more commonly observed in individuals with severe malocclusions and other craniofacial malformations [5,28]. Owing to this complex development and the close association between the central nervous system, peripheral nervous system, and endocrine system, malformation of the sella turcica may be affected by many genetic and nongenetic factors. However, the patterning of malformations within certain genotypes indicates that genes play a central role in these malformations. Thus, attempting to understand these malformation patterns may provide us with new avenues of genetic and craniofacial pathology research.

Conclusion

The results of this systematic review are expected to provide a comprehensive list of morphological variations of the sella turcica, which will aid in the identification of syndromes associated with the craniofacial complex. It may also provide insights into patterns of craniofacial malformations that may be genetically linked, thus adding to the body of evidence relating to genetics and craniofacial malformations.

Authors' Contributions

IAR was responsible for developing the study and writing the manuscript. MC acted in a supervisory capacity and is jointly accountable for the work.

Conflicts of Interest

None declared.

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Abbreviations

CBCT: cone-beam computed tomography
PRISMA-P: Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols

Edited by G Eysenbach; submitted 09.10.19; peer-reviewed by A DaSilveira, A Abd-alrazaq; comments to author 21.08.20; revised version received 24.08.20; accepted 25.08.20; published 05.11.20.

Please cite as:
Roomaney IA, Chetty M
Sella Turcica Morphology in Patients With Genetic Syndromes: Protocol for a Systematic Review
JMIR Res Protoc 2020;9(11):e16633
URL: https://www.researchprotocols.org/2020/11/e16633
doi:10.2196/16633
PMID:33151160

Protocol

The Effect of the COVID-19 Pandemic on Health Care Workers' Anxiety Levels: Protocol for a Meta-Analysis

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Abstract

Background: The COVID-19 pandemic has been declared a public health emergency of international concern; this has caused excessive anxiety among health care workers. In addition, publication bias and low-quality publications have become widespread, which can result in the dissemination of unreliable findings.

Objective: This paper presents the protocol for a meta-analysis with the following two aims: (1) to examine the prevalence of anxiety among health care workers and determine whether it has increased due to the COVID-19 pandemic, and (2) to investigate whether there has been an increase in publication bias.

Methods: All related studies that were published/released from 2015 to 2020 will be searched in electronic databases (Web of Science, PubMed, PsyArXiv, and medRxiv). The risk of bias in individual studies will be assessed using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist. The heterogeneity of the studies will be assessed using the I^2 statistic. The effect size (prevalence rates of anxiety) and a 95% CI for each paper will also be calculated. We will use a moderator analysis to test for the effect of COVID-19 on health care workers' anxiety levels and detect publication bias in COVID-19 studies. We will also assess publication bias using the funnel plot and Egger regression. In case of publication bias, if studies have no homogeneity, the trim-and-fill procedure will be applied to adjust for missing studies.

Results: Database searches will commence in November 2020. The meta-analysis will be completed within 2 months of the start date.

Conclusions: This meta-analysis aims to provide comprehensive evidence about whether COVID-19 increases the prevalence of anxiety among health care workers and whether there has been an increase in publication bias and a deterioration in the quality of publications due to the pandemic. The results of this meta-analysis can provide evidence to help health managers to make informed decisions related to anxiety prevention in health care workers.

International Registered Report Identifier (IRRID): PRR1-10.2196/24136

(JMIR Res Protoc 2020;9(11):e24136) doi:10.2196/24136

KEYWORDS

COVID-19; health care worker; anxiety; meta-analysis; review; protocol; mental health; literature; bias

Introduction

Background and Research Questions

The COVID-19 pandemic has affected more than 18.9 million individuals and resulted in over 709,000 deaths globally [1]. It has, therefore, been declared a public health emergency of international concern [2]. To tide over this crisis, it is important to maintain an adequate health care workforce, which requires not only an sufficient number of health care workers but also the maximization of each health care worker's ability to care for a greater number of patients. Since the outbreak can last

several months, it is also critical that health care workers are able to perform to their full potential over an extended time interval [3].

The COVID-19 pandemic has affected many aspects of people's lives, especially their mental health [4-7]. While health care workers have to concurrently cope with the societal shifts and emotional stressors faced by the general population, they additionally face greater risks of exposure, extreme workloads, moral dilemmas, and rapidly evolving practice environments that differ greatly from what they are familiar with [8,9]. Moreover, facing hitherto unknown challenges in both physical and mental health causes excessive tension and anxiety in health care workers [10]. While anxiety is a common mental condition that can cause emotional distress, obsessive thinking, and compulsive behavior, long-term anxiety results in psychological distress and even affects the daily lives of individuals [11]. Anxiety also impairs the executive functions that underlie our ability to control and focus on our thoughts [12]. Consequently, studying and accurately grasping the anxiety levels of health care workers is necessary to take more appropriate and corrective measures to deal with public health and safety.

Although some researchers have investigated health care workers' anxiety levels during the COVID-19 pandemic [13,14], many new papers on COVID-19 are being released rapidly since the pandemic still poses a serious threat. The present meta-analytic study includes the latest papers, and aims to generate a more comprehensive understanding of the prevalence of anxiety among health care workers. Furthermore, to date, a comparison has not been established between studies on health care workers' anxiety levels, related and unrelated to COVID-19. In the current outbreak situation, will studies conducted in two different periods have different effect sizes? Will levels of anxiety increase significantly? Accordingly, the first aim of our meta-analysis is to examine health care workers' anxiety status and determine the COVID-19 pandemic's influence by comparing COVID-19–related studies with unrelated studies.

In addition, since the onset of the outbreak, knowledge about COVID-19 is direly needed, and medical journals have drastically accelerated the publication process for COVID-19–related articles to accelerate knowledge acquisition [15,16]. In this situation, the preference for publishing papers with significant results may be more extreme, which may seriously compromise the ability to draw valid conclusions from the published literature. Since the publication bias may be highly flawed, the second aim of our meta-analysis is to investigate publication bias by comparing unpublished preprints on COVID-19 with published journal papers about COVID-19.

Hypotheses

We have generated the following two hypotheses:

1. COVID-19 makes health care workers more anxious and thus the studies related to COVID-19 will have a larger effect size. We will investigate this by comparing studies related to COVID-19 vs studies unrelated to it.
2. Publication bias in COVID-19–related studies is widespread. We will investigate this by comparing unpublished preprints about COVID-19 with published journal papers about the disease.

Methods

Search Strategy

This study will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [17]. We will search through electronic databases—Web of Science, PubMed, PsyArXiv, and medRxiv—for all published journal papers (related vs unrelated to COVID-19) and preprints (relevant to COVID-19), whose titles and abstracts include the search terms presented in Textbox 1.

Textbox 1. Search terms.

("Health Personnel" OR "Personnel, Health" OR "Health Care Providers" OR "Health Care Provider" OR "Provider, Health Care" OR "Providers, Health Care" OR "Healthcare Providers" OR "Healthcare Provider" OR "Provider, Healthcare" OR "Providers, Healthcare" OR "Healthcare Workers" OR "Healthcare Worker" OR "Health Occupations" OR "Health Occupation" OR "Health Professions" OR "Health Profession" OR "Profession, Health" OR "Professions, Health" OR "Health professions")

AND

(Anxiety OR Hypervigilance OR Nervousness OR "Social Anxiety" OR "Anxieties, Social" OR "Anxiety, Social" OR "Social Anxieties")

Inclusion and Exclusion Criteria

Studies will be included only if they meet the following inclusion criteria: (1) written in English (which will be decided based on the research team's unified considerations); (2) related to "anxiety among health care workers"; (3) quantitative research designs; (4) submitted during 2015 to 2020; (5) include standardized measures of anxiety with published psychometric data and reasonable evidence of reliability and validity; (6) include a clear description of methods used to assess and score standardized measurement instruments; and (7) include publicly available effect sizes (prevalence) or values that can be calculated (the number of health care workers with anxiety and the sample size).

The exclusion criteria are: (1) studies with insufficient data, (2) duplicate sources, (3) research with unclear methods, and (4) publications about other outbreaks.

Data Extraction

First, duplicate papers that are found in multiple databases will be removed. Subsequently, screening of the titles and abstracts will be conducted, and papers will be removed based on the inclusion and exclusion criteria. Furthermore, the full text of the papers will be checked, and article information will be extracted using a preprepared extraction table that includes the article's title, authors' names, scales used, year of submission, country, sample size, whether the study has been published, whether the study relates to COVID-19, and the effect size

(prevalence of anxiety). The article review and data extraction processes will be performed independently by two of the authors. When there is a disagreement between them, the other authors will resolve the conflict.

Study Assessment Criteria

We will use the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist to assess the quality of observational studies [18]. The checklist consists of 6 scales—title, abstract, introduction, method, results, and discussion—each of which includes multiple items, comprising a total of 32 items. Each item is scored as 0 (not fulfilled) or 1 (fulfilled). In the modified STROBE, scores range from 0 to 32, with scores ≥16 indicating a low risk of bias and scores <16 indicating a high risk of bias. Papers that exhibit a low risk of bias will be selected for the analysis.

Statistical Analysis

First, the heterogeneity of the studies will be determined using the I^2 statistical index, which ranges from 0 to 100; the larger the index, the more heterogeneous are the findings. The categories encompassed by the index will be defined based on the test developed by Higgins et al [19] to measure the extent of heterogeneity: low (25%), moderate (50%), and high (75%). A study with a heterogeneity >50% prompts the use of random effects models. For each research, we will calculate the effect size (prevalence rates of anxiety) and a 95% CI around the effect size. For the data reported, if the original paper does not list the effect size or the number of health care workers with anxiety (which can be used to calculate the effect size), the authors of the paper will be contacted and asked to provide this information. If they are unable to do so, the study will be excluded from the analyses.

Subsequently, we will use a moderator analysis to test for the effect of COVID-19 on health care workers' anxiety levels (related vs unrelated to COVID-19), and publication bias in COVID-19 studies (preprints vs published journal papers). We will also assess publication bias using the funnel plot and Egger regression [20]. For the Egger regression, a *P* value less than the significance level (α=.05) suggests that publication bias is present. If publication bias is present, and studies have no homogeneity, the trim-and-fill procedure will be applied to adjust these missing studies [21].

Finally, sensitivity analyses will be performed to assess the influence of each individual study on the pooled effect size. The statistical significance level is defined as α=.05.

Results

Database searches will commence in November 2020. The meta-analysis will be completed within 2 months.

Discussion

This paper presents a protocol for a meta-analysis that aims to provide comprehensive evidence about whether the COVID-19 pandemic increases the prevalence of anxiety among health care workers and whether there has been an increase in publication bias and a deterioration in the quality of publications due to the pandemic. The results of this meta-analysis can provide evidence to help health managers to make informed decisions for preventing anxiety in health care workers.

Acknowledgments

This research was supported by the Japan Society for the Promotion of Science KAKENHI (16H03079, 17H00875, 18K12015, and 20H04581).

Conflicts of Interest

None declared.

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

Edited by G Eysenbach; submitted 05.09.20; peer-reviewed by N Mohammad Gholi Mezerji, A Azzam, H Alhashmi; comments to author 23.09.20; revised version received 01.10.20; accepted 20.10.20; published 18.11.20.

Please cite as:
Zhang L, Yan M, Takashima K, Guo W, Yamada Y
The Effect of the COVID-19 Pandemic on Health Care Workers' Anxiety Levels: Protocol for a Meta-Analysis
JMIR Res Protoc 2020;9(11):e24136
URL: http://www.researchprotocols.org/2020/11/e24136/
doi:10.2196/24136
PMID:33170800

Proposal

Implementing Individually Tailored Prescription of Physical Activity in Routine Clinical Care: Protocol of the Physicians Implement Exercise = Medicine (PIE=M) Development and Implementation Project

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Abstract

Background: The prescription of physical activity (PA) in clinical care has been advocated worldwide. This "exercise is medicine" (E=M) concept can be used to prevent, manage, and cure various lifestyle-related chronic diseases. Due to several challenges, E=M is not yet routinely implemented in clinical care.

Objective: This paper describes the rationale and design of the Physicians Implement Exercise = Medicine (PIE=M) study, which aims to facilitate the implementation of E=M in hospital care.

Methods: PIE=M consists of 3 interrelated work packages. First, levels and determinants of PA in different patient and healthy populations will be investigated using existing cohort data. The current implementation status, facilitators, and barriers of E=M will also be investigated using a mixed-methods approach among clinicians of participating departments from 2 diverse university medical centers (both located in a city, but one serving an urban population and one serving a more rural population). Implementation strategies will be connected to these barriers and facilitators using a systematic implementation mapping approach. Second, a generic E=M tool will be developed that will provide tailored PA prescription and referral. Requirements for this tool will be investigated among clinicians and department managers. The tool will be developed using an iterative design process in which all stakeholders reflect on the design of the E=M tool. Third, we will pilot-implement the set of implementation strategies, including the E=M tool, to test its feasibility in routine care of clinicians in these 2 university medical centers. An extensive learning process evaluation will be performed among clinicians, department managers, lifestyle coaches, and patients using a mixed-methods design based on the RE-AIM framework.

Results: This project was approved and funded by the Dutch grant provider ZonMW in April 2018. The project started in September 2018 and continues until December 2020 (depending on the course of the COVID-19 crisis). All data from the first work package have been collected and analyzed and are expected to be published in 2021. Results of the second work package are described. The manuscript is expected to be published in 2021. The third work package is currently being conducted in clinical practice in 4 departments of 2 university medical hospitals among clinicians, lifestyle coaches, hospital managers, and patients. Results are expected to be published in 2021.

Conclusions: The PIE=M project addresses the potential of providing patients with PA advice to prevent and manage chronic disease, improve recovery, and enable healthy ageing by developing E=M implementation strategies, including an E=M tool, in routine clinical care. The PIE=M project will result in a blueprint of implementation strategies, including an E=M screening and referral tool, which aims to improve E=M referral by clinicians to improve patients' health, while minimizing the burden on clinicians.

(JMIR Res Protoc 2020;9(11):e19397) doi:10.2196/19397

KEYWORDS

clinicians; Exercise is Medicine initiative; physical activity; exercise referral; conventional treatment; hospital care

Introduction

Over the past century, life expectancy has increased to over 80 years in many developed countries, largely because of reduced mortality rates associated with infectious diseases, childbirth, and malnutrition [1,2]. At the same time, a global pandemic of physical inactivity has occurred that contributes to dramatic increases in lifestyle-related chronic diseases [3,4]. As a result, the increase in life expectancy has not been accompanied by a comparable increase in the number of years spent in good health [2]. To increase these healthy life years, physical activity (PA) plays a crucial role in reducing the risk of a range of noncommunicable diseases. Because of its health benefits, PA improves daily life functioning, wellbeing, and quality of life and reduces healthcare costs [5]. A recent study has conservatively estimated the global financial burden of physical inactivity to be US $68 billion annually [6]. Hence, improving PA has been identified as a "best buy" for public health [5].

In the general population, the association between PA and morbidity is inverse and curvilinear; the biggest health gain can be achieved by getting inactive people to move [7]. Meeting PA guidelines of 150 minutes of moderate to vigorous intensity PA per week and muscle-strengthening activities 2 times per week is internationally recommended [5,8,9]. Also, in patients, increased PA leads to improved health and fitness, leading to maintenance of functional independence and improved quality of life [10,11]. Besides its effects on morbidity, PA is effective in preventing mortality in different patient groups. A recent meta-analysis of 305 RCTs with 339,274 participants indicated that exercise, being a specific subset of PA that is planned, structured, and repetitive, had at least similar mortality benefits to those of drug interventions in patients with lifestyle-related chronic diseases (eg, coronary heart disease, stroke, heart failure, and prediabetes) [12]. In cancer patients, meeting PA guidelines has been shown to reduce the relative risk of mortality up to almost 40%-50% [13].

The prescription of PA in clinical care has been advocated worldwide through the paradigm of "exercise is medicine" (E=M) [14-16]. Prescribing PA to patients can be used to prevent, manage, and cure various lifestyle-related chronic diseases and to prevent the development of both primary and secondary chronic diseases [17-20]. E=M differs from conventional medicine in that it treats the underlying physiological causes of disease and patients become active in managing their own health, whereby it fits the new definition of health as "the ability to adapt and self-manage" [21]. Initiatives for the implementation of E=M in primary care exist [22,23], but it has been suggested that E=M should also be part of the hospital care system (secondary and tertiary care) in terms

of treatment and prescription [24,25]. E=M has great potential because of the authority and important role that clinicians play [26,27]. Periods of impaired health and time spent in the hospital can make patients receptive to behavioral change, creating teachable moments to counsel patients how to implement a physically active lifestyle [28].

Several challenges for implementing E=M at the individual clinician level are described in the literature [29]. First, some clinicians are, due to their medical training, much more likely to opt for the prescription of medication or choose other treatment options, such as surgery, rather than prescribing E=M, which is not part of regular medical training currently [30,31]. Second, clinicians are often unaware of the possibilities for, or feel uncomfortable, referring their patients to exercise professionals in or outside the hospital [29]. Third, clinicians may experience time constraints to discuss E=M with patients [30] or lack feasible tools to prescribe E=M in day-to-day care [29]. Accordingly, if clinicians prescribe E=M, it is often in the form of abstract, brief, general advice, rather than concrete, tailored prescription. To increase uptake of PA prescriptions by patients, robust implementation of personalized E=M into routine clinical care is needed.

A recent overview paper by Bowen et al [29] described several opportunities to deal with these challenges to optimally facilitate sustainable implementation of E=M in routine clinical care. They suggested that E=M can be implemented in routine clinical care via an E=M tool in electronic medical records (EMRs). Such a tool could assess patients' current PA level, cardiometabolic risk, and overall health status related to PA, after which a clinical decision algorithm could help tailor PA prescription for each individual patient [29]. By generating a tailored PA prescription, such a tool has the potential to facilitate the implementation of E=M without requiring extensive knowledge on local PA facilities or major time investment by clinicians.

This paper describes the rationale and design of the Physicians Implement Exercise = Medicine (PIE=M) project, in which 2 diverse university medical centers in the Netherlands (both located in a city, but one serving an urban population and one serving a more rural population) will work towards implementing E=M into routine clinical care. PIE=M will address the following 3 objectives. First, we will determine levels and determinants of PA in different patient populations and compare this to the healthy population, in order to study the need for E=M. We will also determine the current implementation status of E=M and facilitators and barriers of E=M implementation for clinicians and hospital managers in selected clinical departments of both university medical centers. Based on these barriers and facilitators, a tailored set of implementation strategies will be selected to stimulate the implementation of E=M in the 2 university medical centers involved. Second, we will develop an E=M tool that will provide individually tailored PA prescriptions and referrals, in co-creation with clinicians who are the end users of this tool. Third, we will test the feasibility of the new E=M implementation strategies, including the E=M tool, when implemented in routine work processes of clinicians in 2 university medical centers.

Methods

Given its multidisciplinary nature, the PIE=M project will be performed by a large consortium including all relevant stakeholders. This consortium consists of clinicians working in the departments of Rehabilitation Medicine and Medical Oncology of the Amsterdam University Medical Centers (both Amsterdam UMC location VUmc) and the departments of Rehabilitation Medicine, Orthopedics, and Sports Medicine of the University Medical Center Groningen (all UMCG). Moreover, researchers, professionals in technical information technology, implementation experts, sports organizations, municipalities, lifestyle professionals, and patient representatives are involved in the consortium. Throughout this paper, the term "clinicians" refers to physicians and residents working in secondary and tertiary health care. Given the participating medical departments in the PIE=M project, clinicians will be rehabilitation physicians, oncologists, orthopedists, and sports physicians. The health benefits of PA are not assumed to be diagnosis-specific, whereby the PIE=M project targets patients suffering from different physical diseases or disabilities. Throughout this paper, the term "patients" thereby refers to people with different physical diagnoses who are treated within the participating medical departments. Patients, for instance, have musculoskeletal disorders, multiple sclerosis, diabetic neuropathy, osteoarthritis, or cancer.

The PIE=M project consists of 3 interrelated work packages, visually presented in Figure 1. The determinants that will be assessed in the different work packages of the PIE=M project are presented in Table 1, separated at the individual clinician, strategy, and patient levels.

Figure 1. Visual representation of the 3 work packages of the Physicians Implement Exercise = Medicine (PIE=M) project. PA: physical activity; E=M: Exercise = Medicine.

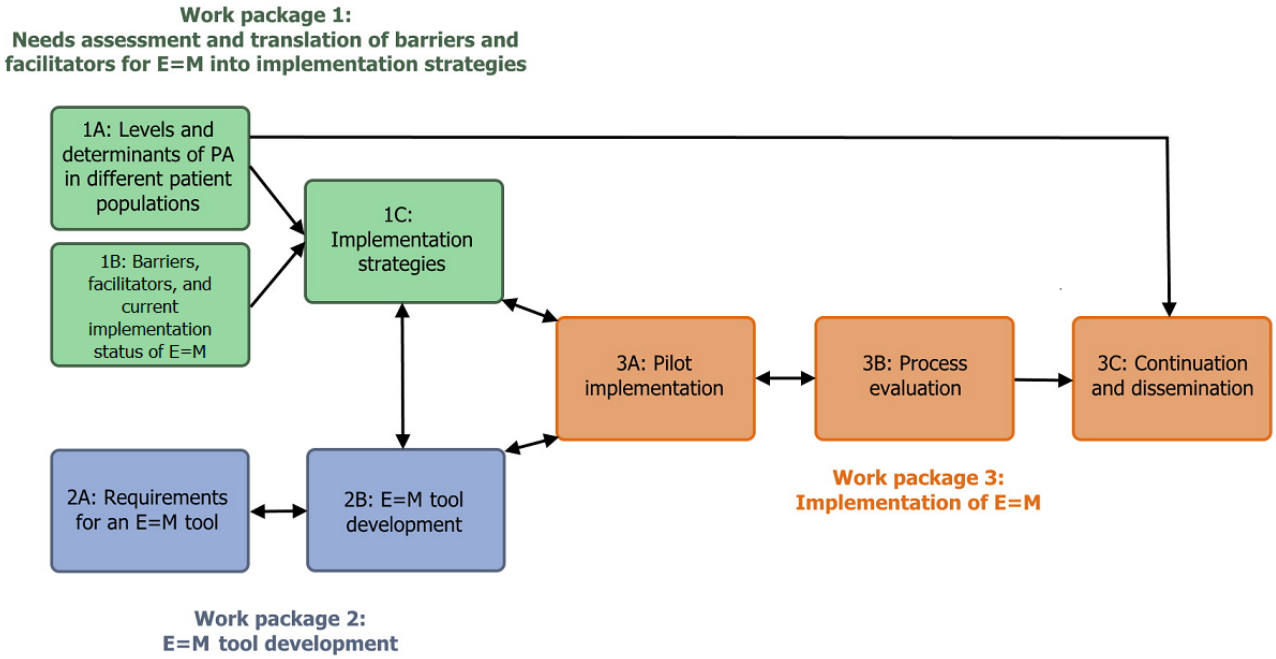

Table 1. Determinants that will be assessed in the different work packages of the Physicians Implement Exercise = Medicine (PIE=M) project.

Work packages	Individual clinician level (methods used)	Strategy level (methods used)	Patient level (methods used)
Work package 1			
1A	N/A[a]	N/A	• Level of PA in different patient populations (Lifelines) • Determinants of PA in different patient populations (Lifelines) • Health benefits of PA in different patient populations (Lifelines)
1B	• Current implementation status of E=M[b] (questionnaire and interview) • Barriers and facilitators for implementation of E=M (questionnaire and interview)	• Barriers and facilitators for implementation of E=M (interview)	N/A
1C	• Implementation strategies (implementation mapping)	• Implementation strategies (implementation mapping)	• Patients' perspective on implementation strategies (panel discussion)
Work package 2			
2A	• Requirements for an E=M tool (questionnaire and interview)	• Requirements for an E=M tool (questionnaire and interview)	N/A
2B	• Reflection on E=M tool designed by information technology (testing and feedback phases)	• Reflection on E=M tool designed by information technology (testing and feedback phases)	• Reflection on E=M tool designed by information technology (testing and feedback phases)
Work package 3			
3A	• Implementation of PIE=M implementation strategies (stepwise implementation)	N/A	N/A
3B	• Reach, effectiveness, adoption, implementation, and maintenance of PIE=M implementation strategies (questionnaires, logbook, field notes, interviews) • Transferability of PIE=M implementation strategies to other hospitals (interviews with clinicians working in nonparticipating hospitals)	• Effectiveness, implementation, and maintenance of PIE=M implementation strategies (interviews)	• Experiences with the E=M implementation (interview)
3C	N/A	• Recommendations for implementation and maintenance of E=M prescription (blueprint)	N/A

[a]N/A: not applicable.

[b]E=M: exercise=medicine.

Work Package 1: Needs Assessment and Translation of Facilitators and Barriers for E=M Into Implementation Strategies

Work package 1 will determine the need for the implementation of E=M by studying levels and determinants of PA in different patient populations and the current implementation status of E=M in the involved clinical departments. Barriers and facilitators regarding implementation of E=M will be investigated, and implementation strategies will be matched to these barriers and facilitators.

1A: Levels and Determinants of PA in Different Patient Populations

To better map the need for E=M, we will identify levels of PA and the factors associated with PA in different patient populations and compare these to the healthy adult population. To do so, data from the Lifelines prospective cohort study [32] will be used. Lifelines is a multidisciplinary, prospective, population-based cohort study with a 3-generation design that

studies the health and health-related behaviors of 167,729 people living in the North of The Netherlands. To recruit participants, the majority of all general practitioners in the 3 northern provinces of The Netherlands invited all their patients between the ages of 25 and 50 years, except people with very severe health conditions with a life expectancy <5 years and people with insufficient knowledge of the Dutch language. Participants invited their family members in order to develop a 3-generation cohort. Moreover, inhabitants could register themselves via the website. Inclusion stopped when the target number of 165,000 participants was reached, which was assumed to be a representative sample [32]. Lifelines data that are of special interest for the PIE=M project include demographics, lifestyle behavior (eg, PA, sitting time, smoking, nutrition, and sleep), health outcomes (eg, blood and urine biomarkers), wellbeing, and mortality. The Lifelines cohort includes healthy people as well as people with disabilities or chronic diseases, such as people with osteoarthritis, diabetes, stroke, rheumatoid arthritis, amputation, cancer, or multiple sclerosis. The Lifelines cohort performed a baseline assessment during 2007-2014. A second assessment was done during 2014-2018. The analyses will use data from the baseline and second screening of Lifelines and will be performed in SPSS 23. The 3 aims of the proposed analyses are: (1) to determine PA levels assessed with the validated Short QUestionnaire to Assess Health enhancing PA (SQUASH) [33] in different patient populations treated within the departments participating in the PIE=M project (eg, stroke, cancer, osteoarthritis) in relation to the "healthy" adult Lifelines population, (2) to determine factors associated with a physically (in)active lifestyle in different patient populations in relation to the healthy adult Lifelines population, and (3) to determine health benefits of PA in different patient populations in relation to the healthy adult Lifelines population. The results will be used to better inform clinicians on the PA levels of their patient population, the factors associated with PA, and the health benefits of PA for their patient population, which can inform their E=M practice.

1B: Barriers, Facilitators, and Current Implementation Status of E=M

The current status of E=M implementation and the barriers and facilitators towards implementation of E=M in Dutch routine clinical care will be assessed using a mixed-methods approach. Clinicians (physicians, residents, physician assistants, nurse practitioners, and therapists) working in the aforementioned participating clinical departments will be invited to complete a short questionnaire. This questionnaire will include questions on the current provision of E=M-prescription, familiarity of clinicians with the Dutch national PA guidelines [9], and perception on roles and responsibilities for prescribing E=M. The questionnaire will be constructed based on questionnaires previously used among general practitioners on the same topic in the Netherlands [34].

Responding clinicians will be asked for their willingness to participate in a semistructured interview to get a more in-depth understanding of the barriers and facilitators towards implementing E=M and the added value and needed content of an E=M tool. The interview guide will expand on the model of Fleuren et al [35] with items concerning E=M as intervention and characteristics of the users, target group, organization, and sociopolitical context. Interviews will be performed until data saturation to ensure all relevant barriers and facilitators are identified. Interviews will be transcribed verbatim and analyzed using a framework analysis [36]. Strategy-level hospital managers of the same clinical departments will be interviewed to study factors that can influence the implementation of E=M prescription in clinical care from a more organizational point of view. For these interviews with managers, small adaptations will be made to the interview questions used in the clinician interviews. Data analysis methods will be similar as those for the interviews with clinicians. Clinicians and strategy-level managers of both hospitals will be interviewed to identify differences between the 2 hospitals.

1C: Implementation Strategies

To address the identified facilitators and barriers, we will develop a set of tailored implementation strategies specific for each hospital. A systematic implementation mapping approach using strong stakeholder participation will be used to match implementation strategies to identified barriers and facilitators [37]. Theory and evidence-informed strategies from the taxonomy of behavior change methods [38] and the Effective Practice and Organization of Care taxonomy [39] will be used. A priori, motivating, and educative strategies and a digital tool like the proposed E=M tool are needed [29]. Selected methods can be, for instance, the distribution of educational material (flyers, posters, video), demonstration meetings, an overview of local PA facilities, introduction of local implementation leaders (eg, influential clinicians at the different departments), and prompts. Although the primary focus of the PIE=M project will be the E=M referral by clinicians, a panel discussion with patient representatives will be organized to reflect on the developed strategies for implementing E=M from a patient perspective.

Work Package 2: E=M Tool Development

Within the second work package, a generic assistive tool will be developed for clinicians. This tool provides tailored E=M prescription and referral to local professionals in or outside the hospital. The E=M tool is based on a clinical decision algorithm that integrates individual patient characteristics (assessed by a short questionnaire) and existing health norms.

2A: Requirements for an E=M Tool

End user (clinician) requirements for an E=M tool will be identified using the results derived from a questionnaire and semistructured interviews with clinicians and strategy-level hospital managers from the clinical departments involved at both university medical centers. Aspects that will be investigated are, for instance, patient characteristics and health norms for which the E=M prescription should be tailored, technical aspects of the tool, and presentation of the E=M prescription. To differentiate among individual patients, it is a priori suggested to tailor the E=M prescription based on patients' motivation regarding PA and exercise. These aspects will be translated into the exact content of the clinical decision algorithm of the E=M tool (eg, which patient characteristics will be assessed, health norms applied) by the researchers. In addition, specific local

information will be gathered for contextual use of the E=M tool, like local E=M referral options and suitability of different patient groups within the medical specialty. In a blueprint for implementing E=M, the actions needed for contextual adaptation will be thoroughly described to facilitate use of E=M in subsequent implementation projects.

2B: E=M Tool Development Process

A generic tool, linked to the EMR, will be developed using an iterative interactive design process to generate a tailored E=M prescription, using individual patient and health condition characteristics. During the design process, clinicians, managers, information technology experts, implementation experts, and patient representatives will reflect on the design of the E=M tool to ensure that the E=M tool will fit the needs of stakeholders (co-creation) and that the E=M tool is consumer friendly and fulfills the general data protection regulation. Design phases (in co-creation with information technology experts) will be alternated by testing and feedback phases in co-creation with clinicians of the clinical departments involved. The E=M tool will be implemented into digital systems that link to the EMR systems (Epic Systems Corporation, Verona, WI) that are currently used by the participating departments.

Work Package 3: Implementation of E=M

The third work package will determine the feasibility of implementing E=M, by implementation of the set of implementation strategies formulated in work package 1 together with the E=M tool designed in work package 2 (herein PIE=M implementation strategies). Pilot studies will run in 4 clinical departments of the 2 university medical centers: Rehabilitation Medicine and Orthopedics (UMCG) and Rehabilitation Medicine and Medical Oncology (Amsterdam UMC location VUmc). In general, these clinical departments have a focus on PA, which makes them suitable to pilot test the feasibility of the PIE=M implementation strategies.

3A: Pilot Implementation

We will stepwise implement the set of implementation strategies of E=M (work package 1) including the E=M tool (work package 2), together referred to as PIE=M implementation strategies. In this stepwise implementation, pilots will be performed sequentially in the 4 clinical departments mentioned in the previous sections, whereby experiences from pilots conducted in the first departments will be taken into account in the implementation strategy in the departments to follow. Pilot studies will be performed between October 2019 and November 2020.

3B: Process Evaluation

The pilot implementation will be monitored and evaluated with a learning process evaluation, which is especially useful when evaluating complex, real-world interventions [40]. A learning process evaluation integrates implementation and evaluation of interventions by iterative plan-do-study-act cycles, which makes it especially suitable for evaluating stepwise implementation processes [41]. Both contextual and explanatory factors related to implementation will be determined, as well as their effect on implementation outcomes across organizations. This makes a learning process evaluation a suitable method for our multicenter pilot implementation [40]. The process evaluation has 3 specific objectives. First, Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) of the implementation of E=M in routine clinical care are investigated [42,43]. Operationalization of the RE-AIM model is provided in Table 2. Reach of implementing E=M will be determined by the absolute number, proportion, and characteristics of patients who are actually participating in the E=M pilot, relative to those eligible for participation. Effectiveness is defined as the impact of the set of PIE=M implementation strategies (work packages 1 and 2) on the perceived successfulness of E=M referral and as satisfaction with implementing E=M using the implemented set of PIE=M strategies (work packages 1 and 2). Adoption is operationalized as the absolute number, proportion, and representativeness of departments and clinicians who are willing to participate in the pilot, relative to those invited for participation. Implementation is operationalized as fidelity, adaptations to the PIE=M implementation strategies, and experiences with the implementation. Maintenance is operationalized as the extent to which the implementation of E=M has become part of routine care in the participating departments. The second aim of the process evaluation is to identify success and failure factors for clinicians regarding the process of implementing E=M using the proposed PIE=M implementation strategies (work packages 1 and 2). Third, recommendations for improvement of E=M in routine clinical care are investigated.

Table 2. Operationalization and methods used in the process evaluation following the RE-AIM framework (work package 3B)

Operationalization	Questionnaire clinician (baseline)	Questionnaire clinician (1 month)	Questionnaire clinician (end pilot)	Interview clinician (end pilot)	Interview department manager (end pilot)	Interview lifestyle coach (end pilot)	Logbook usage E=M-tool	Patient interview	Interview with non-participating hospitals	Field notes
Reach[a]										
Sources and procedures for recruitment of participants, and reported reasons for (non-) participation in E=M		X	X	X	X			X		X
Characteristics of profiled patient population per department (e.g. age, health condition)							X			
Effectiveness[b]										
The impact of the PIE=M innovation strategies on perceived successful referral by clinicians		X	X	X	X	X				
Satisfaction with the PIE=M innovation strategies among patients		X	X	X	X	X		X		
Satisfaction with the PIE=M innovation and implementation strategies among clinicians		X	X	X	X					
Satisfaction with the PIE=M innovation and implementation strategies among managers					X					
Adoption[c]										
Characteristics of participating departments (e.g. size, patients)					X					X
Characteristics of participating clinicians	X									
Implementation[d]										
Fidelity and adaptations to the core principles of the PIE=M implementation strategies		X	X				X			
Views and experiences with implementation of the PIE=M implementation strategies by clinicians		X	X	X	X					
Recommendations for improvement of E=M in routine clinical care and suggestions for future implementation		X	X	X	X					
Success and failure factors to the implementation of the PIE=M implementation strategies		X	X	X	X					

Operationalization	Questionnaire clinician (baseline)	Questionnaire clinician (1 month)	Questionnaire clinician (end pilot)	Interview clinician (end pilot)	Interview department manager (end pilot)	Interview lifestyle coach (end pilot)	Logbook usage E=M-tool	Patient interview	Interview with nonparticipating hospitals	Field notes
Maintenance[e]										
Maintenance of the implementation of the PIE=M implementation strategies			X	X	X	X				
Extent to which other non-involved (university) hospitals are willing to implement the PIE=M implementation strategies									X	

[a]The absolute number, and proportion of patients who are willing to participate in E=M.

[b]The impact of the PIE=M innovation strategies on perceived successful referral.

[c]The absolute number, proportion, and representativeness of settings and clinicians who are willing to initiate a program.

[d]The clinicians' implementation of the key components of the PIE=M implementation strategies.

[e]The extent to which the PIE=M implementation strategies become part of the routine in the participating departments.

Data will be collected using a mixed-methods approach (Table 2). All participating clinicians will be invited for a baseline questionnaire as well as 2 follow-up questionnaires (1 month after baseline and at the end of the pilot). The questionnaire, which was constructed for this study, will include questions on demographic information (eg, age, years of experience, own lifestyle behavior), determinants for implementation, and perceived impact, satisfaction, and experiences with implementing E=M using the set of PIE=M implementation strategies (work packages 1 and 2). In the last questionnaire, a question will be added about the extent to which E=M has become routine care and whether clinicians have suggestions for further improvement of the set of PIE=M implementation strategies. Moreover, the use of the newly developed E=M tool (work package 2) will be tracked using a logbook completed by the participating clinicians during their consultations and field notes made by the researchers.

During and at the end of the pilot, semistructured interviews will be organized with a subsample of the involved clinicians, involved department managers, and eventually other relevant stakeholders, such as lifestyle coaches, in case they have been involved in the pilot departments. During these interviews, we will reflect further on the perceived impact of and satisfaction with the set of PIE=M implementation strategies and the extent to which E=M has become routine care. A subsample of patients who were selected for participating in the pilot will be invited to participate in a short structured face-to-face interview to evaluate their experiences with the E=M implementation. Lastly, clinicians working in nonparticipating hospitals will be invited to participate in an interview to explore the transferability of the set of implementation strategies including the E=M tool to other departments and hospitals in the Netherlands. All semistructured interviews will be transcribed verbatim and analyzed using a framework analysis approach based on the model by Fleuren et al [35].

3C: Continuation and Dissemination

During the implementation process, plans for securing the implementation of E=M prescription in the clinical departments involved will be determined, in collaboration with representatives from the clinical departments. The process evaluation will result in recommendations for the implementation and maintenance of E=M prescription using the set of proposed PIE=M implementation strategies in other clinical departments or other hospitals. These recommendations will be recorded in a blueprint that can guide the implementation of E=M in other clinical departments or other hospitals. Some of the implementation strategies will be generic and applicable in different clinical departments in different hospitals. However, since implementation is highly context-dependent, part of the implementation strategies will be tailored to the specific context of the department and hospital. In addition to generic recommendations, the blueprint will hereby consist of a stepwise procedure to select applicable context-specific implementation strategies.

Patient and Public Involvement

The primary target population of the PIE=M study is clinicians. Clinicians are involved in the project consortium and thereby involved throughout all steps of the project. Also, patients and other public stakeholders (eg, local sports organizations, municipalities) are involved throughout all steps of the PIE=M project, starting already during the writing of the research proposals. Both patients and public organizations are involved in the design, recruitment, and dissemination. Patients are asked to reflect on the burden of the E=M implementation in a panel discussion.

Ethics and Dissemination

The study will be performed in accordance with the Declaration of Helsinki. The medical ethical committees of the UMCG and Amsterdam UMC approved the study design (METc UMCG 2017/517 and Amsterdam UMC 2018/219). Results of the PIE=M project will be published in peer-reviewed international

journals and presented at conferences. Results will be used for further development of the set of implementation strategies and E=M tool, to further facilitate the implementation of E=M in participating departments and other clinical departments and hospitals.

Results

This project was approved and funded by the Dutch grant provider ZonMW in April 2018. The project started in September 2018 and continues until December 2020 (depending on the course of the COVID-19 crisis). All data from work package 1 have been collected and analyzed and are expected to be published in the 2021. Results of work package 2 have been described. The manuscript is expected to be published in 2021. Work package 3 is currently being conducted in clinical practice in the 4 departments of the 2 university medical hospitals among clinicians, lifestyle coaches, hospital managers, and patients. Results are expected to be published in 2021.

Discussion

This paper describes the rationale and design of the PIE=M project, which aims at sustainable implementation of E=M in routine clinical care.

PIE=M will result in a set of strategies to prescribe tailored PA advice and individual referral to local PA professionals, including an E=M tool for clinicians within the currently used EMRs [14,29]. The results of PIE=M are partly generic and partly specific to the context of the participating departments. Work package 1 will result in generic knowledge on current PA levels, and determinants of PA behavior in different patient groups will be generated. This knowledge will help to indicate the need for the implementation of E=M and could potentially be used to better tailor individual PA prescription. The implementation strategies, which are translated from the barriers and facilitators for E=M among clinicians in work package 1, are partly generic and partly specific for the context of the participating departments. The E=M-tool developed in work package 2 will consist of a generic algorithm that can be adapted to the specific local context. During this pilot, the tool will be built into the information technology systems (eg, EMRs) that are currently used in the participating departments. For future implementation in other hospitals or departments, the tool should be linked to information technology systems that are used within the department, providing opportunities for context-specific applications. The development of our E=M tool may thereby serve as an example for other decision aids in different settings aimed at E=M implementation. Work package 3 will result in a generic blueprint describing the generic implementation strategies and a stepwise procedure with tools to select applicable context-specific implementation strategies.

A strength of the PIE=M project is the multidisciplinary collaboration between patients, clinicians working in various clinical departments from 2 university medical centers, researchers from different disciplines, professionals in technical information technology and universities of applied sciences, municipalities, and lifestyle professionals. Another strength of this study is that 2 different hospitals are involved in this project, of which one is located in a very urban area and one is located in a city but serves a more rural area. This involvement enables comparison between the implementation in different organizations and different geographical contexts. We expect this comparison will enhance the recommendations for implementation in other hospitals, which will be described in the blueprint. It should be considered that both hospitals involved are university medical centers providing specialized top clinical care, which might limit the generalizability of the findings to smaller community hospitals. It should also be considered that the participating clinical departments may have a stronger focus on the importance of PA than other clinical departments. Barriers and facilitators might differ in clinical departments with less focus on the importance of PA, which could result in different implementation strategies. However, the developed E=M tool and blueprint for implementing E=M will be generic and applicable in departments with less focus on PA. However, arguably the most important strength of the PIE=M project is the involvement of end users, both clinicians and patients. This ensures applicability in routine clinical practice. By referring patients to existing local PA facilities, both within the hospital and the community, long-term sustainability in daily practice is maximized, contributing to external validity of the study findings.

By developing and pilot testing implementation strategies for E=M, including an E=M tool, the PIE=M project represents a next step within research on implementing E=M. However, when feasibility of the implementation of E=M has been shown, large-scale implementation studies are needed in different clinical departments in different hospitals, as well as studies on the (cost) effectiveness of E=M at the patient level.

The PIE=M project addresses the potential of providing patients with PA advice to prevent and manage chronic disease, improve recovery, and promote healthy aging by developing E=M implementation strategies including an E=M tool in routine clinical care. The PIE=M project will result in a blueprint of implementation strategies, including an E=M screening and referral tool that aims to improve E=M referrals by clinicians to improve patients' health, while minimizing the burden on clinicians.

Acknowledgments

This study was supported by a grant from ZonMw, the Dutch Health Research and Development Council (project number 546001002). The Lifelines Biobank initiative has been made possible by a subsidy from the Dutch Ministry of Health, Welfare and Sport; Dutch Ministry of Economic Affairs; University Medical Center Groningen (UMCG, the Netherlands); University of Groningen; and Northern Provinces of the Netherlands.

Authors' Contributions

All authors contributed to the conception and design of the study. LAK drafted the manuscript. All other authors provided comments and revisions on the draft and read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Report letter of the funder (English translation).
[PDF File (Adobe PDF File), 100 KB - resprot_v9i11e19397_app1.pdf]

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Abbreviations

E=M: exercise=medicine
EMR: electronic medical record
PA: physical activity
PIE=M: Physicians Implement Exercise = Medicine
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
UMC: University Medical Center
UMCG: University Medical Center Groningen

Edited by G Eysenbach; submitted 16.04.20; peer-reviewed by M Molinos, L Damschroder; comments to author 12.06.20; accepted 30.06.20; published 02.11.20.

Please cite as:
Krops LA, Bouma AJ, Van Nassau F, Nauta J, van den Akker-Scheek I, Bossers WJR, Brügemann J, Buffart LM, Diercks RL, De Groot V, De Jong J, Kampshoff CS, Van der Leeden M, Leutscher H, Navis GJ, Scholtens S, Stevens M, Swertz MA, Van Twillert S, Van der Velde J, Zwerver J, Van der Woude LHV, Van Mechelen W, Verhagen EALM, Van Keeken HG, Van der Ploeg HP, Dekker R
Implementing Individually Tailored Prescription of Physical Activity in Routine Clinical Care: Protocol of the Physicians Implement Exercise = Medicine (PIE=M) Development and Implementation Project
JMIR Res Protoc 2020;9(11):e19397
URL: https://www.researchprotocols.org/2020/11/e19397
doi:10.2196/19397
PMID:33136060

Protocol

Reducing Alcohol and Opioid Use Among Youth in Rural Counties: An Innovative Training Protocol for Primary Health Care Providers and School Personnel

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Abstract

Background: Given that youth alcohol use is more common in rural communities, such communities can play a key role in preventing alcohol use among adolescents. Guidelines recommend primary care providers incorporate screening, brief intervention, and referral to treatment (SBIRT) into routine care.

Objective: The aim is to train primary care providers and school nurses within a rural 10-county catchment area in Pennsylvania to use SBIRT and facilitate collaboration with community organizations to better coordinate substance use prevention efforts.

Methods: To build capacity to address underage drinking and opioid use among youth aged 9-20 years, this project uses telehealth, specifically Project ECHO (Extension for Community Healthcare Outcomes), to train primary care providers and school nurses to address substance use with SBIRT. Our project will provide 120 primary care providers and allied health professionals as well as 20 school nurses with SBIRT training. Community-based providers will participate in weekly virtual ECHO sessions with a multidisciplinary team from Penn State College of Medicine that will provide SBIRT training and facilitate case discussions among participants.

Results: To date, we have launched one SBIRT ECHO project with school personnel, enrolling 34 participants. ECHO participants are from both rural (n=17) and urban (n=17) counties and include school nurses (n=15), school counselors (n=8), teachers (n=5), administrators (n=3), and social workers (n=3). Before the study began, only 2/13 (15.5%) of schools were screening for alcohol use.

Conclusions: This project teaches primary care clinics and schools to use SBIRT to prevent the onset and reduce the progression of substance use disorders, reduce problems associated with substance use disorders, and strengthen communities' prevention capacity. Ours is an innovative model to improve rural adolescent health by reducing alcohol and opioid use.

International Registered Report Identifier (IRRID): DERR1-10.2196/21015

(JMIR Res Protoc 2020;9(11):e21015) doi:10.2196/21015

KEYWORDS

alcoholism; adolescent behavior; binge drinking; rural health; underage drinking; adolescent; young adult; alcohol; drinking; behavior; screening; intervention; referral

Introduction

Background

One in three Pennsylvanian eighth-graders has used alcohol, a substantially greater proportion than the national average (23%) [1]. By the 12th grade, nearly 70% of Pennsylvanian youth have used alcohol, compared to 60% nationally [1]. The use of alcohol and other substances by youth has significant negative public health effects, given that youth are more susceptible to risk-related injuries [2]. For example, substance use by youth correlates with increased sexual risk-taking and, due to neurodevelopmental vulnerabilities of the adolescent brain, increased risk of addiction [3,4]. In adolescents, 75% of deaths are the result of unintentional injury, homicide, or suicide, and alcohol is involved in more than one-third of adolescent deaths [5]. The Substance Abuse and Mental Health Services Administration (SAMHSA) has estimated that fewer than 10% of adolescents in need of specialty substance abuse treatment receive it [6]. Together, these factors make addressing underage drinking one of the nation's top substance abuse prevention priorities.

Adolescent Alcohol and Opioid Use

Youth who live in rural communities use alcohol at greater rates than their urban counterparts (37.8% vs 34.3%), highlighting the importance of intervention directed at rural youth [6]. Higher rates of alcohol use among rural youth are attributed to less parental disapproval surrounding use, greater acceptability among peers, greater availability of alcohol, and greater access to alcohol provided by adults [7]. Despite the higher prevalence, rural communities face major barriers to screening and treatment for substance use disorders, including limited resources, fewer providers and facilities, and the sparse distribution of services. In Pennsylvania, there are 48 rural counties and 19 urban counties. Furthermore, 235 of the state's 500 public school districts are considered rural due to the student and town population density and location of student homes, even though some of these districts are in urban counties [8].

In addition to addressing alcohol use, this protocol proposes addressing opioid use, given the screening, brief intervention, and referral to treatment (SBIRT) approach's unique ability to address substance use more broadly. Pennsylvania has the third-highest rate of deaths due to drug overdose in the country (37.9 per 100,000), and this rate has significantly increased in recent years [9]. The SBIRT model is particularly appropriate for addressing opioid use in teens, and the screening tools developed for identifying underage alcohol use have also been validated for identifying opioid use. These include the CRAFFT, S2BI, BSTAD, and 2-question NIAAA screener. Implementing broad substance use prevention strategies within clinics, schools, and community coalitions may help to drive population-level change through a collaborative approach.

Reducing Adolescent Alcohol Consumption

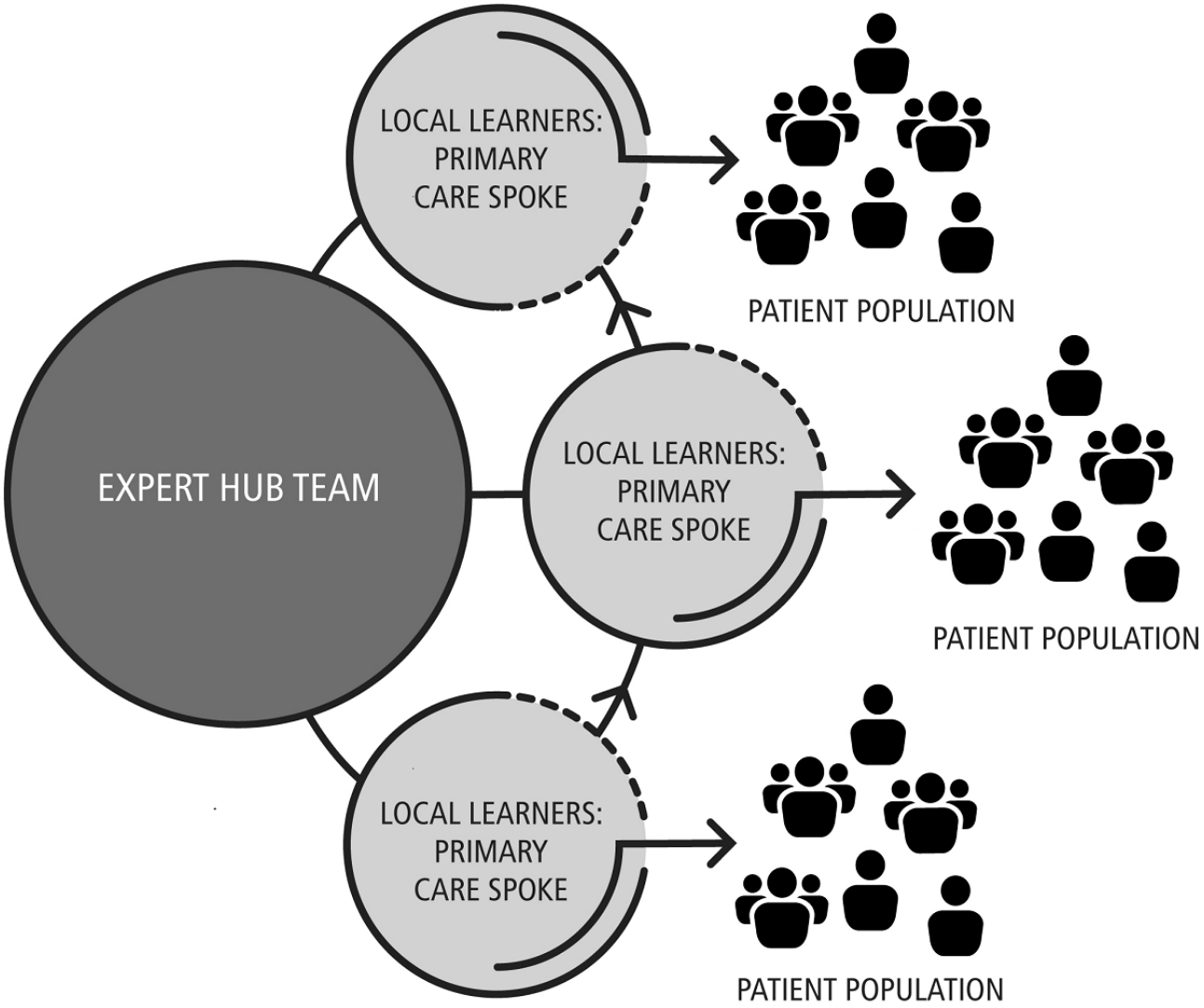
One gap in efforts to reduce underage drinking is the lack of appropriate screening, intervention, and referral for alcohol use among youth. Guidelines recommend that primary care providers incorporate SBIRT into routine care [10]. SBIRT has been defined by SAMHSA as "a comprehensive integrated public health approach to the delivery of intervention for individuals with risky alcohol and drug use, and the timely referral to more intensive substance abuse treatment for those who have substance abuse disorders" [11]. Given that the majority of adolescents (83%) see a physician each year and may be receptive to discussing substance use during these visits, the primary care setting is ideal to offer SBIRT [12]. Screening not only identifies youth currently engaged in alcohol use but also provides positive reinforcement to youth who do not use, a strategy known to delay initiation of alcohol use [13]. However, only 50%-86% of pediatric providers self-report screening for substance use and only a minority of those screen use validated tools [14]. Screening in the absence of a validated tool results in the identification of only 1 in 3 youth with excessive alcohol use [15]. Additionally, providers may be inadequately trained on how to intervene with youth who do report underage drinking, and often communities have few referral options for youth with problematic alcohol use. Therefore, interventions are needed to identify and break down barriers to SBIRT adoption by primary care providers.

SBIRT

SBIRT is most often used in the primary care setting, but the model can be readily adapted to use in community settings. A recent study of high school nurses found that most (64%) reported screening students with suspected substance use and more than 77% of said nurses favored universal alcohol screening in schools [16]. However, only a minority (18%) of school nurses report using a validated screening tool. The most commonly cited barrier to using a validated model is unfamiliarity with screening tools (36%). The authors concluded that the implementation of SBIRT focused on standardized, annual screening has the potential to deliver high-quality care within the school setting, broadening the reach of substance use screening and prevention beyond the clinical setting.

The goal of this protocol is to equip communities with the ability to address underage drinking and opioid use among youth aged 9-20 years through a telehealth platform called Project ECHO (Extension for Community Healthcare Outcomes). Project ECHO was developed at the University of New Mexico and is a model with the power to rapidly transfer knowledge and exponentially increase a community's capacity to deliver best-practice care to underserved populations through case-based discussion and brief lecture. The ECHO model uses videoconferencing technology as a platform for telementoring and collaborative care, with a hub-and-spoke structure (Figure 1). This protocol aims to train primary care providers and school nurses within a rural 10-county catchment area to use SBIRT and also to facilitate collaboration with community organizations to better coordinate substance use prevention efforts in each county (see Multimedia Appendix 1).

Figure 1. The ECHO model uses a hub and spoke model to create an all-teach, all-learn environment. The more providers that are trained, the more patients that are impacted.



Methods

The research team will include several professionals who have been involved in the physical and mental care of adolescents, specifically those with substance use and misuse issues. This team will include a pediatrician and adolescent medicine specialist, a pediatrician/internist with addiction certification, a licensed clinical social worker who has managed inpatient adult and pediatric consult-liaison services for three decades, a project manager, a marketing specialist, and a program director. This team of seasoned professionals will identify a number of topics relevant to the identification and screening of substance use disorders by studying motivational and interview-based brief clinical interventions, the biology of alcohol's effect on the body, risk and protective factors, community-based programming, and the treatment of substance use disorders. There will be a novel curriculum developed specifically for this project, especially as it uses the Project ECHO method to develop and enhance providers' skills working with substance use in adolescents. To our knowledge, a project of this type is novel and has not been done to date in school settings or pediatricians' offices; thus, prior curricula were not available.

This protocol will take advantage of three characteristics that make SBIRT an effective behavioral health intervention: (1) brief, validated, universal pre-screening/screening tools; (2) easy to learn intervention approaches that diverse provider types can use; and (3) incorporation of strong referral linkages to specialty treatment. The Project ECHO model will be used to teach SBIRT to school personnel and primary care providers. Further, this protocol includes the creation of a network of experts and participants to support best practices and identify solutions to overcome barriers related to addressing underage alcohol use. This study (STUDY00010821) has been approved by the Pennsylvania State University Institutional Review Board.

Recruitment

The 10 targeted rural counties in Pennsylvania had an estimated population of 78,833 persons aged 10-19 years in 2017 [17]. Overall, 31%, 46%, and 61% of 8th, 10th, and 12th graders, respectively, reported lifetime alcohol use, compared to 24%, 43%, 56% nationwide, respectively (Table 1) [1]. Likewise, throughout the 10 targeted counties, there was an average of 8.3 alcohol-related crashes per 100,000 crashes. In Pennsylvania as a whole, an average of 4.8 per 100,000 alcohol-related crashes involved youth under 21 years of age. Within the targeted

counties, there are 50 school districts and 631 primary care providers (defined as both family medicine and pediatric providers), all being important targets for the proposed project. Within our specific catchment area, school personnel and primary care providers will be recruited through targeted email listservs. Participants must have access to a zoom-capable device and the internet. However, any school personnel or primary care provider in the catchment area will be eligible to participate given that these prerequisites are met.

Table 1. Ten rural county catchment area description.

County	Total (N=118,086), n	Lifetime use of alcohol, n (%)			Alcohol-related crashes (per 100,000), n	School districts (n=50), n	Primary care providers (n=631), n
		8th Grade	10th Grade	12th Grade			
Blair	16,298	5378 (33)	7823 (48)	9453 (58)	13.6	6	131
Bradford	8060	2902 (36)	4675 (58)	5723 (71)	8.2	6	50
Centre	23,848	8347 (35)	10,493 (44)	15,024 (63)	8.1	5	116
Franklin	21,300	4473 (21)	4686 (22)	7668 (36)	12.3	5	124
Fulton	1915	632 (33)	1245 (65)	1379 (72)	6.8	4	4
Northumberland	11,156	3904 (35)	6024 (54)	7698 (69)	2.2	5	39
Perry	6056	2301 (38)	2967 (49)	3694 (61)	10.9	4	16
Schuylkill	17,675	6717 (38)	10,075 (57)	13,080 (74)	4.2	10	101
Snyder	6299	1827 (29)	3150 50)	4283 (68)	2.5	2	24
Tioga	5479	438 (8)	877 (16)	1918 (35)	14.5	3	26

Proposed Approach

This protocol includes the implementation of an SBIRT training model for primary care clinics and schools to prevent the onset and reduce the progression of substance abuse, reduce substance abuse-related problems, and strengthen prevention infrastructure at the community level (Table 2). Specifically, we will recruit and train 120 primary care providers and allied health professionals and 20 school nurses to participate in SBIRT training (Figure 2). We will use a research-based SBIRT model which includes six characteristics noted by SAMHSA: (1) initial screening is brief; (2) screening is universal; (3) specific behaviors will be targeted; (4) services occur in a public health setting (ie, primary care clinics and schools); (5) program is comprehensive; and (6) model is supported by strong research and experiential evidence [11]. Lastly, project feedback will be obtained annually from local Communities That Care (CTC) coalitions.

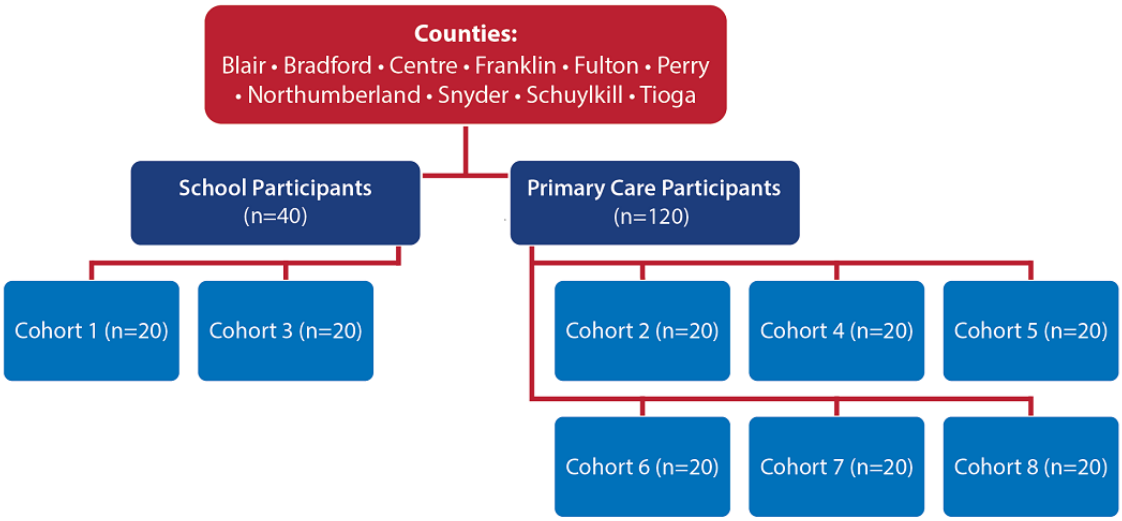
Table 2. Proposed goals and measurable objectives.

Goals	Measurable objectives
Increase the capacity of primary care providers to provide SBIRT[a] to youth aged 9-20 years to reduce alcohol and opioid use and provide treatment or referral for those currently using these substances.	By the end of 2024, our team will have trained 20% of primary care providers in the 10-county catchment through Project ECHO[b] (n=120). This enables approximately 57,600 youth to be served by SBIRT over the proposed project timeline.
Increase the capacity of schools to provide SBIRT to youth aged 9-20 years to reduce alcohol use and opioid use and provide treatment and, if necessary, referral for those currently using these substances.	By the end of 2024, our team will have trained at least 20 school nurses within the 10-county catchment through Project ECHO.
Increase alcohol and substance use prevention resources and programs for primary care clinics and schools to distribute to youth and families.	By the end of 2024, at least 50% of school buildings and primary care clinics will have alcohol/substance use prevention toolkits available for youth and families.

[a]SBIRT: screening, brief intervention, and referral to treatment.

[b]ECHO: Extension for Community Healthcare Outcomes.

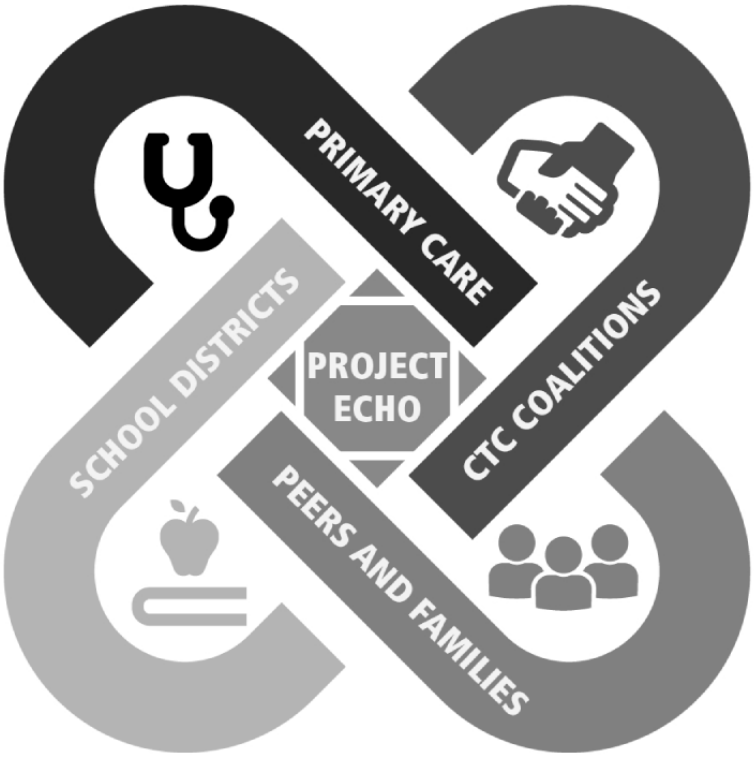
Figure 2. Recruitment into ECHO Cohorts.



Further, this study will follow the SAMHSA-recommended multi-stage screening approach. Clinical staff will prescreen and if a patient prescreens positive, a full screen will be conducted. Low-risk patients will be supported for their health decisions. Moderate-risk patients will receive a brief intervention. Patients with high or severe risk/dependency will be referred for specialty treatment. Referral requires primary care clinics and schools to establish links to appropriate services, which can be a significant barrier. We will reduce this barrier by providing linkages through existing CTC networks that are located throughout communities in Pennsylvania. The 10 counties included in this project also have coalitions in place, some of which will be CTCs supported by the Pennsylvania Commission on Crime and Delinquency. CTC is an evidence-based approach that takes communities through a well-defined and structured process to prevent adolescent problem behaviors and promote positive youth development.

The SBIRT training curriculum will use the approach of the American Academy of Pediatrics' 2016 clinical report [14]. This simplified, clinical approach will support successful research-informed SBIRT implementation across our 10 rural counties. By working with the networks created for primary care physicians and school nurses, we will identify and implement a comprehensive prevention approach (SBIRT) within these settings to include a mix of evidence-based programs, policies, and practices that best address alcohol and opioid use (Figure 3). Additionally, families and peers will have access to fact sheets and handouts that promote health behaviors.

Figure 3. This is a collaboration between primary care providers and school districts, with input from communities that care coalitions and outreach to peers and families.



Project ECHO

The ECHO model has four core principles: (1) use technology to leverage scarce resources; (2) share best practices to reduce disparities; (3) employ case-based learning to master complexity; and (4) monitor outcomes to ensure benefit. Our program will use Project ECHO to train primary care providers and school nurses in our 10-county catchment area to provide SBIRT intervention to reduce rates of underage drinking and opioid use among youth aged 9-20 years. The ECHO model uses videoconferencing technology as a platform for telementoring and collaborative care, with a hub-and-spoke structure (Figure 1). Community-based providers (the spokes) will participate in weekly virtual ECHO sessions with a multidisciplinary specialty team at Penn State College of Medicine (the hub) who will provide technical assistance and training on the use of SBIRT and will facilitate discussions of cases brought forward by providers. These experts include a pediatrician, a board-certified Addiction Medicine specialist who is also a pediatrician, and a social worker. Providers share knowledge, expertise, and experience. Over time, providers become experts, engaged in a wider community of learners and empowered to address substance use in their patients. They have the support of specialists for advice and referral, creating an effective triage system and direct linkage to care.

Through case-based discussions involving all spoke participants and brief lectures provided by experts on the hub, the ECHO model will create a network of learners with demonstrated effectiveness at improving competence, performance, knowledge, attitudes, and confidence in treatment related to substance use disorders [12]. To incentivize participation, continuing education credits will be awarded for attending each session.

Curriculum

Two overlapping curricula have been developed, one for school personnel, tailored to fit the school setting, and a second for pediatricians in the clinical setting. The curriculum includes the topics listed in Table 3. Unlike SBIRT for adults, these sessions will take into account the unique phase of adolescence, including transitions, peer pressure, adverse childhood experiences, and other factors that may impact an adolescent's likelihood to consume alcohol or use substances. We will develop 2 separate curricula in order to address the specific needs of school personnel (nurses, social workers, and guidance counselors) compared with those of primary care pediatricians. Although most of the topics covered will be provided to both groups, the curriculum for the physicians will contain specific information about the formal diagnosis of substance use disorders in adolescents, medical treatment available for substance use disorders, and billing for screening for and treatment of substance use issues. For school personnel, the curriculum will focus on several topics different from the pediatrician group such as recognizing and identifying substance use in school settings, triaging substance use concerns, and the risk and protective factors that are inherent in school settings (eg, school failure, poor school performance, school connections, and support).

Table 3. Proposed curriculum topics.

Curriculum topics	School personnel	Pediatricians
Introduction to SBIRT[a] and brief interventions	✓	✓
Operationalizing screenings and billing for services		✓
Addressing vulnerability during life transitions	✓	✓
Identifying substance use in adolescents	✓	
Diagnosing substance use in adolescents		✓
Beyond alcohol: substance use prevention	✓	✓
Adolescent progress of substance use	✓	✓
How alcohol affects human biology	✓	✓
Referral to psychosocial and medication treatment	✓	✓
Adolescent risk factors vs protective factors	✓	
Medication for substance use disorders		✓
Positive development: building good habits	✓	✓
Review of brief interventions and introduction to communities that care	✓	✓

[a]SBIRT: screening, brief intervention, and referral to treatment.

Proposed Evaluation

We have developed a tracking database within REDCap that will enable us to collect and analyze data from all participating providers and school nurses. The ECHO model aims to evaluate outcomes within Moore's Seven Levels for CME Outcomes Measurements [18]. This progressive approach to evaluation is the recommended framework for evaluating Project ECHO from its founders at the University of New Mexico. Our current database collects baseline and post-program knowledge, skills, attitudes, and confidence, as well as weekly questionnaires that assess provider engagement, intent to make changes in practice, increased ability to provide appropriate care, and decreased professional isolation. REDCap is an encrypted, HIPAA (The Health Insurance Portability and Accountability Act of 1996)-compliant web-based application designed to support data capture for research studies. REDCap access will require user authentication with a password and limits data access based on an individual's role in a project. Further, the study team will access county-level data from a variety of publicly available sources (Multimedia Appendix 2).

Data Analysis

Researchers will compare the outcome measures by treatment type (eg, initiation of buprenorphine/naloxone in the emergency department and type of medication assisted treatment) and referral source using appropriate epidemiologic study designs and statistical methods (eg, a quasi-experiment or an ecologic study design to evaluate the program impact at the community level, chi-square tests for categorical variables or t-tests for continuous variables, or the multivariable generalized linear model, etc). This analysis will allow us to better understand larger trends that occur over the proposed project period.

Community Engagement

By linking CTC partners with primary care providers and school personnel, we aim to strengthen the prevention system and ensure sustainability. This protocol aims to share evaluation data collected from participating providers and school nurses with the CTC's to promote data-driven decision making by the CTCs. The CTCs will then be better able to connect schools and clinics with evidence-based resources in the community, address technical assistance and training needs of providers and schools, and use existing services more efficiently. Further, we will develop effective prevention messages and other prevention strategies for use by the schools and clinical practices within our catchment area. In addition, the study team will make educational and evidence-based resources available to school nurses, pediatricians, or other practice group personnel for distribution to youth and caregivers who are seeking care. Resources will include patient/family health questionnaires and assessments, protocols for parents to follow, fact sheets for practitioners, parents and youth, and handouts for parents to assist them with promoting healthy behaviors.

Results

Our study launched 1 SBIRT ECHO with 34 school personnel in March 2020. School participants from our first ECHO series are from both rural (n=17) and urban (n=17) counties, although 12 of the urban school districts fall within counties that contain rural school districts. Participants include school nurses (n=15), school counselors (n=8), teachers (n=5), administrators (n=3), and social workers (n=3). Before the study began, just 2 of 13 (15%) of these schools indicated that they were screening for alcohol use. The next steps include launching our first ECHO series with pediatricians and primary care providers in the fall of 2020.

Discussion

Overview of Proposed Findings

The overarching goal of this research is to decrease adolescent alcohol consumption and opioid usage by increasing the use of

screening, brief interventions, and referrals to treatment by both school personnel and primary care providers. Because adolescents in rural areas are at higher risk for alcohol and substance use, targeting rural counties with supportive community components is important to curbing adolescent alcohol consumption and resultant negative health outcomes. Using publicly available data such as the Pennsylvania Youth Survey data, SAP referrals, and alcohol-related crashes in underage drivers will allow insight into whether or not this approach is effective [1].

Participants

Prior studies point to the need for interdisciplinary teams in schools to work towards improved health services for students [19]. Although this protocol originally aimed to recruit school nurses, a diverse group of school personnel joined the study including social workers, physical education teachers, health education teachers, and guidance counselors. We anticipate that a group of interdisciplinary participants will further enhance discussion and prove to be more beneficial for participants. Engaging pediatricians and primary care providers is also critical given the underutilization of substance use screening and intervention in this frontline health care setting.

Limitations of Research Design

Although this study does not evaluate student perceptions of SBIRT, prior studies have shown that students who screen negatively for substance use view routine screening favorably. Students that report having used illicit substances view drug and alcohol screenings less favorably [20].

Although this study entails rigorous data collection, several other programs exist in the counties of intervention. Therefore, there is a strong possibility of residual confounding. It will be difficult to determine if successes should be attributed to Project ECHO or other programming in the community.

Because this study is targeting rural communities that have strong community coalitions and resources to help families and adolescents that screen positive for alcohol or substance use, results may be less transferrable to communities that do not have strong coalitions already in place. Additionally, as this study targets a rural catchment area, the results may not be transferrable to urban counties.

Lastly, having a study span of 5 years increases the likelihood of changes in existing data collection measures. For example, if schools stop collecting 30-day alcohol and opioid usage through the Pennsylvania Youth Survey, it will be very difficult to measure adolescent alcohol and substance use.

Study Potential

Currently, the US Preventive Services Task Force's recommendations for children aged 12-17 years is "that the current evidence is insufficient to assess the balance of benefits and harms of screening and brief behavioral counseling interventions for alcohol use in primary care settings" [21]. The task force has similar guidelines related to illicit drug use in that "the current evidence is insufficient to assess the balance of benefits and harms of primary care-based behavioral counseling interventions to prevent illicit drug use, including nonmedical use of prescription drugs, in children, adolescents, and young adults " [22]. Therefore, this study aims to help close the gap in evidence to help move screening, brief interventions and referrals forward to get adolescents the help that they need. The evidence for SBIRT is limited in regards to adolescents. However, prior studies have evaluated Project ECHO in regards to training primary care physicians to address the opioid epidemic. One study in Ontario, Canada found that participation in Project ECHO increased provider knowledge regarding opioids and pain management [23]. Another study from Pennsylvania indicated that 6 months of participation in Project ECHO resulted in significantly decreased wait times for patients seeking treatment for opioid use disorders [24]. These studies demonstrated improved physician knowledge, which enabled primary care providers to optimize care for patients with opioid use disorders.

Although not all states have large rural areas and limited access to care, this study applies to at least 18 other states that have a similar percentage of rural area within their borders [16]. A comprehensive SBIRT model has the potential to address alcohol and other substance use outside of clinical settings, which may be particularly important within rural communities. In this way, engaging and training school nurses from the 10-county catchment area will further increase county capacity to implement, sustain, and improve effective substance abuse prevention services.

Conclusion

Comprehensive substance use disorder prevention involves individual, environmental, and collaborative strategies across schools, homes, communities, and health-focused regulatory bodies. A multipronged approach is the key to changing social norms and expectations for substance use.

SBIRT has been defined by SAMHSA as "a comprehensive integrated public health approach to the delivery of intervention for individuals with risky alcohol and drug use, and the timely referral to more intensive substance abuse treatment for those who have substance abuse disorders" [10]. This project plans to implement a comprehensive SBIRT education model in primary care clinics and schools to prevent the onset and reduce the progression of substance abuse, reduce substance abuse-related problems, and strengthen prevention capacity and infrastructure at the community level. Specifically, we will recruit 120 primary care providers and allied health professionals as well as 20 school nurses to participate in SBIRT training. This is an innovative model to improve rural adolescent health by reducing alcohol and opioid-related harms. The data that support the findings of this study will be available on request from the corresponding author. The data will not be publicly available due to privacy or ethical restrictions.

Acknowledgments

This project is supported by the Substance and Mental Health Services Administration (SAMHSA), through grant 1H79SP081725-01. The content is solely the responsibility of the authors and does not necessarily represent the official views of SAMHSA. This project is also partially supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1 TR002014. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflicts of Interest

None declared.

Multimedia Appendix 1
This will be a 5-year project including IRB approval, data evaluation, 10 ECHO cohorts, annual community advisory board meetings, and outreach strategies including the dissemination of marketing materials.
[DOCX File , 14 KB - resprot_v9i11e21015_app1.docx]

Multimedia Appendix 2
Performance measures will be taken from a wide array of project surveys and public databases.
[DOCX File , 16 KB - resprot_v9i11e21015_app2.docx]

Multimedia Appendix 3
Peer Review Comments.
[PDF File (Adobe PDF File), 126 KB - resprot_v9i11e21015_app3.pdf]

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Abbreviations

CTC: Communities That Care
ECHO: Extension for Community Healthcare Outcomes
SAMHSA: Substance Abuse and Mental Health Services Administration
SBIRT: Screening, brief intervention, and referral to treatment

Edited by G Eysenbach; submitted 03.06.20; peer-reviewed by S Walters, G Tzilos Wernette, C Emezue; comments to author 21.08.20; revised version received 29.09.20; accepted 30.09.20; published 06.11.20.

Please cite as:
Francis E, Shifler Bowers K, Buchberger G, Ryan S, Milchak W, Kraschnewski J
Reducing Alcohol and Opioid Use Among Youth in Rural Counties: An Innovative Training Protocol for Primary Health Care Providers and School Personnel
JMIR Res Protoc 2020;9(11):e21015
URL: http://www.researchprotocols.org/2020/11/e21015/
doi:10.2196/21015
PMID:33155572

Protocol

Determining the Actual Zinc and Iron Intakes in Breastfed Infants: Protocol for a Longitudinal Observational Study

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Abstract

Background: Zinc and iron deficiencies among breastfed infants during the first 6 months of life have been reported in previous studies. The amounts of zinc and iron intakes from breast milk are factors that contribute to the zinc and iron status of breastfed infants.

Objective: This study aims to quantitatively determine zinc and iron intakes by breastfed infants during the first 4 months of life and to investigate the factors that predict zinc and iron status in breastfed infants.

Methods: Pregnant women at 28 to 34 weeks of gestation were enrolled. Zinc and iron status during pregnancy was assessed. At delivery, cord blood was analyzed for zinc and iron levels. Participants and their babies were followed at 2 and 4 months postpartum. Maternal dietary intakes and anthropometric measurements were performed. The amount of breast milk intake was assessed using the deuterium oxide dose-to-mother technique. Breast milk samples were collected for determination of zinc and iron levels. The amount of zinc and iron consumed by infants was calculated. Zinc and iron status was determined in mothers and infants at 4 months postpartum.

Results: A total of 120 pregnant women were enrolled, and 80 mother-infant pairs completed the study (56 provided full breastfeeding, and 24 provided breast milk with infant formula). All data are being managed and cleaned. Statistical analysis will be done.

Conclusions: This study will provide information on zinc and iron intakes in exclusively breastfed infants during the first 4 months of life and explore predictive factors and the possible association of zinc and iron intakes with infant growth and nutrient status.

International Registered Report Identifier (IRRID): DERR1-10.2196/19119

(JMIR Res Protoc 2020;9(11):e19119) doi:10.2196/19119

KEYWORDS

breastfeeding; zinc; iron; zinc deficiency; iron deficiency; deuterium oxide dose-to-mother technique; infant; baby; diet; protocol; prediction; women; growth

Introduction

Micronutrients are essential for infant growth and development. During the first 6 months of life, infants obtain micronutrients from breast milk if they are exclusively breastfed, as recommended by the World Health Organization (WHO) [1]. In addition to micronutrients provided by breast milk, infants use body stores of micronutrients deposited during pregnancy.

Zinc and iron are particularly important micronutrients for infants. Some previous studies have shown that zinc and iron deficiencies are associated with delayed infant growth and development, especially when such deficiencies occur during the early period of life [2-4]. Several reports have shown zinc and iron deficiencies in a high proportion of infants younger than 6 months, and breastfeeding was found to be the associated factor. A study in 2007 in the northeast area of Thailand reported that 50.8% of breastfed infants aged 4 months had a zinc deficiency [5]. When comparing the prevalence of zinc deficiency by feeding types, zinc deficiency was more prevalent among 4- to 6-month old breastfed infants compared with formula-fed infants (14.9% and 5.3% among breastfed and formula-fed infants, respectively) [6]. Regarding iron deficiency, the prevalence of iron deficiency among breastfed infants was found to be higher than among infants fed with formula in several studies [7,8]. A study on the iron status of infants in Bangkok showed that the prevalence of iron deficiency anemia in breastfed infants aged 1 year was 25.7%, which was higher than in formula-fed infants (2.7%) [9]. The percentage of infants with iron deficiency anemia was 4 times higher in 6-month-old compared with 4-month-old infants (26.1% vs 5.7%, respectively), as described in a cohort study of iron status in breastfed infants [10]. Breastfeeding duration was found to be associated with a higher prevalence of iron deficiency [11] and low serum ferritin or other iron markers among infants and children [12,13].

The zinc and iron status of breastfed infants during breastfeeding is associated with several factors. The amount of iron storage during intrauterine life, zinc and iron intakes, and physiologic requirement are proposed to be the factors determining zinc and iron status of breastfed infants [14]. Infants' iron storage depends on maternal nutrient status during pregnancy and can be observed in cord blood levels [15,16]. Daily zinc and iron intakes of exclusively breastfed infants come from zinc and iron in breast milk. Naturally, micronutrient concentrations in breast milk are not constant but dynamically change during lactation. Zinc and iron concentrations in breast milk are high during early lactation and gradually decline thereafter [17-19]. The amounts of zinc and iron in breast milk consumed by infants after 6 months are lower than the estimated daily requirements [20,21]. The majority of zinc and iron intakes in infants during this period need to be provided by complementary foods.

Several hypotheses have been proposed to explain the causes of zinc and iron deficiencies among breastfed infants during the exclusive breastfeeding period. Low micronutrient concentrations in breast milk have been proposed as a factor associated with nutrient deficiency in breastfed infants. Stronger evidence was shown in the case of zinc deficiency compared with iron deficiency [22]. Recent studies have attempted to explore the factors that might be associated with the low micronutrient concentrations in breast milk. There have been reports on genetic variation of zinc transporters resulting in the difference in breast milk zinc concentrations [23,24]. Some studies have reported that socioeconomic status, maternal dietary intake, maternal anthropometric parameters, micronutrient status, and maternal age are associated with zinc and iron concentrations in breast milk [6,25,26]. However, many studies did not confirm these associations [27,28].

Breast milk provides complete nutrition to infants during the first 6 months of life, but zinc and iron deficiencies occur among breastfed infants. While zinc and iron levels in breast milk have been determined and reported in several studies, they do not directly reflect the zinc and iron intake amounts in breastfed infants. The data on breast milk volume taken by infants and the nutrient levels in breast milk better demonstrate the amounts of zinc and iron taken by breastfed infants. However, the measurement of breast milk volume consumed by infants can be challenging. Traditional assessments using the test-weighing method or the measurement of expressed breast milk have considerable inaccuracies. Stable isotope measurement of breast milk intake with the protocol established by the International Atomic Energy Agency (IAEA) is the most accurate method to quantify the infant's breast milk intake [29].

Zinc and iron intake from breast milk is one of the factors determining the zinc and iron status of breastfed infants. The data on nutrient intakes will provide more information regarding the zinc and iron status of breastfed infants and may lead to the prevention of nutrient deficiencies. Our study aims to quantify zinc and iron intakes by measuring micronutrient levels in breast milk and assessing breast milk volume intake by breastfed infants using the deuterium oxide dose-to-mother technique.

Methods

Recruitment

This is a prospective descriptive study at the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. The study protocol was approved by the human research ethics committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University (ID 03-60-31) and the ethical committee of Ludwig Maximillian Universitaet, Munich (Project No. 18-015). Pregnant women visiting the antenatal care (ANC) clinic at Ramathibodi Hospital at 28 to 34 weeks of gestation were eligible for enrollment. The enrollment was performed at the ANC clinic when the pregnant women attended the education class during their second trimester. Inclusion criteria were healthy pregnant women who planned to deliver their babies at Ramathibodi Hospital, intended to breastfeed their babies at least 4 months, lived in the Bangkok metropolitan area, and provided written informed consent. Pregnant women who carried twin or triplet pregnancies or who had any contraindication for breastfeeding were excluded. Women and their babies were followed until 4 months postpartum. Each participant was invited to 4 visits (ie, at enrollment, at delivery, and at 2- and 4-month postpartum). The details of the data collection are summarized in Figure 1. During the study, women who were

unwilling to participate in the study, stopped breastfeeding, moved to another province, or had babies with chronic diseases or serious illness were excluded from continuing study participation. The recruitment period was from March 2018 to September 2019.

Figure 1. Data collected at each visit in the study.

Data collection	Enrollment	Delivery	2 months post partum	4 months post partum
Demographic data	✓			
Perinatal data		✓		
Assessment of dietary intake	✓		✓	✓
Assessment of body composition in lactating women			✓	✓
Infant growth assessment			✓	✓
Blood sample for zinc and iron status	✓ (mother)	✓ (cord blood)		✓ (mother and infant)
Breast milk sample for zinc and iron levels			✓	✓
Measurement of breast milk intake volume			✓	✓

Sample Size Calculation

Sample size calculation was based on the reported mean zinc intake of breastfed infants in a study by Krebs et al [30], which was 1.00 (SD 0.43) mg/day. The sample size was determined using the 1-sample *t* test for mean formula, as follows:

Using the assumption that this study will provide a difference in the mean of 0.15 from the previous study, and given a significance level of .05 and power of 0.8, the calculated sample size of this study was 64:

n=64

The calculated sample size of this study was 64. We estimated that the dropout rate would be up to 30%. Therefore, the calculated sample size was 100 participants:

Data Collection

Demographic Data and Antenatal Data

Demographic data, including maternal age, existing diseases, education level, and socioeconomic status, were obtained by interviewing participants. Antenatal data were retrospectively reviewed from medical records and the maternal pregnancy handbook. Data collected during pregnancy included prepregnant weight and BMI, weight gain during pregnancy, parity, investigations during antenatal care (every pregnant woman had a blood test for anemia and serologic screening during their first visit to the ANC clinic and some had an oral glucose tolerance test to screen for gestational diabetes, depending on clinical indication), and complications during pregnancy (ie, gestational diabetes, preeclampsia, and others).

Perinatal Data

The investigators visited the participants who delivered their babies at Ramathibodi Hospital at the postpartum ward. Mothers received routine postpartum care and education from the ward staff. Data regarding mode of delivery, delivery complications, and perinatal complications of infants were collected. Infant anthropometric data, including birth weight, length, and head circumference, were routinely measured by nurses in the labor room.

Anthropometric Assessment of Lactating Women and Infants

To determine the nutritional status of lactating women and infants, anthropometric measurements were performed at the 2- and 4-month postpartum visits. For lactating woman, weight was measured to the nearest 0.1 kg using a digital scale, and height was measured to the nearest 0.1 cm using a height scale while the woman was standing upright without shoes or hair ornaments. Weight, BMI, fat mass, skeletal muscle mass, and visceral fat area were measured using a body composition analyzer (InBody 720; InBody Co).

For the infant, weight was measured to the nearest 10 grams using a digital baby scale, and recumbent length was measured to the nearest 0.1 cm using a wooden board with a sliding foot piece. Head circumference was determined using a nonstretchable measuring tape. The occipitofrontal circumference was measured twice; the greater value was used to represent the baby's head circumference. Weight, length, and head circumference were calculated to *z* score for age and sex, according to the WHO growth chart from the WHO Anthro calculator. In addition to the anthropometric measurements, the weight and length gain of the infants was calculated to determine the growth rate during the first 4 months.

Assessment of Maternal Dietary Intakes

Dietary intake was important during pregnancy and lactation. There are a lot of factors influencing maternal food intake during these periods, such as beliefs and traditions, lifestyle, anxiety, socioeconomic status, and family support. We assessed maternal dietary intakes during pregnancy (at enrollment) and lactation (at 2- and 4-month postpartum) using 3 dietary intake assessment tools, namely a 24-hour food recall, the food frequency questionnaire (FFQ), and a 3-day prospective dietary record. The FFQ was constructed to determine zinc and iron intake with common foods eaten by Thai people. At participant visits, dietary history (24-hour food recall and FFQ) was recorded by a skilled dietitian or nutritionist. A 3-day food record form was then handed to the participant to complete at home within 2 weeks after the visit. They were asked to send the food record back to the researcher by mail or to bring it back at the next visit. The amounts of nutrient intake, including energy, protein, zinc, and iron, were analyzed using INMUCAL software version 4.0 (Institute of Nutrition, Mahidol University), which is the largest database of nutrients in Thai foods.

Collection and Analysis of Blood Samples

Blood samples for determining zinc and iron status were collected. Maternal blood samples were collected from an antecubital vein during pregnancy (at enrollment) and lactation (at 4-month postpartum). At delivery, cord blood samples were collected right after cord cutting from the umbilical cord on the placental side. Infant venous blood samples were collected at the age of 4 months.

Blood samples were immediately centrifuged to separate plasma and kept frozen at –80 °C. All containers used for sample collection were washed with a nitric acid solution and deionized water in order to avoid contamination with micronutrients from the environment. Zinc concentration was analyzed using flame atomic absorption spectrophotometry (GBC Avanta S; GBC Scientific Equipment). Serum ferritin and complete blood count were analyzed using chemiluminescence (automated) and electrical impedance, respectively, at the Department of Pathology, Faculty of Medicine Ramathibodi Hospital. Remaining plasma samples were kept for further analysis.

Collection and Analysis of Breast Milk

Each lactating woman was asked to collect a breast milk sample at the 2- and 4-month visits. Breast milk samples were collected from one breast by an electrical milk pump. The participant was asked to express breast milk until the breast was empty. The breast milk sample was then evenly mixed, and 15 mL of the breast milk sample was collected for analysis. The remaining breast milk was kept in the milk storage bag and returned to the participant for feeding her infant. The milk samples were kept at –80 °C within 4 hours from the time of collection. All the equipment and containers used in breast milk collection had been washed with a nitric acid solution and deionized water to avoid micronutrient contamination from the environment and were sterilized before use. A separate aliquot of 5 mL of the evenly mixed breast milk sample was transferred for metabolomics analyses.

Zinc and iron levels in the breast milk were analyzed using inductively coupled plasma optical emission spectrometry (ICP-OES). Prior to analysis by ICP-OES, the breast milk sample was digested using nitric acid in a closed vessel under microwave radiation.

Measurement of Breast Milk Volume Intake by Infants Using Deuterium Oxide Dose-to-Mother Method

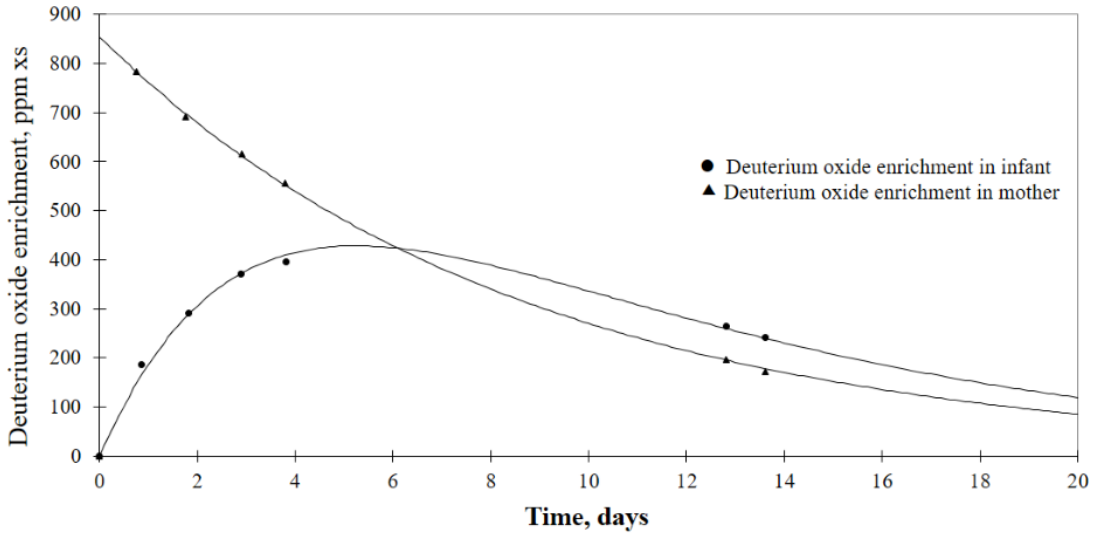
The breast milk volume was assessed at 2- and 4-month postpartum. In general practice, there are two methods of giving breast milk to infants: providing breastfeeding at the breast or expressing breast milk via bottle-feeding. We used different methods to assess breast milk volume from different feeding practices.

Among mothers who provide breastfeeding at the breast, breast milk intake was assessed using the deuterium oxide dose-to-mother technique, strictly following the protocol to assess breast milk intake proposed by the IAEA [29]. Deuterium is a stable (nonradioactive) isotope of hydrogen that is metabolized in the body in the same way as water. Therefore, deuterium oxide is eliminated from the body in urine, saliva, sweat, and human milk.

The principle of the deuterium oxide dose-to-mother technique for measuring breast milk volume is to track the disappearance of deuterium oxide from the maternal body and the presence of deuterium oxide in the infant (Figure 2). Lactating women were given a drink of 30 g of deuterium-labeled water. Saliva samples (2 mL per sample) were collected from mothers and infants to monitor deuterium oxide levels. According to the IAEA protocol, saliva samples were collected at 7 time points: at baseline (day 0) before giving the deuterium-labeled water to the mother and at days 1, 2, 3, 4, 13, and 14 after the dose of deuterium. All samples were collected by the same researchers, both at the hospital (on day 0) and during home visits. Deuterium oxide levels were analyzed and breast milk volumes

were calculated using the equation based on the principles of volume distribution [29].

Figure 2. Deuterium oxide enrichment from the deuterium oxide dose-to-mother technique to measure breast milk intake shows the disappearance of deuterium oxide from the mother's body and the presence of deuterium oxide in the infant. xs: excess.



Results

Study enrollment took place from March 2018 to September 2019. A total of 120 pregnant women participated in this study. There were 3 participants who delivered their babies in other hospitals and were excluded from the study. Among the 117 participants, 56 women provided breastfeeding to their babies and completed the study at 4-month postpartum; they were classified as the breastfeeding group. A total of 24 women could not adequately provide breastfeeding to their babies and gave the infants some infant formula. However, they completed the study and were classified as the mixed-feeding group. A total of 37 women were excluded from the study (18 stopped breastfeeding before 4 months, 12 moved to another province, and 7 were unwilling to continue the study). All data are being managed and cleaned. Statistical analysis will be done.

Discussion

Expected Outcome

This study will provide information on zinc and iron intakes from breast milk in breastfed infants during the first 4 months of life. It may demonstrate the association of zinc and iron intakes with the growth and nutrient status of infants. As this study follows the participants from pregnancy to lactation, the data may provide information about the impact of intrauterine nutrition on the nutrient status of infants after birth. The data regarding dietary intake and nutrient status of mothers during both the pregnancy and lactation period will be provided and the relationship between maternal and infant nutritional status may be demonstrated.

Significance of the Study

This study will provide informative data on zinc and iron intakes by breastfed infants. These data will provide scientific knowledge and might contribute to determining the daily dietary zinc and iron requirements for infants during the first 6 months. Moreover, these data may be useful in devising strategies for preventing zinc and iron deficiency in breastfed infants. As the study will also provide information on the levels of zinc and iron in breast milk and their associations with the dietary intake and micronutrient status of lactating women, these data will have advantages for nutritional promotion during lactation.

Acknowledgments

This study is funded by Mahidol University of Thailand and the Family Larsson Rosenquist Foundation. BK is the Else Kröner-Seniorprofessor of Paediatrics at LMU financially supported by the Else Kröner-Fresenius-Foundation and LMU University Hospitals.

Conflicts of Interest

None declared.

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Abbreviations

ANC: antenatal care
FFQ: food frequency questionnaire
IAEA: International Atomic Energy Agency
ICP-OES: inductively coupled plasma optical emission spectrometry
WHO: World Health Organization

Edited by G Eysenbach; submitted 05.04.20; peer-reviewed by K Kingsley, S Lundgren; comments to author 25.08.20; revised version received 25.09.20; accepted 02.10.20; published 06.11.20.

Please cite as:
Dumrongwongsiri O, Winichagoon P, Chongviriyaphan N, Suthutvoravut U, Grote V, Koletzko B
Determining the Actual Zinc and Iron Intakes in Breastfed Infants: Protocol for a Longitudinal Observational Study
JMIR Res Protoc 2020;9(11):e19119
URL: https://www.researchprotocols.org/2020/11/e19119
doi:10.2196/19119
PMID:33155573

Protocol

Effects of Radiation Therapy and Comorbidity on Health-Related Quality of Life and Mortality Among Older Women With Low-Risk Breast Cancer: Protocol for a Retrospective Cohort Study

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Abstract

Background: The National Comprehensive Cancer Network Breast Cancer Guidelines Committee suggests that the omission of adjuvant radiation therapy (RT) after breast-conserving surgery can be a reasonable option among older women with low-risk breast cancer (early-stage, estrogen receptor-positive, and node-negative) if they are treated with endocrine therapy. However, RT usage in this group of women still exceeds 50%. Conversely, older women tend to forego RT (even when necessary) due to cost, inconvenience, and potential adverse responses associated with RT. Understanding health-related quality of life (HRQOL) change with receipt of RT among older women in the modern era is limited due to the under-representation of this population in clinical trials.

Objective: The proposed study aims to examine the associations of RT with HRQOL trajectories as well as survival outcomes among older women with 5-10 years of follow-up. We will also assess whether prediagnosis comorbidity burden influences receipt of RT and whether the associations between RT and HRQOL trajectory and survival outcomes are modified by the comorbidity burden.

Methods: We will use a retrospective cohort study design with the population-based Surveillance, Epidemiology, and End-Results database linked to the Medicare Health Outcomes Survey (SEER-MHOS). Older women (≥65 years) who were diagnosed with low-risk breast cancer in 1998-2014, received breast-conserving surgery, and participated in MHOS 1998-2016 are eligible for this analysis. The latent class analysis clustering method will be used to identify each patient's prediagnosis comorbidity burden, and HRQOL will be evaluated using the Short Form 36/Veterans RAND 12-Item Health Survey scales. The inverse-weighted estimates of the probability of treatment will be included to control for treatment selection bias and confounding effects in subsequent analysis. The association of RT with HRQOL trajectory will be evaluated using inverse-weighted multilevel growth mixture models. The inverse-weighted Cox regression model will be used to obtain hazard ratios with 95% CIs for the association of RT with survival outcomes. Differential effects of RT on both outcomes according to comorbidity burden class will also be evaluated.

Results: As of October 2020, the study was approved by the institutional review board, and SEER-MHOS data were obtained from the National Cancer Institute. Women with low-risk breast cancer who met inclusion and exclusion criteria have been identified, and prediagnosis comorbidity burden class has been characterized using latent class analysis. Further data analysis will begin in November 2020, and the first manuscript will be submitted in a peer-reviewed journal in February 2021.

Conclusions: This research can potentially improve clinical outcomes of older women with low-risk breast cancer by providing them additional information on the HRQOL trajectories when they make RT treatment decisions. It will facilitate informed, shared treatment decision making and cancer care planning to ultimately improve the HRQOL of older women with breast cancer.

International Registered Report Identifier (IRRID): DERR1-10.2196/18056

(JMIR Res Protoc 2020;9(11):e18056) doi:10.2196/18056

KEYWORDS

radiation therapy; comorbidity; health-related quality of life; survival; early-stage breast cancer; older women

Introduction

Breast cancer is the most prevalent cancer and the second leading cause of cancer-related deaths in American women [1]. Due to the aging of the female population and the increasing incidence of breast cancer with age [2], the number of older women with breast cancer continues to grow. Older women diagnosed with early-stage breast cancer have multiple locoregional treatment options depending on prognostic factors such as tumor type and disease stage. Adjuvant radiation therapy (RT) following breast-conserving surgery (BCS) is standard treatment for early-stage breast cancer, as this course of treatment improves clinical outcomes significantly [3,4]. Older women are often concerned with potential health-related quality of life (HRQOL) declines associated with cancer treatment [5]. These concerns of older women can present clinical challenges when making treatment decisions considering the pros and cons of adjuvant RT within the context of life expectancy.

Many randomized controlled trials (RCTs) have focused on the cancer care of older women. One of them is the CALGB 9343 trial, which reported that the recurrence rates of older women with estrogen receptor (ER)-positive early-stage breast cancer who received endocrine therapy alone were not significantly different from those of women who received both endocrine therapy and RT (4% vs 1%) [6]. Moreover, no significant survival benefits were observed with the addition of RT to endocrine therapy compared to endocrine therapy alone [6]. These remarkable results from the CALGB 9343 trial led to a change in the National Comprehensive Cancer Network (NCCN) Breast Cancer Guidelines in 2004, which suggested the omission of RT as a reasonable option for older women with low-risk breast cancer (early-stage, ER-positive, and node-negative) if they are treated with endocrine therapy [7]. Additionally, 10-20 years of long-term follow-up results of early RCT studies, such as CALGB9343, PRIME II, and BASO II, have further confirmed that adjuvant RT can be omitted in older women with favorable early-stage ER-positive, node-negative breast cancer [8-10].

Despite the aforementioned guideline update, the treatments of older women with low-risk breast cancer vary widely. In prior studies, the patterns of RT omission were not consistent across institutions, even at NCCN member institutions [11-13]. More importantly, RT usage in this group of women still exceeds 50% [14]. A recent survey reported that high proportions of surgeons and radiation oncologists erroneously overestimated survival benefits associated with RT in this group of women [15] because the estimation of life expectancy in older women is not straightforward [11]. Many treatment-decision algorithms include age to estimate life expectancy, but chronological age is not always correlated with one's biological age and mortality. Including geriatric assessment in the algorithm improved compliance with NCCN guidelines without diminishing survival benefits [16]. Since accompanying comorbid conditions at diagnosis are strongly associated with mortality regardless of age [17-19], considering comorbidity burden in addition to age and tumor characteristics will improve the selection of women who can omit RT.

On the other hand, some older women tend to forego RT (even when necessary) due to cost, inconvenience, and uncertainty of potential adverse responses associated with RT. Limited evidence suggests that older women are more concerned about HRQOL declines rather than fear of recurrence when they make treatment decisions [20,21]. However, understanding HRQOL change with the addition of RT among this population is limited due to the under-representation of older women and those with comorbidities in clinical trials [22,23]. Many studies have evaluated adverse effects on HRQOL with receipt of RT, but most of them were cross-sectional designs or assessments of short-term changes within 1 year post RT [18,24-28]. Not many studies have evaluated the long-term effects of RT on HRQOL. In an older study, Lundstedt and colleagues reported that 10.3% of women had weekly pain even after 10-17 years of RT, and this observation was significantly higher among women who received adjuvant RT than those who did not (1.7%, P=.001) [29]. Therefore, we need to update long-term HRQOL with more data since there have been many advancements in RT techniques over the past 3 decades. Moreover, baseline HRQOL is a major predictor of subsequent HRQOL; thus, longitudinal evaluation of HRQOL trajectory in a cohort study design, rather than a cross-sectional evaluation of post-treatment HRQOL, will provide more valid estimates of the impact of RT on HRQOL.

Few studies have investigated the effect of RT among older women with varying comorbidity burden, and to our knowledge, none of the previous studies have evaluated long-term HRQOL trajectories post RT within older women treated in the modern era. Thus, the proposed study aims to examine the effects of RT on long-term HRQOL trajectories and survival outcomes among older women with low-risk breast cancer in an observational setting. Minimizing the potential bias due to treatment selection and controlling for potential differences in confounding factors between treatment groups are essential in observational comparative effectiveness studies without randomized treatment [30]. To mitigate this concern, first, we will only select older women with low-risk breast cancer whose main treatment plan includes BCS and endocrine therapy with

RT being an option. Among this group of women, only 3.3% undergo chemotherapy [1]; thus, the confounding effect of chemotherapy on HRQOL and survival outcomes is minimal. Second, to further balance out the potential confounding factors between the 2 groups, we will use inverse probability of treatment weighting (IPTW) methods, a type of propensity score analysis [31-34], which we have applied successfully in other projects [35,36]. All potential confounding variables will be included in the statistical models when deriving the weights for each group.

This comparative effectiveness study will utilize a national sample of older women to provide much-needed evidence regarding the combined effects of RT and comorbidity on HRQOL (subjective outcome) and survival (objective outcome) in older women. This research has 2 aims.

Regarding Aim 1, we will examine the effect of RT on the HRQOL trajectory over time and its interaction with comorbidity burden in older women with low-risk breast cancer (n=465) using IPTW-adjusted growth mixture models. We hypothesize that the HRQOL trajectory will differ by treatment status and comorbidity burden, and the largest decline will be observed in older women with the highest comorbidity burden.

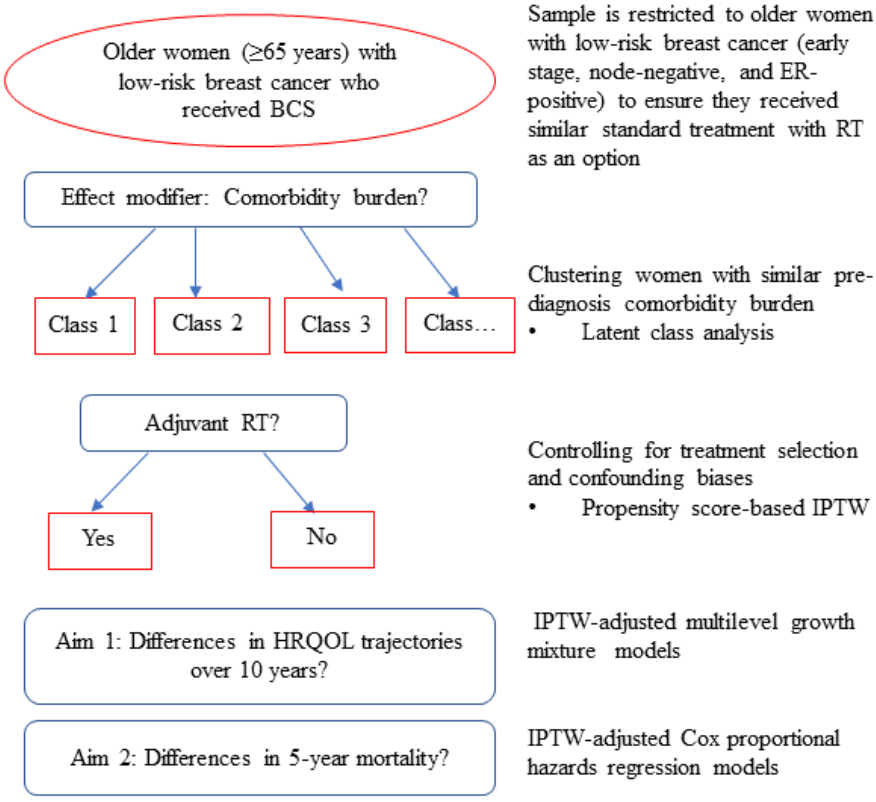
Regarding Aim 2, we will examine the effect of RT on 5-year mortality and its interaction with comorbidity burden in older women with low-risk breast cancer (n=634) using Kaplan-Meier survival analysis and a IPTW-adjusted Cox regression model. We hypothesize that receiving adjuvant RT will improve 5-year mortality, but the magnitude of improvement will differ by comorbidity burden class. We expect that women who have the lowest comorbidity burden and also receive RT will experience the greatest improvement in survival outcomes.

Methods

Overview

This observational study uses a retrospective cohort design, and the study population comprises older women with low-risk breast cancer who received BCS as a primary treatment and took part in the Medicare Health Outcomes Survey (MHOS). As depicted in Figure 1, the women are first clustered according to their prediagnosis comorbidity burden. Next, we will obtain the propensity score-based probability of receiving adjuvant RT based on observed potential confounding variables. Then, inverse probability weights will be calculated and adjusted for in subsequent analyses. We will examine the effect of RT on 2 outcomes: differences in the patterns of HRQOL trajectories over 10 years post diagnosis and 5-year survival outcomes.

Figure 1. Overview of the proposed retrospective cohort study design. The study population will comprise older women with low-risk breast cancer who received breast-conserving surgery (BCS) as a primary treatment in 1998-2014 and took part in Medicare Health Outcomes Survey (MHOS). The women were first clustered according to their prediagnosis comorbidity burden using latent class analysis. Next, the propensity score-based probability of receiving adjuvant radiotherapy (RT) will be obtained, and inverse probability of treatment weights (IPTW) will be estimated and included in statistical models. To examine the effects of RT on 2 outcomes, health-related quality of life (HRQOL) trajectories over 10-year follow-up periods and 5-year survival outcomes, IPTW-adjusted multilevel growth mixture models and IPTW-adjusted Cox proportional hazards regression models will be used, respectively. The data are sourced from the SEER-MHOS Database. ER: estrogen receptor.



We will utilize the Surveillance, Epidemiology, and End-Results (SEER) database linked to the Medicare Health Outcomes Survey (MHOS) for this project. The SEER-MHOS database resulted from the collaborative efforts of the National Cancer Institute (NCI) and the Centers for Medicare & Medicaid Services. SEER collects data on cancer incidence, treatment, and survival, covering nearly 28% of the United States population. SEER includes high-quality, reliable patient characteristic data (eg, demographics, initial treatment and treatment sequence, tumor characteristics, vital status, and cause of death), while the MHOS data provide patient-reported HRQOL outcomes, comorbidity, functional status, and symptoms for a randomly selected sample of the Medicare Advantage Organization enrollees. MHOS is a longitudinal, 2-wave survey administered twice within a cohort at a 2-year interval. Participants who responded to the first baseline survey may have completed the second follow-up survey. In addition, some participants were sampled in more than 1 cohort, resulting in multiple surveys in different years, which allows the evaluation of HRQOL change over time. Therefore, SEER-MHOS is the best available data source for examining the long-term HRQOL trajectory after diagnosis of cancer in a diverse elderly population with varying degrees of comorbidity burden even though SEER-MHOS is limited in its geographical coverage of the United States.

This study has been approved by the Institutional Review Board of the University of Central Florida (approval number: SBE-18-14238). As individuals who participated in MHOS have provided informed consent to participate in research, this study is exempt from the additional requirements of obtaining informed consent from the study participants [37].

Aim 1: Examine the Effect of RT on HRQOL Trajectory Over Time

Study Design and Study Population

A retrospective cohort study design is planned for Aim 1. Older women who were enrolled in Medicare and completed the MHOS between 1998 and 2016 are eligible for the study. The inclusion criteria were as follows: (1) a diagnosis of primary breast cancer between 1998 and 2014 and reported to SEER, (2) low-risk breast cancer, including early-stage (T1-2N0), ER-positive, and node-negative, (3) ≥65 years of age at diagnosis (with 65 years being the threshold for Medicare eligibility), (4) receipt of BCS (lumpectomy, quadrantectomy, or partial mastectomy) as primary treatment for breast cancer, and (5) completion of at least 1 MHOS assessment before and after breast cancer diagnosis to allow for assessing the change in HRQOL. Cases were excluded if they (1) had a previous cancer diagnosis (other than nonmelanoma skin cancer), (2) had more than 1 primary tumor at diagnosis, (3) received treatment outside of standard time frames (ie, treatment initiated 1 year after cancer diagnosis), (4) received RT before surgery, or (5) tumor histology was other than carcinoma. While these eligibility criteria may reduce external validity, they will enhance internal validity.

Measurements

The primary exposure variable will be adjuvant RT. We will consider BCS alone and BCS with adjuvant RT as the treatments. The SEER data provide information on radiation treatment and the sequence of surgery and radiation.

The outcomes of Aim 1 will be HRQOL scores measured over a 5-10 years of follow-up (ie, prediagnosis through post-treatment). MHOS measures HRQOL using the Medical Outcomes Study 36-item Short Form (SF-36) through the year 2005 and the Veterans RAND 12-item Health Survey (VR-12) from the year 2006 onwards. These 2 questionnaires have been validated in many languages and are widely used in HRQOL research, including that involving breast cancer patients [38]. The NCI developed algorithms to convert SF-36 scales to VR-12 scales; hence, the latter will be used across all cohorts in the current study. The VR-12 items correspond to 8 health domains, namely physical functioning, role limitations due to physical problems, role limitations due to emotional problems, bodily pain, social functioning, mental health, vitality, and perceptions of general health. These 12 items are then summarized into 2 summary scores: the physical component summary score and the mental component summary score. These 2 summary scores are standardized scores (mean 50, SD 10), which are normed based on the general US population. A total of 465 women who met the eligibility criteria for Aim 1 completed MHOS multiple times (an average of 3 times). We will sort the data according to the prediagnosis (T_0) and postdiagnosis ($T_1 \ldots T_{10}$) timelines, specifying the time lapse from the cancer diagnosis. The prediagnosis HRQOL (T_0, n=465) will be assessed using the survey conducted within 24 months prior to the diagnosis date recorded in SEER. The postdiagnosis HRQOL ($T_1 \ldots T_{10}$) will be assessed using the survey completed after the diagnosis of breast cancer. We collected 465 data points for the precancer diagnosis, 508 data points within 2 years postdiagnosis, 166 data points for 2-<5 years postdiagnosis, and 92 data points for ≥5 years postdiagnosis. The number of patients who completed MHOS in each time frame is presented in Table 1.

Table 1. Number of patients who completed MHOS in each time frame (N=465).

Survey time to cancer diagnosis (months), t	Prediagnosis and postdiagnosis HRQOL timelines	n (%)
–24<t<0	T_0	465 (100)
0≤*t*<12	T_1	253 (54)
12≤*t*<24	T_2	255 (55)
24≤*t*<36	T_3	79 (17)
36≤*t*<48	T_4	50 (11)
48≤*t*<60	T_5	37 (8)
60≤*t*<72	T_6	29 (6)
72≤*t*<84	T_7	21 (5)
84≤*t*<96	T_8	17 (4)
96≤*t*<108	T_9	8 (2)
108≤t	T_{10}	17 (4)

We considered comorbidity burden as the effect modifier. Prediagnosis comorbidity is an important component of this study, as it likely impacts HRQOL and survival outcomes adversely while also affecting treatment decisions. The presence and number of comorbidities as well as their severity are important. However, the severity of each comorbidity is not available from MHOS, whereas the functional limitations and symptoms related to these comorbidities are. To account for functional limitations and symptoms as a component of comorbidity, we created a new variable named “comorbidity burden class” with 24 self-reported items (ie, 12 chronic medical conditions, 7 functional difficulties, and 5 symptoms) in MHOS (Textbox 1) using latent class analysis. This technique has been applied successfully to identify healthy patients or comorbidity profiles of cancer patients in studies using SEER-MHOS and the National Cancer Database [39,40] when the severity of comorbid conditions is not available. To identify the prediagnosis comorbidity burden class, the survey completed within 24 months before cancer diagnosis was evaluated. Latent class analysis is a subset of structural equation modeling, which is used to categorize subjects into a set of homogeneous groups (eg, k distinct membership classes of comorbidity) according to the observed variables (eg, self-reported chronic medical conditions, functional status, and symptoms). We anticipated that this procedure would suggest 3-5 distinct categories. We selected the most parsimonious number of classes using the Bayesian information criterion to find the best fitting numbers of classes. The classes of comorbidity burden will be tested as effect modifiers.

Textbox 1. Items included in latent class analysis modeling for comorbidity burden class.

Functional status

- Difficulty in moderate activities
- Difficulty bathing
- Difficulty dressing
- Difficulty eating
- Difficulty using the toilet
- Difficulty walking
- Difficulty getting in/out of chairs
- Chest pain with exertion
- Chest pain at rest
- Short of breath at rest
- Short of breath walking
- Short of breath with stairs

Chronic medical conditions

- Angina pectoris/coronary artery disease
- Hypertension
- Myocardial infarction
- Congestive heart failure
- Stroke
- Emphysema, asthma, or chronic obstructive pulmonary disease
- Diabetes, high blood sugar, or sugar in urine
- Crohn disease, ulcerative colitis, or inflammatory bowel disease
- Arthritis of hip/knee
- Heart attack
- Sciatica
- Depression

Based on a literature review, potential confounders included age, race/ethnicity, smoking, body mass index, socioeconomic status (income and education), SEER region, rurality, lag time since treatment, disease stage, tumor grade, and molecular subtype. The year of diagnosis was also included as a covariate in the statistical model to control for variability in diagnostic or treatment criteria over 17 years (1998-2014). Demographics, general information pertaining to treatment status (surgery and radiation), and tumor-related factors (stage, grade, and tumor molecular subtype) were obtained from sources such as the SEER Patient Entitlement and Diagnosis Summary File, the Enrollment Database maintained by the Centers for Medicare & Medicaid Services, and self-reported information.

Statistical Analysis Plan

Regarding the descriptive analyses, the baseline characteristics of the study population will be described in terms of the mean and SD for continuous variables and frequencies with percentages for categorical variables. Descriptive analyses will be conducted to compare demographic, tumor-related, and treatment-related factors for the study population by their treatment status (BCS and RT vs BCS only). Differences in continuous variables and categorical variables will be assessed by *t* tests and chi-square tests, respectively. All analyses will be conducted using SAS 9.4 (SAS Institute Inc.) and R 4.0.1 (R Core Team), and a 2-tailed α level of .05 will denote statistical significance.

The probability of the treatment received by a particular person will be estimated by generalized boosted models using receipt of RT as the dependent variable and the baseline characteristics, such as age at diagnosis, race/ethnicity, smoking status, income, education, SEER region, rurality, disease stage, tumor grade, tumor subtype, and year of diagnosis, as the independent variables. Then, the inverse of the probability of receiving the treatment the patient actually received conditional on the observed covariates will be calculated and included as a weight for each patient in subsequent analyses [41]. Balances in potential confounding factors between the treatment groups will be assessed using diagnostic tools, including chi-square tests for categorical variables, *t* tests for continuous variables, and the standardized mean differences between 2 groups [42]. The

standardized mean difference will be calculated as the difference in means or proportions divided by a pooled estimate of SD. A standardized mean difference≥10% will be considered as evidence of imbalance [43].

Regarding the estimation of RT and comorbidity effects on HRQOL trajectory, we will use a multilevel growth mixture model with surveys clustered within the women to test whether a difference exists in the patterns of HRQOL trajectories with receipt of RT and comorbidity class after controlling for confounders. At level 1, we will first regress woman i's HRQOL change, which describes how each woman's HRQOL depends on time t. This procedure will provide the intercept and slope of the time predictor for each woman. At level 2, we will regress each woman's intercept and slope on her RT treatment (yes/no) and comorbidity class, adjusted for confounders. This procedure will feature how individual HRQOL change trajectories vary across treatment groups (RT) and comorbidity burden classes (COM). Equation (1) presents a simplified model with no covariates, predicting HRQOL from years after diagnosis (TIME), radiation treatment (RT), and comorbidity class (COM). It will estimate the intercepts and slopes for the group of women.

$$HRQOL_{ti} = \gamma_{00} + \gamma_{01}RT_{it} + \gamma_{02}COM_i + \gamma_{10}TIME_{it} + \gamma_{11}RT_iTIME_{it} + \gamma_{12}COM_iTIME_{it} + error \quad \textbf{(1)}$$

where

γ_{00}=Estimated average HRQOL in the year of diagnosis for women who did not receive RT

γ_{01}=Value added to the average HRQOL if the women received RT

γ_{02}=Value added to the average HRQOL due to the comorbidity class

γ_{10}=Change in HRQOL for all women for each year from diagnosis

γ_{11}=Additional change for each year if the women received RT

γ_{12}=Additional change for each year due to the comorbidity class

A significant negative value on γ_{11} will indicate that women who receive RT experience steeper declines in HRQOL over time than those who did not receive RT, while a significant negative value on γ_{12} will indicate stronger HRQOL declines due to the comorbidity burden.

We will also test for the existence of a differential effect of RT on the HRQOL trajectory according to the comorbidity burden class by incorporating interaction terms in the model. If we lack the power to detect statistically significant differences according to comorbidity level but point estimates for the effect of RT indicate that meaningful differences are present across levels of comorbidity, separate estimates will be reported for each comorbidity class. As each participant completed MHOS at different time points, growth mixture modeling is more flexible and sensitive than traditional repeated-measures analysis [44]. It can also capture nonlinear patterns [44].

Regarding the sensitivity/subgroup analysis, if the sample size allows, subgroup analysis by age and tumor stage will be conducted to examine whether the findings are generalizable to all patients satisfying the eligibility criteria.

Aim 2: Examine the Effect of RT on Breast Cancer-Specific Mortality

Study Design and Study Population

A retrospective cohort study design will be used in the context of Aim 2. Older women who were enrolled in Medicare and completed the MHOS will be selected for this study. The inclusion criteria were (1) a diagnosis of primary breast cancer between 1998 and 2010 (to ensure at least 5 years of follow-up after a cancer diagnosis) and report to SEER, (2) a diagnosis of low-risk breast cancer, (3) ≥65 years of age at diagnosis given the Medicare framework, (4) receipt of BCS (lumpectomy, segmental resection, quadrantectomy, or partial mastectomy) as primary treatment for breast cancer, and (5) completion of at least 1 MHOS within 24 months prior to breast cancer diagnosis (to allow the evaluation of the prediagnosis comorbidity burden). Participants will be excluded from the study if (1) they had a previous cancer diagnosis (other than nonmelanoma skin cancer), (2) they had more than 1 primary tumor at diagnosis, (3) they received treatment outside of standard time frames (ie, treatment initiated 1 year after cancer diagnosis), (4) they received RT before surgery, or (5) their vital status was missing.

Measurements

The exposure variables are the same as those of Aim 1, namely BCS alone and BCS with adjuvant RT. We will consider vital status and cause of death as the outcomes. The main outcome for Aim 2 will be mortality (all-cause mortality and breast cancer-specific mortality considering nonbreast cancer mortality as a competing event). The SEER data file provides the vital status of participants and the date and causes of death, which have been verified through the National Death Index. Survival will be calculated from the date of diagnosis to the last known follow-up date or December 31, 2016, whichever comes first. As in the case of Aim 1, the comorbidity burden will serve as the effect modifier. The confounding factors will match those of Aim 1.

Statistical Analysis Plan

The descriptive analyses outlined for Aim 1 will apply to Aim 2 as well. Regarding the IPTW, we will apply the same procedures as in Aim 1 to the dataset to obtain a weight for each woman. The effect of RT on mortality will be assessed via 5-year survival curves of the study population using the Kaplan-Meier method, which will incorporate the IPTW. To estimate the effect of RT and comorbidity on mortality, we will use the weighted Cox proportional hazards model to obtain the IPTW-adjusted relative hazard of 5-year overall and cause-specific mortality from the date of diagnosis. IPTW-adjusted subdistribution hazard ratios with 95% CIs will be reported. The proportional hazards assumption will be assessed using the Schoenfeld residuals test, which measures the correlation between residuals of each covariate and time and evaluates the interactions with time in the survival models.

Sensitivity analysis will be performed to examine whether the censoring may be informative rather than noninformative. We will consider 2 extreme possibilities: events occurred immediately after censoring or later than any other observed events.

Limitations

A significant limitation of this study concerns the lack of data on chemotherapy, endocrine therapy, or other systemic therapy information from the SEER data, which may have a major impact on HRQOL and survival outcomes. To minimize the confounding effects from other treatments on HRQOL, we restricted our study population to women with low-risk, favorable breast cancer whose treatment plan would typically not involve chemotherapy. We assumed that most women in the study population received endocrine therapy according to their ER-positive status. Another limitation concerns the SEER-MHOS data; although they are population-based data, SEER covers certain geographic areas, and MHOS only samples insured women; thus, the overlapping of the 2 databases could be very limited, and only some women/tumor characteristics will be considered in the analysis. However, to the best of our knowledge, this is the best resource to evaluate the long-term effect on HRQOL from RT at the population level.

Results

As of October 2020, the study was approved by the Institutional Review Board of the University of Central Florida (SBE-18-14238), and the permission to use the SEER-MHOS database was obtained from NCI and SEER. Data have been curated for data analysis, women with low-risk breast cancer who met the inclusion and exclusion criteria have been identified, and prediagnosis comorbidity burden class has been characterized by latent class analysis. Further data analysis will begin in November 2020. The results of this study will be disseminated in peer-reviewed journals and presented at medical/scientific conferences. The first set of results of this study, namely those concerning prediagnosis comorbidity burden and HRQOL, will be submitted for publication in peer-reviewed journals in February 2021, and the second set of results regarding the effect of RT on survival outcomes will be submitted in June 2021.

Discussion

This study will provide empirical evidence for the effect of RT on HRQOL trajectory as well as survival outcomes using comparative effectiveness research methods with patient-reported HRQOL outcomes, which provide patients' perspectives on health care options. This research has the potential to improve clinical outcomes of older women with cancer enrolled in Medicare Advantage Organizations by providing information on HRQOL trajectories in addition to potential survival advantages from RT. This project will contribute new knowledge of long-term HRQOL to the existing evidence concerning the use of adjuvant RT after BCS in older women with low-risk breast cancer. By examining the independent and potential interactive effects of RT and comorbidity on HRQOL trajectories and survival outcomes, this evidence can facilitate communication between older women and their health care providers for shared decision making.

Data Statement

The data analyzed in this study are available in the NCI's repository [45]. Permission to use the data is required by the NCI. Investigators interested in using SEER-MHOS data must submit a research protocol as part of their data request.

Acknowledgments

The interpretation and reporting of the SEER-MHOS data used in this project are the sole responsibility of the authors. The authors acknowledge the efforts of the National Cancer Institute (NCI); the Centers for Medicare & Medicaid Services; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-MHOS database. The NCI provided approval for data use after reviewing the protocol. EL received research awards for this study from the University of Central Florida (UCF) Office of Research and the Department of Health Sciences, UCF College of Health Professions and Sciences.

Authors' Contributions

EL was responsible for all aspects of the study, including its conception and design; data collection, analysis, and interpretation; and the creation of the manuscript draft and its submission. RBH and EN contributed to the study design, data analysis, interpretation, and drafting of the manuscript. JLW, MJR, and XL contributed to the study design, data interpretation, and drafting of the manuscript. All the authors critically revised the manuscript and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

BCS: breast-conserving surgery
ER: estrogen receptor
HRQOL: health-related quality of life
IPTW: inverse probability of treatment weighting
MHOS: Medicare Health Outcomes Survey
NCCN: National Comprehensive Cancer Network
NCI: National Cancer Institute
RCT: randomized controlled trial
RT: radiation therapy
SEER: Surveillance, Epidemiology, and End Results

Edited by G Eysenbach; submitted 07.02.20; peer-reviewed by L Wang, IV George; comments to author 05.09.20; revised version received 18.10.20; accepted 20.10.20; published 12.11.20.

Please cite as:
Lee E, Hines RB, Wright JL, Nam E, Rovito MJ, Liu X
Effects of Radiation Therapy and Comorbidity on Health-Related Quality of Life and Mortality Among Older Women With Low-Risk Breast Cancer: Protocol for a Retrospective Cohort Study
JMIR Res Protoc 2020;9(11):e18056
URL: http://www.researchprotocols.org/2020/11/e18056/
doi:10.2196/18056
PMID:33090111

Protocol

QueerVIEW: Protocol for a Technology-Mediated Qualitative Photo Elicitation Study With Sexual and Gender Minority Youth in Ontario, Canada

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Abstract

Background: The experiences of resilience and intersectionality in the lives of contemporary sexual and gender minority youth (SGMY) are important to explore. SGMY face unique experiences of discrimination in both online and offline environments, yet simultaneously build community and seek support in innovative ways. SGMY who identify as transgender, trans, or gender nonconforming and have experiences with child welfare, homelessness, or immigration have been particularly understudied. A qualitative exploration that leverages technology may derive new understanding of the negotiations of risk, resilience, and identity intersections that impact the well-being of vulnerable SGMY.

Objective: The objectives of the QueerVIEW study were to (1) enhance understanding of SGMY identities, both online and offline, (2) identify experiences of intersectionality among culturally, regionally, and racially diverse SGMY in Ontario, Canada, (3) explore online and offline sources of resilience for SGMY, and (4) develop and apply a virtual photo elicitation methodological approach.

Methods: This is the first study to pilot a completely virtual approach to a photo elicitation investigation with youth, including data collection, recruitment, interviewing, and analysis. Recruited through social media, SGMY completed a brief screening survey, submitted 10 to 15 digital photos, and then participated in an individual semistructured interview that focused on their photos and related life experiences. Online data collection methods were employed through encrypted online file transfer and secure online interviews. Data is being analyzed using a constructivist grounded theory approach, with six coders participating in structured online meetings that triangulated photo, video, and textual data.

Results: Data collection with 30 participants has been completed and analyses are underway. SGMY expressed appreciation for the photo elicitation and online design of the study and many reported experiencing an emotional catharsis from participating in this process. It is anticipated that results will form a model of how participants work toward integrating their online and offline experiences and identities into developing a sense of themselves as resilient.

Conclusions: This protocol presents an innovative, technology-enabled qualitative study that completely digitized a popular arts-based methodology—photo elicitation—that has potential utility for contemporary research with marginalized populations. The research design and triangulated analyses can generate more nuanced conceptualizations of SGMY identities and resilience than more traditional approaches. Considerations for conducting online research may be useful for other qualitative research.

International Registered Report Identifier (IRRID): DERR1-10.2196/20547

(JMIR Res Protoc 2020;9(11):e20547) doi:10.2196/20547

KEYWORDS

lesbian; gay; bisexual; transgender; queer; youth; photo elicitation; photo voice; grounded theory; online research; Canada

Introduction

Sexual and Gender Minority Youth (SGMY)

SGMY face unique challenges that impact their sense of self. Their experiences of exclusion and discrimination are important to examine to better understand the unique psychosocial and mental health needs of SGMY and identify instances of resistance and resilience [1]. Minority stress, which includes the stigma of living with a sexual and/or gender minority (SGM) identity [2], impacts the daily lives of SGMY through chronic discrimination, such as microaggressions and name-calling [3], and other acute events, such as physical and sexual violence [4]. Minority stress manifests in higher rates of mental health disorders for SGMY than for their heterosexual or cisgender peers, which may include depression, anxiety, suicide attempts, and posttraumatic stress disorder [5]. Alongside mental health ramifications, SGMY may also be at risk of later developing physical health conditions in response to their minority stress, such as cardiovascular disease, asthma, diabetes, and other chronic conditions [6]. The prevalence of such physical and mental health conditions is considerably higher for those facing multiple and intersecting vulnerabilities [5,6]. Although extant research has quantified the challenges experienced by SGMY generally, as well as several subpopulations [2-7], the experiences of most SGMY cannot be understood in "identity silos" but rather through an exploration of the complexity of the intersections in their daily lives [7]. This qualitative research protocol focuses on the development and implementation of QueerVIEW, a technology-mediated photo elicitation study that examined the intersectionality and resilience of SGMY who also have particular marginalizing experiences. QueerVIEW was a project developed by the Canadian Regional Network of the International Partnership for Queer Youth Resilience (INQYR), an international partnership of researchers working to address the needs of SGMY and their use of information and communication technologies (ICTs) within diverse global contexts. QueerVIEW utilized virtual photo elicitation methods to explore the complex and intersecting identities of SGMY who identify as members of at least one of four priority populations: (1) trans and gender nonconforming youth, (2) youth who have experiences with homelessness, (3) youth with current or past involvement in the child welfare system, and (4) youth who are immigrants, refugees, or newcomers to Canada.

Trans or Gender Nonconforming Youth

Trans is defined as having a different gender than the gender assigned at birth [8-11]. Gender nonconforming and gender diverse is an identity endorsed by people whose gender expression differs from societal expectations of masculinity or femininity [8]. Accurate numbers of trans and gender nonconforming (TGNC) and gender diverse youth remain unavailable at the population level in countries such as Canada and the United States, as national censuses have historically asked for current gender identity via binary options (instead of multiresponse) and have not asked for gender assigned at birth [9]. Available prevalence data are often based on convenience samples recruited by independent researchers [9]. According to reports in the United States, between 0.7% and 1.8% of youth between the ages of 13 and 17 identify as trans [10,11], while Canadian estimates report that approximately 0.6% of the general adult population identifies as trans [12]. A recent study of 6309 SGMY in the United States and Canada found that 14.6% (n=924) identified as trans and 23.9% (n=1506) identified as gender nonconforming [13].

Challenges Faced by TGNC Youth

Youth identifying as TGNC face a particular set of challenges, including feelings of invisibility, hypervisibility, and hostility [14]. Compared with their cisgender (ie, identify with gender assigned at birth) counterparts in the general population, TGNC youth have a higher risk of mental health issues such as psychological distress, self-harm, depression, and suicide, while nonbinary youth are more likely to report self-harm, as reported in the Canadian Community Health Survey [15]. Relatedly, alcohol use and victimization experiences have been found to be higher for TGNC youth than for the general youth population [16]. TGNC youth also reported significantly poorer health outcomes and utilization of health care services than cisgender youth [17]. TGNC adults experienced higher odds of discrimination, depression, and suicide attempts compared with cisgender lesbian, gay, or bisexual individuals [18]. Similarly, depression and anxiety were reported as occurring with higher effect sizes for TGNC college students than for their cisgender lesbian and gay peers [19].

Experiences of Homelessness

Approximately 40% of the 35,000 to 40,000 youth who experience homelessness or housing instability in Canada during an average year identify as SGMY [20]. The term "homelessness" can encompass a range of unstable housing situations, including unsheltered (or absolutely homeless), emergency sheltered (those in overnight shelters or shelters specific to family violence), provisionally accommodated (temporary or insecure housing tenure), and at risk of being homeless (precarious housing or financial situations that may lead to homelessness) [21]. The most frequently cited cause of homelessness among SGMY is identity-based family conflict [22]. Compared with non-SGMY experiencing homelessness, SGMY are more likely to engage in survival sex work when homeless, engage in unsafe sex with their sex work clients, and have higher numbers of sex work clients overall than their cisgender heterosexual peers [23]. TGNC populations appear to be particularly at risk, with a sample of youth (younger than 18 years) and adult trans men experiencing significant and comorbid violence as well as physical and mental health problems. Meanwhile, homeless trans women report higher rates of posttraumatic stress disorder than other homeless individuals [24].

Engagement in Child Welfare

Research from the United States on the prevalence of SGMY engagement in the child welfare system estimates that 15% to 34% of the approximately 350,000 individuals with a history of foster care involvement identify as SGMY at the point of intake [25,26]. Estimates of SGMY among the approximately 63,000 Canadian children in the child welfare system are unavailable, with no child welfare surveys currently collecting data on SGM identity [27] and large-scale reports not reporting on SGMY intake incidence [28]. Systemic limitations on collecting population-based data for Canadian child welfare agencies have been noted elsewhere [29]. SGMY experience higher rates of adverse childhood events than their peers [30] and are at a greater risk of involvement in the child welfare system, often as a result of their SGM status, as they may experience intrafamilial abuse, conflict, and rejection due to their identities [31]. SGMY in foster care report feeling less satisfied with their foster care experience than non-SGMY, are at greater risk for homelessness, and experience more placement breakdowns, resulting in greater emotional distress [32]. Research on SGMY in the child welfare system is often limited by small numbers of consenting participants because youth have concerns about disclosing their identities [33]. While in foster care, SGMY are often the victims of physical abuse, bullying, and harassment from caregivers and other youth [34], resulting in increased rates of posttraumatic stress and other mental health issues [35].

Immigrants, Refugees, and Newcomers

Approximately 21.9% of the Canadian population (37.59 million) was born outside of the country [36]. SGM refugees, immigrants, and newcomers face unique challenges and stressors as a result of their migration and SGM status, including conflict in one or across many of their identity facets or affiliations [37]. Newcomer SGMY, or SGM individuals with landed immigrant status in Canada [38], are recognized as a particularly vulnerable group by the Canadian Immigration and Refugee Protection Act [39]. The Canadian settlement process can vary depending on the applicant's status and type of claim [40], contributing to a large range of experiences for newcomers. SGMY newcomers often have complex interactions with immigration, health care, and employment systems, and frequently have experienced homophobia and racism within their own communities and families, and related to social service provision [41]. Stressors include difficulties accessing health care and employment, and stress associated with refugee claimant hearings. These hearings often emphasize a claimant's ability to disclose and demonstrate their SGM identities, which may be unnecessarily difficult [41]. SGMY newcomers—particularly those who identify as trans females—report experiencing significant discrimination and bullying both in school and in their homes [42]. Many SGM immigrants to Canada discuss feeling disconnected from both their home culture and their Canadian culture because of their SGM identity, although many report that their SGM identity either becomes more important to them than their cultural identity or is integrated to allow them to live authentically [43]. Newcomer or refugee SGMY are a particularly understudied population, thus necessitating a greater understanding of their experiences in the research literature.

Theoretical Approach

This study's key theoretical framework is intersectionality, which not only explores distinct social identities, including their construction and intersections related to power, privilege, and experiences of discrimination, but also serves as a dynamic lens for investigating minority stress and resilience [43,44]. Focusing on a single identity may obscure the significance of other meaningful identities [45]. Intersectionality suggests that categories of oppression (eg, race, ethnicity, gender identity, sexuality, disability, and/or poverty) interact with and complicate an individual's unique context and experience, and may contribute to a compounded experience of marginalization [46]. Although emergent qualitative research has explored the interaction of SGM and racialized identities, there is a paucity of literature utilizing technology and arts-based innovative methods to understand intersectionality factors and the experiences of marginalized SGMY [7].

Rationale for Photo Elicitation

Visual data—such as photographs, videos, art pieces, and diagrams—have received increased interest and use in qualitative research [47], including as a tool to deepen conversations between participants and interviewers. Photo elicitation is a visual data method in which photographs provided by participants that capture relevant concepts under investigation are inserted into, and become the focus of, the research interview [48]. Photo elicitation offers a creative alternative to verbal-only methods of qualitative interviewing that is particularly suited to exploring intersectionalities. Images may evoke deeper elements of human consciousness than words alone, resulting in an interview process that elicits more information and evokes different types of information [48]. The use of photos to guide discussion and stimulate memory [48] has been demonstrated to increase participant-led dialogue [49], and can result in newfound insights compared with studies using more traditional methods to explore the phenomenon of interest [50]. Photo elicitation often results in richer data through the facilitation of rapport building between participant and interviewer [51] and by encouraging participants to provide a richer understanding of their experiences—including emotions, feelings, and ideas—rather than relying on researchers to impose their own assumptions, frameworks, or perceptions [52]. Images can ultimately promote a deepened dialogue and potentially introduce new dimensions that the researcher did not previously consider for their study [53].

Photo elicitation has been proposed as a participant-driven research methodology that is particularly well-suited for research among the adolescent population in general [54], and SGMY in particular. It reduces power differentials between researcher and participant [55], creating a "comfortable space for discussion" [56], and involving participants in a way that does not limit responses. Such advantages may be especially important for data collection with marginalized groups, such as SGMY [57]. By actively taking and selecting relevant photos for the interview, participants maintain agency over their participation in the research process. As a method, photo elicitation has been described as being capable of "empowering and emancipating participants by making their experiences

visible" [57] and centering participant voices [58]. Photo elicitation interviews (PEIs), similar to semistructured interviews without visual cues, provide the researcher with an interview guide centering on relevant areas of interest, as well as the flexibility to allow for unexpected topics to emerge [59].

The increasing availability of ICTs has resulted in new opportunities and enhancements to the research process through digital data collection [60]. Qualitative interviews conducted online have been demonstrated to overcome financial, geographic, and physical mobility barriers for participants [61]. Online reviews [61], focus groups [62], instant messaging [63], and qualitative analysis of public message boards [64] are all well-documented methods for digital data collection in qualitative research. For use with adolescents, online interviewing may be particularly effective, given this age group's comfortability, familiarity, and proficiency with ICTs [65]. Online interviewing with adolescents has demonstrated greater rapport building than in-person interviews and genererated similar amounts of youth self-disclosure [66]. Despite the potential for qualitative virtual PEIs for research with youth, there are no studies that have utilized these methods to date.

The use of technology-enabled photo elicitation methods may be particularly relevant for SGMY, who frequently use such technologies to develop their identities, access resources, and engage in online SGM communities [67]. SGMY also use ICTs to foster their coping skills and resilience [44]. As a result of widespread use and availability of ICTs, which permit easy collection and sharing of visual information (eg, smartphone cameras), youth are constantly engaged in recording their lives and experiences through photographs and videos. Virtual photo elicitation may offer the opportunity to advance insight into the intersectionality of SGMY's lived experiences through the use of participant-recorded real-world data. As such, the QueerVIEW study used PEIs to explore the identity and resilience of SGMY experiencing compounded marginalization or vulnerability within the context of their online and offline lives.

The research aims of QueerVIEW were to (1) enhance understanding of SGMY identities, both online and offline, (2) better understand experiences of intersectionality among culturally, regionally, and racially diverse SGMY in Ontario, Canada, (3) explore SGMY's online and offline sources and processes of resilience, and (4) develop and apply a virtual photo elicitation methodological approach.

Methods

QueerVIEW utilized a constructivist grounded theory framework in a virtual photo elicitation study to explore the intersectional identity experiences of SGMY in Ontario, Canada. Constructivist grounded theory concerns the construction of events, processes, and outcomes in order to study inequality by moving between theorizing and data collection. Constructivist grounded theory applies a critical lens and locates the research process within social, historic, and environmental conditions [68]. This form of inquiry involves co-constructing meaning through the development of emerging questions through the interactive engagement of the researchers with participants by posing critical questions from the inception of the project through the final analysis. For instance, in the case of QueerVIEW, this involved determining a new theme discussed by the participants, and choosing to pursue new questions in future interviews about that subject matter. In this way, constructivist grounded theory results in a deeper level of theorizing and unveiling of new critiques when compared with other qualitative methods [68]. Photo elicitation may be an ideal modality for constructivist grounded theory, as this method of interviewing can dismantle power differentials between participants and researchers while engaging participants in conversations far beyond the limitations of the interview guide [56]. Institutional review board approval was received from the University of Toronto's Health Science Research Ethics Board (Protocol #37041), which included a waiver of parental consent for participants younger than 18 years of age due to the possibility that participants' parents were not aware of their SGMY identities and that knowledge could pose a risk to participants.

Participant Recruitment and Sampling

Participant inclusion criteria for this study included the following: (1) aged between 14 and 29 years, (2) self-identifying as an SGM, (3) residing in Ontario, Canada, (4) able to capture and submit photos, (5) able to speak and understand English sufficiently to participate in the interview, and (6) able to participate in an online interview. To clarify criterion 2, participants were eligible if they self-identified as a gender minority (ie, not cisgender) and/or a sexual minority (ie, not heterosexual). These inclusion criteria were determined by the research coordinator and participants themselves using participants' responses to the screening survey (for criteria 1, 2, and 3) and through interaction with participants for the photo submission and interview scheduling (for criteria 4, 5, and 6). The four groups identified above—TGNC individuals, those with experiences with homelessness, those engaged in the child welfare system, and immigrants, refugees, and newcomers to Canada—were explicitly mentioned as priority populations in the recruitment flyer and screening survey. The age range was purposeful, given that heightened awareness of identity issues often occurs during the developmental periods of adolescence and early adulthood [68,69].

QueerVIEW recruited SGMY through a purposive and venue-based sampling approach. Purposive sampling recruited participants with a flyer, which was shared through the INQYR Canadian Regional Network, and distributed through paid Facebook and Instagram advertisements and via Twitter. Venue-based sampling was conducted concurrently with agencies in Ontario that serve SGMY communities and/or specialize in practice with TGNC youth, as well as youth experiencing homelessness, youth involved in the child welfare system, and newcomers to Canada. Additionally, universities located in Ontario, SGM-specific student clubs, and religious centers were also contacted for distribution of the flyer.

The recruitment flyer (Multimedia Appendix 1) directed potential participants to a QueerVIEW project page on the INQYR website [70], which included additional details about

the study, animated consent videos that described the study's purpose and process in an accessible way, and a link to the screening survey [71]. Further, a live action video of the interviewers was posted on the website and distributed on social media to make participants aware of the interviewers and study, to support self-efficacy, and to reduce anxiety.

Consent

Due to the age of the participants in this study, as well as to the multiple times of engagement, informed consent was collected twice: (1) prior to a screening survey hosted by Qualtrics' online survey software [72], and (2) prior to the interview. In the screening survey, consent information was provided in writing as well as in a specific animated video that used the written form as a script. Participants had the option to either read or watch the informed consent information [73] and, through the use of skip logic, were required to acknowledge they heard or read, understood, and agreed to participation before progressing through the online screener survey. The consent information was scanned for eighth grade readability [74] to ensure understandability and accessibility for all participants. It has been found that consent videos encourage more participants to carefully consider the implications of participation and increase their knowledge of their rights as participants [75]. At the end of the interviews, participants were asked if they would be interested in having their photos publicly displayed in an online gallery. If interested, participants verbally consented, and indicated which photos they did and did not want to be displayed. A separate consent form (Multimedia Appendix 2) will be emailed to participants closer to the gallery launch date (projected for fall 2020).

Data Collection

Stage 1: Online Screening Survey

A brief online screening survey asked potential participants for their age, gender identity, sexual orientation, preferred pronouns, Canadian city and province of residence, current housing situation, and contact information, along with questions about their membership in the four priority subgroups (eg, "have you ever experienced homelessness or any form of housing instability, like couch-surfing, living in a shelter/hotel, or street-involved?").

Stage 2: Participant Selection

The research team monitored the screening survey and met regularly to select participants who initially identified as members of multiple priority subgroups for interviews. Participants who identified with two or more subgroups were initially invited to interviews in order of screener survey completion, with SGMY with at least one priority group identification invited next. Selected participants were contacted by a research assistant through email or text (depending on their stated preference) with an invitation to participate in the study, and this continued until theoretical saturation was achieved.

Stage 3: Photo Selection and Submission

Individuals who agreed to participate were provided with instructions for taking, selecting, and submitting between 10 and 15 photos before the interview (Multimedia Appendix 3). These instructions asked participants to take and/or gather photos that represent the following areas: (1) who you are—how you see yourself in your online and offline lives, (2) how others see you in your online and offline lives, (3) what makes it hard for you to be who you are and what challenges do you face when trying to be yourself, and (4) what helps you be who you are and what gives you strength in the face of challenges. These areas were constructed by the research team (comprised of researchers, students, and people from the priority populations) based on their previous intersectionality research and emerging SGMY experiences to directly link the photo submission process to the research aims identified above. Participants were then instructed to upload their photographs via WeTransfer [76], an encrypted computer-file transfer service, before their interview.

Stage 4: Online Interviews

Two graduate research assistants trained in qualitative interviewing for photo elicitation studies conducted 90- to 120-minute online interviews using Zoom video conferencing. The research team used a Zoom Pro account, which provided up to 24 hours of meeting time, administrative feature controls including recording and screen sharing, customized personal meeting IDs, and a waiting room function. All of these functions were used during the interviews. Virtual interviews were recorded using Zoom's record feature and participants were requested to keep their device's camera on during the interview to collect both audio and video data. If participants required an in-person interview, these were also recorded via Zoom, directing the laptop's camera and microphone toward the interviewer and participant during the meeting. Interviewers toggled between speaker view on Zoom and screen sharing to display the photographs provided by participants.

At the beginning of the interview, participants were provided with a general overview of the study and support with any technology-related questions. A semistructured interview guide (Multimedia Appendix 4) was carefully designed to capture participants' experiences of intersectionality. Questions intended to uncover the personal meaning of minority stress and resilience in light of participants' intersectional social identities [45], such as perceptions of their online and offline lives and how they navigate adversity. During the interviews, SGMY were asked to describe their photos, and the photos were used as prompts whereby interviewers asked for participants to elaborate at times or clarify statements. Participants referred to the photos when describing themselves, their challenges, and their strengths. When needed, the interviewers gently redirected participants' sharing back to the photos provided by asking more in-depth questions about their emotions, senses, and recollections of their experiences (eg, "When you look at this photograph, how did you feel when it was taken? How do you feel now?").

Data Analysis

Data were analyzed using a constructivist grounded theory approach using NVivo 12 software by QSR International [68,77]. Constructivist grounded theory situates the researcher as co-constructing experiences and meaning so that the researcher's reactions, interpretations, and descriptions of the interviews are captured in the analytic process [77]. Six independent coders analyzed and integrated three types of data

from each participant—10-15 photos, video recordings of Zoom interviews, and textual transcripts of Zoom interviews—by importing the data into a single NVivo case and assigning codes based on the photos (which were discussed as part of the interview), interview content, and participant behaviours and affect (eg, facial expression, tone, etc) during the interview [78,79]. This triangulated approach of analysts conducting side-by-side coding of participant photos, nonverbal input from videos, and textual transcripts is one created by the authors to analyze technology-mediated research [80]. This analysis involved organizing the three data sources into initial and focused codes (primarily gerunds) that were combined in a single NVivo file to derive visuals (eg, data maps) for axial coding of the in-depth experiences of participants.

Six independent coders were assigned photos, videos, and transcripts to code simultaneously, with the spoken words as well as vocal intonations and body language of participants being coded as nodes and memos in NVivo [81]. The coding team is comprised of graduate research assistants who are ethnically diverse and predominantly identify as SGMY. Line-by-line coding was used to generate codes from the descriptions of the participants about their identities, technology use, and resilience through their selected images, transcripts, and interviews. Data were triangulated to capture multiple processes occurring simultaneously, such as themes discerned from the content of participants' sharing and process changes such as verbal tone, body language, or displays of affect (eg, crying or laughing), as well as participants' interactions with their environments (such as awareness of their parents in the house, internet disruptions, or introductions of pets). Annotations were used to describe processes occurring in the research process (such as interview interruptions, or instances when transcript content and nonverbal communication were discordant). Line-by-line open coding of the 30 interviews has been completed, each fully coded twice by two independent coders. Axial coding is underway to confirm codes against emerging themes and develop a model that explains intersectional conceptions of resilience and identity. A data map has been created using Mindmeister software (MeisterLabs GmbH) and is being edited by the coding team. To enhance trustworthiness in independent coders, research assistants were trained to utilize grounded theory, employ the "constant comparison" method, and maintain an audit trail. Further, the principal investigator hosted monthly meetings to discuss coding progress [82].

Presentation of Findings

Once analysis is complete, member checking will be conducted whereby participants will be invited to a virtual group meeting to discuss the analysis and how it converges and/or diverges with their individual participation. A draft of this analysis in the form of a written report and a visual will be distributed in advance of this meeting; for participants who cannot attend member checking in the virtual group, they will have the option of emailing a written response to the analysis. Once the results are finalized, study findings will be disseminated to relevant research and practice communities. The results will be presented at local, national, and international social work, qualitative research, and SGM-specific academic conferences and symposia, and submitted for publication in peer-reviewed journals. A summary of the results will be made available on the INQYR website, with infographics, diagrams, and descriptions shared on social media with links to the website. The results will also be detailed in funder reports.

As participants provided specific consent and interest in the research team publishing their photos, the QueerVIEW project will culminate in the creation of an online photo gallery. With participants' consent, voiceovers or text descriptors will describe the images, with a future goal of turning the online gallery into an interactive game interface. Images will have blurred identifiable information, will not feature faces, and will be protected to the greatest extent possible (such as excluding the ability to save image files and barring access from online search engines, such as Google Images). Participants will have access to the online gallery to view their images. An online gallery reception will be hosted for all participants, research team, INQYR partnership members, and interested community members to attend.

Results

Data collection has been completed with a total of 30 interviews. Major emerging themes center on the process of deliberate yet differential approaches to identity formation among SGMY using online and offline mediums. Early results are promising, with virtual photo elicitation serving as a useful tool to deepen the interview process and provide a glimpse into the lives of SGMY participants. Participants took extensive time to consider, select, and submit their photos. SGMY reported caring about their photo selection and the study process because they wanted to select the best photos to represent themselves and because of their potential vulnerability in sharing personal photos.

Discussion

Recruitment Process

The research team noted that the recruitment stage of this study took longer than anticipated at 7 months in length (September 2019 to April 2020), although this is comparable to offline photo-based research [83,84]. However, the COVID-19 global pandemic resulted in an increase in participants finalizing their photo selections and scheduling interviews. The recruitment process was adjusted and streamlined by the research team, with a gentle time limit conveyed to participants, in order to decrease the amount of time between recruitment and interview to facilitate the research process. Among the four highly marginalized priority populations identified above, participants who were immigrants, refugees, or newcomers to Canada and those with child welfare experiences were particularly challenging to recruit. Targeted recruitment strategies with specialized agencies were needed to increase participation in this regard. Future qualitative photo elicitation undertaken by the research team will likely focus on recruiting participants with one or two priority experiences.

Interview Process

The online interview process was very successful, with the research team observing that rapport was built more rapidly online than during in-person interviews of a similar nature,

which corroborates extant literature [83], perhaps as a result of familiarity with online platforms and the comfort with online sharing for SGMY [47]. Participants expressed a sense of emotional catharsis at interview completion, with many stating that they felt better after the interviews and many developing a deeper understanding of their experiences or patterns of behaviour, which aligns with extant photovoice and photo elicitation research [83-86]. Such expressions of catharsis will be explored in the analysis and reported in the context of existing literature on the photo elicitation method's potential for therapeutic benefit.

Limitations

Protocol limitations include the entry criteria of English comprehension and ability to participate in an online interview. While this study prioritized immigrants, refugees, and newcomers to Canada, the study team only had resources available for recruitment and data collection in English. Additional resources for translation services for recruitment, screening, photo submission, and interviewing could have mitigated this language barrier. As this study also prioritized SGMY with experiences of homelessness, access to a device (eg, smartphone) and a private space for the interview could have also been a barrier. Since this study recruited across the Canadian province of Ontario (a large land mass) during the COVID-19 pandemic, and with limited resources, travel for in-person interviews and the provision of devices were not possible. Partnering with community organizations in recruitment may have mitigated the access barrier to some extent, before the COVID-19 pandemic shuttered in-person services, as participants could potentially have used organizational resources to participate in the study.

Conclusion

QueerVIEW is an innovative study that leverages technology and visual arts-based research in a virtual photo elicitation method that advances a creative investigation examining resilience among SGMY. This protocol describes the successful implementation of a completely virtual research study that integrates digital photography with online recruitment, PEIs, data collection, and analysis to deepen exploration of SGMY experiences. The application of this protocol has determined that (1) youth take extroaordinary care in selecting photos, which should be accommodated in recruitment strategies and study timelines, (2) online PEIs can result in increased engagement and sharing by SGMY participants, and (3) technology-enabled PEI studies can contribute to a sense of catharsis for youth participants. The target populations of this study have been chosen based on their experiences of resilience, and the methods offer a means to facilitate their empowerment by fully immersing the research team in their experiences. It is through these methods, which privilege SGMY participant voices about their experiences and accessibility, that the researchers will be able to produce results that portray a robust picture of SGMY intersectional experiences.

Acknowledgments

Dr Craig is the Canada Research Chair in Sexual and Gender Minority Youth. This project is funded by Partnership and Connection Grants from the Social Sciences and Humanities Research Council of Canada (SSHRC Grants #895-2018-1000 and #611-2019-0024), the John R Evans Leaders Fund of the Canada Foundation for Innovation (CFI Grant #37651), and an International Doctoral Cluster Grant from the University of Toronto. Mr Eaton is supported by a salary award from the Ontario HIV Treatment Network. Ms Pascoe and Mr Egag are supported by graduate fellowships from SSHRC.

Conflicts of Interest

None declared.

Multimedia Appendix 1
QueerVIEW flyer.
[PDF File (Adobe PDF File), 575 KB - resprot_v9i11e20547_app1.pdf]

Multimedia Appendix 2
QueerVIEW online gallery consent form.
[DOCX File , 99 KB - resprot_v9i11e20547_app2.docx]

Multimedia Appendix 3
Photo instructions.
[DOCX File , 99 KB - resprot_v9i11e20547_app3.docx]

Multimedia Appendix 4
Interview questionnaire.
[DOCX File , 20 KB - resprot_v9i11e20547_app4.docx]

Multimedia Appendix 5

Peer review reports.
[PDF File (Adobe PDF File), 438 KB - resprot_v9i11e20547_app5.pdf]

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Abbreviations

ICTs: information and communication technologies
INQYR: International Partnership for Queer Youth Resistance
PEI: photo elicitation interview
SGM: sexual and gender minority
SGMY: sexual and gender minority youth
TGNC: trans and gender nonconforming

Edited by G Eysenbach; submitted 07.08.20; peer-reviewed by S Donnelly, C Escobar-Viera, N Mohammad Gholi Mezerji; comments to author 29.09.20; revised version received 08.10.20; accepted 20.10.20; published 05.11.20.

Please cite as:
Craig SL, Eaton AD, Pascoe R, Egag E, McInroy LB, Fang L, Austin A, Dentato MP
QueerVIEW: Protocol for a Technology-Mediated Qualitative Photo Elicitation Study With Sexual and Gender Minority Youth in Ontario, Canada
JMIR Res Protoc 2020;9(11):e20547
URL: https://www.researchprotocols.org/2020/11/e20547
doi:10.2196/20547
PMID:33151153

Protocol

Using Wearable Devices to Monitor Physical Activity in Patients Undergoing Aortic Valve Replacement: Protocol for a Prospective Observational Study

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Abstract

Background: In last few decades, several tools have been developed to measure physical function objectively; however, their use has not been well established in clinical practice.

Objective: This study aims to describe the preoperative physical function and to assess and compare 6-month postoperative changes in the physical function of patients undergoing treatment for aortic stenosis with either surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR). The study also aims to evaluate the feasibility of wearable devices in assessing physical function in such patients.

Methods: This is a prospective observational study. The enrollment will be conducted 1 month before patients' SAVR/TAVR. Patients will be provided with the wearable device at baseline (activity tracker device, Garmin vívoactive 3). They will be trained in the use of the device, and they will be requested to wear it on the wrist of their preferred hand until 12 months after SAVR/TAVR. After baseline assessment, they will undergo 4 follow-up assessments at 1, 3, 6, and 12 months after SAVR/TAVR. At baseline and each follow-up, they will undergo a set of standard and validated tests to assess physical function, health-related quality of life, and sleep quality.

Results: The ethics committee of Vicenza in Veneto Region in Italy approved the study (Protocol No. 943; January 4, 2019). As of October 2020, the enrollment of participants is ongoing.

Conclusions: The use of the wearable devices for real-time monitoring of physical activity of patients undergoing aortic valve replacement is a promising opportunity for improving the clinical management and consequently, the health outcomes of such patients.

Trial Registration: Clinicaltrials.gov NCT03843320; https://tinyurl.com/yyareu5y

International Registered Report Identifier (IRRID): DERR1-10.2196/20072

(JMIR Res Protoc 2020;9(11):e20072) doi:10.2196/20072

KEYWORDS

surgical aortic valve replacement; transcatheter aortic valve replacement; physical function; wearable devices

Introduction

High levels of physical activity are essential for the success of cardiac procedures; it has been established that ad hoc cardiac rehabilitation programs improve patients' functional recovery through exercise therapy [1]. Ad hoc exercises (both preoperative and postoperative) have been demonstrated to reduce the likelihood of postoperative complications (eg, postoperative pulmonary complications and thromboembolism), facilitate physical recovery, and reduce the length of hospital stay [2].

Aortic stenosis is the most common valvular disease in patients aged over 75 years with a prevalence of about 3%, and 1 out of 8 of such patients is affected by moderate/severe disease [3]. For a long time, surgical aortic valve replacement (SAVR) has been the standard of care for treatment of aortic stenosis treatment. However, transcatheter aortic valve replacement (TAVR) has recently emerged as an alternative for the treatment of aortic stenosis in selected patients [4-6], which seems to result in a faster physical recovery compared to SAVR. However, most of the studies on patients receiving SAVR and TAVR have focused on postoperative changes in health-related quality of life (HRQoL). The physical function has been assessed as a parameter of HRQoL (eg, 36-Item Short Form Health Survey [SF-36]), showing that patients receiving TAVR generally show more significant improvements in HRQoL at 3-, 6-, and 9-month follow-ups [7-9] than those in patients receiving SAVR [10]. A few studies have explicitly concentrated on the assessment of physical function. It has been shown that the postoperative changes in physical function of patients undergoing valve replacement are mainly affected by the severity of their condition [11], and physical function in such patients can be improved through ad hoc rehabilitation programs [12-14].

It is worth pointing out that there is a lack of specific data on the trajectories of physical recovery in patients receiving SAVR and TAVR, despite their widely acknowledged key roles in affecting postoperative outcomes, especially among elderly who are more prone to develop postoperative complications. Given the close relationship of physical activity with the outcomes of cardiac procedures, there is a growing interest in improving assessment of physical activity. Undoubtedly, several methods are available to assess physical function (and are widely used in both everyday clinical practice and clinical research) [15]. However, such approaches present several limitations, and the main one is that physical function is self-reported (and self-rated) by the patient. Self-reporting can be biased (eg, recall and desirability biases), and this might pose a barrier to further improvement in patients' recovery from surgery. In the last few decades, several tools have been developed to measure physical function objectively. Particularly, commercially available wearable technologies are increasingly used for both collecting and promoting patients' activity [16] in the health care setting. A recent review in the field has shown a broad spectrum of applications of such technologies for several purposes, including health promotion, health maintenance, and clinical monitoring of patients with various pathological conditions or patients undergoing surgery [17]. The fact that such devices allow for continuous data collection presents a promising opportunity to improve the monitoring of patients, especially those with chronic diseases, allowing for early detection of changes in patients' activity that need to be investigated by the clinicians [18]. However, the use of such devices has not been well established in everyday clinical practice.

This study aims to describe baseline (preoperative) physical function and to assess and compare 6-month postoperative changes in the physical function of patients undergoing treatment for aortic stenosis with either SAVR or TAVR with Edwards valve implants. It also aims to evaluate the feasibility of wearable devices in assessing physical function in such patients.

Methods

This is a prospective observational study.

Study Population

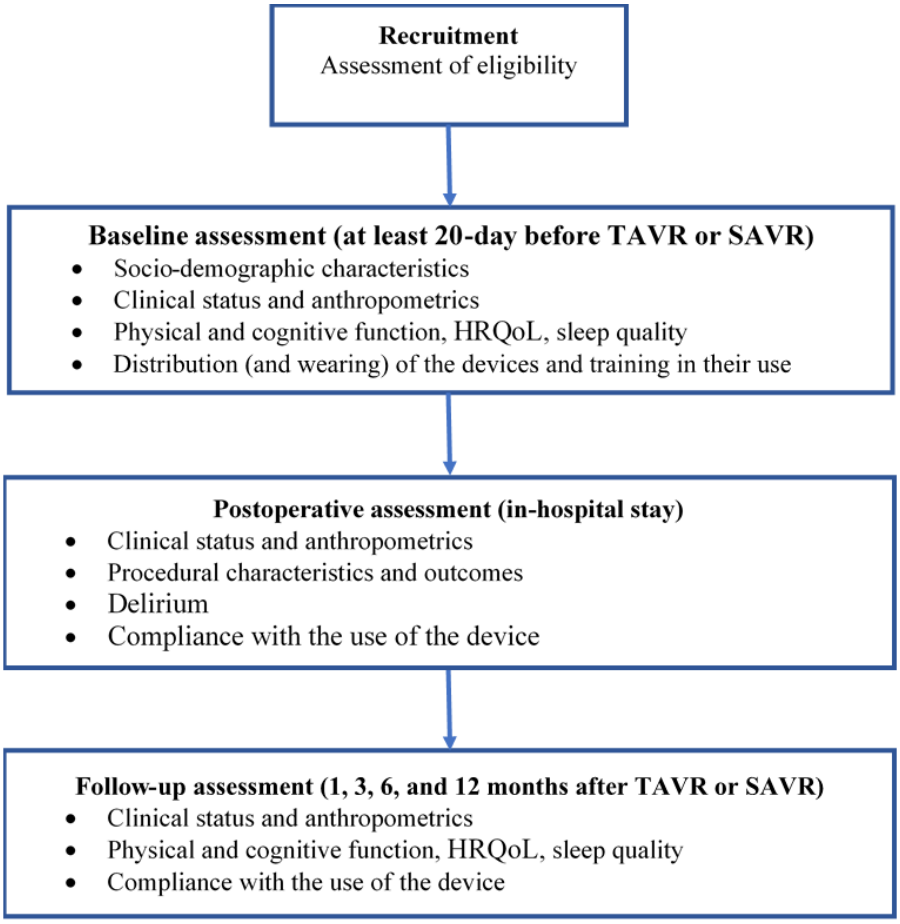
The study will enroll patients undergoing SAVR and TAVR. Aortic valve replacement interventions will be mandated either by patients' symptoms or by indications proposed by the current guidelines and approved by the local heart team.

The inclusion criteria are as follows: (1) age, 75-90 years; (2) severe native aortic valve stenosis symptomatic for heart failure or angina; (3) indication to isolated TAVR or SAVR, approved by the heart team; (4) TAVR through the transfemoral approach; (5) SAVR by any access; (6) implantation of an Edwards valve (Sapien 3 and Sapien XT for TAVR; Inspiris Resilia, Edwards Intuity, and Carpentier-Edwards Perimount Magna Ease for SAVR); (7) not using walking aids; and (8) written informed consent. Patients not fitting the inclusion criteria, those with reduced life expectancy due to severe comorbidities (<1 year), and those with Parkinson disease will be excluded from the study.

Study Procedures and Data Collection

Study procedures are reported in Figure 1. The enrollment will be performed 1 month before SAVR/TAVR. Patients will be provided with the wearable device at baseline. They will be trained in the use of the device, and they will be requested to wear it on the wrist of their preferred hand until 12 months after their SAVR/TAVR. After the baseline assessment, they will undergo 4 follow-up assessments at 1, 3, 6, and 12 months after their SAVR/TAVR.

Figure 1. Flowchart of the study protocol. HRQoL: health-related quality of life; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement.



At baseline and at each follow-up, they will undergo a set of standard and validated tests to assess their physical function, namely, 6-Minute Walk Test (6MWT), Duke Activity Status Index (DASI), Barthel Activities of Daily Living Index, and Instrumental Activity of Daily Living (IADL). Cognitive function will be assessed by Mini Mental State Examination (MMSE). Health-related quality of life will be assessed by SF-36 and Toronto Aortic Stenosis Quality of Life Questionnaire (TASQ). Sleep quality will be assessed by Epworth Sleepiness Scale (ESS).

Study Device

Smartwatch activity tracker devices (vívoactive 3, Garmin) will be used in the study. Devices will be provided to the patients at the time of baseline assessment, along with a Bluetooth-paired smartphone with prepaid data-only SIM card and user interface customized for the study.

Device Data Collection

Data will be collected from the wearable devices employing 2 complementary strategies to access both standard data (made available by Garmin and represented by daily activity statistics obtained through proprietary algorithms) and raw data.

1. Standard data will be collected using the Garmin Health API (application program interface). The standard data will be collected through the Garmin-Connect app installed on the smartphone. Patients will be requested to synchronize the device with their smartphone at least 3 times a week to allow the collection of the data stored in the device.
2. Raw data will be collected using an ad hoc app (developed for the study) powered by Garmin-Connect API. The data stored in the device will be automatically collected every time the phone and the device are close enough to be connected via Bluetooth (less than 8 meters). Patients will be instructed to keep the phone close to bed to allow data collection during nighttime. Once downloaded, the data will be stored in flexible and interoperable data transfer (FIT) files.

Data Management

Site personnel trained in using the device will be available on workdays from 9 AM to 5 PM for technical assistance (by phone) about connection, synchronization, and setting of the smartphones and the devices. The same site personnel will send reminders (by phone) to patients if they do not regularly perform the data download for the standard data collection.

Sample Size

The primary endpoint is represented by the potential gain—assessed through the 6MWT—in recovering physical function within the first 6 months after SAVR/TAVR. A sample size of 154 patients per group has been computed using a Kolmogorov-Smirnov test to evaluate the difference between the growth curves of 6MWT between the SAVR and TAVR

groups. A simulation procedure has been performed assuming the following factors:

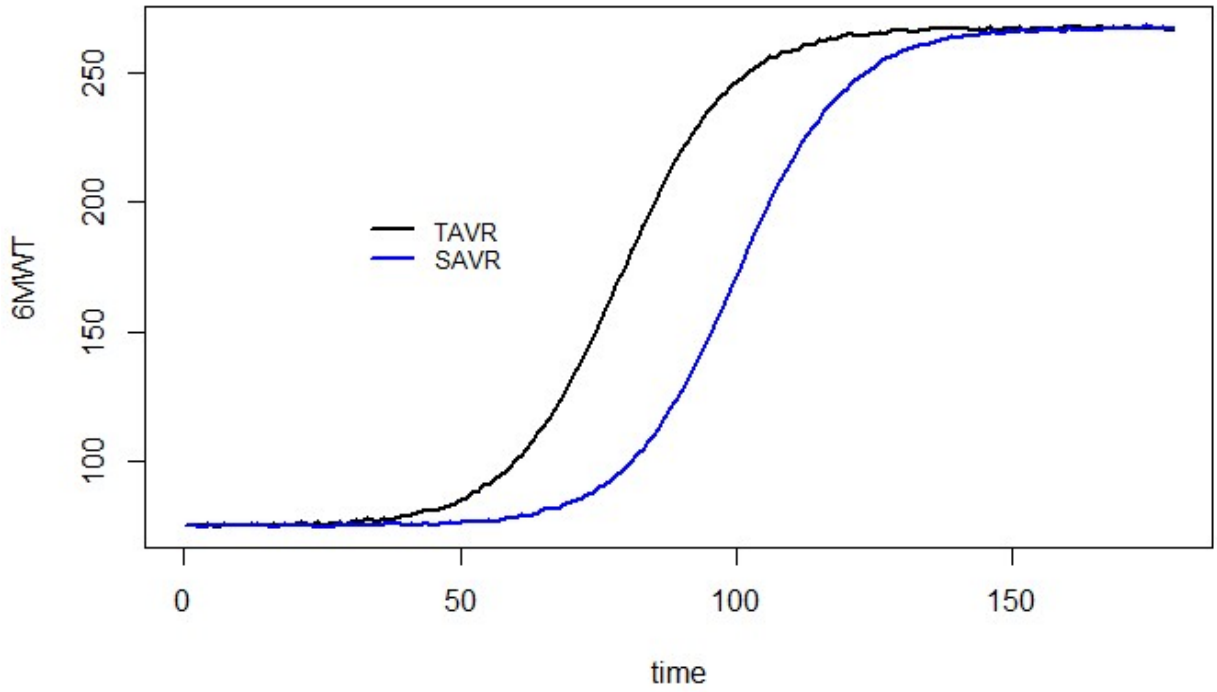
1. Logistic growth function for both groups.
2. Mean growth rate of 10% for both samples, assuming a mean time (useful to recover a carrying capacity of 270 meters) of 100 days for SAVR and 80 days for TAVR (with a mean reduction of recovery time consisting of 20 days).
3. A type I error probability equal to .05.
4. Each scenario consists of a combination of sample sizes from 100 to 200, and a difference between midpoint time recovery ranges from 5 to 30 days.

A statistical power of 0.9 has been reached with a difference between a recovery time of 20 days for 150 patients. For each scenario, 100 simulations have been performed by sampling *n* growth curves (1 for each patient), assuming the following growth function:

In this equation, $\alpha \sim N(0.1, 0.01)$, where α is the growth rate specifying the width of the sigmoidal curve; k is the carrying capacity; and β specifies the time when the curve reaches the midpoint of the growth trajectory.

The curves have been pooled computing the mean within the sample, obtaining a mean SAVR and TAVR growth rate, as shown in Figure 2. Total patients to be enrolled are 340 (170 in each of the SAVR and TAVR groups), considering a dropout rate of 10%.

Figure 2. Simulated growth rate for the 6-Minute Walk Test (6MWT). SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement.



Statistical Analysis

Data will be reported as median (interquartile range) values for continuous variables and as percentage (absolute number) values for qualitative variables. A Wilcoxon-Kruskal-Wallis test will be performed for continuous variables and Pearson chi-square tests for categorical ones.

A propensity score estimation will be provided to balance data in the SAVR and TAVR groups according to the baseline characteristics. A random forest classification algorithm [19] will be employed for propensity score computation.

A genetic algorithm [20] will be considered to match the data, taking into account the similarities in the estimated propensity scores. The algorithm automatically finds the set of matches, which minimizes the discrepancies between groups.

Once the data are matched, treatment groups will be compared to assess the quality of the matching procedure according to the baseline characteristics, reporting the same statistics as previously considered to describe patients receiving SAVR and TAVR.

Finally, a generalized estimating equations model [21] will be estimated on matched data to determine the time effect on the 6MWT performance in both treatment groups; the model will also include other confounding factors potentially affecting 6MWT.

Validity of the Device in Measuring Physical Function

A validation study (ie, device vs observer in measuring the primary endpoint) will be performed during the 6MWT at each follow-up (1, 3, 6, and 12 months) and will involve all the patients enrolled in the study.

The number of steps performed during each 6MWT will be assessed both by the device and manually (using a step counter) by an independent observer. The manual counting of steps will be considered the gold standard. The number of steps recorded

by the device will be compared to those counted manually (the gold standard).

The mean absolute percent error (MAPE) of the number of steps, as the average of the unsigned percentage error, will be computed to assess the agreement between the 2 methods, reporting at 95% confidence interval. A MAPE of less than 5% will be considered excellent, while a MAPE greater than 10% will be considered poor [22]. The validation of Garmin devices will also be performed and reported using Bland-Altman plots [23].

Moreover, the intraclass correlation coefficient (ICC) will be calculated for the number of steps measured manually and that obtained by the Garmin device. An ICC of ≥0.75 will be identified as excellent, 0.65-0.74 as good, 0.40-0.64 as fair, and <0.40 as poor [24].

The concordance between the number of steps recorded by the Garmin device and that by the gold standard (manual counting) will be evaluated at 1, 3, 6, and 12 months after SAVR or TAVR. Considering the multiplicity issues related to measures performed repeatedly, *P* value adjustment will be performed to control the inflation of the type I error rate of the experiment using the Holm procedure [25].

Ethics Approval and Consent To Participate

The study was approved by the ethics committee of the province of Vicenza in the Veneto Region of Italy (Protocol No. 943; January 4, 2019). Each patient or legally authorized representative must provide a written informed consent for the study procedures.

Results

Patient enrollment is ongoing. A total of 20 participants have been enrolled as of October 2020.

Discussion

Objective measurement of physical function presents a promising opportunity to improve the postoperative management of cardiac patients. Demonstrating the validity of wearable devices in monitoring physical recovery in patients undergoing cardiac procedures will provide new insights in the clinical management of such patients, allowing for continuous monitoring and real-time readjusting of patients' therapy. For this reason, the interest in wearable devices is rapidly growing [26]. Wearable devices have been employed to monitor both lifestyle habits (eg, physical activity, dietary habits, or sleep) and clinical parameters (eg, heart rate) in both healthy people and those with acute or chronic diseases. Recently, these devices have been also used in the field of surgical care, mainly in the context of orthopedic surgery [27,28]. However, data on their use in the context of cardiac procedures (and in general, cardiovascular diseases) are scant, despite growing interest.

There are still several limitations in the use of such devices; therefore, their use in everyday clinical practice is not yet well established. Main challenges in the use of these devices are the choice of the device (which should be validated on the population of interest); patients' (or their caregivers') training in the use of the device at home (eg, charging the device or connecting with the Bluetooth); and management of the large quantity of data collected by the device, which requires specific skills.

Lately, several wearable devices have been introduced in the market. A recent review [29] identified 81 studies indexed in PubMed that used one of these wearable devices for purposes of validation or data collection in research projects. The review advised that a research study should choose a wearable device that is most frequently used in the particular sector/care setting. Accordingly, this study will be using the aforementioned Garmin devices. Although we exclude patients with Parkinson disease in this study, it should be noted that another recent study [30] has validated a Garmin device's accuracy in tracking the physical activity of patients with Parkinson disease.

Using wearable devices for the real-time monitoring of lifestyle habits and clinical parameters of patients undergoing cardiac surgery can present a promising opportunity for improving the clinical management and consequently, the health outcomes of such patients. Furthermore, information gained from this study can be helpful in providing patients contemplating intervention for aortic stenosis with practical counseling on expected changes in their functional status months after surgery.

Acknowledgments

This is an investigator-initiated study that received an unrestricted grant provided by Edwards Lifesciences. The funding body was not involved in the design of the study; collection, analysis, and interpretation of data; and writing of the manuscript.

Authors' Contributions

DG, GT, GG, and AD contributed to the study conceptualization and design. ADL, TF, GC, CC, and HO contributed to data acquisition. DA performed data analysis. GL wrote the original draft. CF, LNF, and GD contributed to substantial revision of the original draft.

Conflicts of Interest

None declared.

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Abbreviations

6MWT: 6-Minute Walk Test
API: application program interface
DASI: Duke Activity Status Index
ESS: Epworth Sleepiness Scale
FIT: flexible and interoperable data transfer
HRQoL: health-related quality of life
IADL: Instrumental Activity of Daily Living
ICC: intraclass correlation coefficient
MAPE: mean absolute percent error
MMSE: Mini Mental State Examination
SAVR: surgical aortic valve replacement
SF-36: 36-Item Short Form Health Survey
TASQ: Toronto Aortic Stenosis Quality of Life Questionnaire
TAVR: transcatheter aortic valve replacement

Edited by G Eysenbach; submitted 11.05.20; peer-reviewed by D Leightley, M Tomey, F Palmieri; comments to author 27.06.20; revised version received 21.08.20; accepted 25.08.20; published 12.11.20.

Please cite as:
Lorenzoni G, Azzolina D, Fraccaro C, Di Liberti A, D'Onofrio A, Cavalli C, Fabris T, D'Amico G, Cibin G, Nai Fovino L, Ocagli H, Gerosa G, Tarantini G, Gregori D
Using Wearable Devices to Monitor Physical Activity in Patients Undergoing Aortic Valve Replacement: Protocol for a Prospective Observational Study
JMIR Res Protoc 2020;9(11):e20072
URL: https://www.researchprotocols.org/2020/11/e20072
doi:10.2196/20072
PMID:33180023

Protocol

Web-Based Patient Segmentation in Finnish Primary Care: Protocol for Clinical Validation of the Navigator Service in Patients With Diabetes

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Abstract

Background: An aging population and increasing multimorbidity challenge health care systems worldwide. Patient segmentation aims to recognize groups of patients with similar needs, offer targeted services to these groups, and reduce the burden of health care. In this study, the unique Finnish innovation Navigator, a web-based service for patient segmentation, is presented. Both patients and health care professionals complete the electronic questionnaire concerning patients' coping in everyday life and health state. Thus, it considers the patient perspective on self-care. One of four customership-strategy (CS) groups (self-acting, community, cooperating, and network) is then proposed in response to the answers given. This resulting strategy helps both professionals to coordinate patient health care and patients to utilize appropriate health services.

Objective: This study aims to determine the feasibility, validity, and reliability of the Navigator service in the segmentation of patients with diabetes into four CS groups in a primary care setting. Patient characteristics concerning demographic status, chronic conditions, disabilities, health-related quality of life, and well-being in different CS groups will be described. We hypothesize that patients in the network group will be older, have more illnesses, chronic conditions or disabilities, and require more health care services than patients in the self-acting group.

Methods: In this mixed methods study, data collection was based on questionnaires (user experience of Navigator, demographic and health status, World Health Organization Disability Assessment Schedule 2.0, EuroQol 5D, Wellbeing Questionnaire 12, and the Diabetes Treatment Satisfaction Questionnaire) issued to 300 patients with diabetes and on user-experience questionnaires for and semistructured focus-group interviews with 12 nurses. Navigator-database reports and diabetes-care values (blood pressure, BMI, HbA1c, low-density lipoprotein, albumin-creatinine, smoking status) were collected. Qualitative and descriptive analyses were used to study the feasibility, content, concurrent, and face validity of Navigator. While criterion and concurrent validity were examined with correlations, reliability was examined by calculating Cohen kappa and Cronbach alpha. Construct validity is studied by performing exploratory-factor analysis on Navigator data reports and by hypothesis testing. The values, demographics, and health status of patients in different groups were described, and differences between groups were studied by comparing means. Linear regression analysis was performed to assess which variables affect CS group variation.

Results: Data collection was completed in September 2019, and the first feasibility results are expected by the end of 2020. Further results and publications are expected in 2021 and 2022.

Conclusions: This is the first scientific study concerning Navigator's psychometric properties. The study will examine the segregation of patients with diabetes into four CS groups in a primary care setting and the differences between patients in groups. This study will assist in Navigator's further development as a patient segmentation method considering patients' perspectives on self-care. This study will not prove the effectiveness or efficacy of Navigator; therefore, it is essential to study these outcomes of separate care pathways.

International Registered Report Identifier (IRRID): DERR1-10.2196/20570

(JMIR Res Protoc 2020;9(11):e20570) doi:10.2196/20570

KEYWORDS

patient segmentation; equality; health care services; coordination of care; primary care; Navigator; psychometric properties; questionnaires; eHealth

Introduction

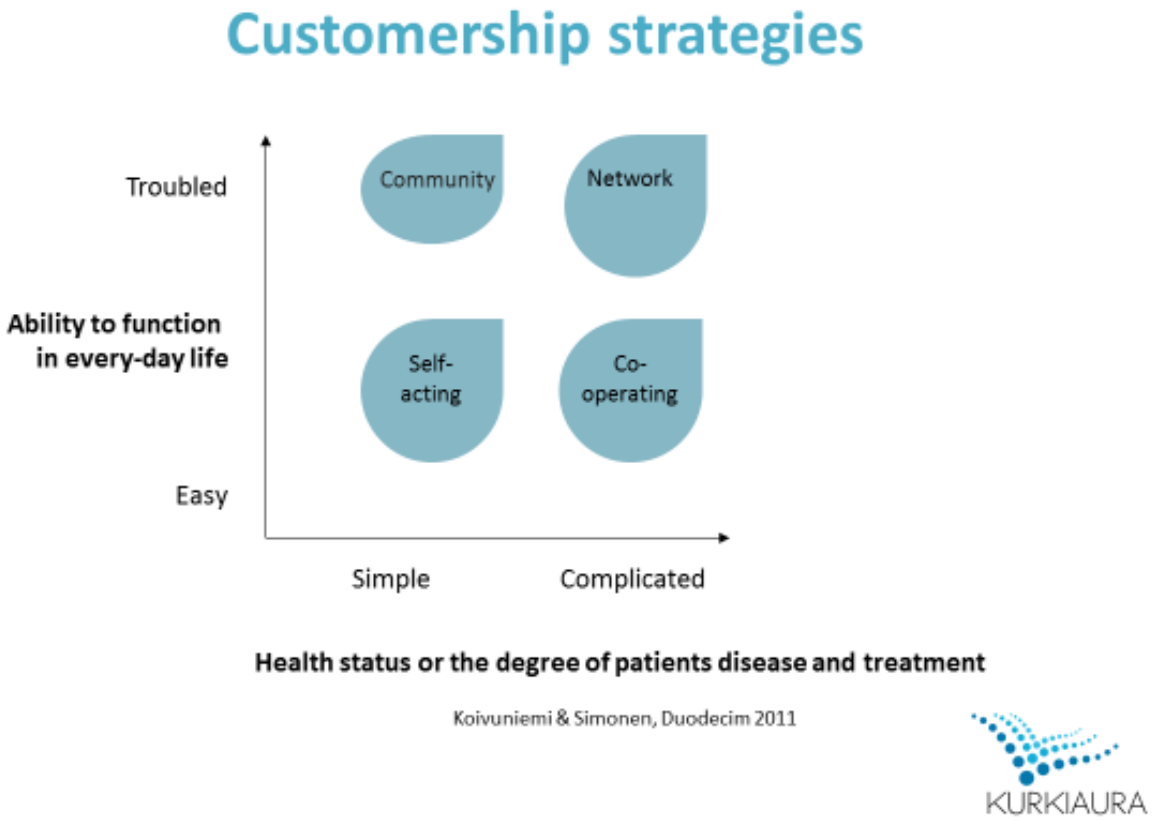
Primary health care systems should deliver services equally for every patient, but an aging population and increasing multimorbidity challenge the capacity of health care systems worldwide [1-5]. Treatment of multiple medical conditions in different health care organizations may lead to fragmentation and incomplete coordination of care, and inefficiency, ineffectiveness, and inequality as unintended consequences of fragmented care [6,7]. Patients' unmet needs lead to poor health outcomes, inappropriate services, and rising costs [1,8,9]. Inequalities in health care appear owing to socioeconomic differences in health and the use of health care services [10-14]. In the 1970s, this was described as The Inverse Care Law [15-17]. One size does not fit all in health services, and one care pathway is not suitable for all patients.

Patient segmentation is an approach that aims to recognize groups of patients with similar health care needs and help care providers to develop services targeted to these groups [18-20]. The origin of patient segmentation was provided in 1970 by Dr Garfield at Kaiser Permanente when recognizing groups of the well, the worried well, early sick, and sick patients were introduced in the new approach to medical care delivery [21]. Another aspect of patient segmentation derives from the field of business and marketing, where, in addition to medical conditions, patients' needs, willingness, and self-efficacy to care are presented to be combined with the production logic of health care services [22,23].

Methods for patient segmentation are either data-driven, where data from different databases and/or electronic health records (EHR) are collected and statistically analyzed [24,25], or expert-driven, where an expert defines the criteria for segmentation [25,26]. The Senior Segmentation Algorithm is a segmentation tool developed at Kaiser Permanente and implemented in the EHR, utilizing EHR data, risk scores, and indicators [27]. Simple Segmentation Tool (SST) is for segmenting the aging population in Singapore and administered by the clinician [28,29]. Different patient segments have been based on medical condition or clinical criteria [30], patient utilization of services [31], and costs of health care [9,32], risk algorithms [33], difficulties in functioning [34], or a combination of factors [29,35]. However, none of these segmentation methods consider personal needs, values, or patients' conditions in individual care. When patient-centered care and health services are planned, patient's self-efficacy and everyday coping should be objectives [36-38]. Moreover, developing separate care pathways for different patient segments could help allocate health care professional resources to the most vulnerable patients and develop and target electronic services to patients capable of managing and navigating in health services.

In Finland, an innovation for patient segmentation has been developed that, remarkably, considers the patients' perspectives regarding their everyday life and self-care resources. Navigator (*Suuntima* in Finnish) is a web-based service for use at appointments. Both patients and health care professionals complete their electronic questionnaires during the conversation. While patients' questions measure their ability to function in everyday life, questions for professionals measure patients' health status or the degree of their diseases and treatments (Figure 1). As a result of these questions, one of four different customership-strategy (CS) groups is proposed: self-acting, community, cooperation, or network. Care pathways differ for each group, thus guiding professionals in coordinating patients' health services as appropriately as possible. The CS group-related care pathway aims to empower patients in self-care by helping them to utilize appropriate health services. The CS group does not guide a patient's medical treatment. The basis of "customership strategies" is in business and marketing; thus, the same terminology has been used here. In health care, the patient is the customer and the nurse or physician the professional.

Figure 1. Dimensions of Navigator and four CS groups.



During Navigator's development, the model was piloted among patients with acute myocardial infarct and patients suffering from alcohol or drug abuse or mental disorders. Segregation of these patients left 60%-66% in self-acting, 10%-20% in the community, 10%-25% in cooperating, and 9%-10% in the network group.

Though Navigator is a general service and suitable to be used with patients with any chronic condition, diabetes was chosen as an example disease because it is a major, seriously complicated, and expensive chronic condition both in Finland and worldwide, requiring multiple medical services [39,40]. In 2019, diabetes was diagnosed in 463 million patients between 20-79 years, and it is estimated that the prevalence increases 51% globally, meaning 700 million patients with diabetes in 2045 [39]. Multifactorial barriers in patients' diabetes management are related to adherence and knowledge about diabetes, cultural aspects, comorbidities, financial resources, and social support [41]. Moreover, barriers in provider and health care systems influence self-care, and self-care barriers are related to complications with type 2 diabetes [42]. Thus, segmenting the vast population of patients with diabetes is essential, and Navigator service might help to recognize and exceed barriers in diabetes management.

This study is the first to address the Navigator service's psychometric properties and the segmentation of patients into CS groups. This study aims to examine the feasibility of Navigator at nursing appointments with patients with diabetes at the health center, study the validity and reliability of Navigator, and characterize patients in each of the four CS groups. The hypothesis is that patients assigned to the network group will be older, more multimorbid and disabled than are patients in the self-acting group.

The detailed research questions are:

1. How user-friendly and time-consuming is Navigator as a web-based service at ordinary appointments, and does it add new issues to nurse-patient discussions (feasibility)? Does Navigator-based segmentation differ from current practice (intuition) in evaluating patient-specific health care service needs (criterion validity)?
2. Are questions studying the health status or everyday ability of patients to function relevant, sufficiently comprehensive, and comprehensible (content validity)?
3. Do all of Navigator's items measure the same construct (internal consistency, reliability), and are all its questions necessary (construct validity)?
4. Is the CS-group segregation result repeatable after two-to-three weeks (test-retest) with the same professional (intrarater) or between professionals (interrater reliability)?
5. How are patients with diabetes segregated in a primary care setting, and what kinds of patients inhabit different CS groups?

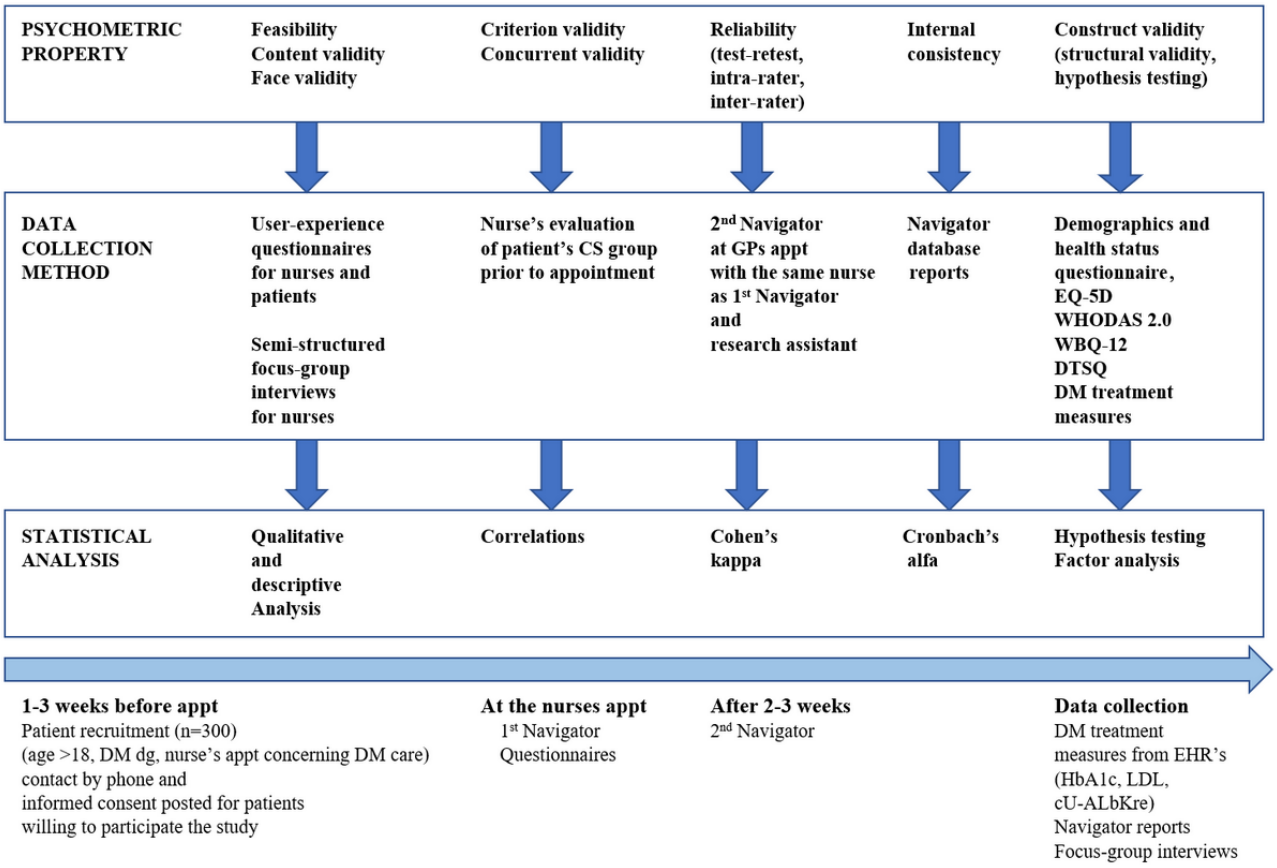
Methods

Study Design

This mixed methods study combines qualitative and quantitative methods. Data collection is based on questionnaires for nurses and patients with diabetes, focus group interviews for nurses, the medical parameters of diabetes care, and Navigator reports from the Pirkanmaa Hospital District database (Figure 2). The study population of 300 patients and 12 nurses were recruited at Valkeakoski social and health center.

COSMIN criteria (consensus-based standards for selecting health-measurement instruments), and quality criteria for the measurement properties of health status questionnaires, were used as a methodological framework to study the content, construct, and criterion validity as well as the reliability of Navigator [43,44]. Patient-reported outcome measures have been developed to capture patients' views on the effect of illnesses and symptoms in their everyday lives and assist communication and decision-making in care between doctors and patients [45]. In this study, Navigator is examined as a patient-reported outcome measure.

Figure 2. Psychometric properties of Navigator, data collection methods and statistical analysis used in study, and timeline of data collection process.



Feasibility, Criterion and Concurrent Validity, Content and Face Validity

Data are gathered with questionnaires for patients and nurses and semistructured focus group interviews for nurses.

The self-generated user-experience questionnaire for patients studies the CS group and the patient's opinion of the care pathway related to it through the Likert scale (from 1, meaning "complete agreement" to 5, meaning "complete disagreement"). Questions determine whether or not any help was needed, for example, from spouses, in answering Navigator's questions. Seven statements study whether questions were easy or difficult or took too long to answer. Statements include that patients' questions helped patients consider their life and everyday coping from a new perspective, that professionals' questions helped patients understand their life situation, and wish to continue to use Navigator in planning their health care services. Furthermore, open questions study whether or not patients disagreed with their CS group allocation and whether new issues concerning their everyday life appeared in the discussion because of the Navigator's questions.

Nurses fill out their user experience questionnaire after every patient with whom Navigator is used. It queries the time spent answering Navigator's questions and whether or not patients required assistance to answer them. Both nurses' and patients' views of Navigator results are queried by way of the Likert scale. Open questions gather information on whether or not, and how, nurses' or patients' views differed regarding CS group allocation. The questionnaire also studies nurse intuition regarding CS group allocation with every patient. The questionnaire queries nurses' previous contact with patients by phone or at appointments during the past year. These questions assess the criterion and the concurrent validity of Navigator.

Another questionnaire collects nurses' experience and work history in primary care and their prior knowledge of

customership strategies. Opinions are obtained using a Likert scale to address Navigator's suitability for patient segregation and the usability of its results in coordinating care for patients with long-term conditions. Nine claims study whether or not the Navigator service was easy and suitable to use, and whether or not questions were too ambiguous or broad to be answered using the Visual Analog Scale (VAS). Users are also asked whether or not Navigator's questions were difficult to understand, helped raise difficult issues with patients, and helped professionals understand the patients' general care at a deep level. The final query is the plausibility of using Navigator and whether new issues appeared in the discussion via its use. Open questions specify if any of Navigator's questions were difficult to understand or too broad. Additionally, nurses are asked to describe if using Navigator was difficult or time-consuming with certain kinds of patients. This questionnaire examines the feasibility and the content validity of Navigator.

Semistructured interviews for three focus groups of four-to-five nurses will be performed after two-to-three months of Navigator use for assessing a more detailed user experience to study the feasibility, the content, and the face validity of Navigator (Multimedia Appendix 1). Interviews will be recorded and transcribed verbatim by an official service provider, and the research team will analyze written material.

Construct Validity

Construct validity consists of structural validity and hypothesis testing. Navigator measures two different constructs: patients' coping in everyday life and patient health status. These two different constructs are evaluated separately. All answers to each Navigator question on the VAS of 1 to 10 are saved in a Pirkanmaa Hospital District database. This information is collected as "Navigator reports."

Questionnaires examine data concerning patients' demographics, medical condition, health-related quality of life, and coping in everyday life.

A self-generated questionnaire is used to collect patient demographics and health status. Patient gender, year of birth, marital status, education, and employment situation is queried. Health-related questions concern self-rated health, duration with a diabetes diagnosis, diabetes medication, knowledge of target values for individual diabetes care, other illnesses or chronic conditions, and medication. Also queried are smoking status, alcohol usage, height and weight, tools needed for physical disability assistance, and the receipt of disability benefits or care allowance for pensioners from the Social Insurance Institution of Finland.

The WHODAS 2.0 (World Health Organization Disability Assessment Schedule 2.0) self-administered 12-item version is used to study health-related disability during the last 30 days. Twelve questions concerning six domains of function (cognition, mobility, self-care, getting along, life activities, and participation) are answered on a 5-point scale ranging from "no difficulties" to "extreme difficulties or could not" [46].

EuroQol 5D (EQ-5D) is a generic health-status measure consisting of the EQ-5D-5L descriptive system and measuring five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with each dimension having five response levels from "no problems" to "extreme problems or unable to." The EQ VAS measures the patient's self-rated health on a vertical VAS whose endpoints are respectively "The best health you can imagine" and "The worst health you can imagine." Patients are asked to evaluate their health on that day. The EQ-5D has Finnish Population Norms [47].

W-BQ12 is a general 12-item well-being questionnaire measuring negative well-being, energy, positive well-being, and general well-being. Patients evaluate their well-being during recent weeks on a 4-point scale from 0 (not at all) to 3 (all the time) [48].

Diabetes-treatment satisfaction questionnaires (DTSQs) are used to collect data on diabetes treatment satisfaction [49].

Medical parameters concerning diabetes care (HbA_{1c}, low-density lipoprotein, albumin-creatinine, blood pressure) are evaluated annually according to the Finnish Current Care Guideline for diabetes [50]. Values are collected from patients' medical records.

Reliability

During the nurse's appointment, Navigator is used for the first time, and the first CS group result is generated. Based on the patient's condition and self-care capability, the nurse then evaluates the patient's need for a physician appointment. Usually, a physician appointment is made with a physician-researcher within 3 weeks. At the beginning of the physician-researcher appointment, Navigator is used for the second time, with the same nurse, the physician, and a research assistant present (2018). All professionals complete their questionnaires independently, and three different results are generated.

Study Population

Patients with diabetes (n=300 based on sample size calculation) were recruited in a primary care setting at Valkeakoski health center. Annual follow-up visits concerning diabetes care are carried out at appointments with first a nurse and then if needed, a physician within a month. Twelve nurses working at Valkeakoski health center at the time of data collection were recruited for the study.

Inclusion and Exclusion Criteria

The inclusion criteria are age exceeding 18 years and a planned annual diabetes care follow-up appointment with a health center nurse. Exclusion criteria are patient disability preventing informed consent for participation in research (eg, Alzheimer disease, intellectual disability) and nonfluency with the Finnish language.

Recruitment

Patients scheduled for an annual diabetes-control appointment with a nurse within three weeks were identified via the electronic patient record system. They were then contacted in advance by phone and informed about the study. Patients willing to read further about the study were sent the informed consent

declaration form by post. Recruitment began in October 2018 and was completed in September 2019.

Data Collection

Before the appointment with a recruited patient begins, the nurse is asked to evaluate the patient's Navigator result intuitively based on knowledge of the patient and medical records (Figure 2). Intuition-based results will also be collected from patients refusing to participate in the study.

At the beginning of the appointment, the nurse confirms the patient's participation, collects the signed consent form, and combines the patient's social security number with their study identification code. All data is encoded for processing, protecting patients and nurses from identification. Patients also receive the study envelope containing study questionnaires. Then the Navigator is used for the first time.

Navigator is used for the second time at the physician-researcher appointment, and diabetes treatment measures are collected. Measures for patients who receive no physician-researcher appointments are collected separately from medical records.

Semistructured interviews for three focus groups of nurses will be performed after Navigator has been used for two or three months, after which Navigator reports are gathered from the database.

Intervention

Development of the Navigator Service

The Navigator service was developed in collaboration with the Finnish Heart Association (FHA) and the Center of General Practice of Pirkanmaa Hospital District in the Kurkiaura project between 2011 and 2015. Navigator was produced by the FHA and is maintained by the Center of General Practice of Pirkanmaa Hospital District in Finland.

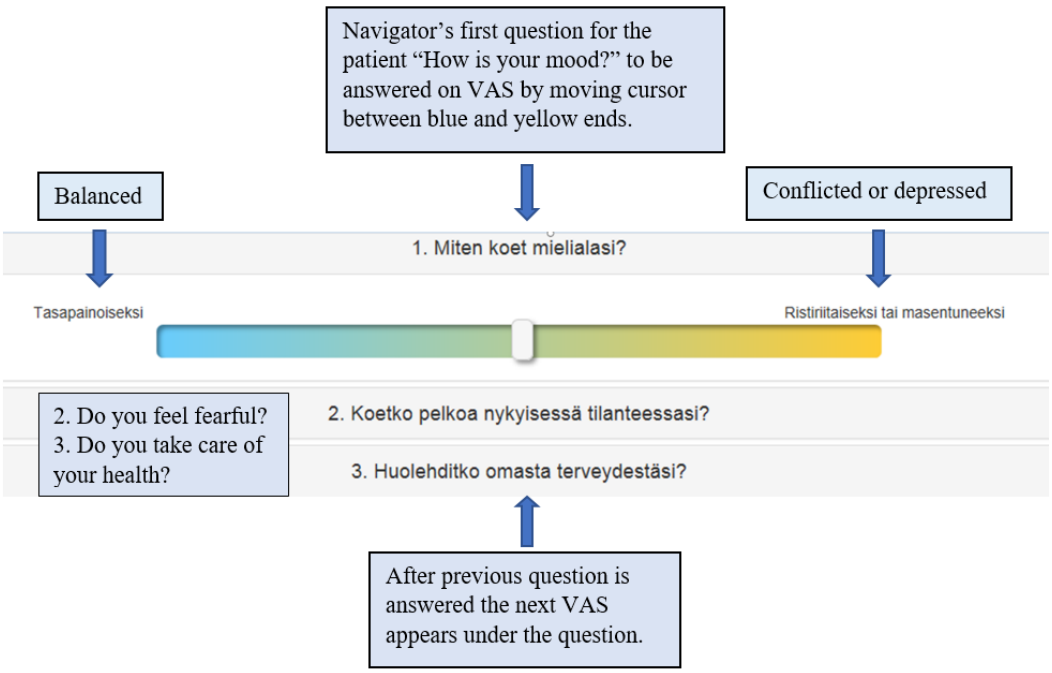
The development process began by describing different kinds of patients based on lifestyle studies. Patient stories describe how different individuals manage private matters and how capable they are of practicing self-care. Professional views of patient care, combined with patients' personal views of self-care, helped to develop the idea of a fourfold table. Issues limiting self-care were studied in a survey of patients with acute myocardial infarct and led to the implementation of separate care pathways for different patient classes. The need then arose to develop a tool to segregate patients into different segments, considering both patient and professional perspectives.

Questions in quality-of-life measurements (eg, 15D) and the international classification of functioning, disability, and health (ICF), were familiarized and reflected upon with previous patient stories to develop themes for patients' questions. Preliminary questions for patients were made and further developed in workshops with patients. A multiprofessional health care group suggested questions for professionals. Questions were agreed upon and further developed in meetings with multiprofessional health care experts (personal communication AR, LK).

Content of the Navigator Service

A 10-question patient and 8-question professional VAS are used (Multimedia Appendix 2, Figure 3). Answers on a scale of 1 to 10 are dichotomized at a certain cut point. The result of all answers is used to propose a CS group appropriate for each patient. Every CS group has its own care pathway, defining the focus of individual care plans, service and care coordinators, making appointments and contacting health care services, and alternatives to appointments and services typically included in certain pathways.

Figure 3. Navigator's first three questions for patients, showing VAS.



Customership Strategy Groups and Care Pathways

Self-Acting Group

Patients in the self-acting group competently manage everyday life with their illnesses and independently coordinate their health care. Health care services aim to support self-care in maintaining the ability to work and function. The individual health care plan for this group is focused on self-care. Planning alternative forms of health care services such as telemedicine options in contacts or as an alternative to appointments is essential with these patients who, according to pilots, make up the majority of all patients.

Community Group

The everyday life of patients in the community group is troubled, although their health status appears simple. Their individual health care plans focus on motivating and empowering their self-care, guiding them to peer group meetings, and building confidential health care relationships. The care coordinator could be a nurse who contacts the patient proactively, such as by phone, and organizes occasional appointments to ensure the appropriate use of health care services.

Cooperating Group

Patients in the cooperating group function in everyday life despite complicated health status. Their individual care plans focus on improving their ability to function and prevent complications and additional illnesses. The coordination of multiprofessional care and appointments is needed, and the coordinator is a health care professional. Electronic health care options could be used in contact with health care services.

Network Group

Patients in the network group are the most vulnerable and in need of intensive support. Their individual health care plans focus on maintaining the ability to function in everyday life at home and preventing hospitalization. Health care is proactive and usually multiprofessional. Services are coordinated by a professional, home visits are considered alternatives to appointments at the health center, and family support is essential.

Sample Size

Sufficient patient population and sample size calculations are needed to compare outcomes of patient variables in different CS groups. The power calculation is based on the WHODAS 2.0 validation study of patients with chronic conditions in Europe. The results of a 36-item WHODAS 2.0 questionnaire gave a mean score of 24.8 (complex scoring scale 0.00-93.5) and a standard deviation of 19.3 [46]. No information on the 12-item WHODAS 2.0 questionnaire results in patients with diabetes was found for this purpose. Using a power of 80% and statistical significance of P=.05, a minimum of 30 patients are needed in each group, as the clinically significant difference between means of separate groups is assumed to be 14 on the WHODAS 2.0 scale (complex scoring 0.00-100). The effect size is moderate (d=0,725) [51]. In Navigator pilots, the smallest group (9%-10% of patients) was the network group, resulting in a total sample size of 300 patients. A sample size calculator was used for the calculation [52].

Statistical Analysis

Feasibility, content, and face validity are examined with patient and professional user experience questionnaires and semistructured focus group interviews for professionals. Data analysis will be qualitative and descriptive. Qualitative thematic analysis will be used to analyze focus group interviews [53].

Criterion and concurrent validity are assessed, comparing nurse-intuited patient CS group allocation to the patient CS group allocation proposed by Navigator. Correlations can be calculated, and visible differences described.

Construct validity consists of structural validity and hypothesis testing. Navigator measures two constructs: the ability to cope in everyday life and patient health, and they are evaluated separately. Exploratory factor analysis is performed on each Navigator data report to evaluate how different factors are loaded. The assumption is that every question is important for determining either patient's coping in everyday life or the patient's health status. Descriptive statistics will be performed on patient values (demographic and health status, diabetes mellitus treatment measures, EQ-5D, WHODAS 2.0, WBQ-12, and DTSQ questionnaire responses) in different CS groups, and differences between groups will be studied by comparison of means. Linear-regression analysis is performed to assess which variables affect variation in CS-group allocation.

Intrarater, interrater, and test-retest reliability are analyzed by calculating Cohen kappa correlations between the first and second Navigator results obtained with the same nurse, in the presence of a physician and a research assistant. The internal consistency of items for both constructs will be analyzed by calculating Cronbach alpha.

Ethical Approval

The Tampere University Hospital Ethics Committee approved this study's ethical aspects in October 2018 (ETL R18070). Data collection at Valkeakoski Health Center was approved by head physician Myllynen in September 2018.

Results

Descriptive results of strengths, difficulties, and time spent using the Navigator service during nurses' appointments may help develop user instructions.

The results of patient segmentation into different CS groups may strengthen the results of previous pilot studies. The characteristics and differences of patients between groups are assumed to relate to Navigator's results: patients managing well in everyday life (self-acting and cooperating groups) could have better results in WHODAS 2.0, EQ-5D, and WBQ-12 than do patients with difficulties in everyday life. Moreover, patients in self-acting and community groups, whose health status is simpler than that of cooperating- and network-group patients, could have fewer chronic conditions, require less medication, and enjoy more successful diabetes mellitus treatment measures.

Exploratory factor analysis may indicate identifiable factors in patients' and professionals' questions. This outcome of construct validity may be used in further developing Navigator's items and be confirmed in future studies.

Correlations between the test and retest results of Navigator will be statistically analyzed using the Cohen kappa coefficient. The reliability outcome is moderate if values are 0.41-0.60, substantial if they are 0.61-0.80, and in almost perfect agreement if they are 0.81-1.00 [54]. In addition, how both patients' and professionals' questions measure the same construct helps assess the reliability and internal consistency of Navigator. Usually, internal consistency is high if Cronbach alpha is >0.7 (values between 0 and 1) [55].

Discussion

Principal Findings

This study is the first to assess the feasibility, validity, and reliability of Navigator, the Finnish innovation for patient segmentation. The study also examined the segregation of patients with diabetes into four customership groups in a primary care setting and the differences between patients in each group.

The Navigator service adds a patient's individual perspective of his/her ability to cope in everyday life to the methods of patient segmentation. EHR databases do not contain information pertinent to patients' capacity to navigate between health services. Therefore, discussing these issues with patients is essential when individual and patient-centered care is planned.

Patient navigation is described as barrier reduction and as 'a bridge over gaps in services' method. Facilitating access to care, communicating with multiple agencies in fragmented health and social care, and navigator persons such as health care professionals, case managers, or laypersons have been reviewed in diverse settings [56,57]. The Navigator service standardizes individual recognition of patients with different needs, and separate care pathways developed for different CS groups help patients navigate between health services.

Note that this study does not assess the effectiveness or efficacy of the four separate care pathways that Navigator proposes. In the future, it will be essential to study how efficient Navigator is in patient navigation and how it affects patient health outcomes.

Risks and Biases

Although several health centers in the Pirkanmaa region have been trialing the Navigator service with patients with different chronic conditions, it has yet to be properly implemented in health care use. Moreover, care pathways related to Navigator CS groups in different chronic conditions remain in development. Therefore, multicenter patient recruitment and regional data collection were unobtainable, and the study population was ultimately drawn from a single health center in Valkeakoski.

The study setting in health care services and particularly exclusion criteria may bias the study population and group segregation. Vulnerable patients may fail to familiarize themselves with the declaration of informed consent, leading to their refusal to participate in the study. In addition, vulnerable patients may not be treated in the health center's ambulatory diabetic guidance clinic, and thus their proportion of the total participants may be low. Furthermore, making appointments at health centers requires an ability to personally deal with the health care system that many vulnerable patients may lack. Nurses' intuitive evaluation of the customership of patients not participating in the study is also collected in order to assess this bias. Moreover, the self-selection bias of participants may impact results.

Timetable and Publications

Data collection was completed in September 2019. Analysis of Navigator user experiences and focus group interviews were performed in Spring 2020. The feasibility assessment of Navigator is expected to be completed in 2020. Further analysis of the psychometric properties of Navigator is expected in 2021, and the results of patient segregation and outcomes in different CS groups are expected in 2022. Further publications are expected in 2020-2022, with a PhD thesis expected to be completed in 2022.

Acknowledgments

The Center of General Practice in the Pirkanmaa, City of Tampere, and General Practitioners in Finland.

Health Psychology Research provided a license to use the WBQ-12 and DTSQs questionnaires.

The authors would like to thank Anna Rikala (AR) and Leena Kuusisto (LK) for interviews concerning the development of the Navigator service; Sari Mäkinen and Leena Kuusisto for practical help in the Navigator study permission process and for delivering Navigator reports from the Pirkanmaa Hospital District database. At the Valkeakoski health center, Elina Kontiainen and Niina Kokkola assisted in organizing the data collection process. Biostatistician Mika Helminen helped with sample size and power calculations.

Conflicts of Interest

TK is a part-time salaried employee, and EK is a former part-time salaried employee of the Center of General Practice in Pirkanmaa. They were not involved in the development of Navigator.

Multimedia Appendix 1
Content of the semi-structured focus-group interview for nurses.
[DOCX File , 15 KB - resprot_v9i11e20570_app1.docx]

Multimedia Appendix 2
Navigator service's questions for patient and professional (translated in English by RR).
[DOCX File , 15 KB - resprot_v9i11e20570_app2.docx]

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Abbreviations

CS group: customership strategies group
DTSQ: Diabetes Treatment Satisfaction Questionnaire
EHR: electronic health record
EQ-5D: EuroQol 5D
FHA: Finnish Heart Association
ICF: International Classification of Functioning, Disability, and Health
WHODAS 2.0: World Health Organization Disability Assessment Schedule 2.0
VAS: Visual Analog Scale

Edited by G Eysenbach; submitted 22.05.20; peer-reviewed by J Leksell; comments to author 05.07.20; revised version received 25.08.20; accepted 14.09.20; published 02.11.20.

Please cite as:
Riihimies R, Kosunen E, Koskela T
Web-Based Patient Segmentation in Finnish Primary Care: Protocol for Clinical Validation of the Navigator Service in Patients With Diabetes
JMIR Res Protoc 2020;9(11):e20570
URL: https://www.researchprotocols.org/2020/11/e20570
doi:10.2196/20570
PMID:33136062

Protocol

EatSmart, a Web-Based and Mobile Healthy Eating Intervention for Disadvantaged People With Type 2 Diabetes: Protocol for a Pilot Mixed Methods Intervention Study

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Abstract

Background: People of low socioeconomic position (SEP) are disproportionately affected by type 2 diabetes (T2D), partly due to unhealthy eating patterns that contribute to inadequate disease self-management and prognosis. Digital technologies have the potential to provide a suitable medium to facilitate diabetes education, support self-management, and address some of the barriers to healthy eating, such as lack of nutritional knowledge or shopping or cooking skills, in this target group.

Objective: This study aims to test the feasibility, appeal, and potential effectiveness of EatSmart, a 12-week, evidence-based, theoretically grounded, fully automated web-based and mobile-delivered healthy eating behavior change program to help disadvantaged people living with T2D to eat healthily on a budget and improve diabetes self-management.

Methods: EatSmart is a mixed methods (quantitative and qualitative) pre-post design pilot study. Sixty socioeconomically disadvantaged people with T2D aged 18 to 75 years will be recruited. Participants will complete self-reported baseline assessments of their basic demographic and clinical data, dietary intake, dietary self-efficacy, and barriers to healthy eating. They will be provided with login access to the EatSmart web program, which includes six progressive skill-based modules covering healthy eating planning; smart food budgeting and shopping; time-saving meal strategies, healthy cooking methods, modifying recipes; and a final reinforcement and summary module. Over the 3-month intervention, participants will also receive 3 text messages weekly, encouraging them to review goals, continue to engage with different components of the EatSmart web program, and eat healthily. Participants will undertake follow-up assessments directly following the intervention 3 months post baseline and again after a 6-month postintervention follow-up period (9 months post baseline). Feasibility will be evaluated using the number of participants recruited and retained and objective indicators of engagement with the website. Program appeal and potential effects on primary and secondary outcomes will be assessed via the same surveys used at baseline, with additional questions asking

about experience with and perceptions of the program. In-depth qualitative interviews will also be conducted 6 months post intervention to provide deeper insight into experiences with EatSmart and a more comprehensive description of the program's appeal.

Results: The EatSmart website has been developed, and all participants have viewed the modules as of May 2020. Results are expected to be submitted for publication in December 2020.

Conclusions: This study will provide data to address the currently limited evidence regarding whether disadvantaged populations with T2D may benefit from digitally delivered behavior change programs that facilitate eating healthily on a budget.

Trial Registration: Australian New Zealand Clinical Trials Registry, ACTRN12619001111167; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12619001111167

International Registered Report Identifier (IRRID): DERR1-10.2196/19488

(JMIR Res Protoc 2020;9(11):e19488) doi:10.2196/19488

KEYWORDS

type 2 diabetes; healthy eating; diet; low socioeconomic position; self-management; digitally delivered; internet; website; mobile phone; text message

Introduction

Overview

Type 2 diabetes (T2D), which is defined by relative insulin deficiency resulting from pancreatic β-cell dysfunction and insulin resistance in target organs [1], is considered the epidemic of the 21st century [2]. T2D is a serious challenge for public health, affecting millions of people worldwide [3]. Globally, the number of people with diabetes has increased four-fold in the past three decades, and it was recognized as the ninth major cause of death in recent years [4,5]. According to the International Diabetes Federation, at the end of 2017, about 425 million people had diabetes, and this number is estimated to reach 628.6 million in 2045 [6]. Moreover, in the year 2018, 318 million adults were diagnosed with impaired glucose regulation that puts them at a high risk of developing diabetes in the future [7].

Individuals of low socioeconomic position (SEP), such as those with lower levels of education, working in low-status occupations, or on a low income, as well as ethnic minority groups, are disproportionately affected by T2D [8]. Unhealthy eating patterns and obesity are key risk factors for T2D [4,9,10]. Previous research has shown that compared with those of higher SEP, people of lower SEP commonly have more unfavorable eating patterns, with diets characterized by lower intake of fruits and vegetables and higher intake of less healthy discretionary foods and beverages [11-13]. While structural barriers, such as limited resources, low accessibility to higher quality foods and cost, contribute to these patterns, nutrition knowledge and skill deficits in cooking, lack of interest in cooking, lower prioritization of health during food selection, and low social support for healthy eating are also well-recognized hurdles with which these groups are struggling [14,15].

Existing initiatives to promote healthy eating among people with T2D include multicomponent face-to-face diabetes self-management classes, community health worker programs, and intensive case-management programs [16]. Traditionally, individuals participate in these programs in medical settings or at community health centers to acquire relevant knowledge about diabetes from clinicians, trained interventionists, or credentialed diabetes educators [17]. While such programs can effectively communicate health information to people with diabetes, they are limited in terms of sustainability and scale [18-22]. Time and access requirements preclude the ability of many individuals to attend multiple educational sessions [23-25]. Such intensive programs also incur high costs related to hiring, training, and maintaining educators, which not all practices are resourced to routinely provide [26].

Driven by advances in web-based technologies and requests by people with T2D for easily accessible information and ongoing support, digitally delivered programs potentially offer a convenient and efficient platform to facilitate the delivery and increase the reach of the self-management support needed by disadvantaged people with T2D [27]. Computers, laptops, and mobile phones or smartphones, hosting mobile applications (apps), are commonly used technologies for delivering digital programs [24]. These programs are secure and cost-effective and allow for the delivery of support in a way that is responsive, transactional, and participatory, and accordingly, more persuasive [17,28]. Furthermore, these programs can be easily distributable since they are not limited to a specific location and can be used in clinics, community health centers, home, or on the move at any convenient time [24,27,29]. With the advent of digital technology programs for health, there have been concerns about creating a digital divide, in which people of low SEP have lower access to the internet and mobile devices compared with higher socioeconomic groups [30]. However, more recent studies have demonstrated that the digital divide is gradually diminishing as the internet and mobile technologies have become more accessible to people from different SEPs [31]. Previous studies with low-income populations, including those with T2D and other chronic conditions, showed that a high proportion of participants knew how to use computers or mobile phones and were willing to expand their knowledge of how to use these technologies and find health information via the internet [32-35]. Moreover, it has been suggested that technology can efficiently play a role in bridging the digital divide and serve traditionally "hard to reach" populations. Thus, technology may provide a unique opportunity to decrease health disparities in underserved populations [31].

Previous reviews suggest that digital-based interventions show promise in increasing knowledge and improving diabetes self-management activities, including medication adherence, engagement in physical activity, and healthy eating behaviors in individuals living with T2D [22,27,36-40]. For example, in a review by Boren et al [41], 18 of 21 studies, which used computerized learning technologies to engage and empower people in diabetes self-management, showed positive outcomes in improving 49 out of 112 diabetes outcomes. They stated that while patients' self management-related behaviors are crucial in diabetes control, computerized learning technology programs can play a major role in improving self-efficacy and diabetes self-care [41].

While digital interventions continue to be developed and researched, their potential for improving diabetes self-management among people of low SEP remains poorly investigated [36], and few have explored the efficacy of these interventions specifically on dietary and healthy eating behaviors [25,42-44]. One example is a study by Arora et al [44], who investigated the effects of educational and motivational text messages on improving healthy eating behaviors, exercising, medication adherence, and foot checks. That intervention led to a daily increase in eating fruits/vegetables by 26.5% and improved diabetes self-efficacy and medication adherence in resource-poor, inner-city patients with diabetes. Another example is the eCare We Care program by Moussa et al [25]. In that study, researchers examined the effect of an evidence-based web program on diabetes knowledge development and skill-building in African American adults with low diabetes literacy [25]. Their findings indicated that the program improved the diabetes and nutritional knowledge of participants [25]. Glasgow et al [45] also investigated the effect of an internet-based diabetes self-management program, with and without additional support, on improving healthy eating, physical activity, and medication taking. Their program improved health behaviors significantly compared to usual care over the 12 months (Cohen *d* for effect size .09-.16) [45].

Although these limited studies show promising results in improving dietary behaviors, they were all heterogeneous in scope. For example, they either concentrated on single nutrition-related health outcomes (eg, weight loss or glycemic control), or combined multiple health behaviors (eg, diet, medication adherence, and physical activity), and utilized different modes of intervention delivery (eg, website, text messages). Therefore, study findings are difficult to integrate and interpret, and there is a need for further research into how disadvantaged populations with diabetes may benefit from digital approaches and whether these programs are feasible, appealing, and can produce long-term and sustainable effects. The EatSmart program was developed to address this gap by designing and evaluating a theoretically grounded, evidence-based web- and phone-delivered healthy eating behavior support program to enable disadvantaged people with T2D to strengthen important skills necessary to eat healthily at low cost.

This project is important as it involves a simple and practical approach tailored to the needs of the many people with T2D who struggle to eat healthily in the context of socioeconomic disadvantage. The program may augment existing clinical management by integrating with people's daily self-management practices of T2D. It also has the potential to reach larger numbers of people with T2D, regardless of geographic location. Moreover, it is designed to be sustainable without intensive ongoing clinical involvement. EatSmart addresses the critical issues of inequities in diabetes-related self-management and associated morbidity.

Hypothesis

We hypothesize that delivery of the 12-week EatSmart program is feasible, appealing to participants, and effective in improving healthy eating behaviors and related attitudes. Specifically, we hypothesize that EatSmart will lead to high program satisfaction and engagement and improvements in self-reported intakes of vegetables, fruits, and foods aligned with dietary recommendations. It will also reduce self-reported intakes of discretionary noncore foods, increase self-efficacy, and reduce barriers to selecting and preparing a balanced healthy diet.

Ethics Approval

Ethics approval has been granted by Deakin University's Human Research Committee and the Western Health Low-Risk Ethics Panel, approval number 49763; version 4, dated 15 March 2019. All participants will be provided with an information sheet explaining the project aim and will be requested to sign a written informed consent form before participating (Multimedia Appendices 1-3).

Methods

Study Design

EatSmart is a mixed methods (quantitative and qualitative) pre-post design pilot study, which is appropriate for evaluating the feasibility, appeal, and potential effectiveness of a novel intervention. Pilot studies are crucial for examining the acceptability of new interventions and improving their delivery to support the future success of more intensive and larger randomized controlled trials [46].

EatSmart focuses on people with T2D who attend diabetes clinics in Melbourne's western suburbs, which, according to the Australian Bureau of Statistics Socioeconomic Index for Areas index of relative advantaged/disadvantaged, comprises a relatively disadvantaged area.

Study Population

Sample Size Estimation

A sample of N=60 (conservatively assuming up to 33% drop-out) has been selected for this pilot study. As this is a pilot study, no formal power calculation was conducted, and this sample size was determined pragmatically to provide adequate data on potential effects on key outcomes, sample variability, recruitment rates, and retention. This number is also adequate for generating rich qualitative and contextual data on intervention engagement, feasibility, and appeal to inform future larger studies.

Participant Recruitment

Sixty people with T2D will be recruited from two outpatient diabetes clinics located at Sunshine Hospital in Melbourne, Australia. Participant recruitment strategies involve (1) distribution of program flyers at diabetes clinics' waiting rooms and to diabetes nurses and specialist offices in Sunshine Hospital; (2) in-person presentations by diabetes educators or researchers at hospital meetings and diabetes-related events; and (3) face to face recruitment of eligible individuals in diabetes clinic waiting rooms by EatSmart researchers.

For postintervention interviews, patients with T2D who participated in EatSmart and completed the 3-month intervention will be invited by telephone, text message, or email to complete a semistructured interview of up to 40 minutes via telephone or Zoom. Recruitment will be successive until no new themes appear (thematic saturation). Up to ten health care providers from Sunshine Hospital diabetes clinics will also be invited by email to take part in a confidential semistructured telephone or Zoom interview of up to 30 minutes.

Eligibility Criteria

Inclusion

Adults aged 18 to 75 years with a diagnosis of T2D, regardless of duration. Participants will be required to own and use a mobile phone, be familiar with receiving and reading text messages, and have mobile data allowance to access the internet or a mobile device (phone/tablet) or computer with internet access. Participants will be socioeconomically disadvantaged, as determined by receiving either a Health Care Card or a pension/benefit as the main source of income, or a stated income up to the cut-off levels used to assess eligibility for the Health Care Card. Annual income thresholds for receipt of a Health Care Card in Australia (as of January 2019) are equal to AU $29,172 (US $20,645) for single adults without children, AU $50,388 (US $35,660) for couples, AU $52,156 (US $36,910) for couples with one child and AU $1768 (US $1251) for each extra dependent child. Due to this study's focus on people from a lower SEP, assessing eligibility can be a sensitive issue. To be respectful when enquiring as to whether or not an individual receives a Health Care Card or low income (ie, is of a low SEP background), a written document with all relevant questions relating to eligibility will be handed to potential participants. This document allows them to check the questions silently in advance, and if they confirm their willingness to answer, the researcher will approach them to complete the recruitment process.

Exclusion

Participants will be excluded if they cannot read or speak English; cannot use mobile text messaging or internet; are pregnant or breastfeeding; are visually or hearing-impaired; have an eating disorder; have compounding comorbidities (like clinical depression), as diabetes management is typically more complex in these cases; are planning to have surgery; or are planning to travel for an extended time in the next nine months.

Intervention

EatSmart is a 12-week evidence-based, theoretically grounded, fully automated healthy eating behavior support program delivered via a website (mobile phone compatible) and text messaging. It is a standalone program that could augment standard diabetes management, which typically involves routine visits and consultation with an endocrinologist and diabetes educator, and sometimes a dietitian (depending on clinical circumstances). If demonstrated to be successful, the EatSmart program could become embedded in clinical practice and promoted by clinical staff as an adjunct treatment option.

The intervention development was informed by Social Cognitive Theory [47], which suggests that people adopt new behaviors through social learning, either through media sources or through imitation of others. Further, it builds on a previous study ("ShopSmart") by Ball et al [11,48], which trialed a behavior change intervention for increasing purchasing and consumption of vegetables and fruits among women of low SEP and resulted in a significant increase in vegetable consumption during the intervention [11].

EatSmart draws on empirical evidence of the key determinants of eating behaviors in people of low SEP, including previous studies suggesting the importance of addressing perceived cost barriers, food planning, budgeting, preparation skills, and nutrition knowledge [49-52].

Intervention mapping was conducted [53] for the planning and development stage to confirm that this program is based on a strong empirical, theoretical, and practical foundation. A literature review identified existing digital and nondigital approaches to increase vegetable and fruit consumption in people of low SEP that addressed the key constructs of Social Cognitive Theory. The findings of the literature review and intervention mapping, in addition to the experiences gained from the ShopSmart study [11], suggested that focusing on skill building for eating healthy and budgeting wisely can be effective strategies.

The research team has developed a set of modules, all of which focus on the specific needs of people of low SEP, particularly affordability and nutrition-related skills. The materials target the proposed theoretical mediators of nutrition self-efficacy, perceived affordability, and other perceived barriers to vegetable and fruit consumption. The intervention components share similarities with those used in the ShopSmart study [11,48]; however, EatSmart materials are targeted for people with T2D. For example, more focus has been placed on encouraging the consumption of leafy vegetables or fruits with a lower glycemic index.

The skill-based modules of the EatSmart website address the following topics:

1. Importance of vegetables, fruits, and whole foods for health
2. Strategies to buy healthy foods on a budget (highlighting the range of low-cost vegetables and fruits available and their uses, and also the value of more affordable options such as tinned and frozen vegetables and fruits)

3. Planning for smart shopping and how to choose healthy foods, with supermarket shopping tours and advice on label reading
4. Trying and incorporating new vegetables, fruits, and whole foods
5. Building cooking confidence and skills by including recipes of healthy and inexpensive meals from various countries and cultures featuring vegetables and fruits; meal planning; simple and convenient meal and snack ideas; and how to modify recipes to be healthier
6. Storing, preparing, and cooking fresh produce, reducing food waste, and "eating out Smart."

The website also offers a range of practical activities, including calculating current and ideal spending on different food groups, videos (eg, virtual shopping tours), and links to other resources (eg, government or not-for-profit health information websites).

EatSmart involves delivering key behavior change techniques, including setting goals for purchasing and consuming key food groups, self-monitoring consumption, engaging social support from family and friends, and problem-solving key barriers to healthy eating. A behavior change taxonomy was used to describe the active ingredients of the intervention [54]. The intervention components and their related BCTs are presented in (Table 1).

As part of EatSmart, participants receive three unidirectional text messages/week (36 in total), at a time they indicate is convenient, to encourage them to maintain healthy eating, review their goals, and continue to engage with different components of the website (Multimedia Appendix 4). Multiple behavioral change techniques, including goal setting on core food group intake, informing about health and social (cost) consequences, instructions on how to perform behaviors, and self-monitoring behavior, were employed to design the text messages.

After consenting to the study, participants complete baseline assessments immediately in person or at a more convenient time by telephone or through a secure weblink. The baseline evaluation requests information on basic demographic and clinical data, dietary intake, dietary self-efficacy, and barriers to healthy eating. Upon completing baseline assessments, participants are shown how to log on to the website using their username and password. Once logged in, participants can access the six intervention modules offered to them consecutively on a biweekly basis. Each module can be completed in around 15 minutes, but no recommendation or limitation regarding timing and usage will be given. Therefore, they can read the materials and engage with the website in a suitable and convenient timeframe.

Following intervention completion at three months, participants undertake the same baseline evaluation (except for demographic details). During the 6-month follow-up period (3 to 9 months post baseline), participants will have free access to all website materials; however, they will not receive text messages. After the 3-month data collection period, all participants who complete the postintervention assessments (regardless of their level of engagement) will receive an AU $50 (US $35) shopping voucher as compensation for their time. Those who complete the online follow-up survey will receive an AU $20 (US $14) shopping voucher, and those who agree to be interviewed will receive an extra AU $20 (US $14) shopping voucher.

Table 1. Summary of intervention components, targeted determinants, and behavior change techniques.

Intervention component	Primary message/resources (web + text message)	Targeted determinant	Behavior change techniques
Module 1	• Importance of a balanced diet for health in diabetes • Addressing cost and time barriers to healthy eating • Resources for setting healthy eating goals	• Knowledge • Health values • Perceived affordability • Perceived barriers: time	• Action planning • Discrepancy between current behavior and goal • Goal setting on core food group intake (behaviors) • Information about health consequences • Information about social consequences (cost) • Instructions on how to perform behaviours • Problem-solving • Self-incentives • Self-monitoring behaviour • Self-rewards for goals
Module 2	• Planning for healthy eating on a budget	• Knowledge and skills (budgeting, planning) • Self-efficacy • Perceived affordability	• Action planning • Demonstration of the behavior • Discrepancy between current behavior and goal • Information about social consequences (cost) • Instructions on how to perform behaviors • Problem-solving • Reviewing behavior goals • Self-incentives • Self-monitoring behavior • Self-rewards • Social rewards for goals
Module 3	• Planning and shopping smart • Label reading • Affordability: focus on tinned/frozen options (eg, fruit, vegetables, fish, legumes) • Saving money and time • Food safety (to reduce waste)	• Knowledge and skills • Perceived affordability • Self-efficacy • Perceived barriers: social (family preferences), time	• Action planning • Conserving mental resources (wallet label reading cards) • Demonstration of the behavior • Discrepancy between current behavior and goal • Goal setting (behaviors) • Identification of self as a role model • Information about health consequences • Information about social consequences (cost) • Instructions on how to perform behaviors • Practical social support • Prompts/cues • Self-incentive • Self-reward • Social reward for goals
Module 4	• Confidence in the kitchen • Storing and cooking fruit and vegetables • Reducing waste • Cooking confidence and skills • Recipe modification • Healthy entertaining	• Knowledge and skills • Self-efficacy • Perceived affordability	• Action planning • Behavior substitution (recipes, takeaway food) • Demonstration of the behavior • Discrepancy between current behavior and goal • Goal setting (behaviors) • Information about social consequences (cost) • Instruction on how to perform behaviors • Practical social support • Problem-solving • Reviewing behavior goals • Self-incentive • Self-reward • Social reward for goals
Module 5	• Eating out • Trying new fruits & vegetables	• Skills • Self-efficacy • Perceived affordability • Perceived barriers: taste	• Action planning • Behavior substitution (eating out) • Demonstration of the behavior • Discrepancy between current behavior and goal • Goal setting (behaviors) • Instruction on how to perform behaviors • Problem-solving • Self-incentive • Self-reward • Social reward for goals

Intervention component	Primary message/resources (web + text message)	Targeted determinant	Behavior change techniques
Module 6	• Message reinforcement	• Knowledge • Skills • Self-efficacy • Perceived affordability	• Conserving mental resources • Discrepancy between current behavior and goal • Instruction on how to perform behaviors • Problem-solving • Reviewing behavior goals • Self-monitoring behavior

EatSmart Website Special Design Characteristics

The website structure has specific design characteristics to address barriers to electronic literacy (e-literacy) [55] so that it is simple and easy to use and omits unnecessary design elements. Furthermore, the elements are arranged in a way that implies importance (visual hierarchy). For example, the most important points about healthy eating habits and take-home messages are arranged at the top of each module (Figures 1 and 2).

Figure 1. Screenshots of EatSmart website.

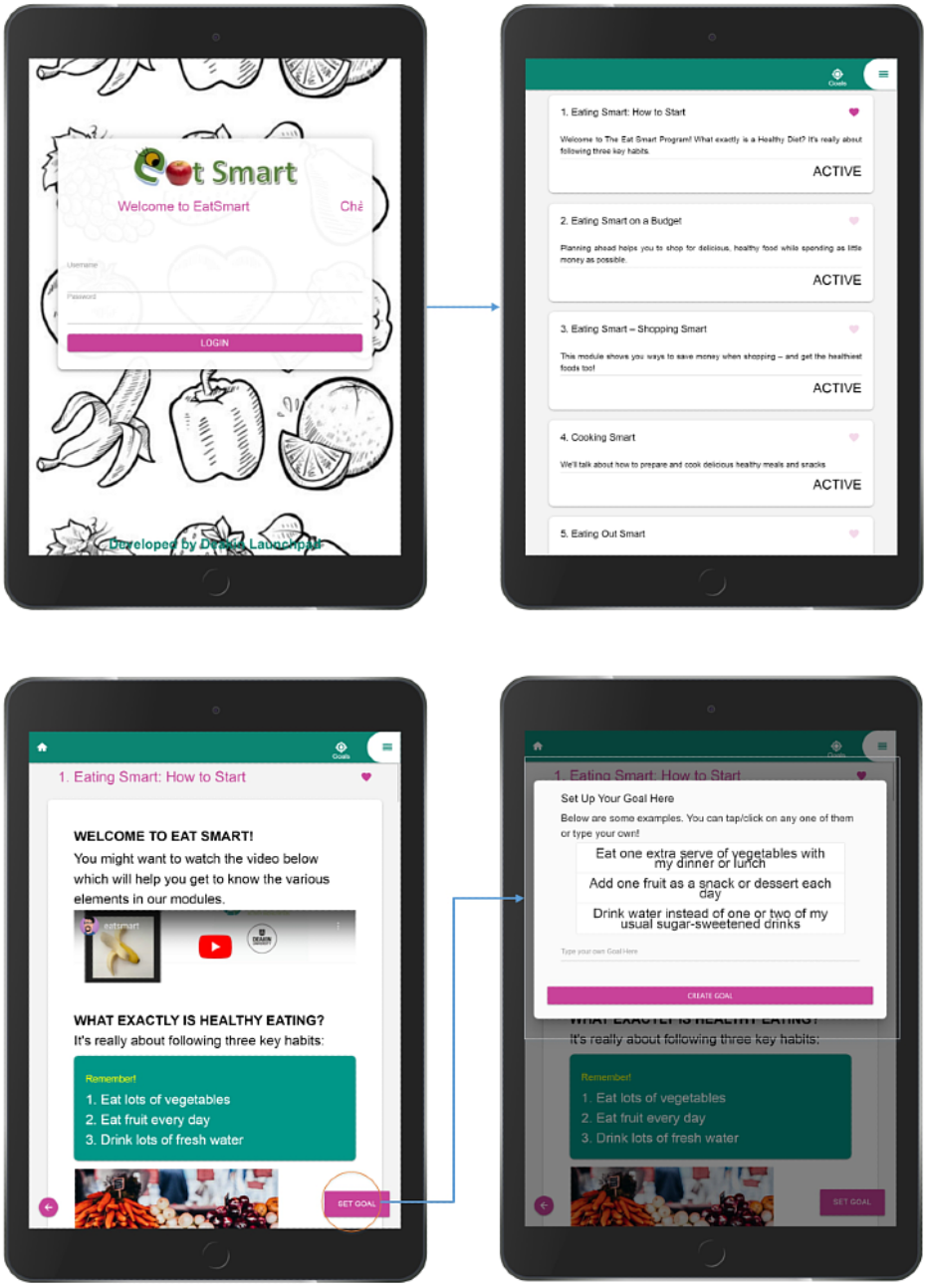
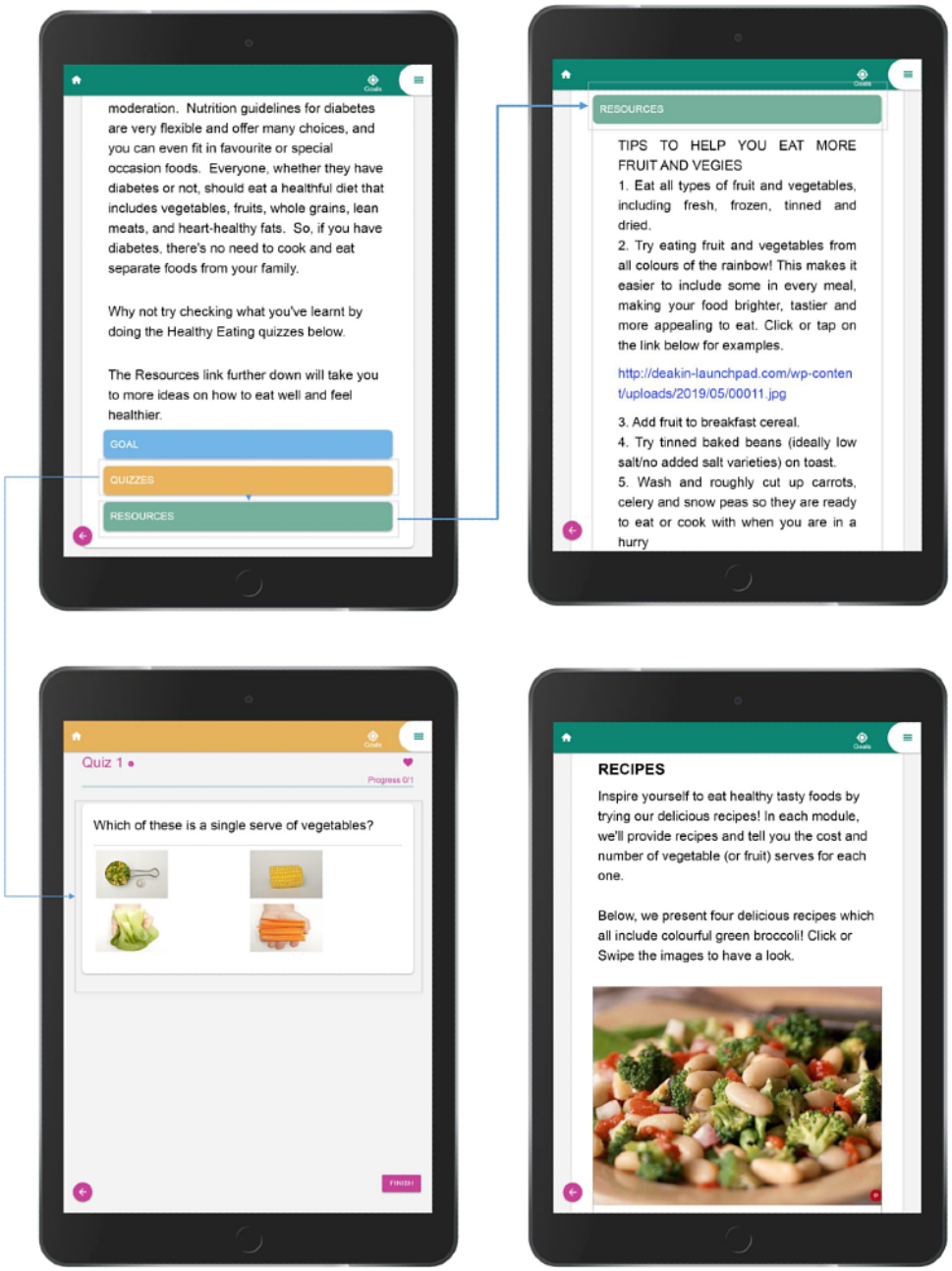


Figure 2. Screenshots of different parts of modules.



The site's navigation, overall look, and feel are consistent across all pages by using the same color schemes, typefaces, backgrounds, and tone of the text messages. All six modules comprise four parts. The first part includes healthy eating and nutritional information, followed by goals, quizzes, and resources, which are color-coded to distinguish them from other features. This approach was adopted to enhance the usability of the website [56]. The website is compatible with mobile and desktop devices and different operating systems and browsers. A simple nonverbal users' guide video [57] is provided at the start of the first module to show participants how to interact with different elements of the website, set their preferred time to receive text messages in their profile, select one of the offered goals, or view videos and recipes.

During website development (before the main project begins), the first four modules were pilot tested with 12 people approached in diabetes clinics at Sunshine Hospital who fell into the project demographic. These participants were asked to complete, with the researchers, a brief survey asking questions about how appealing and understandable they found the website and its modules. No identifying data were collected, although the researchers noted the sex and approximate age of participants in case these factors influenced their views on the modules and/or website design and content. Based on this pilot test, specific suggestions from the participants about content and design of the website (for example, introducing more budget-saving strategies, the inclusion of more simple ethnic recipes, more colorful pictures and visual messages, bigger font size, and easier browsing) have been incorporated to improve interest, readability, tone, and layout in the final development of the intervention for end users.

Outcomes and Measures

This study's primary outcome is pre-post intervention (baseline versus 3 months) changes in the consumption of vegetables and fruits.

Secondary outcomes are:

1. Six-month follow-up changes in consumption of vegetables and fruits (baseline versus 9-month),
2. Pre-post intervention and 6-month follow-up changes in other dietary indicators aligned with dietary guidelines (wholemeal/whole grain bread, milk, water, and some discretionary items),
3. Pre-post intervention and 6-month follow-up changes in dietary self-efficacy (including perceived skills and confidence),
4. Pre-post intervention and 6-month follow-up changes in perceived barriers to healthy eating (including budget/perceived unaffordability, family preferences, taste, and skills),
5. Feasibility and engagement,
6. Appeal, satisfaction, usability, and longer term acceptability of the program.

Study measures across time points are presented in Multimedia Appendix 5. Demographic data including age, sex, education level, country of birth, and family/household composition will be gathered using a standard survey. Clinical data, including the duration of diabetes and current diabetes medications, will also be collected to describe the sample. Dietary intake will be assessed by a survey with short dietary intake questions. The survey includes five multiple-choice questions regarding the consumption of vegetables and fruits and 12 questions asking about the consumption of wholemeal/whole grain bread, milk, water, and some discretionary items. The single fruit and vegetable questions are adapted from those used in Australia's National Nutrition Survey (1995), which were shown to discriminate between groups with different vegetable intakes assessed by a 24-h recall. The self-report Food Frequency questions are based on those used in the ShopSmart study [58]. Additional questions regarding the consumption of starchy vegetables and legumes were also designed and added to the survey to capture important outcomes for this T2D target group. Dietary self-efficacy and barriers as key predictors of dietary changes will be assessed by established self-report survey items, including 27 statements with Likert scale responses [59,60].

Feasibility and engagement will be evaluated by the number of participants recruited/retained, numbers accessing the website, logins and duration of website use, pages engaged with, and numbers receiving/reading the text messages [61]. For this purpose, web tagging is applied to the EatSmart website to record usage systematically. Tagging logs user interaction with particular program features and can provide real-time and historical statistics on engagement [62]. Website analytics allow us to identify whether portal login and usage are continuous, declining, or fluctuating during the intervention and follow-up period. In this intervention, we will consider adherence to the program to be confirmed by at least 66% of participants completing the study. We will also assess the number of website modules visited, as well as text messages read. While there is no set definition of feasibility in the literature for this context, we would consider the approach feasible if participants engage with the majority of materials (ie, on average more than 50% of website pages and text messages). However, we will also explore reasons for lower engagement levels through our semistructured interview to improve the materials for future larger studies. Program appeal, usability, and participants' satisfaction will be assessed by self-report survey questions developed for this study. These include three statements with Likert scale responses and 11 open-ended qualitative questions about using the educational materials, useful features of the website and the messages, and liked and disliked aspects of the EatSmart program.

Participants will complete all self-report surveys, either web-based or telephone-assisted, at baseline and again at 3 and 9 months. The data capture and management tool REDCap (Research Electronic Data Capture) [63] will be used to collect data. Data will be entered automatically by the participant, via an individualized hyperlink or manually (by the research fellow), into REDCap. The data is stored, housed, and backed up within Deakin University in a database that can only be accessed via three layers of security (university firewalls, institute limitations, and project manager login).

Data on program appeal, usability, and participant satisfaction will be supplemented by semistructured interviews at 6 months post intervention to explore longer term maintenance of any behavioral or attitudinal changes.

At 9 months post baseline, participants will be invited by telephone, text message, or email to complete a one-on-one semistructured interview of up to 40 minutes via telephone. Recruitment for interviews will be successive until no new themes appear (thematic saturation). However, based on other qualitative reports in the same area [64-66], we do not expect to recruit fewer than 25 participants. Interview methods are useful for gaining specific information while allowing participants to freely share their viewpoints [62]. These interviews will be conducted to understand participants' experiences of the EatSmart program and answer questions about whether, how, and why the intervention modules created long-lasting behavioral changes. The researcher will use a discussion guide of open-ended questions, and the interview will be audio recorded to ensure all verbal data are captured. The researcher will also write notes after the interview to document related nonverbal data. Participants will answer questions about the various parts of the website, text messages, and content presented within the intervention, their perceived capability for action within their personal situation, and any subsequent healthy eating-related changes.

These interviews will add to the program feedback from the surveys and create a base for understanding the characteristics of patients for whom these healthy changes occur and last. These data will provide us with insight into contextual factors that promote engagement.

At the end of the intervention, we will also conduct one-on-one interviews with up to ten health care providers involved with diabetes care (including endocrinologists, diabetes nurses, and diabetes nurse educators) at Western Health diabetes clinics.

These interviews aim to understand providers' views about successful or unsuccessful elements of EatSmart as a technology-delivered intervention, concerns or barriers regarding using these kinds of interventions, and feedback from their interactions with patients about the intervention's content, impact, or observed benefits. The providers will be invited by email or face-to-face invitations to participate in a confidential semistructured interview of up to 30 min length. Interviews will be conducted at the health care practice or via telephone, as convenient for the provider. The interviews will begin by reviewing the website's modules and text messages to guide the discussion. An open-ended discussion guide, audio recording, and note-taking of every session will be used to capture data. These data will complement the participant interviews to refine and develop the program for future studies.

Statistical Analysis

Statistical analyses of quantitative and qualitative data will be conducted using Stata version 16 [67] and NVivo qualitative data analysis software (QSR International, version 10), respectively. Formal power calculations have not been conducted as this is a pilot study focusing on feasibility, and all of the comparisons and effects will be considered exploratory, regardless of the significance level found. However, the study will generate data on eating behaviors to inform power calculations for a larger subsequent trial.

Participants' baseline and sociodemographic characteristics will be summarized using descriptive statistics. To understand the potential limitations of this intervention's generalizability, characteristics of participants who prematurely exit the program will be compared with those who complete the program [68]. Potential intervention effects on dietary intake, self-efficacy, and perceived barriers will be assessed quantitatively by comparing pre- and postintervention and follow-up survey measures and analyzed using mixed models. Program feasibility measures will be analyzed as proportions, means, and frequencies. The frequency of participant logins and the number of visits to each page of the EatSmart website during the study and follow-up period will be extracted by web server logs and analyzed using descriptive analytical statistics. These analytical data will be used to describe participants' engagement with the program generally and with specific modules during the intervention and follow-up period. Measures of program appeal and usability will be analyzed using descriptive analytical techniques (frequencies, proportions). Descriptive statistics will be derived from the survey responses, such as the reported extent of engagement with different website modules, the number of modules visited, the number of text messages read, and the perceived impact of the EatSmart intervention.

Furthermore, a thematic analysis will be employed for open-ended surveys to identify key program likes and dislikes. For qualitative measures from interviews, audiotapes of the interviews will be transcribed verbatim and de-identified. Transcripts will be imported to NVivo software to enable coding of the interview data and expedite the organization of codes into themes and subthemes. Two researchers will do line-by-line coding on three initial transcripts and then meet to discuss the development of preliminary conceptual themes and subthemes. These initial conceptual themes will then be applied to subsequent transcripts. Open discussions within the research team will resolve discrepancies in data interpretation. The coding process will continue until saturation, such that no further codes or categories can be found in the data. Thematic analysis will be used to describe why and among whom the program works best [69]. Qualitative results will be reported according to consolidated criteria for reporting qualitative research (COREQ) [70]. Incorporation of quantitative and qualitative analyses will thus happen at multiple stages in the evaluation of the program. Results from our different data sources will be combined and then interpreted to improve the validity of our conclusions.

Results

The EatSmart website has been developed, tailored to the needs of people of lower SEP with T2D, and all the modules viewed by participants. Recruitment began in October 2019 and finished in February 2020. Data collection will continue through October 2020. Data analysis and cleaning will be conducted after data collection is complete. We anticipate reporting results in December 2020 by submitting professional publications in peer-reviewed journals and conference presentations.

Discussion

As with many chronic diseases, a disproportionately high burden of diabetes and its associated complications is shouldered by those who are socioeconomically disadvantaged. This target group is often neglected in research trials as they are generally considered too hard to reach and impact [71]. EatSmart is one of the first international studies to deliver theoretically grounded, evidence-based support digitally to enable disadvantaged people with T2D to strengthen skills necessary to eat healthily on a budget, as a key part of diabetes self-management. EatSmart offers a potentially low-cost approach with high reach, with the only cost to participants involving minimal data use to access the website from their existing internet service.

Several approaches have been employed to increase the efficacy of EatSmart. Firstly, in all stages of the website's design, development, and content, the end users' particular needs and perspectives have been evaluated and considered. Secondly, a behavioral support reminder system in the form of regular text messages helps promote continued engagement and address the problem of high attrition rates, a problem common to eHealth studies [72]. Furthermore, the intervention framework is theoretically grounded in Bandura's Social Cognitive Theory [47], emphasizing the importance of factors within the cognitive, socioenvironmental, and behavioral domains and their interactions. Key constructs of Social Cognitive Theory are goals (plans to act that can be deemed as intentions to perform the behavior), self-efficacy (peoples' judgment of their ability to perform a behavior), and outcome expectations (views about the outcomes that are possible to result from a specific behavior).

EatSmart targets nutritional knowledge gaps and misinformation, promotes positive mindsets toward healthy eating (ie, self-efficacy), and facilitates changes in eating behaviors to increase self-efficacy and behavior change. Active learning,

guided practice, reinforcement, and modeling are key features of Social Cognitive Theory contained within EatSmart. Some of the strategies incorporated into the design of EatSmart included goal setting and problem solving for building self-management skills, providing hands-on skill-building activities (eg, cooking activities utilizing healthy ingredients and cooking methods), and direct instruction and modeling by the intervention nutritionist (in videos). Modeling is an important influence, providing individuals with skills and strategies to adopt and maintain behaviors in different situations. The video components of the EatSmart website incorporate modeling, with actors (research team members) providing support in real-world environments such as the supermarket and the kitchen at home. The intervention also draws on empirical evidence of the key determinants of eating behaviors, including our past work suggesting the significance of addressing nutrition knowledge, food planning and budgeting and preparation skills, perceived and actual food costs, and other barriers [11]. Finally, the mixed methods design and the inclusion of in-depth qualitative interviews can provide deep insight into the challenges and promises of employing eHealth healthy eating interventions for disadvantaged people with T2D.

The results of this pilot study will be interpreted with consideration of the following limitations. The study relies on self-reported measures, which may be subject to recall and social desirability bias. The lack of a control group is another limitation, although this is an appropriate design for a pilot study in a relatively new area, with feasibility and exploratory focus. Furthermore, while clinicians and 12 randomly selected patients with T2D were involved in reviewing and providing input to a draft website, there could have been greater involvement from these groups throughout the development of the intervention. However, as it is a pilot study, the feedback survey and interviews will be used to further inform the development of future interventions. Finally, EatSmart is currently only presented in English, which is essential to evaluate the feasibility of this initial pilot trial. Translation to other languages can be a future priority to reach other underserved communities at higher risk of health disparities.

The EatSmart intervention study results will make a valuable contribution to the evidence base on diabetes self-management in a high-risk population. This project will inform scalable public health programs to promote healthy eating and diabetes self-management as an inexpensive adjunct to clinical care among vulnerable populations and contribute new knowledge to digitally delivered health research in Australia and internationally.

Acknowledgments

We are grateful to Diabetes Australia for the Diabetes Australia Research Program grant to support this work and the Institute for Physical Activity and Nutrition (IPAN) at Deakin University. Each named author has contributed to conducting the underlying research and drafting this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant Information and Consent Form.
[DOC File , 106 KB - resprot_v9i11e19488_app1.doc]

Multimedia Appendix 2
Participant Information and Consent Form (Follow up interview).
[DOC File , 109 KB - resprot_v9i11e19488_app2.doc]

Multimedia Appendix 3
HCP Information and Consent Form.
[DOC File , 105 KB - resprot_v9i11e19488_app3.doc]

Multimedia Appendix 4
Text messages provided in the EatSmart program.
[DOC File , 64 KB - resprot_v9i11e19488_app4.doc]

Multimedia Appendix 5
Study measures and assessment tools across time points.
[DOCX File , 29 KB - resprot_v9i11e19488_app5.docx]

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Abbreviations

SEP: socioeconomic position
T2D: type 2 diabetes

Edited by C Hoving; submitted 20.04.20; peer-reviewed by E Lyons, A Lau; comments to author 03.06.20; revised version received 10.08.20; accepted 16.09.20; published 06.11.20.

Please cite as:
Karimi N, Crawford D, Opie R, Maddison R, O'Connell S, Hamblin PS, Ng AH, Steele C, Rasmussen B, Ball K
EatSmart, a Web-Based and Mobile Healthy Eating Intervention for Disadvantaged People With Type 2 Diabetes: Protocol for a Pilot Mixed Methods Intervention Study
JMIR Res Protoc 2020;9(11):e19488
URL: https://www.researchprotocols.org/2020/11/e19488
doi:10.2196/19488
PMID:33155571

Protocol

A Short Intervention Followed by an Interactive E-Learning Module to Motivate Medical Students to Enlist as First Responders: Protocol for a Prospective Implementation Study

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Abstract

Background: In Geneva, Switzerland, basic life support (BLS) maneuvers are provided in only 40% of out-of-hospital cardiac arrests (OHCAs) cases. As OHCA outcomes are markedly improved when BLS maneuvers are swiftly applied, a “first-responder” system was introduced in 2019. When emergency dispatchers identify a possible OHCA, first responders receive an alert message on a specific app (Save-a-Life) installed on their smartphones. Those nearest to the victim and immediately available are sent the exact location of the intervention. First-year medical students only have limited knowledge regarding BLS procedures but might nevertheless need to take care of OHCA victims. Medical students responding to out-of-hospital emergencies are off-duty in half of these situations, and offering junior medical students the opportunity to enlist as first responders might therefore not only improve OHCA outcomes but also foster a greater recognition of the role medical students can hold in our society.

Objective: Our aim is to determine whether providing first-year medical students with a short intervention followed by an interactive e-learning module can motivate them to enlist as first responders.

Methods: After obtaining the approval of the regional ethics committee and of the vice-dean for undergraduate education of the University of Geneva Faculty of Medicine (UGFM), 2 senior medical students will present the project to their first-year colleagues at the beginning of a lecture. First-year students will then be provided with a link to an interactive e-learning module which has been designed according to the Swiss Resuscitation Council’s first aid guidelines. After answering a first questionnaire and completing the module, students will be able to register for practice sessions. Those attending and successfully completing these sessions will receive a training certificate which will enable them to enlist as first responders. The primary outcome will be the proportion of first-year medical students enlisting as first responders at the end of the study period. Secondary outcomes will be the proportion of first-year medical students electing to register on the platform, to begin the e-learning module, to complete the e-learning module, to register for practice sessions, to attend the practice sessions, and to obtain a certificate. The reasons given by medical students for refusing to participate will be analyzed. We will also assess how comfortable junior medical students

would feel to be integrated into the first responders system at the end of the training program and whether it affects the registration rate.

Results: The regional ethics committee (Req-2020-01143) and the UGFM vice-dean for undergraduate education have given their approval to the realization of this study, which is scheduled to begin in January 2021.

Conclusions: This study should determine whether a short intervention followed by an interactive e-learning module can motivate first-year medical students to enlist as first responders.

International Registered Report Identifier (IRRID): PRR1-10.2196/24664

(JMIR Res Protoc 2020;9(11):e24664) doi:10.2196/24664

KEYWORDS

basic life support; cardiopulmonary resuscitation; medical students; undergraduate medical education; out-of-hospital cardiac arrest

Introduction

In Switzerland, as in many other countries, junior medical students only possess limited knowledge regarding basic life support (BLS) procedures [1-6]. Medical students are often off-duty when exposed to out-of-hospital cardiac arrests (OHCAs) or to other emergency situations [7]. Although they feel that the public expects them to respond to such emergencies, medical students consistently report that they are not sufficiently prepared [7,8]. There is little doubt that they could benefit from adequate training in BLS maneuvers and use of automated external defibrillators (AEDs) as these procedures significantly increase survival rates and neurological outcomes after OHCAs [9]. Some systems have strived to overcome this issue, and some medical schools have promoted a mutually beneficial collaboration with ambulance services by offering medical students the opportunity to become first responders [10].

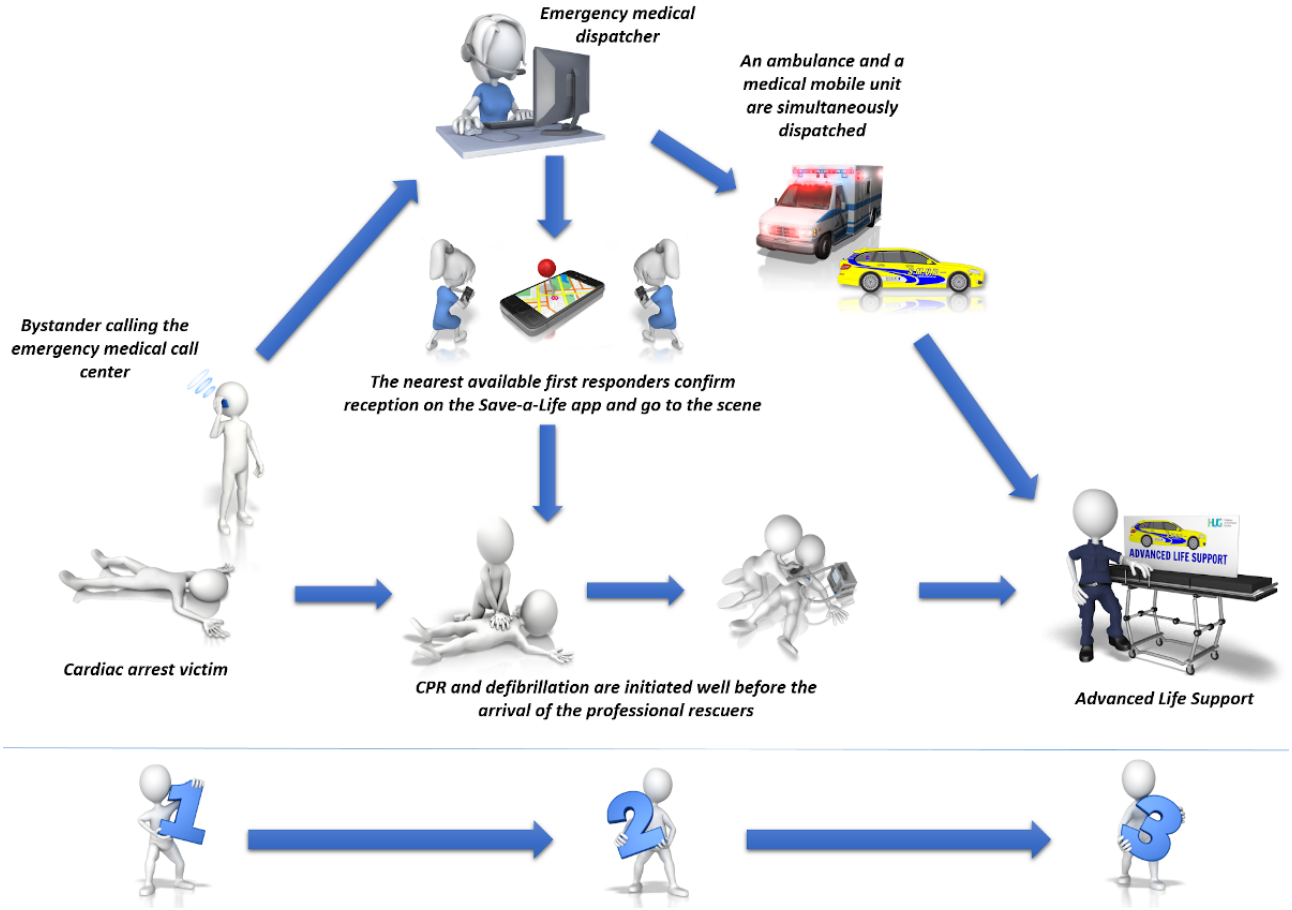
Offering junior medical students the opportunity to enlist as first responders could increase the sheer number of first responders. This could consequently lead to a significant improvement in OHCA outcomes, as BLS was provided in less than 40% of OHCA cases between 2009 and 2012 in Geneva, Switzerland [11]. As an added benefit, this approach might foster a greater recognition of the role medical students can hold in our society, thereby increasing their global motivation toward their studies and building their future medical identity.

Important variations in first responder systems can be observed across different jurisdictions and regions [12,13]. In Geneva, all first responders have been certified as full-fledged BLS–AED providers according to the Swiss Resuscitation Council's (SRC) guidelines or to other certified training procedures. They can be either lay or professional rescuers (firefighters, policemen, physicians, paramedics, or members of other such professions). In this system, all medical emergencies are assessed by professional dispatchers (all with a nursing or paramedic background) working for the emergency medical call center. These dispatchers carefully assess each situation and decide whether first responders should be sent. This decision is even more important given the current COVID-19 (coronavirus disease 2019) context, as unnecessarily exposing first responders, who might be lay people, to a potentially contagious patient should be avoided as often as possible. When an alarm is sent by emergency medical call center dispatchers, all first responders receive a notification through a specific app (Save-a-Life) installed on their smartphones (Figure 1). The first responders who are both nearest to the victim and available at the time of the alert receive information regarding the exact location of the intervention. These first responders are then expected to swiftly find and quickly assess the victim, initiate the appropriate maneuvers, and retrieve the nearest available AED, the location of which is also given through the app.

Given the high workload bearing upon junior medical students, and in the context of the COVID-19 pandemic, a flexible approach based on an inverted classroom principle could prove successful. Distance learning through electronic learning (e-learning) methods has been shown to improve knowledge acquisition and user satisfaction and could efficiently promote engagement [14-16]. Such methods are particularly well adapted to the current context [17].

Our aim is to determine whether providing first-year medical students with a short intervention followed by the possibility of following an interactive e-learning module could motivate them to enlist as first responders.

Figure 1. First responder system in Geneva, Switzerland. CPR: cardiopulmonary resuscitation.



Methods

Study Design

After obtaining the approval of the regional ethics committee (Commission Cantonale d'Ethique de la Recherche) and of the vice-dean for undergraduate education of the University of Geneva Faculty of Medicine (UGFM), senior medical students from the Geneva Medical Students' Association (Association des Etudiants en Médecine de Genève [AEMG]) will present the project to first-year medical students at the beginning of a lecture. In Geneva, medical students follow a 6-year curriculum before graduating, and first attend BLS–AED courses during their second year [18]. Medical and dental medicine students share a common pathway during the first 2 years of this curriculum. The AEMG senior medical students will be fourth- or fifth-year students who are already certified as BLS–AED instructors. After their short intervention, they will provide their younger colleagues with a link to an interactive e-learning module. This module has been designed according to the SRC's guidelines for the training of BLS–AED providers [19] and will be adapted to take the COVID-19 pandemic guidelines into account [20].

Before accessing the e-learning module, students will have to register on a dedicated website. They will then be required to complete a short questionnaire designed to gather demographic data, to assess their baseline knowledge, and their previous qualifications in the field (Table 1). The CHERRIES guidelines [21] will be used to design the questionnaire and to report its results. Students unwilling to register will still be offered the possibility to follow the e-learning module.

Upon completion of the e-learning module, and whether or not they have registered on the website, first-year medical students will be offered the option to register for practice sessions. Students attending and successfully completing these sessions will receive a course certificate which will be valid for 1 year and allow them to register as first responders (Figure 2).

Table 1. Survey structure and questions.

Survey page, field, and question	Type of question
Introduction	
Consent	N/A
Reason for refusal (if applicable)	MAQ[a]
Attrition	
N/A[b]	
1	
Demographics	
Year of birth	Open (Regex[c])
Gender	MCQ[d]
Medical or dental medicine student	MCQ
Previous qualifications	MCQ
Former student or graduate of another health care profession	MCQ
Target specialty	MCQ
2	
General BLS[e] knowledge	
Ever heard of BLS or ACLS[f] before	Yes/No
Meaning of "AED[g]"[h,i]	Open
Year of the last BLS guidelines update	Open (Regex)
Phone number of the emergency medical services dispatch center[h,j]	Open
3	
Prior BLS experience	
Current or past: (1) student of another healthcare profession; (2) BLS instructor; (3) professional rescuer	MAQ
Prior BLS training	Yes/No
Wish to be trained, or more trained, in BLS procedures	Yes/No
4	
Specific BLS knowledge	
Criteria used to recognize out-of-hospital cardiac arrest[h]	MAQ
BLS sequence[h]	Ordering
Artery for pulse assessment[h]	MCQ
Compression depth[h]	MCQ
Compressions-to-ventilations ratio[h]	MCQ
Compression rate[h]	MCQ
Compression-only cardiopulmonary resuscitation[h]	Yes/No
Treatment of a choking patient, conscious, unable to either cough or talk[h]	MCQ
Self-assessed confidence in the ability to perform resuscitation	1-10 Likert scale

[a]MAQ: multiple answer question (more than 1 answer accepted).

[b]N/A: not applicable.

[c]Regex: regular expression validation.

[d]MCQ: multiple choice question (only 1 answer accepted).

[e]BLS: basic life support.

[f]ACLS: advanced cardiovascular life support.

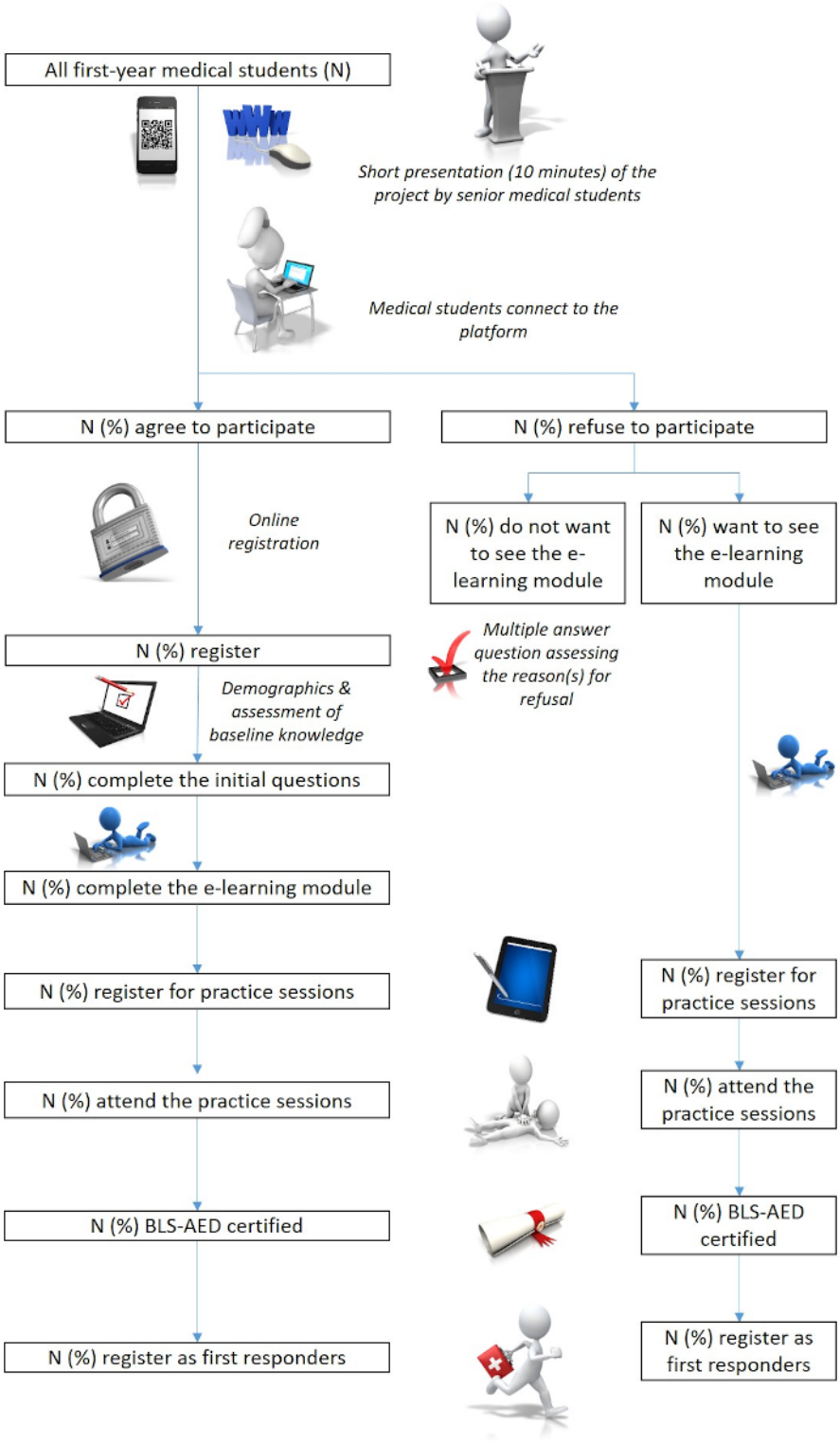
[g]AED: automated external defibrillator.

[h]Questions used to assess the baseline knowledge (score out of 10 questions).

[i]All answers containing “defibrillator” in English or in French will be considered as correct (not case sensitive, spelling mistakes accepted).

[j]Acceptable answers: 112, 144, and 911 which all work in Geneva, Switzerland. 144 is the official Swiss number.

Figure 2. Study design.



Enrolment and Consent

A short presentation of the study lasting approximately 10 minutes will be made to first-year UGFM medical students by 2 AEMG senior medical students. First-year medical students will then be provided with a regular URL as well as with a QR code to access the online platform.

Information regarding the study's purpose and its estimated duration will be displayed on the main page. Medical students willing to participate will then have to register on the platform using a valid email address. An electronic consent form will be displayed along with the registration form, and registration will be considered as consent to participate. Participants refusing to participate will be prompted to enter the reason for this refusal. Identity and contact details of the investigators will be given, and information regarding data handling will be provided in accordance with the European General Data Protection Regulation (GDPR) [22]. No financial incentive will be given to promote participation.

Sample Size, Inclusion, and Exclusion Criteria

At UGFM, 521 first-year medical students are currently registered and will represent a convenience sample. First-year medical students who are already registered as first responders will be excluded.

Online Platform, Initial Questionnaire, and Learning Material

An internet platform will be developed under the Joomla 3.10 content management system (Open Source Matters) [23].

After registration, the students will be shown a first questionnaire designed to gather demographic data and to assess their baseline knowledge. This questionnaire is adapted from a recent study by Sturny et al [6], which used questions prepared according to the 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations [24].

Given the context of the COVID-19 pandemic, the e-learning module will be adapted from an already existing module used to teach BLS–AED courses to UGFM second-year medical students according to a "flipped-classroom" principle.

Practice Sessions and Certification

Upon completion of the e-learning module, first-year medical students will be able to register for practice sessions. These sessions will last 1 hour and will be delivered by senior medical students. All these senior medical students will be required to possess a BLS–AED instructor certificate delivered by an SRC-certified instructor.

Upon successful completion of the practice session, first-year medical students will receive a certificate enabling them to enlist as first responders.

Data Collection, Outcomes, and Statistical Analysis

All data will be stored on an encrypted MySQL compatible database (MariaDB 5.5.5, MariaDB Foundation) located on a Swiss server.

The primary outcome will be the proportion of first-year medical students enlisting as first responders at the end of the study period. Secondary outcomes will be the proportion of first-year medical students electing to register on the platform, to begin the e-learning module, to complete the e-learning module, to register for practice sessions, to show up to the practice sessions, and to obtain a certificate. The reasons given by medical students for refusing to participate will be analyzed. We will also assess how comfortable junior medical students would feel to be integrated to the first responders system at the end of the training program and whether it affects the registration rate.

These proportions will be displayed using descriptive statistics (n [%]). Student *t* test will be used to determine a potential association between baseline knowledge and the probability of obtaining a certificate and of enlisting in the first-responder system. The same test will be used to determine whether students who feel more comfortable after their training are more likely to enlist. A sensitivity analysis will be performed according to whether the students immediately agreed to participate and register on the platform or if they rallied the study after seeing the e-learning module.

Results

This study protocol has been submitted to the local ethics committee (Req-2020-01143), which issued a declaration of "no objection" as such studies do not fall within the scope of the Swiss Federal Act on Research involving Human Beings [25].

The vice-dean for undergraduate education of the UGFM has also approved the protocol and its underlying concept.

The study is scheduled to begin in January 2021. After discussion with the different stakeholders, we estimate that the procedure would be successful if 10% of first-year medical students had enlisted as first responders at the end of the study period.

Discussion

Main Considerations

The success of the approach described in this study protocol will depend on numerous factors. The short intervention performed by senior medical students will be of particular importance, as it will condition whether first-year medical students choose to connect to the online platform. As participation will not be compulsory, junior medical students might more easily heed the advice of their more senior colleagues rather than the recommendation of the teaching staff or of senior physicians [26-28].

The interactivity of the e-learning module will also be an important factor. E-learning is a generic term covering many different kinds of electronic teaching and learning materials [29]. Some e-learning methods have proven more successful than others, and enhanced interactivity has been postulated to increase learner engagement and knowledge acquisition [14-16]. The existing version of the e-learning module will therefore be adapted not only to comply to the COVID-19 guidelines [20],

but also to improve its interactivity. Although this will most probably contribute to improving knowledge acquisition, practice sessions will nevertheless still be needed as practical skills can hardly be acquired through e-learning alone [30,31].

The practice sessions will need to be carefully planned. Once again, instructors should be senior medical students rather than senior physicians, as this will be less intimidating to junior medical students [26]. Combining e-learning with hands-on practice will result in a blended learning method which should enhance knowledge and skill acquisition [32,33]. Blended learning has also been shown to significantly increase motivation in undergraduate students [34]. This learning method will also allow students to spend less time in direct contact with an instructor, and courses including 45-minute practical sessions have been shown to be at least as effective as classical 6-hour courses [35]. This rather short duration should help further promote participation and limit attrition. Despite these advantages, specific safety measures, including frequent handwash and keeping a safe distance between participants, will have to be enforced given the COVID-19 pandemic context [20].

Some limitations can already be pointed out. First, the short intervention which will be used to motivate junior medical students to connect onto the web platform might not be followed by all first-year students. The participation rate might therefore be underestimated as some potential participants will not get the information and the link to the platform. Moreover, though the medical students who will follow the e-learning module without registering on the platform will still be able to register for practice sessions, we will not be able to gather data regarding their baseline knowledge. This might lead to a bias as we will aim to identify a potential association between baseline knowledge and the probability of obtaining a certificate and of enlisting in the first-responder system. A sensitivity analysis will therefore be performed to assess for such a bias. Finally, though we will strive to assess the reasons underlying the refusals to follow this learning path, we will only be able to analyze the data entered by the students who have elected to browse the study website. We might therefore miss some important clues as to how the attention of these students could be drawn.

Conclusion

Offering junior medical students the opportunity to enlist as first responders might not only improve outcomes in OHCA victims, but also foster a greater recognition of the role medical students can hold in our society, thereby increasing their motivation. This study will determine whether providing first-year medical students with an interactive e-learning module can motivate them to enlist as first responders.

Conflicts of Interest

None declared.

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Abbreviations

AED: automated external defibrillator
AEMG: Association des Etudiants en Médecine de Genève
BLS: basic life support
CPR: cardiopulmonary resuscitation
OHCA: out-of-hospital cardiac arrest
UGFM: University of Geneva Faculty of Medicine

Edited by G Eysenbach; submitted 02.10.20; peer-reviewed by LA Lee; comments to author 26.10.20; revised version received 26.10.20; accepted 27.10.20; published 06.11.20.

Please cite as:
Suppan L, Herren T, Taramarcaz V, Regard S, Martin-Achard S, Zamberg I, Larribau R, Niquille M, Mach F, Suppan M, Schiffer E
A Short Intervention Followed by an Interactive E-Learning Module to Motivate Medical Students to Enlist as First Responders: Protocol for a Prospective Implementation Study
JMIR Res Protoc 2020;9(11):e24664
URL: http://www.researchprotocols.org/2020/11/e24664/
doi:10.2196/24664
PMID:33155574

Protocol

Artificial Intelligence–Powered Smartphone App to Facilitate Medication Adherence: Protocol for a Human Factors Design Study

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Abstract

Background: Medication Guides consisting of crucial interactions and side effects are extensive and complex. Due to the exhaustive information, patients do not retain the necessary medication information, which can result in hospitalizations and medication nonadherence. A gap exists in understanding patients' cognition of managing complex medication information. However, advancements in technology and artificial intelligence (AI) allow us to understand patient cognitive processes to design an app to better provide important medication information to patients.

Objective: Our objective is to improve the design of an innovative AI- and human factor–based interface that supports patients' medication information comprehension that could potentially improve medication adherence.

Methods: This study has three aims. Aim 1 has three phases: (1) an observational study to understand patient perception of fear and biases regarding medication information, (2) an eye-tracking study to understand the attention locus for medication information, and (3) a psychological refractory period (PRP) paradigm study to understand functionalities. Observational data will be collected, such as audio and video recordings, gaze mapping, and time from PRP. A total of 50 patients, aged 18-65 years, who started at least one new medication, for which we developed visualization information, and who have a cognitive status of 34 during cognitive screening using the TICS-M test and health literacy level will be included in this aim of the study. In Aim 2, we will iteratively design and evaluate an AI-powered medication information visualization interface as a smartphone app with the knowledge gained from each component of Aim 1. The interface will be assessed through two usability surveys. A total of 300 patients, aged 18-65 years, with diabetes, cardiovascular diseases, or mental health disorders, will be recruited for the surveys. Data from the surveys will be analyzed through exploratory factor analysis. In Aim 3, in order to test the prototype, there will be a two-arm study design. This aim will include 900 patients, aged 18-65 years, with internet access, without any cognitive impairment, and with at least two medications. Patients will be sequentially randomized. Three surveys will be used to assess the primary outcome of medication information comprehension and the secondary outcome of medication adherence at 12 weeks.

Results: Preliminary data collection will be conducted in 2021, and results are expected to be published in 2022.

Conclusions: This study will lead the future of AI-based, innovative, digital interface design and aid in improving medication comprehension, which may improve medication adherence. The results from this study will also open up future research

opportunities in understanding how patients manage complex medication information and will inform the format and design for innovative, AI-powered digital interfaces for Medication Guides.

International Registered Report Identifier (IRRID): PRR1-10.2196/21659

(JMIR Res Protoc 2020;9(11):e21659) doi:10.2196/21659

KEYWORDS

artificial intelligence; smartphone app; patient cognition; complex medication information; medication adherence; machine learning; mobile phone

Introduction

Background

For decades, the US Food and Drug Administration (FDA) and drug manufacturers provided detailed Medication Guides to the public to effectively communicate crucial patient safety [1]. The guides include warnings, precautions, and other lists of adverse drug reactions [2]. Unfortunately, the information presented in these Medication Guides often contains complicated medical jargon. As a result, the information is difficult to read, especially among patients with lower literacy skills [3]. One study found that only about half of the participants understood the information presented [4]. In another exploratory study, researchers used a mixed methods approach that combines eye-tracking technology, a survey, and qualitative data to explore self-reported measures of drug-risk reading and actual information recall. More than 80% of participants (n=29) claimed to have read or comprehended only half or more of the risk information. However, eye-tracking measures revealed limited to no understanding of risks and minimal unaided recall [5].

Consequently, patients cannot identify pivotal warnings from the guides, as evidenced by an increase in all medication-related hospitalizations by 117% from 1997 to 2008 [6]. Limited research in this area suggests that minimal patient engagement with information may contribute to unrecognized adverse effects that can lead to poor adherence. Furthermore, patient cognition and low literacy levels have a negative impact on medication adherence [7-9]. Therefore, the solution may not be whether or not the information was presented but rather *how* the information presented supports the cognition of the patient [10]. Moreover, understanding the patient's cognitive processes could ultimately impact both intentional and unintentional medication nonadherence. Intentional nonadherence relates to stopping or altering prescribed medications through a perceived purpose, whereas unintentional medication nonadherence relates to specific circumstances that impede compliance, including forgetting to take a dose [11]. Both intentional and unintentional nonadherence lead to poor outcomes and uncontrolled disease states. Additionally, studies have detected a relationship between nonadherence and health literacy [12,13]. One study in particular investigated asthmatic patient perspectives of medication nonadherence to inhaled corticosteroids and observed that a factor for noncompliance was suboptimal knowledge of medications [14]. Moreover, health literacy is positively associated with cognition [15]. Thus, patients with lower health literacy and lower cognition have more serious adverse drug events [16]. By understanding cognition, novel solutions to medication nonadherence can potentially be developed. Previous studies in understanding cognitive processes mainly focused on the decision making of clinicians to support cognition [17-19]. Research on the aspects of understanding the patient's cognition is still limited. Thus, a gap exists in the understanding of how patients manage complex medication information cognitively in the digital environment.

Currently, the patient's cognition can be supported through effective medication information communication using digital platforms, such as smartphone apps. In particular, recent advancements in artificial intelligence (AI) embedded into smartphone apps have the potential for a significant impact to monitor and eventually comprehend different features of the patient's cognition [20,21].

We hypothesize that interactive information visualization using human factors design principles delivered through a smartphone platform has the potential to improve medication information retention. Infographics or interactive visualizations using pictures and illustrations have been effective for complex information communication and have proven the age-old saying "a picture is worth a thousand words" [22-25]. Furthermore, AI-based smartphone devices have proven to be effective in clinical trials and chronic disease management to improve medication adherence [21,26]. Utilizing advanced machine learning algorithms, smartphone apps have the potential to improve medication information delivery to patients. Specifically, algorithms based on AI can help advance our understanding of patients' cognitive processes and provide solutions through digital health technology.

Objective

Our goal is to improve the design of an innovative, AI-powered user interface based on human factors methodology to support the patient's cognition, enhance the ability to comprehend medication information, and ultimately improve medication adherence. The aims are listed below:

1. Aim 1: identify barriers to medication information comprehension.
2. Aim 2: iteratively design and evaluate the AI-powered medication information visualization interface.
3. Aim 3: test the prototype for better comprehension and adherence to medication information.

Methods

Overview

We will use RxNorm and the Unified Medical Language System to design the AI infrastructure to unify medication and biomedical terminologies systematically. Generic medication names for the most prescribed and commonly used oral medications will be obtained from RxNorm. A recursive neural network (RNN)–based methodology was used for developing the AI-based algorithm. Artificial neural networks (ANNs) are modeled after the human brain and structured to recognize and recall information. An RNN is a type of ANN algorithm that operates on structured inputs of an acyclic graph. It is a type of architecture used in machine learning for various applications, such as predicting the weather, processing images, and language composition. We implemented this architecture and used deep learning algorithms using Amazon SageMaker for integrating the AI aspects into the smartphone app. We will use AI to monitor features of user analytics, use predictive tools to understand user interaction, and create a dynamic user environment of the app that changes based on the user's previous input. The deep learning methodology of RNNs will guide us to develop such features. The user's input will be reused to train the machine learning model.

Aim 1: Identify Barriers to Medication Information Comprehension

Methods Overview

We will conduct a mixed methods study following these three steps:

1. Step 1: identify patients' perceptions of fear and biases regarding medication information from a focus group study.
2. Step 2: the eye-tracking study will provide design configurations for the interface.
3. Step 3: psychological refractory period (PRP) will help us understand functionalities based on user profile variations.

Step 1: Observational Study

In the first phase, we will conduct multiple group interviews (ie, focus group methodology) for patients to interact to gain new knowledge and generate meaningful suggestions, opinions, and feedback [27]. Each focus group will have 5 patients. We will ask each patient to provide us with the name of a new medication, and we will print the Medication Guide per FDA to facilitate discussions. The study measures are (1) specific medication information on the leaflet that is hard to comprehend, (2) trigger points for information avoidance and perceived familiarity, and (3) patients' suggestions. An initial coding framework will be developed by two coders to establish themes and subthemes from the transcript data. Refinement of coding will follow, and any disagreement between two coders will be resolved by consulting with a third coder.

Step 2: Eye-Tracking Study

In the second phase, we will design a web-based mock interface representing medication information in an interactive visualization format. We will use medication information from the FDA's Medication Guides that are provided to patients for designing this mock-up. We will use the open-source software platform Pupil, a wearable, mobile, eye-tracking headset with one scene camera and one infrared-spectrum eye camera for dark pupil detection [28]. The video streams are read using Pupil capture software for real-time pupil detection, gaze mapping, recording, and other functions. We will use a mobile platform to display this information. Patients will be asked to wear the Pupil device and browse the web-based mock-up of medication information on a mobile device. They also will be asked to perform a series of tasks; for example, "find the most common side effect of the drug," "find the storage instructions," "find instructions on whether you can break the pill in half and take it," etc. Patients will be asked to browse the interface data and provide overall feedback in a short semistructured verbal interview that will follow the task segment. The study measures are (1) specific areas in medication information where attention is focused, (2) real-time gaze movement using the Pupil software algorithm, and (3) accuracy, response time, and eye-movement data. For the data analysis, the Gaze History Length option for each surface decides how many recent gaze positions will be used to calculate the heat map based on gaze history. We will use annotation software to label timestamps of specific video gazing to understand the attention locus. Two researchers will assess the transcribed audio interviews to generate trigger points, user-centered design recommendations, and user preferences.

Step 3: Psychological Refractory Period Paradigm Study

In the third phase, we seek to understand users' variations in their ability to complete two tasks in rapid succession for a goal-directed behavior; in our proposed research design, this understanding will be unpacked by determining the limits of dual-tasking by self-regulation and task-based measurement. The specific methodology for data collection is the PRP task, a tool provided by the National Institutes of Health Science of Behavior Change (SOBC) program [29-31]. The PRP gives specific instructions, which participants must follow as stated on the screen. The time, variation, and accuracy are measured through PRP and results are readily available to be downloaded after the session. The results will help us understand functionalities based on user profile variations, including age, health literacy, or any other physical and mental conditions. Patients will be given the test from the SOBC site from a web browser on a laptop computer. The study measures are (1) response time and (2) task-switching time. For the data analysis, we will note the variations of the response time based on patients' ages and backgrounds to help create design features of buttons and clickable interface functional requirements in the design for the interface.

Study Subjects and Recruitment Methods

We will recruit 50 patients from our outpatient clinic sites. A research assistant will conduct a telephone interview for cognitive status to ensure potential participants meet the minimum cutoff score of 34 during cognitive screening based on TICS-M test for sound cognitive status and health literacy level [32]. Participants will come to our main site at a lab at the Western University of Health Sciences, Pomona, California. Inclusion criteria will be patients who are aged 18-65 years and have started at least one new medication to develop visualization

information. The observational study (30 minutes), eye-tracking study (20 minutes), and PRP (10 minutes) will take around one hour, including instructions and filling out consent forms. Patients will be offered a US $100 gift card and access to a pharmacist consultation for the duration of the study.

Data Collection

We propose to collect the following data: (1) observation notes and audio recordings, (2) video data from Pupil on specific locations on gaze mapping, surface detection, and audio streaming data, (3) notes from user observations and audio of the short interviews after the eye-tracking study, and (4) task-switching and task-processing time from PRP.

Sample Size Justifications

Previous observation and eye-tracking studies used 10-90 participants and 5-40 participants, respectively [17,33,34]. We plan to recruit 50 patients for this aim.

Limitations

Patients may experience peer pressure to show conformity to medication information. We will have the moderator clarify to patients that the questions have no right or wrong answers. Some errors may result from gaze mapping, surface detection, and algorithm data. Therefore, we will calibrate the software and hardware before each study.

Aim 2: Iteratively Design and Evaluate the AI-Powered, Medication Information Visualization Interface

Methods Overview

We will use an AI-based smartphone interface platform for our iterative design of the medication information interface. To develop such a platform, we will use the Amazon SageMaker engine for creating an AI-powered interface with our RNN-based algorithm. This interface will be able to take into account users' interactions and translate the data into a data analytics–based back-end server. This prototype will be developed in Java and Python languages for both android and iOS platforms.

Human Factor–Based Iterative Design

We will use a human factor–based methodology to iteratively design the app from the functional requirements from Aim 1 using user-centered design principles [12,23,34]. We will use the usability inquiry approach for the iterative design to understand the users' likes, dislikes, and needs [35,36]. The multidisciplinary research team, including 20 clinicians with diverse clinical backgrounds and 12 researchers, will then iteratively review and revise the app based on the written and verbal feedback related to the usability (ie, think-aloud methods), efficiency, and ease of use for 4 months or until no further revisions are identified. App usability will not be measured remotely. A research assistant will recruit clinicians and other team members for the iterative design process related to the front end of the prototype app. We will ask users to interact with the mock-up in the mobile interface and provide them with tasks using think-aloud methods. Think-aloud methods will provide rich verbal data about specific changes and functionalities of the initial mock-up [35,37]. We will audio record and screen record sessions, using Camtasia (TechSmith Corporation), to analyze verbal feedback from the think-aloud method and measure the mouse movements. We will analyze the data from the think-aloud sessions and screen recordings to identify design functionalities, and we will change the design based on feedback. The think-aloud sessions and screen recordings will provide us with specific user comments and interface design preferences. Our design team will incorporate those changes and take users' feedback in an iterative process unless a final design agreement has been reached.

Contextual Medication Information for the Visualization

Two medication information expert pharmacists will develop contextual medication information—10 pieces of crucial information—that the patients should know [38]. This information may include indications for use, essential warnings, contraindications, storage information, typical side effects, and directions for use. We will use this information in the design of the visualization as well as use just the text version of the information as an intervention for Aim 3.

Usability Testing of the App

Two usability surveys will be emailed to users. The *first survey* instrument, which has been validated and created from the research on smartphone apps from the industry, is specifically designed for mobile interface design [39,40]. This Likert scale–based survey is based on a heuristic evaluation for easy, quick, and reliable assessment of the mobile user interface design [39]. The *second survey* instrument is the hierarchical task measure developed by the SOBC program. Hierarchical task analysis helps us to understand how users categorize tasks in hierarchical steps in their minds [41]. The hierarchical reinforcement learning task measures participants' abilities to discover and use higher-order structures in their environment. Participants are presented with 18 stimuli composed of three dimensions: shape, orientation, and border color. The task requires that participants respond to stimuli by pressing one of three keys in response to each of the stimuli. In a "flat" condition, the keys are randomly associated with the shapes so that the participant must learn each association independently. We will iteratively change the design of the visualization based on the survey results.

Study Subjects and Recruitment Methods

We will recruit patients (18-65 years of age) at clinic sites during the discharge process with access to, and the ability to use, a smartphone device. A research assistant will conduct the modified Telephone Interview for Cognitive Status (TICS-M) test for cognitive status to ensure potential participants meet the inclusion criteria of a minimum cutoff score of 34 for sound cognitive status and health literacy level [32]. Patients will be given a US $50 gift card for participation. We will load our medication information tool remotely into the users' app and send out an e-survey for ratings and feedback. The data from the usability surveys will be sent to a HIPPA (Health Insurance Portability and Accountability Act)-protected secured server.

Data Analysis

For the hierarchical task, the results will be shown in graphs with the percentage of error of participants' abilities to simplify tasks. We will correlate the means of the graphs with the results from the survey instruments for a personalized design.

Sample Size Justifications

Previous studies have included usability surveys with 96-404 participants [40,41]. We plan to recruit 300 patients from our outpatient clinics at the Western University of Health Sciences.

Limitations

We may receive numerous users' input about the interface. The research team will apply only the changes that correspond to the current literature of design conforming to patient safety [42].

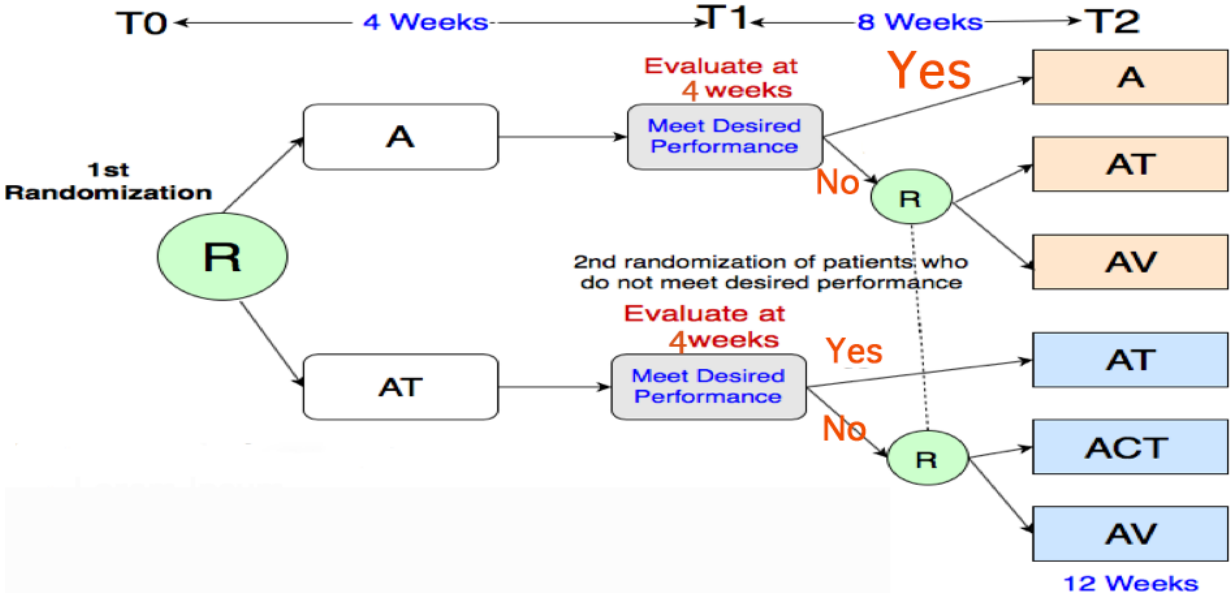
Aim 3: Test the Prototype for Better Comprehension and Adherence to Medication Information

Our hypothesis for this aim is that the AI-powered visualization tool in the app improves medication information comprehension and adherence when compared with written medication information and contextual plain-text information.

Study Design

The study has a single-blind and sequentially randomized design. The full design of the study will include two arms with 2 (modality: app versus app with text) × 2 (format: an app with visualization versus an app with contextual medication text information) × 2 (context: contextual medication information versus information without context) + 1 (control: app) design. The design is depicted in Figure 1. The randomized trial using binary options (*yes* or *no*) provides the stratification needed to identify groups that are prone to get benefits from the different presentations of medication information. The results from the sequential randomized design will help us detect statistically significant differences using a larger sample size. The first randomization helps with filtering patients who have better information recall regardless of the app. The second randomization helps with finding the actual effects of the tool when compared with different interventions.

Figure 1. Study design. The participants are randomized first at R: one group uses only the app (A) and another group is given the app with medication information text (AT). At time point 1 (T1), after 4 weeks, both groups are evaluated for information recall (>80%). Then, after a second randomization (R), the participants are divided into the following groups: app with medication information text (AT), app with contextual medication information text (ACT), and app with visualization (AV). T0: baseline; T2: time point 2 (after 12 weeks).



Intervention

The study will include three intervention conditions loaded into the smartphone app platform. We can better compare the effects of the medication information visualization tool by comparing the outcomes of these three interventions to understand the impacts of our visualization. In the first condition, the app with medication information text (AT), the medication text information will be loaded into the app platform. This medication text is the Medication Guide, which is approved by the FDA. In the second condition, the app with contextual medication information text (ACT) is shown as a printed-text version. This contextual information (ie, 10 pieces of crucial information patients should know) that we included in our visualization will be shown only as the text version in this intervention. In the third condition, an app with visualization (AV), the interactive app will be loaded with our medication information visualization tool, including the visual format of the contextual information.

Study Subjects and Recruitment Methods

We will recruit patients (18-65 years of age) from our clinics. Inclusion criteria will include participants who have access to a smartphone, can provide their consent, do not have any cognitive impairment, and who have at least two medications on profile for which we have created a visualization. At the time of recruitment, we will ensure that the patients meet the minimum cutoff score of 34 during cognitive screening using the TICS-M test and health literacy level [32]. Eligible patients will be allocated in a 1:1 ratio to the two arms of the study according to a computer-generated random sequence stratified by third-party software.

Procedure

In the first randomization, patients will be randomized into two groups at baseline. The control group (ie, the app-only [A] group) will have the smartphone app with no visualization, and the intervention group will have the app with text information only as in the current Medication Guide (AT) [43]. At 4 weeks, patients from both the control and intervention groups from both arms, who have scores of 80% or higher in the information recall survey, will continue in the study with the same intervention, in either the A or AT group. Those who do not meet the performance cutoff will be rerandomized further into two groups for each arm. In the second randomization at 4 weeks, the control group from the first arm (A) will have the smartphone app with just text information about medication (AT), and the intervention group will have the smartphone app with the prototype of medication information visualization (AV). The control group from the second arm (AT) will have the app with contextual medication information in a text format (ACT), and the intervention group will have the app with our visualization design (AV). This part of the study will continue for 8 weeks. The monitoring is not a continuous process. Only the principal investigator will have access to the main file and will check the adherence and patient analytics at 4 and 8 weeks.

Survey Tools

Three survey measures will be used. The first survey will be used to understand information recall; we will design a timed questionnaire, with *true* or *false* responses, for each medication in a patient's regimen that includes the 10 pieces of crucial medication information we embedded into the visualization interface. Each patient will be tested on different medications at 4 and 12 weeks to show understanding and knowledge. For example, if a patient takes simvastatin, metformin, and losartan, only those specific medication-related questions will be asked. The second survey will help us to understand the patient's perception of medication knowledge. We will use a validated survey instrument to assess patients' attitudes, confidence, and perceived medication knowledge [44]. This instrument was validated with high internal consistency (Cronbach α=.833). The third survey will use the 8-item Morisky Medication Adherence Scale (MMAS-8). The MMAS-8, whose scores range from 0 to 8 with lower scores indicating lower adherence, is a widely used tool for self-reported medication adherence; the scale was found to be reliable and significantly associated with adherence control (P<.05), with 93% sensitivity as well as 53% specificity for low adherence in a validation study [37].

Data Collection

We will collect demographics data at baseline. Data will be collected at 4 and 12 weeks. The 12-week time point will be considered the primary endpoint for the study. The AI platform on the smartphone app's back end will provide patient analytics on the usage of the mobile app (ie, intake of medications in the app diary and access frequencies).

Study Measures

The following study measures will be conducted:

1. Medication information comprehension from the first survey (primary outcome) [45]; the comprehension measure will be a composite of three subscales:
   a. Relevance to understanding patients' attitudes,
   b. Patients' levels of confidence and knowledge of medication use, measured using a Likert scale, and
   c. Information recall subscale, measured using a dichotomous scale (ie, true or false).
2. Survey on patients' perceptions of medication information.
3. Medication adherence (secondary outcome) will be operationalized by the following:
   a. MMAS-8 [46] survey score; the dichotomous response categories are yes or no for each item, and
   b. Analytics of the patients' daily intake of medications diary from the smartphone app.

Data Analysis

Demographic information will be presented using descriptive statistics. We will analyze the groups using *t* tests to detect differences between the means for continuous data. Chi-square analysis will be used to evaluate differences between arms for primary and secondary outcomes. We will use the univariate analysis of variance to calculate the mean differences between groups. If the distribution is not normal, we will use general linear modeling for the data analysis [47,48]. The AI-based analytics data from the smartphone will show us the patients' medication intake and we will correlate that score with our interventions.

Sample Size Justifications

To detect a 1-point improvement on the Likert scale and 80% power at the 5% significance level, the study would require 100 subjects in each group with 1:1 allocation for the second randomization (ie, AT: AV and ACT: AV). To allow for an 11% loss due to dropouts and those lost to follow-up, we would need to recruit 888 patients, allowing up to 50% of the patients to move to the second randomization following the first randomization with a score of 80% or higher in the medication recall questionnaire survey with assigned intervention. Recruitment of 888 patients is also sufficient to detect a 1-point improvement on the MMAS-8 (the secondary outcome), with 80% power at 5% significance. Therefore, our target is to recruit 900 patients.

Limitations

We expect to enroll a large number of patients for this sequential randomized design. We do not anticipate significant problems because our clinics are excellent sites for recruitment. The recruiting advantage is due to the academic affiliations with faculty and residents. However, given our large sample size requirements, to the extent that we cannot recruit around 888 patients, our study will lack rigor.

Results

We will conduct preliminary data collection for the studies in 2021. Results are expected to be published in 2022.

Discussion

Overview

This protocol addresses the problem of creating an AI-powered smartphone app to engage and predict user analytics. This unique idea builds upon an understanding of how users interact with complex medication task information and interactively visualize crucial medication information that frequently is ignored. Previous studies have also successfully shown that informatics platforms have the potential to empower patients [49]. While AI-based algorithms have been used in predicting health outcomes [20,50], very few studies have looked into the user's interaction analytics and ways to build better visualization techniques to engage the user [51-54]. This protocol focuses on creating uniform data standards that are crucial for efficient health information exchange [55]. This protocol provides future researchers and visualization designers with a new and innovative way to design and improve health care smartphone apps.

Conclusions

This study will lead the future of innovative AI-powered smartphone app design and act as the aid to improve medication risk comprehension, which may ultimately improve medication adherence. The results from this study also open up future research opportunities to understand how patients manage complex medication information and will inform the format and design for innovative AI-powered digital interfaces for Medication Guides.

Acknowledgments

We give our appreciation to the Western University of Health Sciences for helping and supporting the ideas in this proposal. Also, we acknowledge internal funding that supports this research from the Western University of Health Sciences, College of Pharmacy.

Conflicts of Interest

None declared.

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Abbreviations

A: app only
ACT: app with contextual medication information text
AI: artificial intelligence
ANN: artificial neural network

AT: app with medication information text
AV: app with visualization
FDA: US Food and Drug Administration
HIPPA: Health Insurance Portability and Accountability Act
MMAS-8: 8-item Morisky Medication Adherence Scale
PRP: psychological refractory period
RNN: recursive neural network
SOBC: Science of Behavior Change
TICS-M: modified Telephone Interview for Cognitive Status

Edited by G Eysenbach; submitted 20.06.20; peer-reviewed by R Holden, R Mickelson; comments to author 25.08.20; revised version received 08.10.20; accepted 13.10.20; published 09.11.20.

Please cite as:
Roosan D, Chok J, Karim M, Law AV, Baskys A, Hwang A, Roosan MR
Artificial Intelligence–Powered Smartphone App to Facilitate Medication Adherence: Protocol for a Human Factors Design Study
JMIR Res Protoc 2020;9(11):e21659
URL: http://www.researchprotocols.org/2020/11/e21659/
doi:10.2196/21659
PMID:33164898

Protocol

Improving the Management of Atrial Fibrillation in General Practice: Protocol for a Mixed Methods Study

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Abstract

Background: Atrial fibrillation (AF) is one of the commonest arrhythmias observed in general practice. The thromboembolic complications of AF include transient ischemic attack, stroke, and pulmonary embolism. Early recognition of AF can lead to early intervention with managing the risks of these complications.

Objective: The primary aim of this study is to investigate if patients are managed in general practice according to current national guidelines. In addition, the study will evaluate the impact of direct oral anticoagulant use with respect to AF complications in a real-world dataset. The secondary aims of the study are to develop a dashboard that will allow monitoring the management of AF in general practice and evaluate the usability of the dashboard.

Methods: The study was conducted in 2 phases. The initial phase was a quantitative analysis of routinely collected primary care data from the Oxford Royal College of General Practitioners Research and Surveillance Center (RCGP RSC) sentinel network database. AF cases from 2009 to 2019 were identified. The study investigated the impact of the use of anticoagulants on complications of AF over this time period. We used this dataset to examine how AF was managed in primary care during the last decade. The second phase involved development of an online dashboard for monitoring management of AF in general practice. We conducted a usability evaluation for the dashboard to identify usability issues and performed enhancements to improve usability.

Results: We received funding for both phases in January 2019 and received approval from the RCGP RSC research committee in March 2019. We completed data extraction for phase 1 in May 2019 and completed analysis in December 2019. We completed building the AF dashboard in May 2019. We started recruiting participants for phase 1 in May 2019 and concluded data collection in July 2019. We completed data analysis for phase 2 in October 2019. The results are expected to be published in the second half of 2020. As of October 2020, the publications reporting the results are under review.

Conclusions: Results of this study will provide an insight into the current trends in management of AF using real-world data from the Oxford RCGP RSC database. We anticipate that the outcomes of this study will be used to guide the development and implementation of an audit-based intervention tool to assist practitioners in identifying and managing AF in primary care.

International Registered Report Identifier (IRRID): RR1-10.2196/21259

(JMIR Res Protoc 2020;9(11):e21259) doi:10.2196/21259

KEYWORDS

atrial fibrillation; medical record systems, computerized; general practice; cross-sectional studies; qualitative research

Introduction

Atrial fibrillation (AF) is one of the commonest arrhythmias observed in clinical practice [1]. Globally, the incidence of AF is rising. The thromboembolic complications of AF can lead to significant disabling consequences for patients, including transient ischemic attack, stroke, and pulmonary embolism. Early recognition of AF in general practice can lead to early intervention with managing the risks of these complications.

Current guidelines on the management of AF by the National Institute for Health and Care Excellence (NICE) advise identifying and managing the underlying causes of AF, treating the arrhythmia, and assessing and managing the risk of stroke in these patients [2]. Risk of stroke is determined by the CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke/transient ischemic attack–VAScular disease) assessment tool [3], which guides the practitioner on commencing anticoagulation treatment to manage this risk. The risk of starting a patient on anticoagulation is assessed using the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly) score, assessing for major bleeding risks [4].

Anticoagulation therapy aims to reduce the risk of thromboembolic events. This has been achieved using warfarin (a vitamin K antagonist) for many years. The introduction of direct oral anticoagulants (DOACs) such as apixaban and rivaroxaban to clinical practice has changed how AF is managed in clinical practice [5]. In comparison to warfarin, DOACs are observed to have similar or better mortality and vascular outcomes [6]. They have the added benefit of requiring no monitoring, as opposed to warfarin use [7]. Though studies have highlighted that increased number of patients in clinical practice are receiving treatment for AF [8], whether they are managed according to national or local guidelines is unclear. Better understanding of current management trends of AF in population will guide practitioners on how best to employ interventions in clinical practice to increase awareness of AF and early recognition.

The aim of this study is to understand the disease and prescribing trends related to AF in general practice. We also aim to develop a system to monitor practice-level indicators for AF of the same trends and evaluate the usability of this system. The primary objective of this study is to investigate if people with newly diagnosed AF treated with DOACs versus warfarin have any difference in stroke or all-cause mortality in long-term follow-up. The secondary objectives of this study are to develop an AF dashboard as an intervention method at a practice level and to evaluate the usability of the AF dashboard.

Methods

Study Design

This study combines qualitative and quantitative methods and therefore, was planned as a mixed method study [9-11]. It was run within the Oxford Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) sentinel network of general practices. The mixed method study was conducted in 2 phases. Phase 1 was a quantitative analysis of AF data. We conducted a repeated cross-sectional study to identify those patients diagnosed with AF during 2009-2019 and identified current therapeutic management of their AF. Phase 2 involved development and evaluation of a dashboard for monitoring data quality for AF. The dashboard provides the general practices in the RCGP RSC sentinel network an access to quality indicators related to AF management that are updated weekly.

Phase 1: Quantitative Analysis of AF Data

Data Source

The initial phase involved a repeated cross-sectional retrospective analysis of data extracted from the RCGP RSC database, a surveillance network, which collects data from computerized medical records (CMR) from more than 3.5 million patients and over 300 general practices in England. CMRs are used during consultations to record patient conditions and prescriptions [12,13]. Anonymized clinical coded data from participating general practices were uploaded weekly to a secure network at the Clinical Informatics Research Group [12,14]. This study used NICE guidelines as the standard to compare the management of AF across this database.

Case Ascertainment

We used Read codes and CTV3 codes used in primary care CMR systems to identify patients with AF. Pay-for-performance (P4P) for chronic disease management has improved data quality related to AF in the recent past [15]. We excluded patients who had a previous stroke and those not on British National Formulary–recommended dose of DOAC. We included patients over 18 years with code for the diagnosis of AF who had been registered at any point between 2008 and 2019.

Exposures and Outcomes

We considered the exposure as continuous anticoagulant prescription for the first time after receiving an AF diagnosis. Although almost all anticoagulant prescriptions in the United Kingdom are issued from primary care if an anticoagulant is started in a hospital, we measured exposure from the first general practice prescription. We excluded patients who had an interval of greater than 90 days between anticoagulant prescriptions.

Outcomes are first records of stroke and all-cause mortality based on previously published Read codes [16,17] Stroke was included regardless of etiology, an approach used in other studies [18,19]. Study participants were followed for stroke and all-cause mortality till the end of the study period.

Covariates

We included variables likely to be used as indicators in prescribing anticoagulants: age-band, gender, and deprivation reporting Index of Multiple Deprivation (IMD) quintile. IMD is a national measure of socioeconomic status, which can be derived at an individual level from first part of postcode. We adjusted for comorbidities from that part of the stroke risk score (CHA_2DS_2-VASc), namely, heart failure, hypertension, stroke or transient ischemic attack, and myocardial infarction or

peripheral vascular disease at baseline. We also included smoking status as a covariate.

Statistical Analysis

Analysis of data extracted from general practice CMR was carried out using the statistical software R. We studied the influence of the anticoagulation regimen by evaluating the cause-specific hazard ratio and the subdistribution hazard ratios of both events. Additionally, we estimated cumulative incidence for both events by direct regression, utilizing the inverse of the probability of censoring weights method [15] with time-varying effects [20]. We will report and interpret both cause-specific and subdistribution analyses. The cause-specific hazard ratio is often interpreted as estimating etiological association, estimating associations between covariates, and the rate at which events occur in those participants who are event-free. The cause - specific hazard ratio can be interpreted as a rate ratio. Whenever the proportional hazards assumption was violated, we interpreted all hazard ratios as time-averaged effects.

We will determine the (adjusted) incidence and prevalence of AF for each year along with the proportion of incident and prevalent cases treated with nothing, antiplatelet medications only (eg, aspirin), and anticoagulant therapy (warfarin/types of DOACs). We will also determine the number of strokes, transient ischemic attacks, deaths, and bleeds in the incident and prevalent cases per year.

Phase 2: Development of a Dashboard for Monitoring AF

We developed an online dashboard for the general practices to understand the quality of their data across a variety of AF-related indicators. The AF dashboard provided 4 categories of information: (1) case ascertainment—incidence, prevalence, standardized prevalence, and any indicators related to P4P prevalence; (2) indications for therapy and risk factors; (3) management choices; and (4) quality. The dashboard was developed using Tableau data visualization software (Salesforce Inc). The initial dashboard is hosted on the public dashboard cloud server and accesses a publicly accessible database server (located within information technology infrastructure of the University of Oxford), which hosts only aggregated data to comply with the requirements of information governance. The dashboard allowed users to view the AF indicators only from their own practice.

We used the Think Aloud method to validate the usability of the AF dashboard. During usability experiment, study participants were instructed to verbalize their thoughts while concurrently conducting predefined tasks on the dashboard [21]. The design of the Think Aloud experiment involved participants engaging in 5 tasks. Participants were asked to verbalize their thought process while engaging in each of the tasks [22]. During the initial 4 tasks, the participants interacted with the 4 main sections of the dashboard. They observed the given information and interpreted it with respect to that particular aspect of AF management in their practice. As a fifth task, participants considered the overall dashboard and described the overall state of AF management in their practice in comparison to the RCGP RSC sentinel network.

Participants

We invited staff from general practices to cover a range of roles from primary care, including general practitioners, nurses, and practice managers. We provided remote participation for those who could not attend in person. We aimed to invite staff from practices participating in the RCGP RSC sentinel network. Our target sample size was about 30 participants based on the guidelines from previous studies [23].

Data Capture and Analysis

We recorded participant feedback and screen activity using GoToMeeting screen sharing software, version 10.5 (LogMeIn Inc). The audio component of the recordings was exported and transcribed by a professional transcription service. The transcripts were analyzed using NVivo, version 12 (QSR International), a qualitative analysis software. We followed a 3-step approach to analyze the transcripts.

1. *Mapping verbalized tasks to sections:* Each verbalized task description was extracted and mapped to the corresponding section of the dashboard. A "verbalized task" is the narrative description provided by a participant when interacting with particular component in the dashboard. We organized the verbalized tasks according to the template given in (Table S1 in Multimedia Appendix 1). The verbalized tasks were mapped to the dashboard sections, and similar feedbacks were grouped.
2. *Mapping verbalized tasks to usability problem classes:* For each section, we mapped the verbalized tasks to matching usability problem classes. We adapted the usability problem classification method used by Peute et al [21] and identified occurrences for each usability problem class (Table S2 in Multimedia Appendix 1). We also classified the identified verbalized tasks based on whether they were positive feedback, negative feedback, or suggestions for new features.
3. *Summarizing usability issues across sections/usability problem class:* The completed templates were analyzed to determine the critical sections and key usability problem classes that required attention.

Ethical Considerations

For phase 1, approval was granted by the research committee of the RCGP RSC. The study did not meet the requirements for a formal ethics board review as per the NHS Health Research Authority's research decision tool [24]. The study was conducted in line with the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines [25]. For phase 2, personal data were not collected from the study participants. Participants were informed that their verbal responses and screen activities would be recorded. All participants received oral and written information about the study.

Dissemination

The protocol and data produced from this work will be submitted for publication in a peer-reviewed journal covering the domains of cardiology, epidemiology, and primary care. Additional opportunities include presentation at seminars, conferences, and meetings.

Results

We received funding for both phases in January 2019 and received approval from RCGP RSC research committee in March 2019. We completed data extraction for phase 1 in May 2019 and completed analysis in December 2019. We completed building the AF dashboard in May 2019. We started recruiting participants for phase 1 in May 2019 and concluded data collection in July 2019. We completed data analysis for phase 2 to in October 2019. As of October 2020, the publications reporting the results are under review.

Discussion

The RCGP RSC sentinel network has a large dataset, which is representative of information regarding primary care practices on management of AF. The quantitative analysis will report on the current trends of anticoagulant prescribing using a real-world data set in the United Kingdom and the overall population effect of the use of DOAC use.

Missing/incomplete data could be a potential issue in this analysis. We intend to reduce the effect of this issue by incorporating an ontological approach, considering practice level variations in the anticoagulation prescribing.

The qualitative analysis of the dashboard will indicate the priority of sections that require an improved user experience. We intend to enhance the dashboard using the outcomes of the usability study and deploy to general practices in the RCGP RSC sentinel network.

As the incidence of AF has increased over the years, there is a greater focus on early recognition of AF in general practice to allow for early intervention. This study will give insights into the current trends in management of AF using real-world data from the Oxford RCGP RSC database. We anticipate that the outcomes of this study will be used to guide the development and implementation of an audit-based intervention tool for use in primary care settings to assist practitioners in identifying and managing AF.

Acknowledgments

The work was supported by Daiichi Sankyo. The funder did not have any involvement in study design, access to data, or influence in this analysis.

Conflicts of Interest

FDRH has received occasional fees from Bayer and Boehringer Ingelheim for speaking or consulting on atrial fibrillation–related stroke risk.

Multimedia Appendix 1
Supplementary file with Table 1 and Table 2 described in the study design of phase 2.
[DOCX File , 15 KB - resprot_v9i11e21259_app1.docx]

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Abbreviations

AF: atrial fibrillation
CHA2DS2-VASc: Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke/transient ischemic attack–VAScular disease
CMR: computerized medical records
DOAC: direct oral anticoagulant
HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly
IMD: Index of Multiple Deprivation
NICE: National Institute for Health and Care Excellence
P4P: pay-for-performance
RCGP RSC: Royal College of General Practitioners Research and Surveillance Center
RECORD: REporting of studies Conducted using Observational Routinely-collected Data

Edited by G Eysenbach; submitted 10.06.20; peer-reviewed by F Palmieri, N Pahlavani; comments to author 19.06.20; revised version received 18.08.20; accepted 25.08.20; published 09.11.20.

Please cite as:
de Lusignan S, Hobbs FDR, Liyanage H, Ferreira F, Tripathy M, Munro N, Feher M, Joy M
Improving the Management of Atrial Fibrillation in General Practice: Protocol for a Mixed Methods Study
JMIR Res Protoc 2020;9(11):e21259
URL: https://www.researchprotocols.org/2020/11/e21259
doi:10.2196/21259
PMID:33164903

Protocol

Implementation and Evaluation of a Text Message–Based Addiction Counseling Program (Text4Hope-Addiction Support): Protocol for a Questionnaire Study

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Abstract

Background: With the emergence of the COVID-19 pandemic, providing counseling to people with drug or alcohol addiction while maintaining physical distance has been challenging. This protocol describes the use of text messaging (as used in the Text4Hope-Addiction Support program) as a convenient, evidence-based, cost-effective, and accessible population-level mental health intervention with high user satisfaction proven in prior research.

Objective: The project goal is to implement a program of daily supportive text messaging (Text4Hope-Addiction Support) to reduce drug or alcohol cravings as well as anxiety and depression, typically associated with alcohol and substance use disorders. The aim of this study is to evaluate the prevalence of cravings, anxiety, and depressive symptoms; demographic correlates of the same; and the outcomes of the Text4Hope-Addiction Support intervention in mitigating cravings, anxiety, and depressive symptoms.

Methods: Self-administered, anonymous, online questionnaires will be used to assess cravings for the primary substance of addiction (Brief Substance Craving Scale), anxiety (Generalized Anxiety Disorder-7), and depressive symptoms (Patient Health Questionnaire-9). Data will be collected at baseline (onset of receiving text messages), program midpoint (6 weeks), and program end (12 weeks).

Results: As of October 2020, data collection is in progress; and it is expected to be completed by fall 2021. Data analysis will include parametric and nonparametric techniques, focusing on primary outcomes (ie, cravings, anxiety, and depressive symptoms) and metrics of use, including the number of subscribers and user satisfaction.

Conclusions: This Text4Hope-Addiction Support project will provide key information regarding the prevalence rates of cravings, anxiety, and depressive symptoms among persons with alcohol and substance use disorders; demographic correlates of cravings, anxiety, and depression; and outcome data related to this scalable population-level intervention. Information from this study will be valuable for addiction care practitioners; it will inform the policy and decision making regarding population-level addiction treatment and support during emergencies.

International Registered Report Identifier (IRRID): DERR1-10.2196/22047

(JMIR Res Protoc 2020;9(11):e22047) doi:10.2196/22047

KEYWORDS

addiction; support drugs; alcohol; Text4Hope; mobile phones; text messaging; anxiety; depression; mHealth; COVID-19

Introduction

Background

Substance addiction can cause significant impairment in a person's physical, social, and psycho-occupational level of functioning. The lifetime prevalence of substance use was estimated to be 9.9% [1]. Substance abuse and mental illness have globally affected nearly 1 billion people in 2016 [2]; and unfortunately, only 1 in 6 people receives the necessary help toward addressing substance abuse [3]. Alcohol can create a higher level of disability; and sadly, only 24.1% of those with alcohol use disorder ever receive treatment [4]. Not surprisingly, the total number of worldwide deaths due to alcohol misuse alone is higher than the combined number of deaths from tuberculosis, HIV/AIDS, and diabetes [3]. In Canada, substance abuse accounts for about 21% of all deaths and 23% of potential years lost [5].

A systematic review of the 2010 Global Burden of Disease study reported that mental disorders and substance use disorders were 2 leading causes of years lived with disability [6]. The economic cost of substance abuse in Canada was estimated at Can $40 billion (US $30.4 billion) in 2002, with a per capita cost of Can $1267 (US $964) [7].

Substance abuse is common and frequently co-occurs with mood and anxiety disorders. A systematic review and meta-analysis [8] showed a very strong association of alcohol abuse with major depressive disorder (MDD) (OR 2.42, 95% CI 2.22-2.64) and with any anxiety disorder (OR 2.11, 95% CI 2.03-2.19). Similarly, the associations of abuse of illicit substances with MDD and any anxiety disorder were OR 3.8 (95% CI 3.02-4.78) and OR 2.91 (95% CI 2.58-3.28), respectively [8]. The strength of these associations may suggest that the levels of anxiety and depression are potential biomarkers in people with substance use disorder [9,10].

The relationship between substance abuse and mental illness has been argued to account for a significant number of emergency department (ED) visits (mean 5.2), when compared to substance use disorder alone (mean 2.5) [11]. Similarly, substance abuse and comorbid mood disorder, especially MDD, are associated with a high risk of suicide [12,13] and increased health care service utilization [14], which may partly explain the high number of ED visits.

Adequate support for persons with addiction is likely to reduce their ED presentation and can potentially optimize the acute bed utilization needed to support the COVID-19 bed surge and beyond.

There are multifactorial risk factors that can lead to the development of substance abuse. This can include genetic, social, and psychological factors. Familial studies have reported an increased risk of addiction in persons with a genetic predisposition [15,16], but this increased vulnerability is subject to the interplay between gene and environment. Sociodemographic factors such as peer pressure, unemployment, and geographical location can influence the onset and outcome of substance abuse [17]. Psychological factors predicting a person's vulnerability to substance abuse include a history of trauma, high psychopathology of anxiety, and depression [18,19].

It is important to understand how natural disasters, such as the COVID-19 pandemic, influence the onset of substance abuse and mental illness. This study will examine the association between COVID-19, addiction, anxiety, and depression. A recent study reported that about 53.8% of the sampled population reported a moderate-to-severe level of anxiety during the COVID-19 pandemic [20].

During the COVID-19 pandemic, centers that adopted strategic services to meet the demand of bed surge capacity for COVID-19 cases have seen a reduction in the rate of psychiatric admissions and a decrease in mental health–related ED visits [21]. However, this is likely to precipitate relapse and possibly increases the risk of self-medication with alcohol or other illicit drugs.

There are different approaches to the treatment of substance abuse. Unfortunately, the treatment of comorbid substance abuse and mood disorder remains a challenge for clinicians. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid substance use disorders reported that there was no significant level 1 evidence on treatment of comorbid mood disorder and substance abuse [22]. A meta-analysis compared the outcomes of contingency management (CM), cognitive behavioral therapy (CBT), and relapse prevention for substance use disorder with about 50.7 % of persons meeting the criteria for alcohol dependence. The result reported a better short-term benefit in the intervention group than in 67% of participants in the control group. This is statistically significant, as the aggregate effect size of active treatment was high (d=1.02). The result also showed a disappointing long-term outcome with high dropout rates in CBT (35.3%) and CM (29.4%). The relapse rate showed only 31% abstinence in the treatment group and 13% abstinence in the control group [23]. Another network meta-analysis reported that the combination of CM and community reinforcement was acceptable and effective in patients with a better short- and long-term abstinence, especially in persons with stimulant use disorder [24]. The result showed that the combination of CM plus CBT and CM alone were superior to the treatment-as-usual approach (standardized mean difference [SMD] 0.75, 95% CI 0.31-1.19 and SMD 0.62, 95% CI 0.43-0.80, respectively). Similarly, the combination of CM plus CBT and CM alone had the longest duration of abstinence compared to the treatment-as-usual approach (SMD 0.74, 95% CI 0.43-1.06 and SMD 0.60, 95% CI 0.43-0.76, respectively).

A systematic review of data between 1999-2015 suggested the evolution of text messages as a useful tool in the management of mental illness and addiction [25]. Recent studies have shown the benefits of using an electronic medium, such as the internet

or recorded video, for psychoeducation and prevention of substance abuse [26]. However, persons with substance abuse disorder tend to have low motivation, which can limit the use of video or web-based interventions [27,28]. Mobile phones are increasingly becoming standard tools of communication across all age groups. A survey of 389 people with addiction showed that about 83% of the survey participants owned cellphones [29], and the results of a recent randomized controlled trial showed promising benefits of using supportive text messages in the treatment of MDD with comorbid alcohol abuse. However, the study was limited by its small sample size [30]. Other studies on supportive text messages reported improvement in both abstinence and mental health in about 75%-83% of patients with MDD and comorbid alcohol abuse [31]. Our study was designed to use CBT-based supportive text messages for the treatment of substance use disorder. This daily text messaging program was designed and launched as an addiction counseling modality to complement virtual counseling services during the COVID-19 pandemic to reduce cravings, promote recovery, and observe social distancing.

Objectives

This protocol describes the implementation of the Text4Hope-Addiction Support program in Canada, a low-cost, evidence-based, supportive text messaging service. The objective of the project is to implement a self-subscribing daily supportive text message program to close the addiction counseling gap and reduce cravings, anxiety, and depression-related drug and alcohol addiction among Canadians during the COVID-19 pandemic. The research questions of this study are as follows:

1. What are the prevalence rates of cravings, anxiety, and depressive symptoms in Canada during the COVID-19 pandemic?
2. What are the demographic correlates of cravings, anxiety, and depressive symptoms?
3. Will the Text4Hope-Addiction Support program help to reduce cravings, anxiety, and depressive symptoms among Canadians experiencing psychological distress during the COVID-19 pandemic?

Methods

Recruitment, Evaluation Methodology, and Measurement Plan

In the Text4Hope-Addiction Support program, people self-subscribe to receive daily supportive text messages for 6 months by texting the word “Open2Change” to 393939. The program has been the subject of wide publicity, including social media campaigns run by the local provincial mental health foundation and Alberta Health Services, the single provincial government health care provider. Recruitment posters are also used to advertise the program in addiction treatment facilities across Alberta.

The messages built into the program are aligned with an addiction counseling framework, with content written by a clinical psychologist and psychiatrist. This content was then reviewed and revised by a multidisciplinary team consisting of addiction counselors, psychiatrists, and mental health therapists. Some examples of the messages are as follows:

1. In early recovery, your feelings may be more noticeable without masking by substance use. Use more self-care strategies and social support to get you through.
2. Challenge your thoughts about urges. Urges are uncomfortable, but are not unbearable. Urges are distracting, but will not drive you crazy.
3. Addiction is often cue-based. Identify people, places, and things that trigger the desire to use.

The messages are preprogrammed into an online software that delivers messages daily at 8 AM. At the onset of the first message, respondents are welcomed to the service and are invited to complete an online baseline survey capturing demographic information (age, gender, employment status, relationship status, ethnicity, and educational level); COVID-19–related self-isolation/quarantine information; and responses on the Brief Substance Craving Scale (BSCS) [32], Generalized Anxiety Disorder-7 (GAD-7) scale [23], and the Patient Health Questionnaire-9 (PHQ-9) [25]. Survey questions are programmed into REDCap, an online survey tool operated by the University of Alberta. No incentives are offered to respondents. Participation in the program is entirely voluntary. Noncompletion of the survey does not impact the delivery of supportive text messages; this is clearly stated to subscribers in the text messaging program information provided at subscription. Subscribers can opt out of the program at any time by texting “Open2Change” to 393939. Participant consent is indicated via submission of subscribers’ survey responses. Survey responses will be stored within the University of Alberta REDCap account, and data will be exported and analyzed by the Text4Hope research team. Ethics approval has been granted by the University of Alberta Health Research Ethics Board (Pro00086163).

Sample Size Considerations

The Canadian Community Health Survey 2018 [33] reports that 20% of Canadians experience an alcohol or substance use disorder. Alberta’s population is approximately 4.4 million; and we project that 2.5% of those with alcohol and substance abuse disorders would actively seek help for their addition during the COVID-19 pandemic. Accordingly, we expect about 22,000 Canadians to subscribe to the Text4Hope-Addiction Support program within 12 months of its launch. Based on the response rate of 21.7% for our prior Text4Mood survey [34], we anticipate around 4400 responses to the Text4Hope-Addiction Support surveys in 1 year.

Outcome Measures

Primary outcomes are changed scores at 6 and 12 weeks from baseline on the BSCS, GAD-7, and PHQ-9 scales. Secondary outcomes are (1) interactions between demographic characteristics of subscribers and primary outcomes and (2) subscriber satisfaction/experience.

Proposed Timeline and Milestones

The first stage of the study involved the creation and review of supportive text messages, targeting cravings, anxiety, and

depression and programming of those messages into the software. This stage was completed on April 20, 2020. The second stage involved the launch of the Text4Hope-Addiction Support program, which occurred on May 22, 2020. The remainder of the project will be focused on data collection, analysis, and reporting.

Hypotheses

This study will test the following hypotheses:

1. High rates of craving, anxiety, and depression will be reported at baseline, affecting more than half of the sample population.
2. Specific risk demographics and COVID-19–related factors related to the experience of cravings, anxiety, and depression during the pandemic will be identified.
3. The intervention will result in a 25% or greater reduction in cravings, anxiety, and depressive symptoms (as measured by the BSCS, GAD-7, and PHQ-9 scales) at 6 and 12 weeks from baseline. This hypothesis is based on the results of a randomized controlled trial of daily supportive text messaging, which showed that there was close to 25% additional improvement in the Beck Depression Inventory scale–measured mood in the intervention group compared to the control group [30].
4. At least 80% of subscribers will express satisfaction with the Text4Hope-Addiction Support program and perceive the daily supportive text messages as contributing to their overall mental well-being.

Results

We expect the data collection to be completed by October 2021 and study results to be available in spring 2022. We would implement and evaluate the Text4Hope-Addiction Support program with the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) Framework [26] and the Alberta Quality Matrix for Health [27]. We would include the following dimensions in the evaluation: acceptability (subscriber satisfaction/experience); accessibility (ease of subscription to and utilization of the Text4Hope-Addiction Support program); appropriateness (numbers of persons with drug and alcohol problems subscribing to the program); and effectiveness (6- and 12-week changes in the BSCS, GAD-7, and PHQ-9 scales). It may also be possible to examine efficiency (cost avoidance and efficiencies through reduced need for face-to-face counseling) and safety (self-reports of decreased crisis and urgent service calls and decreased emergency medical services utilization rates).

We will evaluate the efficacy of Text4Hope-Addiction Support with the reductions of cravings, anxiety, and depression at 6 weeks and 12 weeks. Data analysis will include standard use of parametric and nonparametric techniques (eg, within-subject general linear models), including multiple comparison type 1 error corrections. A power analysis with effect sizes from previous studies by Agyapong and colleagues [30,31,34] indicates sufficient effect size for expected Text4Hope-Addiction Support program subscribers' sample size.

Discussion

The impacts of COVID-19 on health, lifestyle, psychological safety, and well-being are difficult to overstate. The psychological impact is likely to be more significant for those with mental health conditions and substance use disorders. Mental health support for groups vulnerable to mental health risks during infectious outbreaks requires innovative techniques that can serve the high number of people requiring support while respecting the need to maintain physical distance.

This protocol describes the use of mobile health (mHealth) technology as a convenient, cost-effective, and accessible means for implementing a psychological intervention for people with substance use disorders during the pandemic. This program is empirically supported in previous research, which show good outcomes as well as high user satisfaction.

This study will evaluate outcomes according to the standardized and empirically validated questionnaires. It will provide key information regarding the prevalence rates of substance use cravings, anxiety, and depression during the COVID-19 pandemic; demographic correlates; and outcome data (cravings, anxiety, and depression). Information from this study will thus be critical for practitioners as well as useful for informing policy and decision making regarding psychological interventions during the COVID-19 pandemic, especially for persons with mental health and substance use disorders. We hope that the outcome of this study will inform the integration of supportive text messaging into treatment programs readily available to persons with substance use disorders.

Acknowledgments

Support for the project was received from Alberta Health Services and the University of Alberta. This study was supported by grants from the Mental Health Foundation, Calgary Health Trust, University Hospital Foundation, Alberta Children's Hospital Foundation, Royal Alexandra Hospital Foundation, and Alberta Cancer Foundation. The funding bodies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the results for publication.

Authors' Contributions

VIOA conceived and designed the study, including the Text4Hope- Addiction Support program. MH created the bank of supportive text messages. RS contributed to create the Text4Hope-Addiction Support program. VIOA and AAA drafted the initial manuscript.

All authors critically reviewed the manuscript and contributed to the final draft of the manuscript. All authors reviewed and approved the final draft of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BSCS: Brief Substance Craving Scale
CANMAT: Canadian Network for Mood and Anxiety Treatments
CBT: cognitive behavioral therapy
CM: contingency management
ED: emergency department
GAD-7: Generalized Anxiety Disorder-7
MDD: major depressive disorder
mHealth: mobile health
PHQ-9: Patient Health Questionnaire-9
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
SMD: standardized mean difference

Edited by G Eysenbach; submitted 02.07.20; peer-reviewed by L Gomez-Pathak, E Kleiman; comments to author 15.08.20; revised version received 12.09.20; accepted 24.09.20; published 17.11.20.

Please cite as:
Agyapong VIO, Hrabok M, Vuong W, Gusnowski A, Shalaby R, Surood S, Greenshaw AJ, Aulakh A, Abba-Aji A, Singh M
Implementation and Evaluation of a Text Message–Based Addiction Counseling Program (Text4Hope-Addiction Support): Protocol for a Questionnaire Study
JMIR Res Protoc 2020;9(11):e22047
URL: http://www.researchprotocols.org/2020/11/e22047/
doi:10.2196/22047
PMID:33200993

Protocol

Quality Assessment of an Integrated Care Pathway Using Telemonitoring in Patients with Chronic Heart Failure and Chronic Obstructive Pulmonary Disease: Protocol for a Quasi-Experimental Study

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Abstract

Background: Chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) often coexist and are associated with a high morbidity and reduced quality of life (QoL). Although these diseases share similarities in symptoms and clinical course, and exacerbations of both diseases often overlap, care pathways for both conditions are usually not integrated. This results in frequent outpatient consultations and suboptimal treatment during exacerbations, leading to frequent hospital admissions. Therefore, we propose an integrated care pathway for both diseases, using telemonitoring to detect deterioration at an early stage and a single case manager for both diseases.

Objective: This study aims to investigate whether an integrated care pathway using telemonitoring in patients with combined CHF and COPD results in a higher general health-related QoL (HRQoL) as compared with the traditional care pathways. Secondary end points include disease-specific HRQoL, level of self-management, patient satisfaction, compliance to the program, and cost-effectiveness.

Methods: This is a monocenter, prospective study using a quasi-experimental interrupted time series design. Thirty patients with combined CHF and COPD are included. The study period of 2.5 years per patient is divided into a preintervention phase (6 months) and a postintervention phase (2 years) in which end points are assessed. The intervention consists of an on-demand treatment strategy based on monitoring symptoms related to CHF/COPD and vital parameters (weight, blood pressure, heart rate, oxygen saturation, temperature), which are uploaded on a digital platform. The monitoring frequency and the limit values of the measurements to detect abnormalities are determined individually. Monitoring is performed by a case manager, who has the opportunity for a daily multidisciplinary meeting with both the cardiologist and the pulmonologist. Routine appointments at the outpatient clinic are cancelled and replaced by telemonitoring-guided treatment.

Results: Following ethical approval of the study protocol, the first patient was included in May 2018. Inclusion is expected to be complete in May 2021.

Conclusions: This study is the first to evaluate the effects of a novel integrated care pathway using telemonitoring for patients with combined CHF and COPD. Unique to this study is the concept of remote on-demand disease management by a single case manager for both diseases, combined with multidisciplinary meetings. Moreover, modern telemonitoring technology is used instead of, rather than as an addition to, regular care.

Trial Registration: Netherlands Trial Register NL6741; https://www.trialregister.nl/trial/6741
International Registered Report Identifier (IRRID): DERR1-10.2196/20571

(JMIR Res Protoc 2020;9(11):e20571) doi:10.2196/20571

KEYWORDS

chronic heart failure; chronic obstructive pulmonary disease; integrated care pathway; telemonitoring

Introduction

Background

Chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) often coexist because they share similar risk factors, of which smoking and low-grade systemic inflammation are the most significant [1]. The prevalence of CHF in patients with COPD is approximately 20%, while the reported prevalence of COPD in patients with CHF ranges from 10% up to 50%, depending on the population studied and diagnostic criteria used to define COPD and CHF [1,2]. Both diseases share a chronic, progressive character and are associated with a poor quality of life (QoL) [3,4]. Health-related QoL (HRQoL) is negatively affected by the presence of comorbidities as well as frequent hospital admissions [3,5,6]. In fact, data from the Alliance for Home Health Quality and Innovation show a 60-day hospital readmission rate of 33% for elderly patients with combined CHF and COPD [7]. Obviously, this not only affects patient-related outcomes but it also causes a major economic burden. In addition to the overlap in pathophysiology, symptoms, and clinical course, CHF and COPD both require complex medication regimens associated with interactions between CHF and COPD medications. Concerning nonpharmacological treatment, both diseases require strict adherence to therapy and lifestyle recommendations. However, despite these similarities, in current daily practice, patients with CHF and COPD are treated in separate care pathways according to the CHF and COPD guidelines. Although these guidelines acknowledge the fact that diagnostic and therapeutic strategies should be integrated, no specific recommendations on integrated management are provided [8,9]. Recent studies show that there is a clear need for a more holistic approach for patients with chronic conditions [10,11]. In a survey among health care professionals, the following shortcomings in current COPD care pathways were identified: a lack of communication among health care providers, poor patient engagement, and a lack of a unified system targeting COPD and CHF [12]. Qualitative interviews in patients with CHF revealed that they experience a lack of cooperation among health care professionals in multiple health care sectors and insufficient patient education and counselling [13]. A qualitative study in patients with COPD showed that they struggle with the same problems as patients with CHF and that they opt for the introduction of a care coordinator and request self-monitoring and telehealth solutions [14].

Telehealth might provide a solution to these shortcomings. However, in 2017, only 40% of Dutch hospitals offered eHealth solutions to patients with CHF [15]. For patients with COPD, this is less well implemented. Worldwide, these percentages are even lower. The third global survey on eHealth, published in 2016 by the World Health Organization [16], showed that only 22% of the responding countries used an established remote patient monitoring solution. Telemonitoring studies on CHF as well as COPD show mixed results due to differences in telemonitoring interventions, study populations, and study end points [17,18]. Factors that might improve the effects of telemonitoring include personalization of telemonitoring regimes according to the patients' needs, monitoring of comorbidities, and utilization of integrated care pathways rather than the application of telemonitoring as an add-on to regular care.

Given the overlap between CHF and COPD, the high costs of separate care pathways, and the call for a more holistic approach by patients and health care professionals, we propose a combined telemonitoring approach in an integrated care pathway. Unique to this approach is combined, on-demand disease management using modern technology (eg, face-to-face contact via videoconferencing) and delivering personalized care by one case manager for both diseases. Moreover, telemonitoring will be used instead of, rather than as an add-on to, regular care. In this way, telemonitoring is tailored to the patient's demands, while covering more than one chronic disease.

Objectives

The primary goal of this study is to investigate whether an integrated pathway using telemonitoring in patients with combined CHF and COPD results in a higher general HRQoL compared with traditional care pathways. Secondary end points include (1) disease-specific HRQoL, (2) level of self-management, (3) patient satisfaction, (4) compliance to the program, and (5) cost-effectiveness.

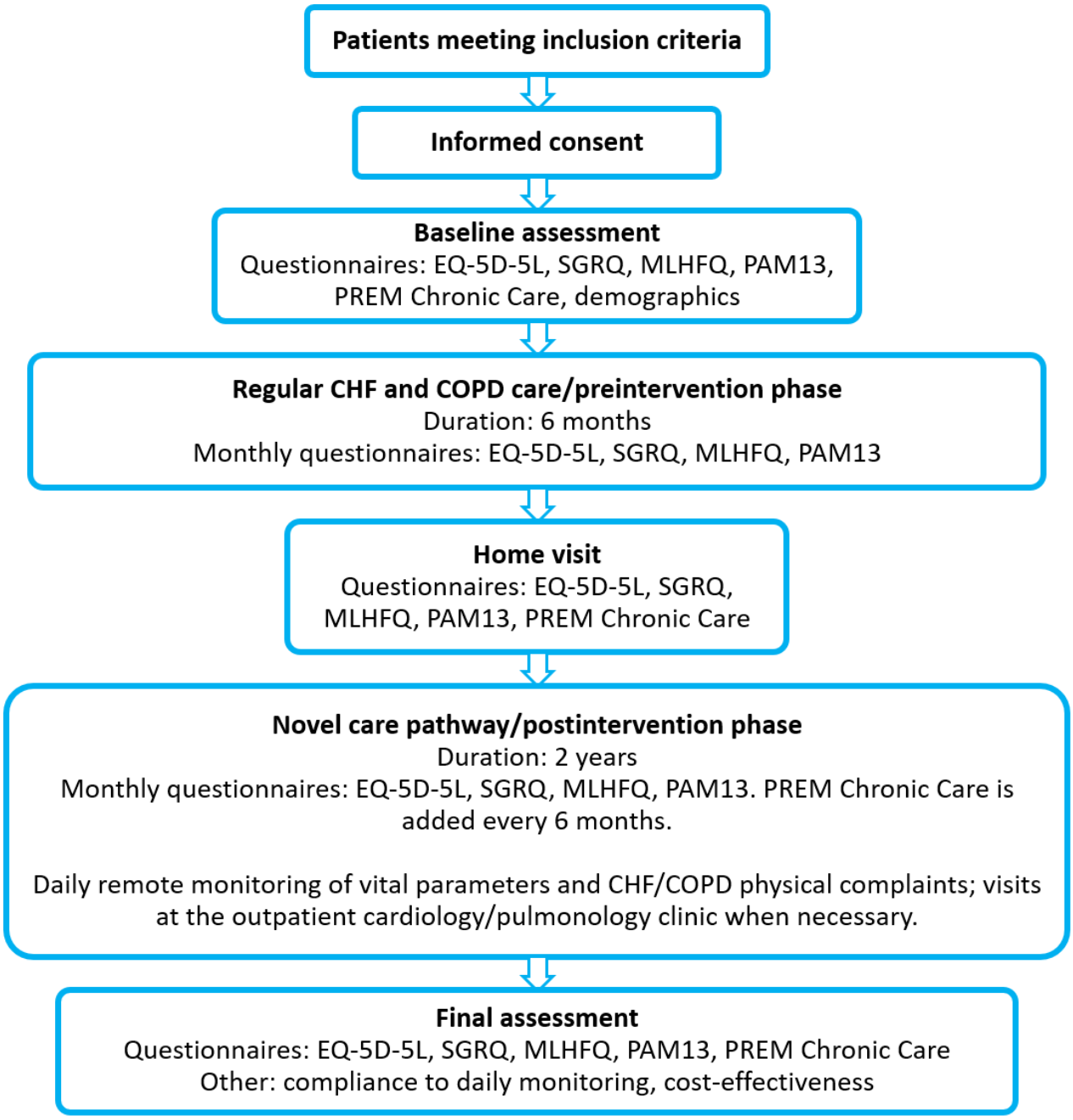
Methods

Study Design

This study was designed as a monocenter, prospective trial using a quasi-experimental interrupted time series design with a study period of 2.5 years. The study period starts with 6 months of regular care, after which the novel care pathway (see "Intervention") will be introduced. End points are assessed monthly during these 2.5 years, resulting in 6 data points before introduction of the intervention and 24 data points after the start of the intervention. An interrupted time series design is the strongest quasi-experimental design to evaluate the longitudinal effects of interventions [19] and is more often used to evaluate the effects of interventions in the health care setting [20,21]. To achieve a balance between an acceptable wait time for the patient to start the intervention and to obtain sufficient preintervention data, a preintervention period of 6 months (6 data points) was chosen pragmatically.

An overview of the participants' timeline and measurements is provided in Figure 1. The study will be performed in cooperation with the departments of cardiology and pulmonology at Máxima Medical Center in Eindhoven/Veldhoven, Netherlands.

Figure 1. Flowchart of the study design. CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; MLHFQ: Minnesota Living with Heart Failure Questionnaire; PAM13: 13-item Patient Activation Measure; PREM: Patient-Reported Experience Measure; SGRQ: St George's Respiratory Questionnaire.



Eligibility Criteria

Eligible patients will be recruited by their cardiologist, pulmonologist, or CHF/COPD nurse, either at the outpatient clinic or at the cardiology/pulmonology ward. Patients (aged 16 years or older) who meet the diagnostic criteria for both CHF and COPD, regardless of etiology and severity (defined by the New York Heart Association [NYHA] class and the Global Initiative for Chronic Obstructive Lung Disease [GOLD] group, respectively), are considered for participation. CHF is defined as having symptoms that may be accompanied by signs that are caused by a structural and/or functional cardiac abnormality [8]. Patients will be included regardless of left ventricular ejection fraction (ie, diagnosed with heart failure with reduced ejection fraction [HFrEF], heart failure with preserved ejection fraction [HFpEF], or heart failure with mid-range ejection fraction [HFmrEF]).

COPD is defined as having symptoms and signs with matching spirometric findings [9]. Eligible patients should be treated for both CHF and COPD at Máxima Medical Center in Eindhoven/Veldhoven, Netherlands. Moreover, they must have been admitted to the hospital at least once during the previous year because of an exacerbation of CHF and/or COPD. Patients

are required to have a personal computer, laptop, or tablet with an internet connection. Additionally, sufficient digital skills are needed. For patients without sufficient digital skills, informal caregivers could be involved to assist the patients. A complete list of inclusion and exclusion criteria can be found in Textbox 1. All subjects are requested to provide written informed consent before study entry (see Multimedia Appendix 1 for a sample informed consent form).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Diagnosed with both chronic heart failure (heart failure with reduced ejection fraction, heart failure with mid-range ejection fraction, or heart failure with preserved ejection fraction) and chronic obstructive pulmonary disease, regardless of etiology.
- At least one hospital admission due to an exacerbation of chronic heart failure and/or chronic obstructive pulmonary disease during the last year.
- Aged 16 years or older.
- Able to speak and read the Dutch language.
- Life expectancy of more than 2.5 years.
- Sufficient digital skills (or assistance from an informal caregiver).

Exclusion criteria

- Not having an internet connection.
- Psychological disorders preventing the patient from study participation.

Developmental Phase

The design of the intervention is based on the outcomes of a health care innovation project related to CHF and COPD care at Máxima Medical Center in Veldhoven, Netherlands. The aim of the project was to evaluate the current CHF and COPD care pathways and ideate new concepts to improve health care for these chronic patients. The results of this project were used to construct the current study.

The first part of the developmental phase consisted of two focus group meetings. Each group consisted of four patients who were diagnosed with combined CHF/COPD and had at least one hospital admission due to an exacerbation of CHF and/or COPD in the past year. Each patient was accompanied by a relative or spouse. The meetings were led by a specialized nurse. The interviews were aimed at revealing the most important themes and areas of concern, with respect to both the current care pathway and a future telemonitoring-guided care pathway. The main conclusions are summarized in Textbox 2.

The second part of this phase consisted of the assessment of the level of self-management and health care consumption of patients with combined CHF and COPD. To assess the level of self-management, the 13-item Patient Activation Measure (PAM13) was sent to 37 patients, of which 23 patients responded. The PAM13 reflects 4 levels of patient activation, where level 1 reflects the lowest level of self-management and level 4 reflects the highest level. The mean level of patient activation among these 23 patients, based on the PAM13 results, was 2, indicating that these patients lacked the knowledge and confidence to manage their diseases. An overview of the average annual health care consumption by these patients can be found in Table 1. Both the patients' opinions and data on level of self-management and health care consumption were used to design the study intervention.

Textbox 2. Main conclusions of focus group meetings (n=8).

Current care pathway

- Patients experience a lack of communication among different health care providers.
- More information about the use of medication, changes in medication, and knowledge about drug side effects and interactions is needed.
- Patients would like to learn how to better manage their chronic heart failure and chronic obstructive pulmonary disease.

Future telemonitoring-guided care pathway

- Patients would appreciate a quick intervention for an upcoming exacerbation.
- It would be beneficial to have one contact person for both diseases.
- Daily monitoring would provide a feeling of safety and prevent patients from waiting too long before consulting a health care professional for their chronic heart failure/chronic obstructive pulmonary disease–related physical complaints.
- Daily monitoring would provide feelings of safety; however, when clinically stable, the monitoring frequency should be reduced to gain trust in their own body.

Table 1. Average annual health care consumption by patients with combined chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) (n=23).

	Number/year
Hospital admissions	2.3
Days admitted to the hospital	14.6
Visits to an emergency department	0.3
Visits to a cardiologist/pulmonologist	5.6
Telephonic appointments with a cardiologist or pulmonologist	1.7
Visits to a CHF/COPD nurse	2.1
Telephonic appointments with a CHF/COPD nurse	1.6
Cardiac examinations (electrocardiogram, ultrasound, Holter monitoring)	4.4
Spirometry	2.0

Usual Care

During the first 6 months of the study period, patients receive regular care by their cardiologist, pulmonologist, and CHF or COPD nurse (ie, by appointments at the outpatient clinic).

Intervention

The intervention starts with a home visit by the patient's case manager (a specialized CHF/COPD nurse). The major goals of this home visit are (1) to familiarize themself with the patient, (2) to get an impression of the home environment of the patient, (3) to take a cardiac and pulmonary anamnesis and to evaluate the medication use, (4) to provide the patient with instructions for the use of the sensors and digital platform, and (5) to involve informal caregivers in the telemonitoring process (if needed).

During the home visit, the following sensors are provided to the patient: a blood pressure monitor (iHealth Track, iHealth Labs Inc), a pulse oximeter (iHealth Air, iHealth Labs Inc), a weighing scale (iHealth Lite, iHealth Labs Inc), and a thermometer (Thermoval Basic, Hartmann BV). In addition, participants are instructed on the use of a personalized and secured digital platform (Mibida BV). Safety and privacy are warranted by using encryption and signature layers. To improve usability, the platform was developed and tested before the start of the study. This was done together with a patient with CHF and COPD. For patients, the platform is equipped with the following functionalities:

- daily entry of vital parameters—although there is a possibility for automatic transfer of iHealth sensor data to the digital platform (via Bluetooth), study participants enter their data manually. This is to assure data safety, as storing medical data on the iHealth app and corresponding cloud is undesirable. Moreover, dealing actively with measured parameters, by reading numbers on the sensors and then manually entering them on the digital platform, might enhance insight into their own vital parameters and promote self-management.
- daily entry of physical complaints related to CHF and COPD—the questionnaire consists of 5 short questions. If a patient answers "yes" (eg, to the question about whether they suffer from coughing), additional questions appear to get a more complete overview of the patient's clinical status and to try to differentiate between CHF- and COPD-related physical complaints.
- a graphical overview of measured vital parameters over periods of time.
- a modality for videoconferencing with the case manager.
- a modality to send chat messages to the case manager.
- a tab with reports made by the case manager (eg, to refer to changes in medication being made).
- a tab with upcoming appointments (ie, video calls or appointments at the outpatient clinic, if needed).

During the first month of the intervention, all participants are instructed to complete the short questionnaire on physical complaints related to CHF and COPD and to perform sensor measurements (blood pressure, heart rate, weight, oxygen saturation, and body temperature) on a daily basis. For each measured vital parameter, personalized reference values are set, categorizing values into normal, slightly abnormal, or abnormal. These reference values are set in a multidisciplinary setting with the case manager, cardiologist, and pulmonologist. Case managers perform daily reviews (except during the weekends) based on a list of all participants. This list gives a practical overview of the clinical status of each patient. All measurements that raise an alarm, or questionnaires that indicate physical complaints, are indicated in the list of participants. The patient with the most alarming parameters appears at the top of the list. If a patient appears to be clinically unstable based on the parameters, a video call will take place to get a more complete overview of the patient's status. Moreover, the patients are provided with a central phone number to get in touch with the case manager when experiencing acute physical complaints.

Every afternoon, a multidisciplinary meeting of the cardiologist, pulmonologist, and case manager is scheduled to discuss patients that need supervision and to define their treatment strategy. After the first month, the measurement frequency is personalized to the patient depending on his or her clinical stability and preferences. Once every three months, the case manager will have a more extensive video call with the patient to discuss, for example, medication use, lifestyle recommendations, self-management skills, etc.

Regular appointments at the outpatient clinic with the cardiologist, pulmonologist, and CHF/COPD nurse do not take

place during the postintervention phase. Appointments will only be planned if deemed necessary, based on the telemonitoring parameters or on the patient's medical history. Thus, telemonitoring will not be used as an addition to regular care but rather will replace regular care, fitting with the patient's needs.

Outcomes

The primary outcome measure is general HRQoL. The secondary outcome measures are disease-specific HRQoL, level of self-management, patient satisfaction, compliance to the telemonitoring program, and cost-effectiveness. General HRQoL, disease-specific HRQoL, and level of self-management are assessed monthly during the entire study period (both preintervention and postintervention). Patient satisfaction of chronic care is assessed at baseline and then every 6 months. All questionnaires used to assess the end points will be sent to patients via email, using a web-based database software program (Castor Electronic Data Capture, Ciwit BV). Compliance to the telemonitoring program and cost-effectiveness will be assessed at the end of the study period.

General HRQoL: EQ-5D-5L

The primary outcome measure is general HRQoL. To measure general HRQoL, the validated questionnaire EQ-5D-5L is used. The EQ-5D-5L consists of 5 questions in 5 domains and a visual analog scale to grade QoL. It is a valid and responsive measure of health status in both patients with respiratory disease and patients with cardiovascular disease [22,23]. This questionnaire will also be used in cost-effectiveness analysis by calculating quality-adjusted life-years (QALYs).

Due to the progressive nature of both CHF and COPD, a gradual decline in HRQoL is expected. We therefore hypothesize that the intervention will result in a reduced decline or improvement of HRQoL as compared with the preintervention phase. This study primarily focuses on HRQoL, as patient value in chronic care and research is often underrecognized.

Disease-Specific HRQoL: Minnesota Living with Heart Failure Questionnaire (MLHFQ) and St George's Respiratory Questionnaire (SGRQ)

In addition to general HRQoL, disease-specific HRQoL will be assessed to evaluate the effect of both CHF and COPD on patients' QoL. Heart failure–specific QoL is assessed by the MLHFQ. This questionnaire consists of 21 items, rated on 6-point Likert scales. The MLHFQ provides a total score for HRQoL, as well as subscores in the physical and emotional domains. The commonly used MLHFQ has shown good psychometric properties [24].

The SGRQ is a widely used and validated questionnaire among patients with COPD [25,26]. It consists of 50 items, some of which are scored on a Likert scale and others dichotomously. The SGRQ results in a total score and three subscale scores (symptoms, activity, and impact).

Level of Self-Management: PAM13

Self-management is assessed by the previously validated PAM13 [27,28]. PAM13 is a 13-item questionnaire scored using 4-point Likert scales. The PAM13 reflects 4 levels of patient activation. Level 1 reflects a passive role and a lack of confidence in maintaining or improving health status, while level 4 reflects the ability to adopt and maintain new behaviors.

Patient Satisfaction: Patient-Reported Experience Measure (PREM) Chronic Care

Patient experiences are assessed using the PREM Chronic Care questionnaire. This questionnaire was developed by InEen, Patiëntenfederatie Nederland, and Zorgverzekeraars Nederland and is designed for quality improvement of chronic integrated care. It is a validated 26-item questionnaire with different types of questions (ie, multiple choice, open-ended, 6-point Likert scale) about the patient's experience with chronic care [29]. The PREM is sent to the patient at baseline and then every 6 months during the study period.

Compliance

Compliance to the telemonitoring program will be evaluated at the end of the study by reporting the percentage of completed monitoring sessions. A monitoring session comprises uploading the requested vital parameters and the corresponding questionnaire on physical complaints. An adherent patient is defined as a patient who completes at least 80% of the requested monitoring sessions. A nonadherent patient completes less than 20% of the requested number of monitoring sessions. A partially adherent patient completes 20% or more but less than 80% of the requested number of monitoring sessions. This classification is based on previous literature on adherence to a therapeutic regimen [30].

Cost-Effectiveness

For the cost-effectiveness analysis, the effects of the period before and after the intervention will be compared and related to their difference in costs. The effect is expressed in quality-adjusted life-years (QALYs) and will be calculated using index values derived from the monthly administered EQ-5D-5L [31]. The costs and QALYs of the preintervention period (6 months) will be compared with the monthly data from the first 6 months after the intervention has started. Only the first 6 months postintervention will be taken into account to enhance the quality of the comparison with the preintervention period. Although costs could be higher in the first 6 months postintervention because of training and set-up, QoL deteriorates over time in patients with COPD and CHF. Therefore, we decided to analyze only the first 6 months postintervention. In a sensitivity analysis, we will calculate the costs and QALYs for the whole postintervention period and calculate the monthly average for comparison with the preintervention period. The economic evaluation will be performed from a health care perspective. In-hospital costs will include telephonic and face-to-face contacts with the cardiologist, pulmonologist, heart failure nurse and pulmonary nurse, as well as ambulance transports, emergency department visits, hospital admissions, and associated in-hospital examinations (ie, electrocardiogram, cardiac ultrasound, spirometry, etc). These data are derived from the electronic patient files. Face-to-face and telephonic consultations with the general practitioner (GP) or nurse practitioners will be gathered by contacting the GP. The

pharmacist will be asked to provide an overview of delivered medications for CHF and COPD. Prices will be gathered using the Dutch Manual for Costing in economic evaluations and market prices [32], the Dutch Pharmacotherapeutic Compass [33], and the financial division of the hospital. Costs related to the intervention include costs for the sensors, digital platform, home visit, telephonic and video calls, and costs associated with a multidisciplinary meeting.

Sample Size

A power calculation is not possible because of the study design. Previous research tried to provide guidance on sample size calculation in an interrupted time series design, which appeared to be complex and needed various factors to be considered, such as the expected effect size, the location of the intervention in the time series, and the sample size per time point [34]. For this study, we chose a sample size of 30 participants. This was a pragmatic choice, based on the expected inclusion rate and the expected large effect size. The effect size is expected to be large because patients with CHF and COPD have a low QoL [35,36], and the study intervention is particularly designed to meet the patients' needs and preferences (via interviews).

Statistical Analysis

Descriptive statistics will be used to describe the population with regard to baseline characteristics and demographics. Continuous data will be presented as mean (SD) if normally distributed. Categorial data will be presented as n (%). For each outcome measure (eg, general HRQoL, disease-specific HRQoL, and level of self-management), each participant will create 6 data points before and 24 data points after the start of the intervention. Patterns in these data points will be analyzed using segmented regression analysis [19]. Regression estimates will be used to express the level and trend (ie, slope) of the outcome measures in both the preintervention phase and the postintervention phase in relation to the intervention. The presence of autocorrelation will be tested using the Durbin-Watson statistic [37]. If autocorrelation is present, we will adjust for it. Moreover, we will adjust for seasonality and time between last hospital admission and inclusion in the study. Missing data points will be imputed. Analysis will be performed using the statistical software package SPSS (version 26.0; IBM Corp).

Results

Ethics Approval

The study and its amendments were approved by the local ethics committee of Máxima Medical Center (see Multimedia Appendix 2 for the primary medical ethical approval form). The study will be conducted in accordance with the declaration of Helsinki and is registered at the Netherlands Trial Register (NTR) with registration number NL6741.

Trial Status

Following ethical approval of the study protocol, the first patient was included in May 2018. Inclusion is expected to be complete in May 2021. With a study period of 2.5 years per patient, data collection is expected to be complete in November 2023.

Discussion

The aim of this study is to improve the QoL of patients with combined CHF and COPD by introducing a novel, integrated care pathway using a remote, on-demand treatment strategy that was designed with input from patients. By providing feedback on the patient's health status on a regular basis, improved levels of self-management are expected. This novel care pathway might lead to a higher efficacy in chronic care for patients with combined CHF and COPD and might therefore be accompanied by a reduction in health care costs.

Previous studies on telemonitoring in patients with CHF or COPD, which mainly focused on hard end points such as (re)hospitalization or mortality, showed conflicting results [38,39]. To improve the effectiveness of telemonitoring, we designed a novel intervention with several distinct features. First, telemonitoring will not be used as an add-on to regular care but rather will be incorporated in a well-defined care pathway. In this way, we aim to improve the cost-effectiveness of telemonitoring as compared with the interventions used in previous studies [40]. Second, the intervention is tailored to the disease stage. An unstable patient population at high risk of hospital readmission was selected using a telemonitoring intervention, which focuses on detecting clinical deterioration by daily monitoring of vital parameters and physical complaints. Clinically stable patients with CHF and COPD, without previous hospitalizations and with a low disease burden, might not benefit from a telemonitoring intervention focused on vital parameters; instead, these patients might benefit from a telemonitoring intervention focused on education and self-management, and replacing regular hospital visits with e-consultations. Finally, the intervention will target both CHF and COPD by assigning a case manager for both diseases. To our knowledge, this is the first study evaluating the effects of combined disease management using telemonitoring. Bernocchi et al [41] evaluated the effects of a novel care program for patients with combined CHF and COPD, but the program primarily focused on telerehabilitation. As mentioned previously, there is a need for a more holistic approach for patients with multiple chronic conditions. Therefore, future chronic care should focus not only on combined monitoring of two chronic conditions, but also on other prevalent chronic conditions, such as diabetes mellitus and chronic kidney disease.

Conclusion

The remote patient monitoring CHF/COPD trial will provide important insights into the effects of a novel, combined care pathway for patients with CHF and COPD. Unique to this novel care pathway is that it is designed with the input of patients. Moreover, it offers disease monitoring using modern technology, delivering care on demand, having one case manager for both diseases, and providing an improved collaboration between the cardiologist and the pulmonologist.

Acknowledgments

The study was submitted and approved by the Medical Ethics Committee of Máxima Medical Center, Netherlands. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study entry.

Authors' Contributions

CH participated in the design of the study, conducted the trial and drafted the manuscript. JK and HK participated in the design of the study and helped to draft the manuscript. RS, AS and LG helped to revise the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent form.
[DOCX File , 18 KB - resprot_v9i11e20571_app1.docx]

Multimedia Appendix 2
Primary decision form of the medical ethical committee.
[PDF File (Adobe PDF File), 240 KB - resprot_v9i11e20571_app2.pdf]

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Abbreviations

CHF: chronic heart failure
COPD: chronic obstructive pulmonary disease
GOLD: Global Initiative for Chronic Obstructive Lung Disease
GP: general practitioner
HFmrEF: heart failure with mid-range ejection fraction
HFrEF: heart failure with reduced ejection fraction
HFpEF: heart failure with preserved ejection fraction
HRQoL: health-related quality of life
MLHFQ: Minnesota Living with Heart Failure Questionnaire
NYHA: New York Heart Association
PAM: Patient Activation Measure
PREM: patient-reported experience measure
QALY: quality-adjusted life-year
QoL: quality of life
SGRQ: St George's Respiratory Questionnaire

Edited by G Eysenbach; submitted 22.05.20; peer-reviewed by A Snoek, S D'Arcy; comments to author 10.07.20; revised version received 23.07.20; accepted 28.07.20; published 19.11.20.

Please cite as:
Herkert C, Kraal JJ, Spee RF, Serier A, Graat-Verboom L, Kemps HMC
Quality Assessment of an Integrated Care Pathway Using Telemonitoring in Patients with Chronic Heart Failure and Chronic Obstructive Pulmonary Disease: Protocol for a Quasi-Experimental Study
JMIR Res Protoc 2020;9(11):e20571
URL: https://www.researchprotocols.org/2020/11/e20571
doi:10.2196/20571
PMID:33211017

Protocol

Developing a Standardized and Reusable Method to Link Distributed Health Plan Databases to the National Death Index: Methods Development Study Protocol

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Abstract

Background: Certain medications may increase the risk of death or death from specific causes (eg, sudden cardiac death), but these risks may not be identified in premarket randomized trials. Having the capacity to examine death in postmarket safety surveillance activities is important to the US Food and Drug Administration's (FDA) mission to protect public health. Distributed networks of electronic health plan databases used by the FDA to conduct multicenter research or medical product safety surveillance studies often do not systematically include death or cause-of-death information.

Objective: This study aims to develop reusable, generalizable methods for linking multiple health plan databases with the Centers for Disease Control and Prevention's National Death Index Plus (NDI+) data.

Methods: We will develop efficient administrative workflows to facilitate multicenter institutional review board (IRB) review and approval within a distributed network of 6 health plans. The study will create a distributed NDI+ linkage process that avoids sharing of identifiable patient information between health plans or with a central coordinating center. We will develop standardized criteria for selecting and retaining NDI+ matches and methods for harmonizing linked information across multiple health plans. We will test our processes within a use case comprising users and nonusers of antiarrhythmic medications.

Results: We will use the linked health plan and NDI+ data sets to estimate the incidences and incidence rates of mortality and specific causes of death within the study use case and compare the results with reported estimates. These comparisons provide an opportunity to assess the performance of the developed NDI+ linkage approach and lessons for future studies requiring NDI+ linkage in distributed database settings. This study is approved by the IRB at Harvard Pilgrim Health Care in Boston, MA. Results will be presented to the FDA at academic conferences and published in peer-reviewed journals.

Conclusions: This study will develop and test a reusable distributed NDI+ linkage approach with the goal of providing tested NDI+ linkage methods for use in future studies within distributed data networks. Having standardized and reusable methods for systematically obtaining death and cause-of-death information from NDI+ would enhance the FDA's ability to assess mortality-related safety questions in the postmarket, real-world setting.

International Registered Report Identifier (IRRID): DERR1-10.2196/21811

(JMIR Res Protoc 2020;9(11):e21811) doi:10.2196/21811

KEYWORDS

National Death Index; data linkage; all-cause mortality; cause specific mortality; distributed analysis; multisite research

Introduction

Public Health Significance and Study Motivation

Certain medications may increase the risk of death and specific causes of death (eg, sudden cardiac death [SCD]), but these risks may not be identified in premarket randomized controlled trials owing to the relatively small sample sizes and the highly selected patient populations in these trials. The capacity to examine the risk of death in postmarket safety surveillance activities is an important part of the US Food and Drug Administration's (FDA) mission to protect public health. Although the FDA Adverse Event Reporting System (FAERS) [1] identifies drug safety signals [2] and is vital to this mission [3], FAERS has a number of known limitations. Similar to most spontaneous reporting systems that rely primarily on voluntarily reported adverse events, FAERS is susceptible to underreporting, variable data quality, lack of denominator information, and frequent absence of details necessary to evaluate clinical events and associations with a specific medication [4-6].

Other components of the FDA's postmarket medical product safety surveillance system complement FAERS in many ways but often do not systematically capture death or cause-of-death information. For example, the FDA's Sentinel System [7,8] includes a distributed network of electronic health plan databases. The health plans that participate in the Sentinel System or other multicenter research networks routinely capture data on in-hospital deaths and medically attended deaths but often do not have complete capture of out-of-hospital deaths or cause-of-death information. Although some health plans perform routine or ad hoc linkages with local or state death registries or Social Security Administration (SSA) data to address these data gaps, such linkages are often specific to a particular study or site.

In addition, some multicenter research networks use a distributed data approach in which individual study sites or health plans maintain physical and operational control over their electronic health data behind their respective firewalls. A distributed network approach promotes data sharing by protecting patient privacy, data security, and proprietary interests [9-12]. The development of a systematic method to link distributed databases to a data source that includes both death and cause-of-death information, such as the National Death Index (NDI), would enhance the FDA's ability to answer mortality-related safety questions in the postmarket setting.

NDI and Cause-of-Death Information

The NDI, a self-supporting service within the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention, is a centralized database of death record information compiled from the vital statistics offices of states and other jurisdictions. The NDI provides death information including death date and death certificate number (referred to as the NDI data) and cause of death from death certificates (referred to as NDI Plus or NDI+ data) upon request [13]. Although the SSA also provides the fact of death, it does not provide cause-of-death information, and a 2011 determination by the SSA that data submitted electronically by states cannot be publicly shared in the SSA death master file has since limited its coverage [14].

The limitations of the cause-of-death information derived from death certificates, the foundation of state death records, and subsequent NDI information have been well described [15]. In brief, although efforts have been made to improve the completeness and accuracy of cause-of-death reporting in the United States, the cause-of-death information in the death certificate ultimately represents medical opinions. The certifier (eg, attending physician, medical examiner, coroner) provides a clinical judgment informed by their training, knowledge of medicine, and available medical history of the decedent [16]. Certifier requirements (eg, coroner or medical examiner) can also vary according to state laws [17]. Variation in all of these elements can lead to inaccurate documentation by the certifier, and studies have found that causes of death listed on the death certificates, and subsequently coded in NDI+ data, may be misclassified by 16% to 40%, depending on the cause [18,19]. Misclassification may increase when the death is sudden and unobserved [20,21] and also when more narrowly defined causes of death are listed [22]. Errors introduced during translation of the causes of death on death certificates to the International Classification of Diseases, 10th Revision (ICD-10) codes are much less common [23,24].

Despite the known limitations of death certificate data, researchers have used these data to examine national death data

trends and changes in causes of death over time [22,25,26] and have used death certificate data with other data sources to more accurately define specific causes of death, such as SCD [27]. Notwithstanding the above mentioned limitations, the NDI is currently the only complete national source of death and cause-of-death information accessible to large-scale population-based epidemiologic studies in the United States.

Primary and Secondary Objective of the Study

Overview of the Study Objectives

The primary objective of this study is to develop reusable administrative and technical processes for linking multiple health plan databases with NDI+ data to allow the FDA to assess death and specific causes of death as outcomes in medical product safety and effectiveness studies in distributed networks of electronic health plan databases. We will pilot the developed approach through a use case comprising antiarrhythmic medication users and nonusers. The outcomes of interest in the use case are all-cause mortality and SCD, but cardiovascular death may also be examined if it is feasible within the study timeline.

The secondary objectives focus on using the linked health plan and NDI+ data to estimate the incidences and incidence rates of mortality and specific causes of death within the use case and comparing them with estimates reported in the literature. Examining the incidences and incidence rates of mortality and death from specific causes within the use case will provide an opportunity to assess the performance of the workflows and processes developed under the primary objectives.

Primary Objectives

1. Develop and pilot an administrative workflow that facilitates efficient, coordinated, multicenter institutional review board (IRB) review and approval for linking health plan data with NDI+ data.
2. Create and pilot a distributed technical process for linking health plan and NDI+ data that:
   - uniformly identifies records to be submitted to the NDI from each health plan
   - avoids sharing of identifiable patient information between participating health plans or with the coordinating center and allows health plans to work directly with the NDI
   - uses standardized criteria to select and retain confirmed or best match from linked NDI+ data across multiple health plans
   - harmonizes linked information across multiple health plans by saving NDI+ data in a standardized format

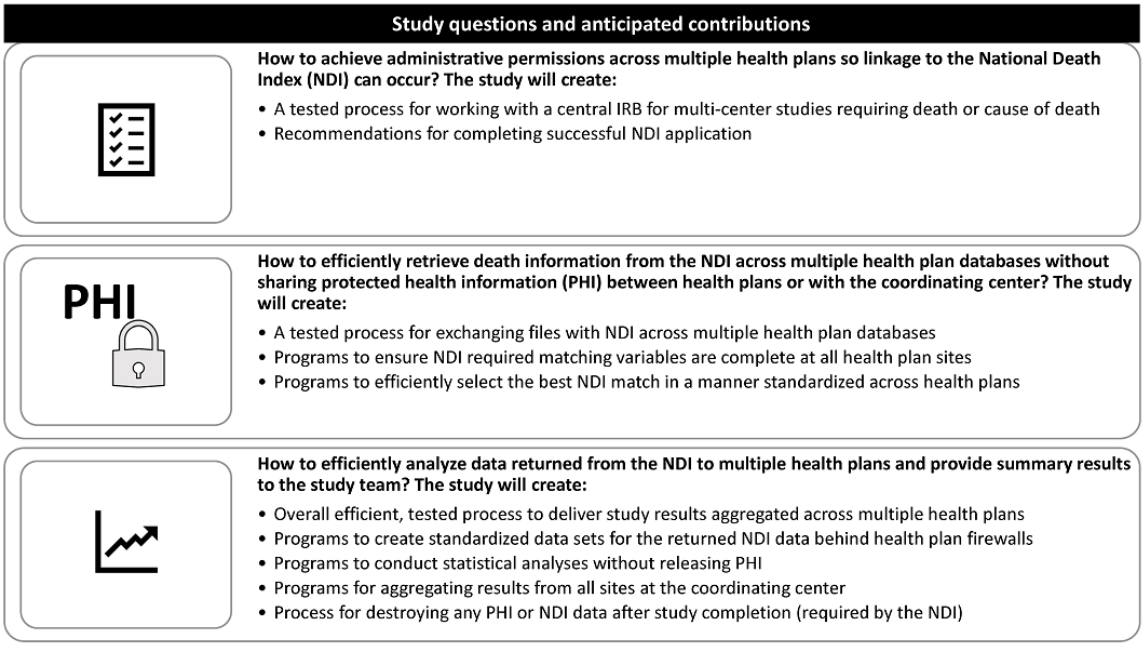
Secondary Objectives

The secondary objectives are as follows:

1. Estimate the incidences and incidence rates of all-cause mortality, SCD, and potentially cardiovascular death within a high-risk use case cohort (ie, individuals using antiarrhythmic medications) and an average-risk cohort (ie, individuals not on antiarrhythmic medications).
2. Assess the performance of the developed workflows and processes for linking health plan and NDI+ data by examining the incidences and incidence rates of all-cause mortality, SCD, and potentially cardiovascular death within the use case cohorts, and comparing them with estimates previously reported in the literature.

Figure 1 provides an overview of the questions this study will address and anticipated contributions.

Figure 1. Overview of study questions and anticipated contributions. NDI: National Death Index; IRB: Institutional Review Board; PHI: Protected Health Information.



Methods

Use Case and Rationale

For this study, we chose antiarrhythmic medications as the use case. The arrhythmogenicity of antiarrhythmic medications is well known, and several antiarrhythmic medications are known to be associated with elevated risks of all-cause mortality and SCD [28-30]. SCD associated with arrest, generally defined as the sudden cessation of heart function, is a major cause of mortality and a major public health concern. Ventricular fibrillation is often associated with SCD and is a pulseless arrhythmia with irregular and chaotic electrical activity and ventricular contraction in which the heart immediately loses its ability to pump [31]. Ventricular fibrillation is the initial electrocardiogram rhythm in 75% of outpatient cases of SCD [32]. Torsade de Pointes is a specific form of polymorphic ventricular tachycardia that if rapid or prolonged can lead to ventricular fibrillation and SCD [33].

There are approximately 20 cardiovascular medications and well over 100 noncardiovascular medications suspected of causing SCD, ventricular fibrillation, or Torsade de Pointes [28]. For example, although class III antiarrhythmic medications are used to treat atrial or ventricular arrhythmias, they prolong repolarization and cardiac refractoriness and can increase an individual's propensity for Torsade de Pointes [34]. In addition, individuals with arrhythmias are at a high risk of death and SCD. Therefore, we expect all-cause mortality as well as SCD to be more common in antiarrhythmic medication users than in a cohort not exposed to these medications. As the incidences of mortality and SCD in the US population are well described [35-37], identification of a cohort at average risk of these outcomes will provide an efficient reference point for antiarrhythmic medication users and an opportunity to assess the performance or *validity* of the linkage to NDI+ data.

Participating Organizations

This project will be led and coordinated by the Harvard Pilgrim Health Care Institute (HPHCI), which will work closely with the FDA and participating health plans in all aspects of the project. A total of 6 health plans—Aetna, a CVS Health company; HealthPartners Institute; Kaiser Permanente Colorado; Kaiser Permanente Northwest; Kaiser Permanente Washington; and Vanderbilt University (which provides access to Tennessee Medicaid data)—will participate in this project. They represent a diverse group of health plans, including national insurers, regional health plans, and integrated delivery systems, and cover both commercial and public insurance programs. Although the project will leverage the Sentinel infrastructure and be built on the successful collaboration among participating institutions, it will be conducted outside of the Sentinel Initiative and will be relevant to other distributed data networks. The project is a research activity subject to the Office for Human Research Protections regulations, following the 45 Code of Federal Regulations 46 [38] on the protection of human subjects, and will undergo IRB review.

Development of Multisite Administrative Workflows to Support Linkage to NDI+ Data

Overview of the Administrative Workflows

This project will develop reusable and flexible administrative workflows required to support simultaneous linkage of multiple health plan databases with NDI+ data. As the lead project site and coordinating center, the HPHCI will develop and facilitate administrative processes for IRB workflow as well as submission of the master NDI application on behalf of the participating health plans. The HPHCI will lead the development of the NDI application package, coordinate review by participating health plans and the FDA as well as the execution of legal agreements (as necessary), and will submit the master NDI application that will include IRB documents and approvals.

The HPHCI will review, consider, and accommodate the requirements of institutions involved in this project to ensure that the developed workflows for NDI and IRB application review and approval are flexible enough to be reused in future studies. This may require review and response to any of the following: health plan institutional requirements, FDA requirements, relevant federal requirements (eg, revised Common Rule [39] and other requirements), relevant state or local jurisdiction requirements (eg, laws concerning death data), institutional IRB requirements, or NCHS/NDI requirements. For example, preliminary work with participating health plans suggested the need to consider any state or local laws pertaining to death data within project workflows. Balancing such requirements as well as any other identified prerequisites or constraints will be a key focus of the developed multisite administrative workflow. In the following paragraphs, we describe our anticipated processes for implementing coordinated multisite, central IRB review and approval, as well as multisite NDI application review and approval.

IRB Application Workflow

The revised Common Rule requires the use of a central IRB for multisite research, with certain exceptions (82 Fed. Reg. at 7265 [final rule §.114]) [39]. In addition, the NDI currently requires all studies requesting NDI+ data to undergo IRB review. This project will develop and pilot an administrative workflow that facilitates efficient, coordinated, multicenter IRB review and approval for linking health plan data with NDI+ data in accordance with the revised Common Rule.

The IRB at Harvard Pilgrim Health Care, the parent organization of the HPHCI, is responsible for managing and supporting scientific and ethical review of research studies submitted by the HPHCI. The HPHC IRB also enters into reliance agreements for multisite studies as a reviewing IRB and a relying IRB. The HPHC IRB holds a Federalwide Assurance (FWA) with the US Department of Health and Human Services [FWA00000100] and thus is compliant with human subjects regulations within 45 Code of Federal Regulations 46 [38,40]. As the lead study institution, the HPHCI will aim to have the HPHC IRB serve as the IRB of record, with all participating sites ceding their IRB review to the HPHC IRB. However, if the use of a single IRB entity is determined not to be feasible or acceptable to the NCHS, the NDI board, or participating health plans, the HPHCI

will work with each participating health plan to attain IRB approval.

The study team will describe the necessary administrative workflow processes and highlight any encountered governance challenges (eg, local institutional policies or procedures) and potential solutions. Furthermore, the study team will address any complications with individual study sites obtaining approval to cede to the HPHC IRB in the final developed workflow. The anticipated central IRB workflow is as follows:

1. The HPHCI will submit an IRB application to the HPHC IRB and obtain HPHC IRB approval for the study. The HPHCI and collaborating health plans to cede review by initiating and executing reliance agreements with respective health plan IRB(s). Reliance agreements must be in place for local health plan IRBs to cede review and for the HPHC IRB to serve as the lead reviewing IRB. We anticipate the cede process will proceed as follows:
    - The HPHCI will provide the HPHC IRB application and approval to participating health plans for review. The HPHCI will work with health plans to address any concerns or amendments needed to satisfy approval to cede to the HPHC IRB. Individual health plan–specific policies and procedures may apply and will be documented.
    - Participating health plans will prepare all necessary cede request documents required by site IRB(s) and the HPHC IRB. Health plans will submit a cede request to the HPHC IRB.
    - The HPHC IRB will review the submitted cede requests and may require additional health plan–specific materials in determining approval to accept the request (eg, documentation of human subjects training from key personnel).
    - The lead HPHC IRB and the IRB(s) at participating health plans will fully execute reliance agreements, formally known as IRB authorization agreements, to officially confirm the HPHC IRB as the lead reviewing IRB of record for the study.
2. Following the completed cede process, the HPHC IRB will be responsible for continuing review as well as amendment and reviewing of any unanticipated problems. Participating health plans will be responsible for timely communication and reporting to the HPHC IRB for any unanticipated problems encountered at their site for this study.

The anticipated central IRB workflow process will be updated as new procedures or processes are encountered. A final recommended IRB workflow will be created after the process is piloted and will include lessons learned, requirements for each involved institution (eg, FDA, HPHCI, participating health plans), relevant flowcharts, and recommendations for future studies.

NDI Application Workflow

The HPHCI will lead the NDI application development and subsequent application review by the FDA and the health plans before submission of the final application package to the NDI. The published guidelines for obtaining NDI application approval by the NDI board will inform the developed workflow [41]. The HPHCI will also work with staff at the NDI to ensure all requirements are met in accordance with the NDI guidelines. Process development may be iterative, with the NDI providing guidelines and the HPHCI subsequently working with health plans and the FDA to ensure guidelines are met. Preliminary work has identified the need for specific process development in IRB approval for the protection of human subjects, final disposition of identifiable data, and NDI-required agreements.

The HPHCI will document lessons learned from piloting the administrative workflows that will inform the development of a flexible and reusable process intended to guide future studies. The HPHCI will review the NDI and IRB stipulations encountered during this study and ensure appropriate processes and guidelines are built to accommodate them. As the NDI and IRB administrative workflows are interdependent, we will use an iterative process outlining and updating the IRB and NDI administrative workflows as new stipulations or requirements are encountered. Thus, the overall administrative workflow will include recommendations for IRB and NDI application development for use in future studies.

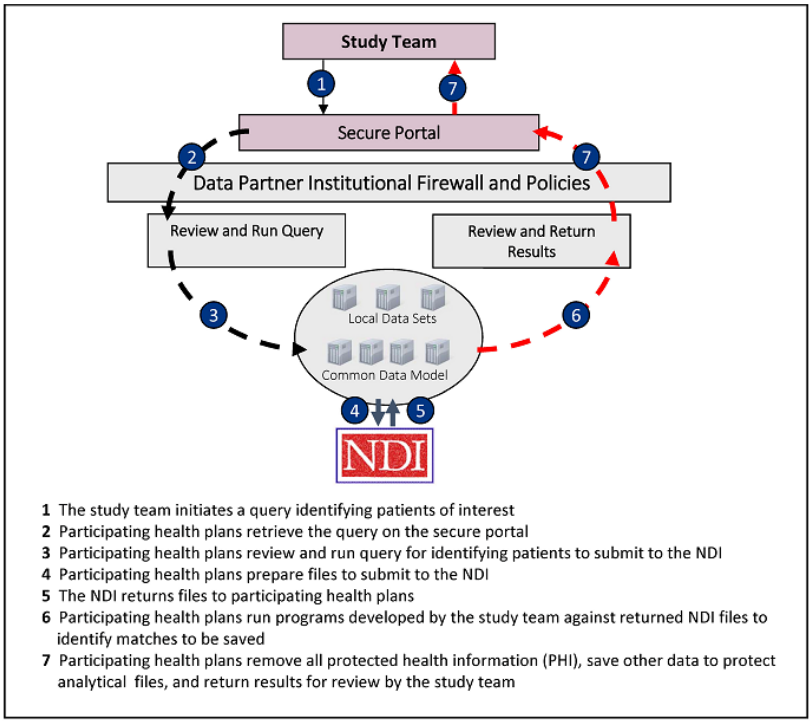
Development of Distributed Process for Linkage Between Health Plan and NDI+ Data

Overview of the Distributed Linkage Process

The HPHCI, in collaboration with the FDA and participating health plans, will develop a distributed linkage process that allows health plans to work directly with the NDI to eliminate sharing of identifiable patient information between participating health plans or with the coordinating center. The HPHCI will develop the distributed NDI+ data linkage process with input from the participating health plans and pilot the process within the study use case. Health plans will identify and submit individuals meeting specific criteria within the use case cohorts to the NDI for matching. The HPHCI will also work with each participating health plan to develop and ensure a standardized NDI+ data linkage process across databases. Figure 2 provides a high-level overview of the anticipated distributed process for linkage between health plan data and NDI+ data.

Piloting the process with the study use case will elucidate adjustments that could be made to improve efficiency and provide flexible options for future studies. We will summarize practical lessons learned from the participating health plans and the NDI. Although the NDI User's Guide [42] describes the general process for NDI+ data linkage within a single site, the developed technical workflow will need to enable linkage to NDI+ data at multiple study sites. Accomplishing timely and standardized linkage to NDI+ data across multiple sites requires defining and implementing a set of NDI submission criteria, ensuring adequate file preparation and quality control processes across sites, standardizing the selection and retention of NDI matches, and storing information retrieved from the NDI in standardized table(s) so that study analyses can be implemented. We anticipate the following tasks will be required to build a distributed process for linkage between health plan and NDI+ data.

Figure 2. Overview of the distributed National Death Index data linkage process. NDI: National Death Index; PHI: Protected Health Information.



Defining NDI Submission Criteria

This project will develop, pilot, and recommend case identification and NDI submission criteria for future multicenter studies. Multimedia Appendix 1 includes the case identification and NDI submission criteria this project will use to determine which individuals will be initially selected for sending to the NDI, thereby obtaining death and cause-of-death information. We anticipate submitting patients with deaths recorded in health plan data or patients with potential deaths to the NDI for linkage. We will define potential death as health plan disenrollment between cohort entry and cohort exit plus 365 days, without subsequent reenrollment or medical utilization >60 days after disenrollment. It is possible that these NDI submission criteria will be refined or redesigned as they are piloted within the study use case. We will describe the final developed case identification and NDI submission algorithm and provide this information for use in future studies.

Preparing Files for Submission to the NDI

The NDI publishes information that health plans must provide to conduct an NDI+ data search as well as the required file structures in their NDI User's Guide [42]. Health plans will need to access these required data elements from their source systems and transmit complete records to the NDI for matching. To ensure that files submitted to the NDI are of sufficient completeness, the HPHCI will develop distributed programs for local execution by the health plans to identify any potential data or formatting issues. Any lessons learned during these file preparation and quality control processes will be documented for future use and incorporation into the technical workflow.

Standardizing NDI+ Data Linkage Across Multiple Health Plan Databases

After files intended for submission to the NDI have been checked to ensure sufficient completeness and quality, each health plan will submit their selected health plan members for matching directly with NDI+ data. Health plan data files will be transferred to the NCHS via either password-protected encrypted CDs or a secure file transfer protocol site, according to the health plan and NCHS or NDI requirements. When NDI staff return data files directly to health plans, health plans will load the returned files to their computer servers behind their firewalls. These data sets will remain behind their firewalls and will not be shared with the HPHCI, the FDA, or other health plans. We will summarize the processes, challenges, and requirements in the technical workflow.

Selecting and Retaining the Best NDI Match

When the NDI performs matching, multiple possible matches for each individual submitted may be provided within the NDI-returned data files. The NDI User's Guide [42] provides guidelines for selection and retention of NDI matches, from among multiple possible matches for each individual submitted. This requires researchers to assess the quality of each possible NDI record match listed and determine which possible matches are *best* matches. The NDI recommends a multistep process when determining the best match among possible multiple matches, including using the NDI-provided probabilistic matching scores to distinguish true matches from false matches. The HPHCI, guided by the principles within the NDI User's Guide [42], will develop a standardized process for ascertaining and keeping confirmed or best matches locally at the participating health plan sites. This will be implemented in distributed programs to examine all possible matches and

identify matches that are considered best based on specific criteria.

We will design the process to be flexible and reusable, and we anticipate a multistep process using variables within the returned NDI data files for match selection. Processes will assess the distribution of NDI-provided matching variables such as the *Status Code* (indicates NDI assessment of probability of truly being alive or dead), *Class Code* (indicates the fact that some NDI-identifying data items used in the matching criteria are more important for determining true matches than others), assessment of item-by-item matches between health plan and NDI information, and probabilistic matching scores (score for each potential match). We will implement rules for retaining NDI matches in distributed program(s).

The NDI returns a cause-of-death code only for records that rank first in the list of possible NDI matches. If our match selection process identifies a match that was not ranked first by the NDI, this record will not have the cause-of-death information in the initial NDI+ data files. In such instances, the HPHCI will work with the NDI to attain this missing cause-of-death information. However, it is possible that the NDI will be unable to supply the cause-of-death information or may have time delays for the return of this information. If this occurs, the HPHCI may not be able to include newly supplied cause-of-death information in final use case analyses and will pilot the process for requesting and attaining this information and document lessons learned.

The HPHCI will develop a proposed standardized table structure that can be used in future studies to store information retrieved from the NDI. The HPHCI will work with the health plans to develop the ultimate table structure. The data included in this table will be maintained behind each health plan's firewall, thereby preserving the distributed nature of health plan databases. The HPHCI will document these processes and programs in a report for future use.

Draft Use Case Specifications

Use Case Inclusion and Exclusion Criteria

This study will use data captured within participating health plan databases between 2000 and 2017 (or earliest or latest available health plan data) and the most recent NDI+ data available at the time of NDI application.

Cohort 1 will include new users of select antiarrhythmic medications for men aged 45 years and older and women aged 55 years and older on the date of cohort entry between 2000 and 2017 (or earliest available health plan data). The list of select antiarrhythmic medications of interest and new-user definition is described under the *Exposure Identification for the Use Case* section**.** We chose different age cutoff values for men and women because risks of all-cause mortality and SCD vary considerably by sex. The goal is to improve the specificity of mortality and specific causes of death outcomes identified through NDI+ matching. Younger individuals are less likely to experience mortality and SCD than older individuals, and within age groups, women are less likely to experience mortality and SCD than men. The risk for SCD has been shown to increase in women after the age of 55 years [43]. All-cause mortality is also rare in younger age groups. Choosing a higher age cutoff for women is intended to decrease *false-positive* matches and minimize the number of NDI submissions.

We will use the entire cohort for the all-cause mortality analysis and potentially the cardiovascular death analysis. For analyses focused on SCD, we will restrict the cohorts to individuals under the age of 75 years to maintain consistency with a study by Chung et al [27], which developed and validated a computerized algorithm to identify community originating SCD. As the risk of mortality increases with age, Chung et al [27] found death certificates to be less reliable for identifying SCD in older individuals and removed patients aged ≥75 years to minimize false positives. Although it may be difficult to capture nursing home stays within the participating health plan databases, to maintain consistency with the algorithm by Chung et al [27], we will exclude individuals with evidence of a nursing home stay in the baseline period. Cohort 1 entry will begin on an individual's first prescription dispensing for an oral dosage form of an antiarrhythmic medication of interest that was preceded by a 365-day baseline period with medical and pharmacy benefits (gaps in enrollment <45 days bridged), during which the individual has ≥1 encounter with a diagnosis recorded in any care setting or an outpatient dispensing of any medication.

To mimic typical drug safety study situations in which no future information is available to determine medication users' vital status, individuals with more than one episode of new use during the study period will contribute only their first episode. This study design choice also helps avoid the selection bias that use of future information may generate. The protocol allows gaps in enrollment of <45 days because it is believed that these may not represent true gaps in coverage but rather administrative changes. Index date will be the date of the first eligible dispensing for a select antiarrhythmic drug of interest.

Cohort 2 will be drawn from average-risk individuals who are not current (ie, on day of cohort entry) or past (ie, before 365 days) users of antiarrhythmic medications of interest. We will match cohort 2 at a one-to-one ratio with cohort 1 based on age, sex, and health plan. Index dates will also be matched to cohort 1. We will require individuals in cohort 2 to have a 365-day baseline period with medical and pharmacy benefits (gaps in enrollment <45 days ignored as specified above in cohort 1) and at least one medical encounter or outpatient pharmacy dispensing claim in the previous 365 days. As in cohort 1, cohort 2 will include the entire cohort for the all-cause mortality analysis and potentially the cardiovascular death analysis but will be restricted to individuals younger than 75 years and with no evidence of a nursing home stay in the baseline period for the SCD analyses. It is worth noting that individuals included in either cohort 1 or 2 may in fact have used antiarrhythmics medications outside of the study period or before enrolling in a participating health plan.

Use Case Exposure Definitions

We will identify select oral antiarrhythmic medications of interest using National Drug Codes. New use will be defined by excluding individuals with dispensings of class I and III antiarrhythmic drugs (all routes of administration), including amiodarone, disopyramide, dofetilide, dronedarone, flecainide,

mexiletine, procainamide, propafenone, quinidine, and sotalol [44,45], in the 365-day baseline period. Individuals with dispensings of intravenous lidocaine in the 365-day baseline period will also be excluded. Baseline exposure to adenosine A1 agonists, digoxin, phenytoin, class II β-blocker agents, and calcium channel blockers (class IV) agents will be ignored.

When creating treatment episodes, we will apply a stockpiling algorithm [46] to account for the possibility that members may refill prescriptions before the end of days' supply of their previous prescription. For example, if a member receives a 30-day dispensing for sotalol on January 1, and then receives a second 30-day dispensing on January 20, the stockpiling algorithm will adjust the second dispensing so that it starts on January 31, after the first dispensing has been used in full. The treatment episode will thus be 60 days in total, through March 1 (assuming February has 28 days). We will also implement a 14-day episode gap when creating treatment episodes to account for imperfect adherence. An episode gap is the maximum number of days of interrupted days-supply allowed between two claims for the same drugs of interest. If the number of days between when one prescription claim runs out and the next claim is smaller than or equal to the episode gap, the algorithm *bridges* these two claims to build a continuous treatment episode. However, if the number of days between the two claims of the same treatment exceeds the episode gap, the treatment episode ends at the end of the 14-day period. The episode gap is assessed after the claim service dates are adjusted by the stockpiling algorithm. Because we are interested in the risk of all-cause mortality and SCD for the class of medications in general and not individual antiarrhythmic medications, our analyses will focus on users of any antiarrhythmic medications of interest as a group, and the results will not be stratified by individual medication.

Use Case Follow-Up and Censoring Plan

For cohort 1, follow-up time will begin with the cohort entry-defining antiarrhythmic medication dispensing (ie, day 1 of follow-up=dispensing date) and will continue based on the treatment episode as described above. For cohort 2, follow-up time will begin on the same day as the individual's corresponding match from the antiarrhythmic medication user cohort. Follow-up will be censored upon the earliest of the following occurrences:

1. Death or specific causes of death, as determined from NDI+ data; date of death will be the last day of follow-up (both cohorts).
2. Health plan disenrollment (gaps of enrollment <45 days will be ignored); the last day of enrollment will be the last day of follow-up (both cohorts).
3. End of database time; database end date will be the last day of follow-up (both cohorts).
4. Initiation of an antiarrhythmic medication of interest; the day before the date of medication initiation will be the last day of follow-up (cohort 2 only).
5. Excessive allowable gap between dispensings, defined as >14 days between two consecutive dispensings for a study antiarrhythmic medication of interest, the last day of follow-up included will be the end of days' supply of the most recent dispensing of the study antiarrhythmic medication of interest +14 days (cohort 1 only).

The analysis will follow use case cohorts for death, SCD, and potentially cardiovascular death until censored. As linking to NDI+ data allows us to follow patients for survival through the end of the study period, if feasible, we will also conduct an analysis that ignores the censoring criteria and follows use case cohorts for death and SCD, and potentially cardiovascular death through the end of NDI+ data.

Use Case Outcomes

The primary outcomes of interest are all-cause mortality and SCD. If timeline and study resources permit, we will assess cardiovascular death as a secondary outcome of interest. Ideally, the selected outcome algorithms would: (1) facilitate the assessment of the performance or *validity* of the linkage to NDI+ data; (2) allow for comparing the incidences and incidence rates of all-cause mortality and specific causes of death with rates previously reported in the literature, or other national death information sources; and (3) use data retrieved from the NDI, and possibly information within health plan databases. To inform future studies, we will try to capture both medically attended and nonmedically attended deaths. We will identify these outcomes using NDI+ data and will evaluate each outcome separately. Although we will attempt to replicate SCD or cardiovascular death algorithms that have been previously validated by other studies, it may be necessary to modify or tailor the algorithms to data elements available within the health plan databases that have been converted into the Sentinel Common Data Model format [47]. Multimedia Appendix 2 [27,48,49] describes the operational definitions of the outcomes. We also provide the high-level details in the following paragraphs.

We will determine all-cause mortality through linkage to the NDI+ data (all deaths, including both medically attended and nonmedically attended deaths). Two algorithms for SCD will be used, both of which exclude persons aged ≥75 years. For the primary SCD definition, we will adapt an algorithm focused on community-originating events defined by Chung et al [27] for use within the health plan databases. This algorithm uses information available in claims data to exclude patients with certain conditions (Table 1 [50]) as well as cause-of-death information provided by the NDI (Table 2) [27]. The definition of secondary SCD will focus on events that occur in medical care settings. Studies examining ventricular arrhythmia diagnosis in hospital settings (ie, inpatient or emergency department) have found inpatient diagnosis codes for ventricular arrhythmia to have high positive predictive values, regardless of diagnosis code position [49,51,52]. To identify SCD outcomes originating in medical settings, we will adapt these algorithms for use within health plan databases. Secondary emergency department or inpatient diagnoses consistent with ventricular arrhythmia or sudden cardiac arrest were selected to attempt to identify events occurring in medical settings, as principal diagnosis codes would generally define conditions established after study to be chiefly responsible for admission [53]. If feasible, we may also include a sensitivity analysis exploring the principal emergency department or inpatient diagnoses consistent with ventricular

arrhythmia or sudden cardiac arrest. Finally, we may examine cardiovascular death if it is determined to be feasible by the study team, and we would define cardiovascular death with cause-of-death codes typically used by national death data sources, such as the underlying cause of death consistent with a cardiovascular cause [25]. The algorithm parameters are outlined in more detail in Multimedia Appendix 2.

Table 1. High-risk conditions likely to be miscoded as sudden cardiac death per Ray et al[a].

Condition	Operational definition[b]
Cancer	Diagnosis of cancer (except for nonmelanoma skin cancers) or select antineoplastic agents. Includes the following neoplasms uncertain behavior ICD-9-CM[c] codes[d] 235-238, *except*: 238.2 (skin), 238.9 (site unspecified), 237.70, 237.71 (neurofibromatosis), 238.4 (polycythemia vera), 238.7 (lymphoproliferative disease), and 285.22 (anemia in neoplastic disease)
HIV	Diagnosis of HIV or use of antiretroviral agents appropriate for HIV or pentamidine (also used for other major immunocompromised patients)
Renal	Diagnosis or procedure code for dialysis outside of the hospital (includes 996.73). Includes end-stage renal disease diagnosis (285.21, 585.5, 585.6), also outside of the hospital
Liver	Diagnoses 570-573
Respiratory	Diagnosis of respiratory failure, cardiorespiratory failure, or pulmonary heart disease. Also includes tracheostomy (excluding temporary), home oxygen, or home ventilator
Organ transplant	Includes kidney, heart, lung, liver, bone marrow, and pancreas. Includes complications of transplanted organ (996.8)
Serious neuromuscular	Multiple sclerosis (340), amyotrophic lateral sclerosis (335.20), Duchenne muscular dystrophy (335.21), Huntington chorea (333.4), quadriplegia, paraplegia, or spinal cord injury. Recent stroke (inpatient with primary discharge diagnosis of 430, 431, 433.x1, 434, 436) with hemiplegia/hemiparesis (342, 438.2)
Cardiovascular congenital anomalies	Common truncus (745.0) transposition great vessels (745.1), tetrology (745.2), common ventricle (745.3), endocardial cushion defect (745.6), pulmonary atresia (746.0), tricuspid atresia (746.1), hypoplastic left heart (746.7), coarctation of aorta (747.1), other anomalies of aorta (747.2), total anomalous pulmonary venous connection (747.41). A single diagnosis is sufficient for exclusion
Other congenital anomalies/childhood conditions	Sickle cell (282.6), cerebral palsy (343), spina bifida (741), Down syndrome (758.0), hydrocephalus (742.3), microcephalus (742.1), encephalocele (742.0), severe mental retardation (318.1, 318.2), cystic fibrosis
Other end-stage illness	(a) Hospice care; (b) diagnosis of coma, vegetative state, debility (799.3); (c) total parenteral nutrition, percutaneous endoscopic gastrostomy, enteral feeding, malnutrition (260, 261, 262, 263) when these are for outpatients; (d) gangrene (040, gas gangrene; 785.4 gangrene: single diagnosis sufficient); (e) intravenous medications outside of the hospital, as indicated by procedures for intravenous access outside a hospital stay period
Drug abuse	Includes all medications and drugs with abuse potential and with the exception of alcohol (unless hospitalization with primary discharge diagnosis: 291.x, 303.x, 305.0, 980.0, 980.9, E860.0, E860.1, E860.9) and tobacco. Codes are 292.0 (drug withdrawal syndrome), 304.x (drug dependence), 305.2-305.9 (drug abuse, except alcohol/tobacco, 305.9 is abuse not otherwise specified, may be nonspecific, but better to exclude), 965.01 (accidental poisoning, heroin), 969.6 (poisoning, psychodysleptic [hallucinogens]), 970.81 (cocaine poisoning, added in 2010), E8500 (heroin poisoning), E8541 (psychodysleptic poisoning)

[a]Ray et al [50].

[b]Unless otherwise indicated, codes are ICD-9-CM diagnostic codes and a 3- or 4-digit code implies inclusion of all subcodes. Further, a single diagnosis is sufficient for exclusion.

[c]ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification.

[d]ICD-9-CM codes will be mapped to ICD-10-CM codes during the study.

Table 2. Underlying cause-of-death diagnostic codes consistent with sudden cardiac death.

International Classification of Diseases, 10th Revision Code	Description
I10	essential hypertension, not otherwise specified
I11.9	hypertensive heart disease, without heart failure
I20	angina pectoris
I21	acute myocardial infarction
I22	subsequent myocardial infarction
I23	certain current complications following ST elevation and non-ST elevation myocardial infarction
I24	other acute ischemic heart disease
I25	chronic ischemic heart disease
I25.2	old myocardial infarction
I42.8, I42.9	cardiomyopathy, not otherwise specified
I46	cardiac arrest
I47.0	re-entry ventricular arrhythmia
I47.2	ventricular tachycardia
I49.0	ventricular fibrillation and flutter
I49.8	other specified cardiac arrhythmias
I49.9	cardiac arrhythmia, unspecified
I51.6	cardiovascular disease, unspecified
I51.9	heart disease, unspecified
I70.9	atherosclerosis, not otherwise specified
R96.1	death in <24 hours
R98	unattended death

Use Case Analytic Plan

For both cohort 1 and cohort 2, we will generate a baseline characteristics table. Table 3 includes the proposed list of baseline characteristics and Table 4 includes the initial code lists. We will examine demographic variables, health care utilization intensity measures, and select comorbid conditions during the 365-day baseline period. Expert opinion and review of the literature will inform variable selection. If feasible, we will also consider examining a claims-based measure of frailty [54].

Separately for all-cause mortality, SCD, and cardiovascular death, we will estimate the incidences and incidence rates as the number of outcome events during the observation period as defined in the outcome section below, divided by total persons in cohort (for incidences) or person-time (for incidence rates) of observation. All incidences or incidence rates will also be stratified by cohort. We will further estimate the incidences and incidence rates by age group (<65, 65-74, ≥75 [for all-cause mortality only]), sex, and cohort entry year. To facilitate comparison with previously published estimates, incidence will be presented per 1000 persons and incidence rates will be presented per 1000 person-years. For SCD, we will further estimate the incidences and incidence rates by selecting comorbidities (coronary heart disease [35,36,55,56] and diabetes mellitus [55,57,58]). If feasible, to facilitate comparisons with the literature, we will include analyses using multiple age subgroups (eg, age subgroup 1: 45-54, 55-64, 65-74, 75-84, and ≥85 years; age subgroup 2: 45-46, 47-51, 52-56, 57-61, 62-66, 67-71, 72-74; and 45-54, 55-64, 65-74) [35,64].

Although medical records, autopsy reports, ambulance, or other similar records might be used to validate death information attained from the NDI, this type of evaluation is beyond the scope of this study. If project timelines permit, we will consider two other indirect approaches to evaluate the performance of the NDI+ data linkage. The first strategy would involve comparing rates of mortality and SCD with rates previously reported in the literature. We will describe and examine the incidences and incidence rates of mortality and SCD in the use case cohorts and compare them with estimates previously reported in the literature. This comparison will provide indirect evidence for outcome definition accuracy. For all-cause mortality, we will compare our estimated incidence rates with those from the CDC Wonder data [65]. For SCD, we will compare the incidence rates estimated in cohort 1 with the range of incidence rates reported in the literature (Table 5). In general, we will examine and compare the incidences and incidence rates in cohort 2 with national data sources such as CDC Wonder and studies included in the literature because such data sources and studies focus on the overall population and are thus are comparable with our cohort 2.

Table 3. Baseline characteristics associated with users of antiarrhythmic medications (cohort 1) and among the average-risk population (cohort 2) identified at participating health plans, 2000 to 2017 or latest health plan and National Death Index Plus data availability.

Demographics	Cohort 1[a]	Cohort 2[a]
Age groups (<65, 65-74, ≥75)		
Mean age, in years (±SD)	N/A[c]	N/A
Median age, in years (±SD)	N/A	N/A
Sex, % female	N/A	N/A
Health care utilization intensity measures during the baseline period		
#hospitalizations	N/A	N/A
#emergency department visits	N/A	N/A
#ambulatory care visits	N/A	N/A
#unique medications dispensed	N/A	N/A
Comorbid conditions, identified during the baseline period		
Arrhythmia/conduction disorder, by type	N/A	N/A
Atrial fibrillation and flutter	N/A	N/A
Paroxysmal ventricular tachycardia	N/A	N/A
Ventricular fibrillation and flutter	N/A	N/A
Paroxysmal supraventricular tachycardia	N/A	N/A
Unspecified paroxysmal tachycardia	N/A	N/A
Premature beats	N/A	N/A
Other specified or unspecified cardiac dysrhythmia	N/A	N/A
Cerebrovascular disease	N/A	N/A
Coronary heart disease	N/A	N/A
Diabetes mellitus	N/A	N/A
Heart failure/cardiomyopathy	N/A	N/A
Cardioverter-defibrillator/pacemaker	N/A	N/A
Hyperlipidemia	N/A	N/A
Hypertension	N/A	N/A
Kidney disease	N/A	N/A
Circulatory system disease	N/A	N/A
Seizure disorder	N/A	N/A
Smoking[b]	N/A	N/A
Obesity[b]	N/A	N/A
Charlson comorbidity score		
0	N/A	N/A
1	N/A	N/A
≥2	N/A	N/A
Risk of Torsades de pointes (TdP), per CredibleMeds [28]		
Known risk	N/A	N/A
Possible risk	N/A	N/A
Conditional risk	N/A	N/A
To be avoided by congenital long QT patients	N/A	N/A

[a]This table represents planned study analyses, and cells are blank because analyses are not yet complete.

[b]Although these covariates are often not well-captured in claims data, given the importance of these factors we will include them with the understanding under capture of these elements is expected within source data.

[c]N/A: Not yet available

Table 4. International Classification of Diseases, 9th Revision, Clinical Modification, diagnosis, and procedure codes for identifying comorbidities and other conditions.[a]

Baseline table conditions	Codes
Atrial fibrillation and flutter	ICD-9[b]-CM: 427.31 and 427.32
Paroxysmal ventricular tachycardia	ICD-9-CM: 427.1
Ventricular fibrillation and flutter	ICD-9-CM: 427.4X
Paroxysmal supraventricular tachycardia	ICD-9-CM: 427.0
Unspecified paroxysmal tachycardia	ICD-9-CM: 427.2
Premature beats	ICD-9-CM: 427.6X
Other specified or unspecified cardiac dysrhythmia	ICD-9-CM: 427.8X or 427.9X
Cerebrovascular disease	ICD-9-CM: 430.X-432.X 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.x, 436 362.34, 433.00, 433.10, 433.20, 433.30, 433.80, 433.90, 435.x, 437.0, 437.1, 437.9, 438.x 38.11, 38.12, 38.41, 38.42 325.X, 437.6 781.4, 784.3, 997.0
Coronary heart disease [35,36,55,56]	ICD-9-CM: 410.XX, 412.XX, 412, 413.X, 414.XX
Diabetes mellitus [55,57,58]	ICD-9-CM: 250.XX
Heart failure/cardiomyopathy [35,59,60]	ICD-9-CM: 402.X1, 404.X1, 404.X3, 428.XX
Cardioverter-defibrillator/pacemaker	ICD-9-CM: 996.01, 996.04, V45.X, V53.31, V53.32; ICD-9-CM Volume 3 procedure codes: 00.50—00.54, 37.7X, 37.8X, 37.94, 37.95, 37.96, 37.97, 37.98, 89.45—89.49 CPT-4[c] Category II codes: 00530, 33200—33249, 33262—33264, 93280, 93288, 93294, 93296, 93297, 93640, 93641, 93642 CPT-4 Category III codes: 0319T—0328T Healthcare Common Procedure Coding System codes (HCPCS): C1721, C1722, C1777, C1779, C1785, C1786, C1882, C1895, C1896, C1898, C1899, C2619, C2620, C2621, E0610, E0615, E0617, G0297, G0298, G0299, G0300, G0448, K0606, K0607, K0608, K0609
Hyperlipidemia	ICD-9-CM: 272.0X, 272.1X, 272.2X, 272.3X, 272.4X, 272.7X
Hypertension	ICD-9-CM: 401–405 (excluding 402.01, 402.11, 402.91)
Chronic kidney disease [58,61,62]	ICD-9-CM: 585.3, 585.4, 585.5
Circulatory system disease, thereby capturing rheumatic fever, rheumatic heart disease, hypertensive disease, ischemic heart disease, diseases of pulmonary circulation, other heart disease, cerebrovascular disease, arterial disease, and venous disease	ICD-9-CM: 390.X–459.X
Seizure disorder	ICD-9-CM: 345x, 780.3x (not 780.31)
Smoking tobacco [55][e]	Presence of any the following codes on any claim type: ICD-9-CM: 305.1, 649.0X, 989.84, V15.82; CPT-I: 83887, 99406, 99407; CPT-II: 1034F, 1035F, 4000F, 4001F, 4004F; HCPCS: C9801, C9802, G0375, G0376, G0436, G0437, G8093, G8094, G8402, G8403, G8453, G8454, G8455, G8456, G8688, G9016, S4990, S4991, S4995, S9075, S9453; NDC[d]: nicotine replacement, varenicline, Zyban (brand only)
Obesity [55,63][e]	278.0X
Conditions included in the SCD[f] subgroup analyses	
Coronary heart disease [35,36,55,56]	410.XX, 412.XX, 412, 413.X, 414.XX
Diabetes mellitus [55,57,58]	250.XX

[a]Codes will be mapped to ICD-10-CM (ICD-10: International Classification of Diseases, 10th Revision) codes during the study

[b]ICD-9-CM: International Classification of Diseases, 9th Revision.

[c]CPT-4: Current Procedural Terminology-4.

[d]NDC: National Drug Code.

[e]Although obesity and smoking are often not well-captured in claims data, we will include them with the understanding under capture of these elements is expected within source data.

[f]SDC: sudden cardiac death.

Table 5. Published incidences or incidence rates of sudden cardiac death and all-cause mortality among users of antiarrhythmic medications and among the average-risk population.

Patient characteristics	Events per person or person-years, and/or risk of sudden cardiac death by patient characteristics		Events per person or person-years or risk of all-cause mortality by patient characteristics[a]	
	Antiarrhythmic medication users[b]	Average-risk population, without respect to antiarrhythmic use	Antiarrhythmic medication users	Average-risk population, without respect to antiarrhythmic use
Overall	N/A	0.5-1.5/1000 persons, Deo et al [66], Chugh et al [36], Straus et al [67]	N/A[c]	N/A
Female	N/A	Female<male, Zheng et al [43], Kannel et al [68], Stecker et al [37]; Beginning at age 35, incidence increases monotonically until age 85 (Zheng et al [43], Chugh et al [36], Straus et al [67])	N/A	N/A
55-64 years	N/A	1.0/1000 persons	N/A	N/A
65-74 years	N/A	2.8/1000 persons	N/A	N/A
Male	N/A	Male>female, Zheng et al [43], Kannel et al [59], Stecker et al [37]; Beginning at age 35, incidence increases monotonically until age 85 (Zheng et al [43], Chugh et al [36], Straus et al [67])	N/A	N/A
45-54 years	N/A	1.2/1000 persons	N/A	N/A
55-64 years	N/A	2.8/1000 persons	N/A	N/A
65-74 years	N/A	6.0/1000 persons	N/A	N/A
Year	N/A	Given that sudden cardiac death incidence declined from 1979-1998 [69], it may be reasonable to expect a small decline in incidence from 2001-2002 to 2009-2010. This is likely driven by a reduction in coronary heart disease. Yet, any small decline could be halted by the increasing incidence of heart failure [70]	N/A	N/A
1990-1995	N/A	1.0/1000 person-years (for 1990s) [71]	N/A	N/A
1996-1999	N/A	0.91-1.0/1000 persons [67]	N/A	N/A
2000-2004	N/A	0.79/1000 persons [67]	N/A	N/A
2005-2009	N/A	N/A	N/A	N/A
2010-2014	N/A	N/A	N/A	N/A
2015-2017	N/A	N/A	N/A	N/A
Comorbidities			N/A	
Coronary heart disease		2-12X increased risk, Chugh et al [36], Kannel et al [56,59], Albert et al [72]	N/A	N/A
Presence	N/A	4.6-25.1/1000 persons	N/A	N/A
Absence	N/A	1.5-3.6/1000 persons	N/A	N/A
Diabetes mellitus		2-3 times increased risk, Jouven et al [73,74], Albert et al [72], Vasiliadis et al [58]; 1.3/1000 person-years in sulfonylurea users Leonard et al [75]	N/A	N/A
Presence	N/A	N/A	N/A	N/A
Absence	N/A	N/A	N/A	N/A

[a]Estimates from CDC Wonder or other national death data sources.

[b]Estimates located at the time or protocol development were included, blank cells indicate no available information at the time of protocol development.

[c]N/A: Not yet available.

The second strategy would be to examine the concordance between NDI data and health plan death data. Several participating health plans collect death information through linkage with the state death records. If timeline and resources permit, this project will attempt to identify time periods in which death information is considered well populated within each health plan and examine the concordance of this information with information attained through linkage to NDI data. At health plans that do not attain death information from state death records, if timeline and resources permit, we will consider examining discharge disposition (ie, discharged expired) for in-hospital deaths included in health plan databases, and comparing this information with NDI data. Although we expect agreement between both data sources, such comparisons will assist in any evaluations of matching with NDI data and would also provide indirect evidence for accuracy (Table 6).

Table 6. Example concordance matrix, all-cause mortality (to be repeated for each health plan and time period of interest[a]).

NDI[b] data	Health plan data	
	Health plan 1 death=yes[c]	Health plan 1 death=no[c]
NDI death=yes	A	C
NDI death=no	B	D

[a]Death data within the health plan databases are known to be incomplete. Time period of interest will be time periods in which participating health plans are confident in the completeness of their death data. Additional stratifications, such as stratifying results by data source (eg, hospital discharge disposition) may be conducted.

[b]NDI: National Death Index.

[c]No gold standard, can only describe concordance and discordance (ie, "a" and "d" concordance, "b" and "c" discordant).

Proposed Use Case Workflow

Below, we summarize a high-level overview of steps to execute the use case.

1. Study team will finalize the following:
   - Use case specifications
   - Criteria for NDI patient record submission
   - The limited set of identifiable data elements needed for NDI+ matching
   - Analytic plan
2. The HPHCI will develop a cohort identification program that will query health plan databases formatted in the Sentinel Common Data Model. This program will identify individuals who meet the criteria entry into the cohorts as well as for matching with the NDI at the participating health plans; the program will be distributed to participating health plans for local execution.
3. Participating health plans will populate files to be sent directly to the NDI from their operational data source with the NDI required patient identifiers (eg, name, date of birth, age, social security number).
4. The HPHCI will develop a data quality assurance and check program that will ensure that the data files to be sent to the NDI are completely populated, meet NDI's minimal criteria as eligible for matching, and are correctly formatted. The program will be distributed to participating health plans for local execution.
5. Participating health plans will individually submit the necessary quality-checked data files to the NDI.
6. The NDI will conduct matching activities and return files to health plans.
7. The HPHCI will develop a program to remove all identifiable data, identify matches to be saved, and create analytic files with minimally necessary information from health plan data and the NDI. The program will be distributed to participating health plans for local execution.
8. The HPHCI will develop an analytic program to generate information necessary to conduct the statistical analysis for the use case. The program will be distributed to participating health plans for local execution, and only summary-level information will be shared between health plans and the coordinating center.
9. The HPHCI will retrieve output produced by health plans and complete the statistical analysis.
10. The HPHCI will lead the writing of the final project report and standard operating procedures.

Results

We will use the linked health plan and NDI+ data sets to estimate the incidence and incidence rate of mortality and specific causes of death within the use case and compare the results with previously reported estimates. These comparisons provide an opportunity to assess the performance of the developed NDI+ linkage approach and lessons to future studies requiring NDI+ linkage in distributed database settings. This study is approved by the Harvard Pilgrim Health Care IRB in Boston, MA. We will present results and the reusable NDI+ linkage approach to the FDA, at academic conferences, and publish in peer-reviewed journals. We have attained NDI approval and are summarizing the administrative processes that we developed and implemented for use in other studies. Currently, the study team is in the process of developing and testing the distributed NDI+ linkage process as described above and anticipates having initial results in early 2021.

Discussion

Use Case Limitations

Given that the outcomes of death, SCD, and cardiovascular death could be rare in the general population; large cohorts will be required to adequately address the use case. Although we anticipate potentially large available sample sizes within the

use case, estimates of incidences and incidence rates in small subgroups may be imprecise. If it is not feasible to perform linkage for all the identified individuals, we will develop a sampling scheme that will still allow us to pilot the linkage methods.

The incidences and incidence rates estimated from our study may not be directly comparable with those reported in the literature. For example, our proposed use case exclusion conditions and matching of persons in cohort 2 with persons of cohort 1 by age, sex, health plan, and index dates (thereby making the population in cohort 2 more similar to the antiarrhythmic medication users in cohort 1), may make our population of interest different from other populations studied previously. In addition, privately insured patients may have lower mortality rates compared with the general population owing to better health care access. Due to these anticipated differences, the comparison between the incidences and incidence rates derived from our study and the literature-reported estimates will be performed qualitatively.

Some of the outcome algorithms used in this study have been validated in other data sources but have not been validated specifically within the participating health plan databases. For example, the SCD algorithm by Chung et al [27] was originally developed and implemented within a population including Tennessee Medicaid recipients aged 30-74 years. While the participating health plans in this study include mainly commercially insured populations, Medicaid beneficiaries included in the study by Chung et al may be different (eg, more vulnerable, economically disadvantaged). However, in our study, one participating health plan also provides Tennessee Medicaid data, and thus analyses stratified by health plan may inform potential population differences. In addition, the Chung et al study relied on both death certificate data and state hospital discharge data when developing a computerized algorithm to identify SCD. Although not all information included in the Chung et al study is available to participating health plans, the selected algorithms can be adapted to utilize data elements available within health plan data. The potential inability to replicate validated computerized algorithms developed in other data sources in their entirety is a study limitation.

Health plan disenrollment will be used as a proxy to select individuals for linkage to NDI+ data. Most individuals who disenroll from their health plans have not died but instead have lost or changed their insurance coverage. If individuals in an average-risk cohort are healthier and more likely to change health insurance plans, they may have higher rates of disenrollment than antiarrhythmic medication users. These higher rates of disenrollment are unlikely to reflect death and may lead to a disproportionate number of submissions to the NDI that do not result in a death record. We expect that the incidence of death and SCD will be low and disenrollment rates will be high (approximately 20%-30% per year). Therefore, we expect that our NDI+ data linkage activity will yield false positives. However, given the goal of this project is to determine an algorithm for identifying individuals to submit to NDI in future studies, lessons learned concerning false positives during analyses examining concordance between health plan death data and NDI data as well as ways to refine the disenrollment algorithm will inform future NDI+ data linkage studies.

In general, study results will be highly dependent on the quality of the NDI+ data linkage. Some identifiers that would be highly desirable to use as keys for linkage may not be uniformly available across all health plans. For example, provision of social security number information to the NDI will likely increase the number of correct matches. However, social security number information is not always complete in health plans. A lack of social security number submittal could result in a greater number of multiple matches returned by the NDI, which requires resolution and selection. The study team is designing strategies to optimize the selection of the best match. However, regardless of whether a social security number is submitted, it is possible that an incorrect match could be selected. In addition, if personal identifiers submitted by the health plans are incorrect, mismatches between health plan and NDI+ data could also occur. Such mismatches will most likely result in misclassifying patients who are dead as alive (ie, unable to locate a death in NDI+ data). The study team has anticipated these potential issues and is designing quality assurance steps where possible. To inform future studies, we will summarize lessons learned about ways to maximize the quality of the NDI+ data linkage.

Study Strengths

The NDI is currently the best data source of death and cause-of-death information for large-scale population-based epidemiologic studies in the United States. We anticipate the development of standardized processes to attain and analyze death and cause-of-death information from the NDI will provide avenues for multisite research networks to efficiently obtain more complete death information. As many health plans that participate in multisite research networks do not have complete capture of out-of-hospital deaths or cause-of-death information, the ability to efficiently attain this information from the NDI may provide opportunities to answer a wider variety of mortality-related research questions. We also anticipate that our newly developed NDI+ linkage methods will enhance the FDA's ability to answer mortality-related safety questions in distributed networks.

Although conducted independently of the Sentinel Initiative, our study will leverage the infrastructure of a well-known distributed network, the FDA Sentinel System [7,8], to develop and test reusable administrative and technical processes for linking multiple health plan databases with NDI+ data. Leveraging the Sentinel System infrastructure will ensure that health plan databases are standardized and research ready. As our study sites are health plans that participate in the Sentinel System, administrative processes or NDI+ data linkage programs we will develop could be reused by the Sentinel System as well as other multisite studies using distributed research networks. As the Sentinel System publishes its common data model publicly [7,8] and in some instances provides translation code to help certain data sources with data conversion, other researchers would have the ability to directly transform other health plan databases into the Sentinel Common Data Model and directly use any developed NDI+ data linkage programs from this study for NDI+ data linkage. In addition, we will test

our newly developed NDI+ data linkage methods among a diverse group of participating health plans (ie, national insurers, regional health plans, and integrated delivery systems, which cover both commercial and public insurance programs). We anticipate that our testing will ensure that developed NDI+ data linkage processes will be applicable to multiple settings.

Another strength of this study is our focus on developing a distributed process for NDI+ data linkage in multisite research studies. A distributed approach allows individual study sites to maintain physical and operational control over their electronic health data behind their respective firewalls, thus promoting data sharing by protecting patient privacy, data security, and proprietary interests [9-11]. We will develop methods that will allow health plans to work directly with the NDI and eliminate sharing of identifiable patient information between participating health plans or the coordinating center.

Finally, we chose our antiarrhythmic medications use case to robustly test the NDI+ data linkage processes within a cohort at high risk of death (antiarrhythmic medication users) and a cohort at average risk of death (nonusers matched by age and sex to antiarrhythmic medication users). This use case should provide sufficient sample sizes for patients who are dead and alive. To indirectly validate our newly developed linkage methods, we plan to examine the concordance between NDI data and health plan death data as well as compare rates of mortality and SCD with rates previously reported in the literature. Information we will gather as part of these indirect validation activities will provide some metrics for the performance of our NDI+ data linkage methods.

Anticipated Study Contributions

We anticipate this project to provide future studies with a tested administrative workflow that facilitates efficient, coordinated, multicenter IRB review and approval for linking health plan data with NDI+ data in accordance with the revised Common Rule. We will also provide recommendations for completing a successful NDI application, along with lessons learned that may help future studies navigate the process more efficiently. We will develop a standardized and reusable distributed technical process for efficiently attaining and analyzing death and cause-of-death information from the NDI across multiple health plan databases without sharing protected health information between health plans or with the coordinating center. Our study will also provide considerations for determining which patients to submit to the NDI for matching. We will leverage lessons learned by developing and testing our NDI+ data linkage methods with the goal of improving the ability to answer mortality-related research questions within multisite studies based in distributed data networks.

Acknowledgments

This project is supported by the US Department of Health and Human Services (HHS), Assistant Secretary of Planning and Evaluation, Patient Centered Outcomes Research Trust Fund, through the Food and Drug Administration contract number HHSF223301710132C, project titled, “A Reusable Method to Link Health Plan Data with the National Death Index Plus to Examine the Associations Between Medical Products and Death and Causes of Death.” This paper reflects the views of the authors and does not necessarily represent the FDA’s views or policies.

A previous mini-Sentinel project workgroup laid an important groundwork for this project and included the following members and organizations: Steven Bird, Victor Crentsil, David Graham, Terry Harrison, Monika Houstoun, Stephanie Keeton, Susan Lu, Katrina Mott, Rita Ouellet-Hellstrom, Simone Pinheiro, Marsha Reichman, Marry Ross Southworth, and Anne Tobenkin of Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration; Eric Frimpong and Margie Goulding of Harvard Pilgrim Health Care Institute; Sascha Dublin, Monica Fujii, Kristina Hansen, Jennifer Nelson, and Robert Wellman of Group Health Research Institute; Susan Andrade of Meyers Primary Care Institute; Nancy Lin of OptumInsight Life Sciences Inc; Todd Lee of University of Illinois at Chicago; Rajat Deo and Sean Hennessy of Center for Pharmacoepidemiology Research and Training, Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania; and James Floyd, Bruce Psaty and David Siscovik of University of Washington Department of Biostatistics.

Furthermore, the authors acknowledge the helpful input and contributions to the current project as follows: Noelle Cocoros, Qoua Her, April DuCott, Matthew Lakoma, Christine Draper, Zilu Zhang, Elizabeth Dee, and Susan Forrow of Harvard Pilgrim Health Care Institute; Jacqueline M Major, Deloris Willis, Carla Walls, Denise Jones, and Rita Noel of Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration; Sonal Singh of Meyers Primary Care Institute; and Samantha Soprano of Center for Pharmacoepidemiology Research and Training, Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania.

Authors' Contributions

CF collaborated with coauthors on the study design and wrote the protocol. All authors reviewed and approved the final manuscript.

Conflicts of Interest

CEL serves on the Executive Committee of the University of Pennsylvania's Center for Pharmacoepidemiology Research and Training. The Center receives funds for education from Pfizer and Sanofi. He recently received honoraria from the American College of Clinical Pharmacy Research Institute and the University of Florida College of Pharmacy. CEL's research is funded

by the American Diabetes Association, Food and Drug Administration, and National Institutes of Health. CEL is a Special Government Employee of the Food and Drug Administration.

Multimedia Appendix 1
Proposed National Death Index submission criteria to be used to determine which individuals will be initially selected for sending to the NDI, thereby obtaining death and cause-of-death information.
[PPTX File , 47 KB - resprot_v9i11e21811_app1.pptx]

Multimedia Appendix 2
Operational definitions of outcomes of interest in the use case.
[PPTX File , 53 KB - resprot_v9i11e21811_app2.pptx]

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Abbreviations

FAERS: FDA Adverse Event Reporting System
FDA: United States Food and Drug Administration
FWA: Federalwide Assurance
HPHCI: Harvard Pilgrim Health Care Institute
ICD-9: International Classification of Diseases, 9th Revision
ICD-10: International Classification of Diseases, 10th Revision
IRB: institutional review board
NCHS: National Center for Health Statistics
NDI: National Death Index
NDI+: National Death Index Plus
SCD: sudden cardiac death
SSA: Social Security Administration

Edited by G Eysenbach; submitted 29.06.20; peer-reviewed by N Mohammad Gholi Mezerji, G Luo; comments to author 22.07.20; revised version received 04.08.20; accepted 11.08.20; published 02.11.20.

Please cite as:
Fuller CC, Hua W, Leonard CE, Mosholder A, Carnahan R, Dutcher S, King K, Petrone AB, Rosofsky R, Shockro LA, Young J, Min JY, Binswanger I, Boudreau D, Griffin MR, Adgent MA, Kuntz J, McMahill-Walraven C, Pawloski PA, Ball R, Toh S
Developing a Standardized and Reusable Method to Link Distributed Health Plan Databases to the National Death Index: Methods Development Study Protocol
JMIR Res Protoc 2020;9(11):e21811
URL: https://www.researchprotocols.org/2020/11/e21811
doi:10.2196/21811
PMID:33136063

Original Paper

Length of Initial Prescription at Hospital Discharge and Long-Term Medication Adherence for Elderly, Post-Myocardial Infarction Patients: Protocol for an Interrupted Time Series Study

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Abstract

Background: Based on high-quality evidence, guidelines recommend the long-term use of secondary prevention medications post-myocardial infarction (MI) to avoid recurrent cardiovascular events and death. Unfortunately, discontinuation of recommended medications post-MI is common. Observational evidence suggests that prescriptions covering a longer duration at discharge from hospital are associated with greater long-term medication adherence. The following is a proposal for the first interventional study to evaluate the impact of longer prescription duration at discharge post-MI on long-term medication adherence.

Objective: The overarching goal of this study is to reduce morbidity and mortality among post-MI patients through improved long-term cardiac medication adherence. The specific objectives include the following. First, we will assess whether long-term cardiac medication adherence improves among elderly, post-MI patients following the implementation of (1) standardized discharge prescription forms with 90-day prescriptions and 3 repeats for recommended cardiac medication classes, in combination with education and (2) education alone compared to (3) usual care. Second, we will assess the cost implications of prolonged initial discharge prescriptions compared with usual care. Third, we will compare clinical outcomes between longer (>60 days) versus shorter prescription durations. Fourth, we will collect baseline information to inform a multicenter interventional study.

Methods: We will conduct a quasiexperimental, interrupted time series design to evaluate the impact of a multifaceted intervention to implement longer duration prescriptions versus usual care on long-term cardiac medication adherence among post-MI patients. Intervention groups and their corresponding settings include: (1) intervention group 1: 1 cardiac center and 1 noncardiac hospital allocated to receive standardized discharge prescription forms supporting the dispensation of 90 days' worth of cardiac medications

with 3 repeats, coupled with education; (2) intervention group 2: 4 sites (including 1 cardiac center) allocated to receive education only; and (3) control group: all remaining hospitals within the province that did not receive an intervention (ie, usual care). Administrative databases will be used to measure all outcomes. Adherence to 4 classes of cardiac medications — statins, beta blockers, angiotensin system inhibitors, and secondary antiplatelets (ie, prasugrel, clopidogrel, or ticagrelor) — will be assessed.

Results: Enrollment began in September 2017, and results are expected to be analyzed in late 2020.

Conclusions: The results have the potential to redefine best practices regarding discharge prescribing policies for patients post-MI. A policy of standardized maximum-duration prescriptions at the time of discharge post-MI is a simple intervention that has the potential to significantly improve long-term medication adherence, thus decreasing cardiac morbidity and mortality. If effective, this low-cost intervention to implement longer duration prescriptions post-MI could be easily scaled.

Trial Registration: ClinicalTrials.gov NCT03257579; https://clinicaltrials.gov/ct2/show/NCT03257579

International Registered Report Identifier (IRRID): DERR1-10.2196/18981

(JMIR Res Protoc 2020;9(11):e18981) doi:10.2196/18981

KEYWORDS

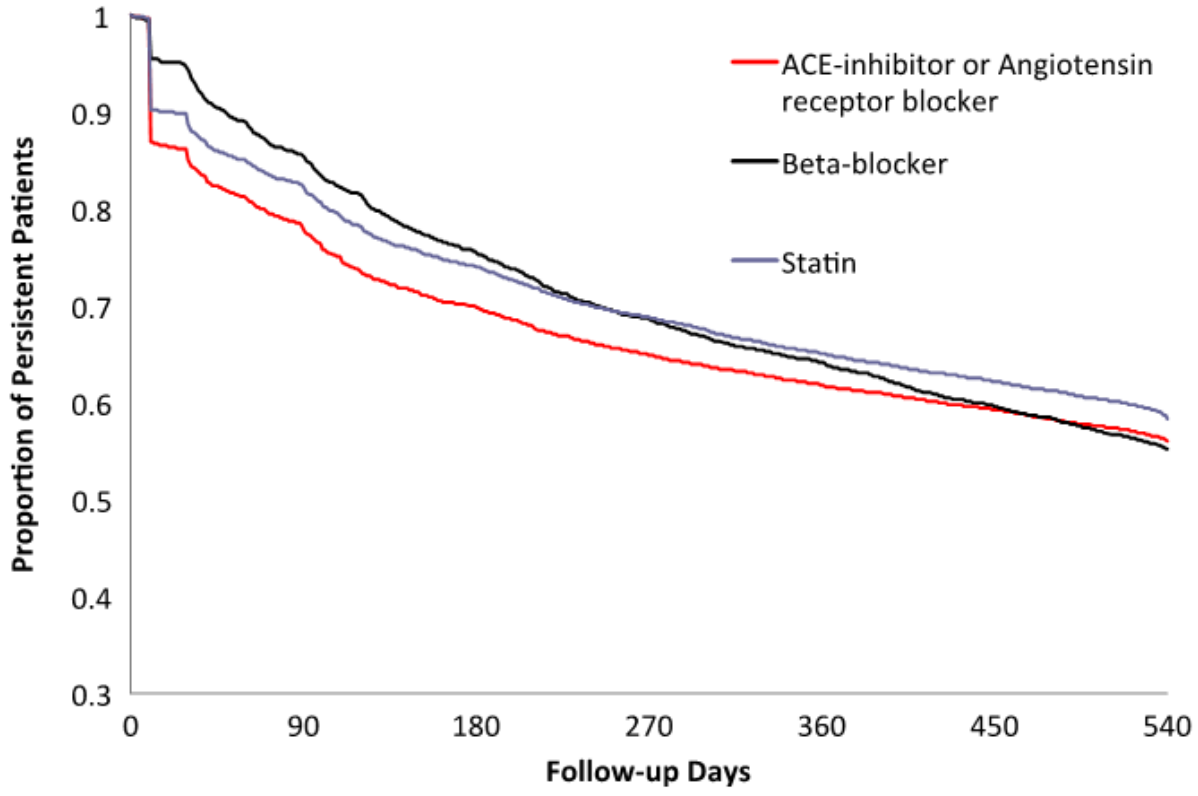
post-myocardial infarction; adherence; standardized discharge prescription form; secondary prevention; policy change; medication; elderly; intervention; prescription; discharge; prevention; cardiology; heart

Introduction

Background

International guidelines recommend the long-term use of secondary preventative cardiac medications following a myocardial infarction (MI) [1-3]. The medication classes used for secondary prevention post-MI include both a primary antiplatelet (aspirin) and secondary antiplatelet (eg, prasugrel, clopidogrel, or ticagrelor), statins, beta blockers, and angiotensin system inhibitors (ie, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker). These medications provide an expected 60% relative risk reduction of recurrent cardiovascular events [1,2]. However, studies have shown that postdischarge cardiac medication adherence tends to steadily decline over time (Figure 1) [4-12]. Multiple studies have shown an increased risk of morbidity and mortality associated with medication nonadherence in patients with coronary artery disease (CAD) [10-14].

Figure 1. Persistence with secondary prevention medications after angiography. ACE: angiotensin-converting enzyme.



Although medication adherence is a complex phenomenon with multiple interacting factors, there is emerging evidence that a simple step taken by health care providers at the time of hospital discharge plays an important role in long-term adherence. In a population-based observational study of over 18,000 patients conducted by our research team, greater long-term adherence

to cardiac medications was observed in Ontario patients receiving longer initial prescriptions (>60 days versus <31 days) at the time of discharge [4]. Specifically, a higher proportion of patients receiving longer duration prescriptions had greater than 80% proportion of days covered (PDC) in the 18 months following hospital discharge for angiotensin system inhibitors (adjusted odds ratio [OR] 4.1, 95% CI 3.6-4.7), beta blockers (adjusted OR 2.4, 95% CI 1.9-3.1), and statins (adjusted OR 3.0, 95% CI 2.6-3.4) [4]. Two earlier studies found similar results. Batal et al [15] analyzed a cohort of 3386 patients from a large US health care center and found higher adherence to statins in patients with mostly 60-day prescriptions as compared to those with mostly 30-day prescriptions (adjusted risk ratio 1.4, 95% CI 1.3-1.6). Steiner et al [16] examined maintenance of medication in 290 outpatients from Veteran Affairs Centers in the United States and found that those with longer prescriptions for digoxin (ie, at least a 90-day supply) were more likely to regularly acquire the medication over 9 to 14 months. While these 3 observational studies suggest an association between prescription duration and long-term medication adherence, evidence from a prospective study is required to support implementation of this policy as a best practice.

Rationale and Study Objectives

Poor medication adherence was identified by the World Health Organization in 2003 as a worldwide challenge in the management of chronic diseases [17]. The consequences of suboptimal adherence include undesirable health outcomes as well as increased health care costs. Both provider-level and system-level factors play important roles in optimizing adherence. We have previously shown that inappropriate beliefs regarding risk perception and outcome expectancies, prescription refill burden, and unintentional forgetfulness due to lack of habituation all contribute to the observed general decline in medication adherence over time [18-20]. Providing longer prescriptions at the time of discharge can address all of these barriers. However, prescriptions covering ≥90 days are currently provided to only 21% of all cardiac patients and to no more than 54% of MI patients, suggesting an opportunity for this change to benefit many patients [4,21].

We know of no guidelines or practice standards for physicians that recommend the prescription of maximum duration (ie, ≥90 days) for cardiac medications at discharge. The use of standardized hospital-based medication discharge practices has been shown to minimize medication errors and to optimize guideline-recommended therapies [22]. However, no prospective study has evaluated the effects of implementing an institutional policy or standardized discharge cardiac medication prescriptions of maximum duration on long-term medication adherence. Therefore, it is hypothesized that longer prescription duration at discharge will promote better long-term cardiac medication adherence.

The specific objectives of this study include estimating and comparing the effects on long-term cardiac medication adherence of (1) a standardized discharge form featuring prescription duration of 90 days with 3 repeats in post-MI patients in combination with education, (2) education only, and (3) usual care (ie, no intervention regarding prescription duration) and assessing the economic implications of the prolonged initial discharge prescriptions as compared to usual care. To our knowledge, this project is the first interventional study to investigate how modifying prescription duration impacts medication adherence.

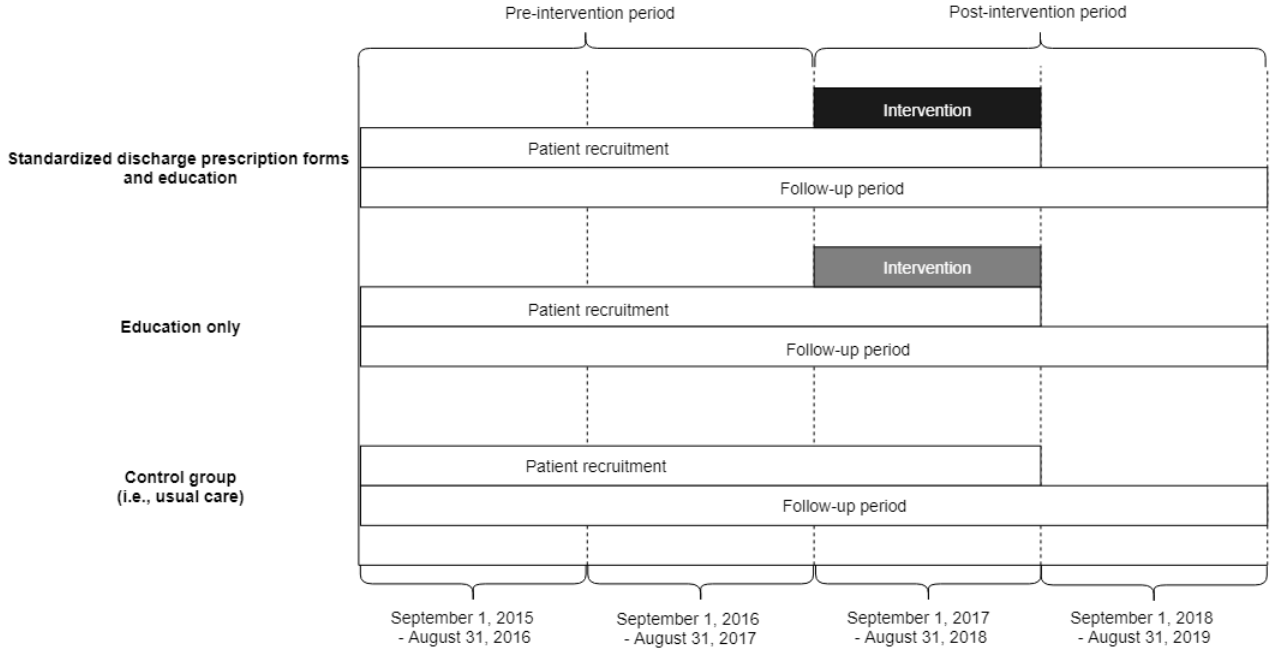
Methods

Trial Setting and Design

The Myocardial Infarction Prescription Adherence Duration (MIPAD) study will use a quasiexperimental, interrupted time series design to evaluate the impact of standardized prolonged discharge prescription forms and education versus usual care on long-term cardiac medication adherence among elderly, post-MI patients in Ontario who were discharged from hospital following a cardiac catheterization procedure between September 1, 2015 and August 31, 2018.

After the first 24 months within the study window (ie, the pre-intervention period: September 1, 2015 through August 31, 2017), a total of 6 sites (2 of which are cardiac centers, where advanced cardiac procedures are performed in Ontario) across 3 hospital corporations (Hamilton Health Sciences [HHS], St. Joseph's Healthcare Hamilton, and Niagara Health System [NHS]) were nonrandomly allocated to receive at least one of the two planned intervention packages for the subsequent 12 months (ie, the post-intervention period: September 1, 2017 through August 31, 2018; Figure 2). These 6 intervention sites were chosen as a convenience sample based on the investigators' affiliations. Irrespective of intervention package received (detailed fully in the following sections), all interventions were implemented starting September 1, 2017 at each of these sites. All 6 intervention sites are within the same health care region in southwest Ontario, Canada, which serves approximately 1.4 million people. All other Ontario hospitals will collectively act as a contemporaneous control group [23,24].

Figure 2. Intervention and control groups in the Myocardial Infarction Prescription Adherence Duration (MIPAD) study.



Intervention Packages

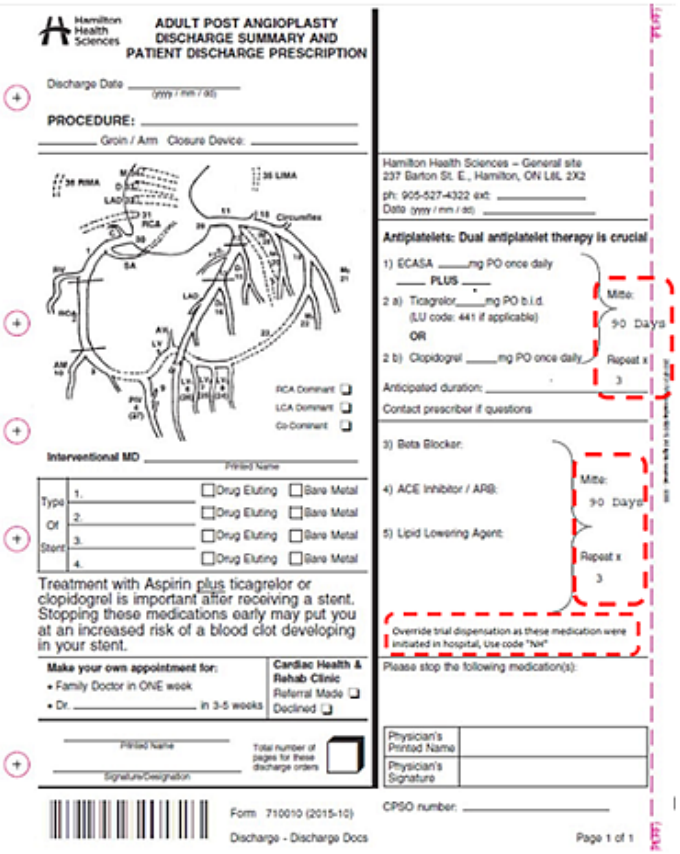
Groups

The MIPAD study team delivered a multifaceted intervention to reduce morbidity and mortality among post-MI patients through improving long-term adherence to secondary prevention medications. Intervention group 1, comprised of 1 cardiac center and 1 noncardiac hospital (both belonging to the same hospital corporation), received both revised standardized discharge prescription forms and education. Intervention group 2, comprised of the other 4 sites across 2 hospital corporations (including 1 cardiac center), received education alone. The remaining Ontario hospitals, comprising the parallel control group, did not receive any intervention (ie, usual care) [23,24]. The knowledge-to-action framework informed the hypothesis, intervention development, and evaluation of this study [25].

Standardized Discharge Prescription Forms

We implemented a revised standardized discharge prescription form available on all wards where MI patients are managed. The revised prescription form has a default of a 90-day supply with 3 repeats for recommended cardiac medications (ie, primary antiplatelet [aspirin], statin, beta blocker, angiotensin system inhibitor, and secondary antiplatelet). Current discharge prescription forms leave the dispensation amount and repeats to the discretion of the individual physician. To encourage community pharmacists to dispense 90 days' worth of medications at discharge, in accordance with the revised discharge prescriptions, the Ontario Pharmacists Association recommended that the following statement be included on the discharge prescription: "Override trial dispensation as these medications were initiated in hospital, Use code NH." This is a standard mechanism to ensure patients with drug coverage from a provincial payer (ie, the Ontario Drug Benefit [ODB] Plan) receive the correct amount of medications on their first fill post-discharge. See Figure 3 for a copy of the discharge prescription form and highlighted revisions. The intervention may be tailored by the physician to allow shorter discharge prescription durations for cost consideration in patients less than 65 years of age and without medication insurance. Monthly monitoring with intervention group 1 ward visits ensured standardized prescription forms were being implemented.

Figure 3. Example discharge prescription from Hamilton Health Sciences with intervention revisions circled.



Education

The education-based intervention consists of both components detailed in the following sections.

For educational outreach to the hospital staff, educational rounds for all involved health care providers (eg, physicians, residents, nurses) at each of the 6 sites took place at the start of the intervention period to outline the evidence regarding longer prescriptions at discharge and encourage this change in discharge practices. In a preliminary survey of 82 health care providers in the study region, 95% said they would use standardized discharge prescriptions with 3 months of cardiac medication supplies and 3 repeats but less than 50% admitted that they currently provide medication supplies to cover a year (Schwalm, unpublished data). Further education (eg, emails, mailouts, site visits) occurred every 3 months during the intervention period.

For educational support of community pharmacies, in addition to the statement "Override trial dispensation as these medications were initiated in hospital, Use code NH" added to the discharge prescriptions, outreach via personal emails and newsletters to community pharmacies in the study region was undertaken with help from the Ontario Pharmacists Association and Ontario Pharmacy Evidence Network. This outreach was intended to help ensure fidelity of the intervention when medications were dispensed at discharge.

Data Sources

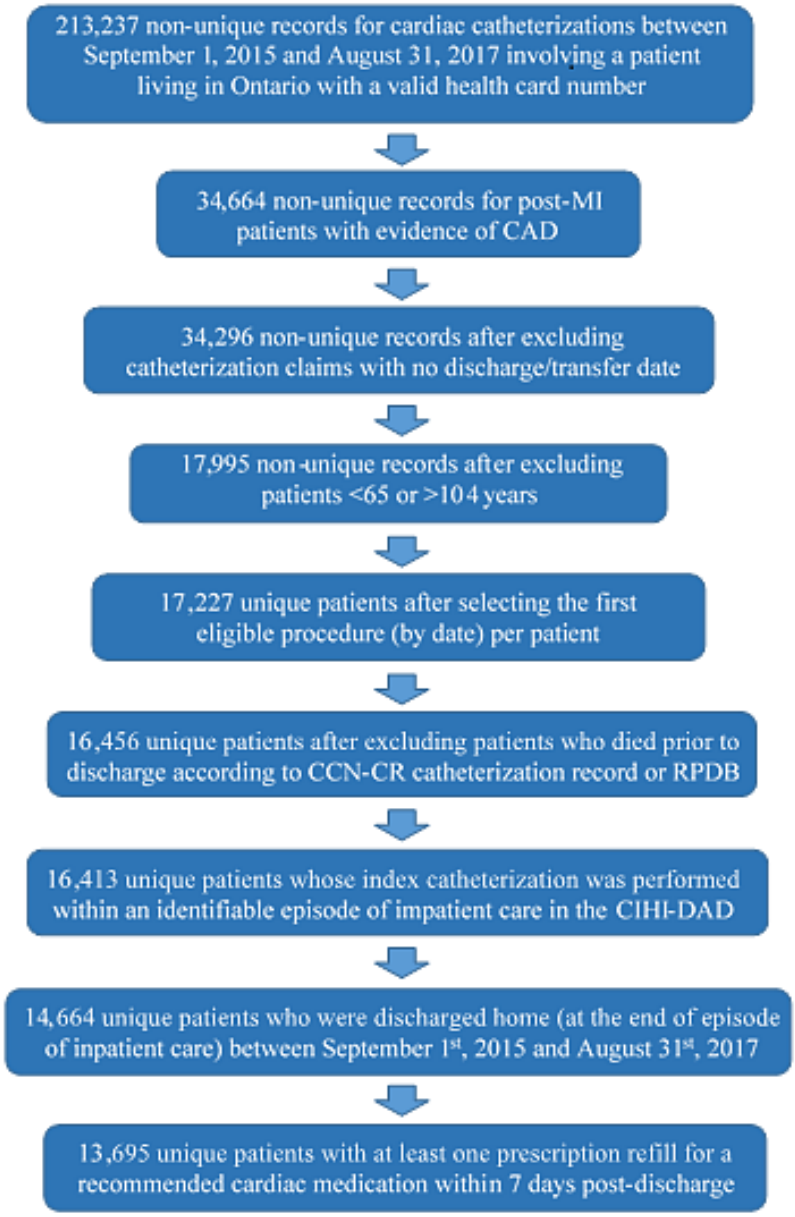
The following administrative databases held at ICES McMaster will be linked and analyzed for the MIPAD study: (1) CorHealth Cardiac Registry (CCN-CR), which is a clinical database containing information such as demographics, comorbidities (eg, diabetes, hypertension, prior heart disease), and procedure-specific details (eg, referral date, patient wait time, complications, results) for patients who undergo a cardiac procedure (eg, cardiac catheterization, percutaneous coronary intervention, or coronary artery bypass graft surgery) in Ontario [26]; (2) Canadian Institute for Health Information Discharge Abstract Database, which captures demographic, clinical, and administrative information on all hospital inpatient discharges (including deaths, sign-outs, and transfers) in all provinces and territories except Quebec; (3) National Ambulatory Care Reporting System, containing data for all ambulatory care provided in hospital (eg, day surgeries and emergency department visits) or in the community across Canada; (4) ODB database, which captures all prescription medication dispensations for Ontario residents covered under the ODB plan (including those aged 65 years and older); (5) Ontario Health Insurance Plan database, covering physician billings for procedures and consultations; and (6) Registered Persons Database, containing demographic information (including date of death) on all persons registered under the Ontario Health Insurance Plan, which is the majority of Ontario residents. The CCN-CR has been used for numerous quality assurance and research projects, including 1 observational and 1 randomized controlled trial (RCT) conducted by the principal investigators of the MIPAD study [4,27]. Several provinces and territories (including Ontario) also use the Canadian Institute for Health Information Discharge Abstract Database to capture day surgeries [28]. Of the 5 recommended cardiac medication classes post-MI, aspirin (primary antiplatelet) is poorly captured in the

ODB, as most dispensations are private pay. Correspondingly, measurement of medication adherence in this study will only concern statins, beta blockers, angiotensin system inhibitors, and secondary antiplatelets.

Recruitment

Our study population will consist of patients aged 65 years and older who were discharged home from an Ontario hospital between September 1, 2015 and August 31, 2018 following a cardiac catheterization post-MI with evidence of CAD [29]. First, we will identify any CCN-CR claims for a cardiac catheterization with the primary referral reason being a ST-elevation myocardial infarction (STEMI) or non-STEMI with evidence of CAD, defined as left main artery stenosis ≥50% or major epicardial coronary artery stenosis ≥70% (Multimedia Appendix 1) [29]. Patients will be excluded if they meet any of the following criteria: site of procedure missing on their index claim, invalid or missing health card number, non-Ontario resident, <65 years of age (ie, patients who are not automatically eligible for ODB due to age) or ≥105 years of age, or died prior to discharge. Lastly, we will restrict to patients who filled a prescription for at least one medication from one of the 4 recommended cardiac medication classes (ie, statin, beta blocker, angiotensin system inhibitor, or secondary antiplatelet) within 7 days of discharge. This 1-week window was specified based on pre-intervention data, which determined that 93.4% of patients meeting all other exclusion criteria filled at least one recommended cardiac medication within 7 days (with 87.2% having their first fill within 1 day of discharge). We will herein refer to this initial prescription fill as a patient's index fill. If patients have multiple eligible index cardiac catherization claims within the accrual window — an uncommon occurrence based on pre-intervention data — we only include the patient's first claim (ie, earliest by date). Figure 4 fully summarizes the application of eligibility criteria to accrue study participants within the pre-intervention period.

Figure 4. Flow of participants into the study during the pre-intervention period (preliminary data used for power calculation). Notes: Patient age determined at procedure date – 120 days. CAD: coronary artery disease; CCN-CR: Cardiac Care Network – Cardiac Registry; CIHI-DAD: Canadian Institute for Health Information - discharge abstract database; MI: myocardial infarction; RPDB: registered persons database.



Outcome Measures

Primary Outcome

The primary outcome will be long-term cardiac medication adherence assessed at 365 days from discharge. To calculate the primary outcome per patient, first we will identify the number of unique cardiac medication classes (out of 4) — statins, beta blockers, angiotensin system inhibitors, and secondary antiplatelets (ie, prasugrel, clopidogrel, or ticagrelor) — that were dispensed, as per ODB claims on the patient's index fill date. The PDC will then be calculated per class [30,31], as it is generally a more conservative measure of adherence than the medication possession ratio [30,32]. If patients have 2 or more filled prescriptions for drugs in the same medication class with overlapping days supplied, we will assume the supply was used in sequence, as multiple doses of a drug in the same class would not typically be administered simultaneously [33]. The sum of class-specific PDC values across all classes will then be derived for each patient. Patients with an average PDC ≥80% among those medication classes dispensed at their index fill will be considered as adherent to their cardiac medication regimen [34]. For patients who die during their 1 year of follow-up, their PDC per class will be calculated over the time elapsed (in days) between their index fill and death date. It is not expected that this intervention will increase the number of cardiac medications prescribed to post-MI patients at the time of discharge but rather improve the long-term adherence to the cardiac medications initiated at discharge.

Secondary Outcomes

Class-specific adherence (defined as a dichotomous outcome) will also be independently defined as PDC ≥80% for a given drug class at 1 year from discharge. Class-specific medication persistence (defined as a dichotomous outcome) will also be independently defined as having claims for any type of medication within that class from discharge date through the following 365 days with no period of 30 days or more without supply (ie, a discontinuation). The number of unique cardiac medication classes (range, 1-4) filled by a patient at their index fill will also be modelled to investigate whether either intervention meaningfully altered the number of medication classes per patient. Additionally, at the time of a patient's index fill, we will measure the number of days supplied per medication class and the average number of days supplied across all unique medication classes — both outcomes will be dichotomized (ie, ≥90 days supplied versus <90 days supplied).

In addition to medication adherence–based and persistence-based outcomes, we will assess health care utilization and adverse clinical outcomes at 365 days from discharge including the frequency of outpatient primary care visits, frequency of outpatient cardiology visits, hospitalization for cardiovascular disease, hospitalization due to repeat acute MI, hospitalization due to stroke, repeat cardiac catheterization, coronary revascularization, and death. For both visit-based outcomes, visits occurring on the same day as discharge will be excluded.

Statistical Analysis

Primary Outcome Analysis

Our primary analytical approach will use segmented linear regression analyses of the aggregate monthly data in each group. To promote stability of the time series, we will pool data across the hospitals within each intervention group (ie, standardized discharge prescription forms plus education [intervention group 1] or education only [intervention group 2]). Within each of the 2 intervention groups, we will then independently analyze the aggregated monthly proportions of patients adherent to their cardiac medication regimen at 1 year (expressed as a percentage) using segmented linear regression. In case of nonlinearity of the monthly series, segmented logistic regression analysis of the monthly proportions will be used. Terms will be included for time (in months; treated as continuous [range, 0-35]), intervention (an indicator denoting observations from the post-intervention window), and time post-intervention (defined as time-23 if observation from post-intervention period; 0 otherwise) [35,36]. Serial autocorrelation will be accounted for using first-order autoregressive errors. Visual assessment of model residuals plotted against time will be used to assess goodness of fit. Intervention effects estimated using segmented linear autoregressive error models will be expressed as absolute post-intervention changes in the intercept and slope with corresponding 95% CIs. Post-intervention changes in intercept (or level) and slope (or trend) can respectively be interpreted as the immediate and gradual effects of the intervention on the primary outcome over time [35,36]. Additionally, we will express the overall intervention effect (ie, as combined intercept and slope changes) at the end of the study, on the absolute scale, by comparing the fitted post-intervention trend to the projected secular trend in the final month of observation [35].

The aforementioned segmented regression analyses will compare pre-intervention to post-intervention levels and trends within intervention groups; therefore, groups will act as their own internal controls. Additionally, we will compare these changes to changes observed in the control group (ie, all other hospitals in Ontario). Analysis of the parallel control group — which will be identically specified to the intervention group analyses — will help address threats to internal validity, such as co-occurring interventions or other policy changes that could be rival explanations for any observed changes in our intervention series. In other words, if we detect a post-intervention effect in the parallel control group, it suggests that changes in the underlying patient population or another (unidentified) intervention could have occurred around the same time across Ontario hospitals that might explain away any observed intervention effects.

To account for potential differences in patient case mix over time and among sites, we will conduct additional secondary analyses of the primary outcome with the patient as the unit of analysis. We will use segmented binary logistic regression analysis with terms as specified in previous paragraphs and with the addition of the following patient covariates: age, sex, type of MI (STEMI vs non-STEMI), prior MI, prior cardiac medication use, and site.

Secondary Outcome Analysis

Consistent with the secondary analyses of the primary outcome described in the preceding section, all secondary outcomes will be analyzed using patient-level segmented regression analyses with terms for time, intervention, time after intervention, and the following covariates: age, sex, type of MI, prior MI, prior cardiac medication use, and site. The remaining secondary outcomes (time to hospitalization for cardiovascular disease, hospitalization due to repeat acute MI, hospitalization due to stroke, repeat cardiac catheterization, coronary revascularization, and death) will be analyzed at the patient level using Cox proportional hazards regression. Death will be treated as a censoring event for analyses of nonfatal, time-to-event outcomes.

Power Calculation

Using the simulation approach developed by Zhang et al [37], we determined that 24 pre-intervention and 12 post-intervention data points (collected at monthly intervals) in each of the 2 intervention groups will achieve 80% power to detect an immediate absolute increase (ie, intercept change) of 10% in the monthly proportion of patients deemed adherent to their recommended cardiac medications using a likelihood ratio test at the 5% level of significance. The anticipated baseline proportion of patients with cardiac medication adherence (ie, average PDC ≥80%) is 75%. The simulation assumed a mean square error for the monthly proportions of 3.1% with 60 patients per month per site, a pre-intervention trend of 0, and an autocorrelation parameter of 0.3.

Health Economic Evaluation

We hypothesize that this intervention package is at least cost neutral and potentially demonstrates cost savings when compared to current practice. The cost implications of longer cardiac prescriptions at discharge are expected to be very minimal, with a surplus of medications likely administered in only a minority of cases. We will collect data that will allow us to determine (1) the added costs of medication surplus (ie, wastage) with longer prescriptions in the intervention versus usual care or control periods, (2) the difference in health system costs associated with cardiovascular disease events in the intervention versus usual care or control periods, and (3) the potential for cost savings due to projected reduction in cardiovascular disease events and reduced prescription fees with longer discharge prescriptions.

Process Evaluation

Analysis to assess the fidelity of the intervention will be undertaken. Specifically, 50-100 random patient charts from the 3 sites (HHS, St. Joseph's Healthcare Hamilton, NHS) will be reviewed to assess discharge prescription duration and compare findings against ODB data to assess the level of agreement between the length of the discharge prescription and pharmacy dispensation. In this sample population, we will assess the proportion of patients who received a prolonged duration discharge prescription as reported in hospital charts compared to the proportion who received a prolonged duration discharge prescription in the ODB record. Selection of participant charts for evaluation will be identified from local (HHS, NHS) access to CorHealth registries. These local registries are available for hospital use for approved research and quality assurance work.

Results

The primary outcome is long-term cardiac medication adherence assessed at 365 days from discharge. We calculated that 24 pre-intervention and 12 post-intervention intervals in each group will achieve 80% power to detect an immediate increase (intercept change) of 10% in the monthly proportion of patients with adherence (ie, proportion of days covered ≥80%) to their cardiac medication regimen at 1 year.

Discussion

Based on previous observational studies [4,15,16], it is expected that long-term cardiac medication adherence among post-MI patients will improve following the implementation of a standardized discharge prescription length of 90 days with 3 repeats, in conjunction with educational outreach and support, as compared to usual care. Specifically, it is expected that the PDC will improve in each cardiac medication class. The PDC is considered a validated measure of medication adherence [38], and patients with a PDC ≥80% have been shown to have better clinical outcomes [34]. We do not expect that this intervention will increase the number of cardiac medications prescribed to post-MI patients at discharge; rather, we anticipate that standardized discharge prescription forms (in combination with education) will improve long-term adherence to the cardiac medications initiated at discharge.

Previous studies have demonstrated that a 10% increase in cardiac medication adherence in the setting of secondary prevention can result in a 6.7% relative reduction in major adverse cardiac events (MACE), including but not limited to death, MI, stroke, and revascularization procedures [38,39]. Assuming the 1-year MACE rate is 14.7% (based on a very large and high-quality RCT) [40] and estimating that there are approximately 3000 MIs in the study region in 1 year, we would expect the implementation of our intervention to prevent over 30 MACE per year and significantly reduce direct health care expenditures. This estimate only accounts for direct hospitalization costs and does not reflect other costs including rehabilitation, home care, and indirect community care costs. The cost implications of longer cardiac prescriptions at discharge are expected to be very minimal, with a surplus of medications likely administered in a minority of cases.

Strengths

This study has several strengths. First, revised standardized discharge prescriptions forms are a low-cost and sustainable intervention. If this concept is demonstrated to be effective, the change to prescription duration could be easily implemented into existing discharge policies and even electronic medical records. Second, there is minimal risk associated with this intervention as the 5 discharge cardiac medications are all recommended for a minimum of 1 year post-MI and often lifelong. Cost limitations would be the only foreseeable risk, which are being evaluated as part of the health economic analysis. Finally, the use of administrative databases facilitates a larger study population — including an external control group consisting of all other Ontario hospitals not allocated to an intervention — at lower research operating costs.

Limitations

While this study proposal highlights the evaluation of a simple, yet novel, approach to improve cardiac medication adherence post-MI, there are methodological limitations. First, the use of administrative databases limits (1) the evaluation of prescription fills rather than swallowing of pills and (2) the assessment of medications and patients not covered by the ODB plan, including aspirin and those <65 years old, respectively. Second, while the interrupted time series analysis can support causal inference, the design is not as robust as an RCT. We do plan to collect appropriate province-wide data throughout this study to inform the design of a future randomized trial. Finally, it is acknowledged that some patients who are classified as nonadherent may have moved away from Ontario, and thus, their prescription claims may be under a different provincial plan for part of the follow-up, leading to potential underestimation of their cardiac medication adherence. The information obtained from this study will help inform the design of a multicenter RCT as an alternative approach to evaluate this proposed intervention.

Conclusions

In conclusion, the MIPAD study is the first prospective study to evaluate the effects of implementing an institutional policy or standardized discharge cardiac medication prescriptions of maximum duration on long-term medication adherence. The

results of this study have the potential to redefine best practices regarding discharge prescribing policy for patients post-MI. Instituting a policy of standardized maximum-duration prescriptions at the time of discharge post-MI is a simple intervention that has the potential to significantly improve long-term medication adherence, thus decreasing cardiac morbidity and mortality. If effective, this low-cost intervention could be easily scaled. Furthermore, since nonadherence is not unique to post-MI patients, this intervention could improve medication adherence in patients with other chronic diseases.

Authors' Contributions

JDS and NI designed and supervised the study and data analysis and drafted and reviewed all versions of the protocol. JG, MN, and LD helped to design the study, interpret the data, and commented on the protocol. ZB and MT helped design the study, drafted the analysis plan, performed preliminary analyses, and participated in writing of the protocol. KT assisted with health economic analysis. TM and EO provided substantive contributions to the drafting and revision of the protocol. All authors read and approved the submitted manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Identification of Cardiac Care Network - Cardiac Registry (CCN-CR) claims for a cardiac catheterization with the primary referral reason being a ST-elevation myocardial infarction (STEMI) or non-STEMI with evidence of coronary artery disease.
[DOCX File , 12 KB - resprot_v9i11e18981_app1.docx]

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Abbreviations

CAD: coronary artery disease
CCN-CR: Cardiac Care Network - Cardiac Registry
HHS: Hamilton Health Sciences
MACE: major adverse cardiac events
MI: myocardial infarction
MIPAD: Myocardial Infarction Prescription Duration Study
NHS: Niagara Health Services
ODB: Ontario Drug Benefit
OR: odds ratio
PDC: proportion of days covered
RCT: randomized controlled trial
STEMI: ST-elevation myocardial infarction

Edited by G Eysenbach; submitted 06.04.20; peer-reviewed by L Brosseau, S Badawy; comments to author 21.09.20; revised version received 01.10.20; accepted 02.10.20; published 04.11.20.

Please cite as:
Schwalm JD, Ivers NM, Bouck Z, Taljaard M, Natarajan MK, Dolovich L, Thavorn K, McCready T, O'Brien E, Grimshaw JM
Length of Initial Prescription at Hospital Discharge and Long-Term Medication Adherence for Elderly, Post-Myocardial Infarction Patients: Protocol for an Interrupted Time Series Study
JMIR Res Protoc 2020;9(11):e18981
URL: https://www.researchprotocols.org/2020/11/e18981
doi:10.2196/18981
PMID:33146624

Protocol

A Mental Health Surveillance System for the General Population During the COVID-19 Pandemic: Protocol for a Multiwave Cross-sectional Survey Study

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Abstract

Background: The COVID-19 outbreak can potentially be categorized as a traumatic event. Public health surveillance is one of the cornerstones of public health practice, and it empowers decision makers to lead and manage public health crises and programs more effectively by providing timely and useful evidence.

Objective: This paper presents the protocol for a study that aims to identify, track, and monitor trends in the population in Saudi Arabia at risk of major depressive disorders and anxiety during the COVID-19 pandemic.

Methods: This study utilizes continuous, cross-sectional, national-level mental health screening via computer-assisted phone interviews, conducted in four waves on a monthly basis (between May and August 2020). Arabic-speaking adults, aged ≥18 years, and living in Saudi Arabia were recruited via a random phone list. This surveillance system used the proportional quota sampling technique to achieve an equal distribution of participants, stratified by age and gender, and region, within and across the 13 administrative regions of Saudi Arabia. A sample size of 4056 participants per wave was calculated to achieve enough power to detect changes in mental health status. The questionnaire includes the Arabic version of the Patient Health Questionnaire-9 (PHQ-9) to measure depressive symptoms and the General Anxiety Disorder-7 (GAD-7) to measure anxiety. In addition, it will collect data on sociodemographic variables and potential risk factors.

Results: Study recruitment began in May 2020. The data analysis was completed in October 2020, and the final report is expected to be published by the end of December 2020.

Conclusions: Monitoring the population's mental health status during the COVID-19 pandemic will inform decision makers of any potential deterioration in mental health on a national level and among subgroups, including across regions, age groups, and gender groups. It will allow decision makers to recognize issues and intervene sooner. It will also provide valuable scientific data to help understand the effects of epidemics and pandemics on mental health. As far as we know, this is the only study that attempts to monitor the mental health status of the general population on a monthly basis.

International Registered Report Identifier (IRRID): DERR1-10.2196/23748

(JMIR Res Protoc 2020;9(11):e23748) doi:10.2196/23748

KEYWORDS

mental health; depression; anxiety; screening; surveillance; COVID-19

Introduction

In January 2020, the World Health Organization (WHO) announced the outbreak of a new coronavirus disease—COVID-19 [1]. In March 2020, the WHO declared COVID-19 to be a pandemic, and this time of crisis began to generate mental stress in the population [1]. The COVID-19 outbreak can potentially be categorized as a traumatic event, as individuals in the community, in addition to isolation, can experience, witness, or be confronted with events that threaten death and/or serious injury to oneself or others [2-4]. The WHO's Department of Mental Health and Substance Use issued a series of messages to support mental and psychosocial well-being in different target groups during the outbreak [1]. In addition, calls for immediate prioritization and collection of high-quality data on the mental health effects of the COVID-19 pandemic across populations and vulnerable groups were issued by mental health experts [3-6].

Although only a few studies have been published looking at the effect of the COVID-19 pandemic on the general population's mental health on a national level, evidence of mental health deterioration is emerging. For example, in the United Kingdom, a national study covering 17,452 participants found that clinically significant levels of mental distress rose from 18.9% in 2018 to 27.3% in April 2020 [7]. Furthermore, a study in the United States found that in April 2020, 13.6% of adults reported symptoms of serious psychological distress, relative to 3.9% in 2018 [8]. These results suggest that the effect of COVID-19 on the mental health of the general population is significant. In addition, this effect has escalated within a short time in both of these countries, which demands further and more frequent investigations on trends of increase in psychological distress using standardized measurements.

Public health surveillance is one of the cornerstones of public health practice, and it empowers decision makers to lead and manage public health programs more effectively by providing timely and useful evidence [9]. Public health surveillance is defined as the systematic, ongoing collection, management, analysis, and interpretation of data, followed by timely dissemination of these data to public health programs to stimulate public health action [10]. Public health surveillance data can be utilized in many activities that are critical to public health research and practice. These activities include estimating the scope and magnitude of health problems, facilitating public health planning, identifying changes in health practices, detection of epidemics or public health crises, monitoring changes, and describing the natural history of a health event in a community [9].

Routine surveillance systems for mental health in many countries in the eastern Mediterranean region are rudimentary or absent, which makes it difficult to understand the needs of local populations and to plan accordingly [11]. Key components of mental health surveillance and information systems are (1) a national-level commitment to ensure that relevant high-quality information is collected and reported; (2) a minimum data set of key mental health indicators; (3) routine data collection that is supplemented by periodic surveys; (4) quality control; and (5) technology and skills to support data collection, sharing, and dissemination [11]. Mental health surveillance systems can be utilized in various situations by different professional groups, including public health and mental health practitioners, academic organizations, and decision makers. For example, officials have used mental illness surveillance data to track trends in mental illness and psychological distress associated with exposure to military combat or large-scale disasters [2,12]. Thus, surveillance data are imperative to the public health goals of reducing the incidence, prevalence, severity, and economic impact of mental health conditions via the provision of timely data to decision makers and the creation of opportunities for early intervention. Mental health screenings are now included in established health surveillance surveys, such as the Centers for Disease Control and Prevention's (CDC) National Health Interview Survey (NHIS), the National Health and Nutrition Examination Survey (NHANES), and the Behavioral Risk Factor Surveillance System (BRFSS) [13].

National-level screening can be used to accurately estimate the prevalence of certain mental illness symptoms across populations, and by repeating surveys over time in a surveillance system, such screening can be used to detect and characterize mental health trends [12]. Screening generally cannot be used to diagnose mental health conditions with the same level of specificity as an individual clinical examination conducted by a psychiatrist [12]. Instead, data can be collected on a variety of subjective manifestations in changes in thinking, mood, behavior, and associated distress that correspond with clinical disorders [12]. Questionnaires that have been validated empirically to distinguish between persons with and without specific mental illnesses or general psychological distress are used in screening surveys to generate high-quality mental health data [12].

This paper presents the protocol for a study that aims to identify, track, and monitor trends on the population in Saudi Arabia at risk of major depressive disorders and anxiety during the COVID-19 pandemic. We also aim to assist decision makers to allocate resources and support where they are most needed.

Methods

Study Design

This study utilizes continuous, cross-sectional, national-level mental health screening via computer-assisted phone interviews, conducted in four waves on a monthly basis (between May and August 2020). This study used the QPlatform data collection system, which had integrated eligibility and sampling modules, to control the distribution of the sample [14]. All questions had

to be answered for the questionnaire to be successfully submitted to the database. To ensure the quality of our mental health surveillance system, we considered all relevant attributes by evaluating the public health surveillance systems issued by the CDC [15]. The interview takes approximately 8 minutes to complete.

Participants, Setting, and Recruitment

Participants were Arabic-speaking adults, aged ≥18 years, from Saudi Arabia. They will be recruited via a random phone number list generated from the Sharik Association for Health Research, a research participants' database [16]. The Sharik database is a database of individuals interested in participating in health research that currently has more than 64,000 potential participants and grows on a daily basis, covering the 13 administrative regions of Saudi Arabia [16].

Participants were contacted by phone on up to three occasions. If the participant did not respond, another potential participant with a similar demographic profile (age, gender, region) was invited to participate. All data collectors received training on research ethics, data quality, and use of the data collection electronic system, as well as specific training on how to administer the screening tools used in this study.

Sample Size

This surveillance system used the proportional quota sampling technique to achieve an equal distribution of participants, stratified by age and gender, and region within and across the 13 administrative regions of Saudi Arabia. We used two age groups based on Saudi Arabia's median adult age of 36 years. This led to a quota of 52 strata for this study, which may have helped increase the diversity of the sample and reduced the risk of nonprobability sampling bias.

The sample size was calculated based on the depth of the subanalysis we needed to reach, which compares the age and gender groups across regions with a medium effect size of approximately 0.3 with 80% power and 95% CI [17]. Thus, each quota required 78 participants, and a total sample of 312 per region, to form a grand total of 4056 participants per wave. Once the quota sample was achieved, participants with similar characteristics were not eligible to participate in the study and were excluded automatically via the data collection system. Quota sampling is an automated process with no human interference, as the sampling process is controlled automatically by the data collection system, which eliminates the potential for human sampling bias [14].

Questionnaire Design and Validation

Data collection included general demographic variables, such as age, gender, region, educational level, and marital status. It also included variables related to COVID-19, such as employment category (eg, health care professional, security, etc), concerns and worries about COVID-19, and COVID-19 incidence in family, friends, etc. In addition, other health-related risk factors, such as a history of noncommunicable diseases, obesity, physical activity, and smoking, were collected.

The main mental health screening tool used was the Patient Health Questionnaire-9 (PHQ-9) [18-20]. The PHQ-9 was selected over other depression screening tools since (1) it has been validated for use among various age groups, including adolescents, adults, and the elderly [21,22]; (2) it has been shown to have consistent performance regardless of the mode of administration (eg, patient self-report, interviewer-administered in person or by telephone, or touch-screen devices) [21,22]; (3) it has demonstrated validity and reliability when screening for depression, anxiety, and somatic and panic disorders in a Saudi sample [20,23,24]; and (4) it has been used for mental health screening in various international surveys and surveillance systems (eg, the US CDC uses the PHQ-9 in the BRFSS and the NHANES), which also allows for international comparison [12].

Finally, anxiety was measured using the Generalized Anxiety Disorder-7 (GAD-7), which has also shown good validity and reliability in various studies [25]. The GAD-7 also demonstrated good validity for general population screening, including in the Arabic language among the Saudi population [26-29].

After the first draft of the survey was finalized, a linguistic validation was conducted via a focus group of 8 participants, who were asked to discuss and answer the survey as a group. According to the results of the focus group and feedback from the researchers and interviewers, the questionnaire was further edited, and a final version was produced. Following this, a pilot stage study with a small sample size will be conducted via phone interview to assess internal consistency and test the surveillance system operation plan.

Outcome Measures

To determine the prevalence of the high risk of depression and anxiety in our sample, we used two PHQ-9 thresholds recommended in the literature. The first threshold is a score >10, comprising pooled estimates of 10 studies with the best trade-off between sensitivity (0.89, 95% CI 0.75-0.96) and specificity (0.89, 95% CI 0.79-0.94) [30]. The second threshold is a score ≥15, which has shown the highest specificity at 0.96 (95% CI 0.94 to 0.97) [30].

In terms of the GAD-7, pooled sensitivity and specificity values appeared acceptable at a cutoff point of 8 (sensitivity: 0.83, 95% CI 0.71-0.91; specificity: 0.84, 95% CI 0.70-0.92), and cutoff scores between 7 to 10 also had similar pooled estimates of sensitivity and specificity [27]. In addition, on the GAD-7 anxiety scale, a score of ≥10 was deemed to be the optimum cutoff in the literature and according to previous studies of the Saudi population [25,29].

Statistical Analysis

Data were weighted to equal the adult population in Saudi Arabia, according to the General Authority of Statistics 2017 Census Report [31]. Quantitative variables will be presented by mean and SD values if they have a normal distribution, or median and range, as appropriate, and will be compared using the *t* test. Categorical variables will be presented as percentages and CIs, and will be compared using the Pearson chi-square test. As this study uses automated electronic data collection, there are no missing values; the QPlatform also includes a data integrity check to prevent users from entering invalid data (eg, the maximum age is 99) [14].

Ethical Considerations

The study was performed in accordance with the Declaration of Helsinki and followed the Saudi Arabia Research Ethics Standards. Consent was obtained verbally at the beginning of the phone interview. All of the obtained data are deidentified and cannot be used to identify individual participants. Ethics approval was obtained from the Sharik Association for Health Research institutional review board (approval number: 01-2020).

Results

Project Timeline

The first wave of the project started in the third week of May 2020. The next waves began in the third week of each month (June, July, and August). Data collection took around 2 weeks for each wave. The data analysis was completed in October 2020, and the final report is expected to be published by the end of December 2020. The results will be reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for cross-sectional studies [32].

Dissemination

The main study outcome will be disseminated to decision makers via a statistical dashboard developed for this project. The dashboard was updated within 72 hours after completion of data collection each month to ensure that the findings reached decision makers in a timely manner. The findings from this study will be disseminated locally and internationally through publication in peer-reviewed journals and conference presentations at the national and international levels.

Data Availability

Once the project is completed, data will be available upon request via the Saudi National Health Research Center.

Discussion

Overview

The COVID-19 pandemic has created a complicated system of stressors affecting the general population in a multilayered manner, including the following: abrupt changes to lifestyle, uncertainties about the future, deterioration of livelihood, social isolation, imposed quarantine, stigmatization, loss of loved ones, deprivation of culturally appropriate mourning rituals, and, finally, the threat of contracting COVID-19 [4]. In addition, generalized fear and fear-induced overreactive behaviors among the public may impede infection control. Thus, monitoring mental health status during the COVID-19 pandemic can inform decision makers about any potential deterioration in mental health on a national level and among subgroups, including across regions, age groups, and gender groups [33]. It will allow decision makers to recognize issues and intervene sooner, as well as identify vulnerable populations to provide tailored mental health interventions to potentially produce better outcomes. This project is among the first large-scale mental health surveillance system in Saudi Arabia. The continuous monitoring of mental health status during the COVID-19 pandemic will assist in understanding the effect of various social and economic measures implemented to control disease transmission, as will the effects of mental health interventions. In addition to its main aim, it will provide specific, valuable lessons to learn from for the future development of surveillance systems for mental health and for other public health issues.

Upon the success of this surveillance system, it may be linked to electronic pathways to provide clinical diagnosis and telemedicine-based interventions to treat and manage clinical and subclinical mental health issues. Telemedicine-based programs can play an important role during the COVID-19 crisis, given their unique potential for scalability [34]. There is already established evidence supporting the general population's willingness to use a mental health app and discuss their results with their doctors, which can then lead to a clinical diagnosis of mental health conditions [21,22].

As COVID-19 may develop into a cultural or societal trauma, the monitoring of mental health status in the general population plays an important role in postpandemic recovery efforts [4]. For example, knowing when there is an increase in mental health conditions and the types of these conditions in society can help in the planning and scaling of mental health services, and stimulate innovation in mental health intervention delivery. This can help increase the chances of successful recovery efforts and transition to normal life after COVID-19. This can also provide an opportunity and prepare society to deal effectively with future population-level crises. At the same time, it is a chance to increase the population's awareness of the importance of mental health and related issues, like mental health stigmatization.

The lack of a national screening baseline in Saudi Arabia generally, and, specifically, using the same screening tools as in this project, poses a challenge to understanding the effect of the first wave of COVID-19; however, the authors assume that, with the continuous health and economic measures implemented during the study period and given the sensitivity of the screening tools to mental health changes, the accumulation of data from the four waves will provide a clear picture of the mental health effects of COVID-19.

The use of proportional quota sampling provides more statistical power to detect changes, not only at national levels but also at regional levels, which can help further in stratifying data in relation to the most affected regions and subpopulations in order to provide a more in-depth picture of the effects of COVID-19. However, we acknowledge that using nonprobability sampling involves some risk of bias. Currently, in Saudi Arabia, the only way to conduct a random representative national survey is via household interviews. However, such a method is not possible during COVID-19 restrictions and lockdowns; it is also very expensive to implement this on a monthly basis. Thus, this study also considered the cost of conducting such a project, which becomes more cost effective via quota sampling. Finally, to improve the sampling accuracy, 52 strata were used to allow for the inclusion of a more diverse sample.

Conclusions

This mental health surveillance system protocol provides a comprehensive approach to monitor the mental health status of the general population on a monthly basis during the COVID-19

pandemic. It was developed utilizing the highest standard of public health surveillance systems. The results of this project will provide valuable data for decision makers about mental health status changes during different phases of the epidemic in Saudi Arabia. It will also provide valuable scientific data to help in understanding the effect of such crises on mental health, since this is, to the best of our knowledge, the only study that attempts to monitor the mental health status of the general population on a monthly basis.

Acknowledgments

The authors wish to express their gratitude and appreciation to King Abdulaziz City for Science and Technology for funding this study (grant number 5-20-01-000-0001). The funder had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all study data and had the final responsibility for the decision to submit this research for publication. The Authors would like to thank Dr. Nahar Alazmi, for providing the support to carry out this project. Also we would like to thank Dr. Mohamed AlKelya, for his leadership and guidance through all stages of this project. We also would like thank Dr. Rufaidah AlDabbagh, who provided insight and expertise that greatly assisted the project.

Authors' Contributions

All authors made major contributions to the design and development of this study. All authors reviewed, revised, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BRFSS: Behavioral Risk Factor Surveillance System
CDC: Centers for Disease Control and Prevention
GAD-7: General Anxiety Disorder-7
NHANES: National Health and Nutrition Examination Survey
NHIS: National Health Interview Survey
PHQ-9: Patient Health Questionnaire-9
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

WHO: World Health Organization

Edited by G Eysenbach; submitted 21.08.20; peer-reviewed by J Li, K Goniewicz; comments to author 29.09.20; revised version received 07.10.20; accepted 03.11.20; published 26.11.20.

Please cite as:
BinDhim NF, Althumiri NA, Basyouni MH, Alageel AA, Alghnam S, Al-Qunaibet AM, Almubark RA, Aldhukair S, Ad-Dab'bagh Y
A Mental Health Surveillance System for the General Population During the COVID-19 Pandemic: Protocol for a Multiwave Cross-sectional Survey Study
JMIR Res Protoc 2020;9(11):e23748
URL: http://www.researchprotocols.org/2020/11/e23748/
doi:10.2196/23748
PMID:33156802

Protocol

Point-of-Care Approaches for Meningitis Diagnosis in a Low-Resource Setting (Southwestern Uganda): Observational Cohort Study Protocol of the "PI-POC" Trial

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Abstract

Background: A timely differential diagnostic is essential to identify the etiology of central nervous system (CNS) infections in children, in order to facilitate targeted treatment, manage patients, and improve clinical outcome.

Objective: The Pediatric Infection-Point-of-Care (PI-POC) trial is investigating novel methods to improve and strengthen the differential diagnostics of suspected childhood CNS infections in low-income health systems such as those in Southwestern Uganda. This will be achieved by evaluating (1) a novel DNA-based diagnostic assay for CNS infections, (2) a commercially available multiplex PCR-based meningitis/encephalitis (ME) panel for clinical use in a facility-limited laboratory setting, (3) proteomics profiling of blood from children with severe CNS infection as compared to outpatient controls with fever yet not severely ill, and (4) Myxovirus resistance protein A (MxA) as a biomarker in blood for viral CNS infection. Further changes in the etiology of childhood CNS infections after the introduction of the pneumococcal conjugate vaccine against *Streptococcus pneumoniae* will be investigated. In addition, the carriage and invasive rate of *Neisseria meningitidis* will be recorded and serotyped, and the expression of its major virulence factor (polysaccharide capsule) will be investigated.

Methods: The PI-POC trial is a prospective observational study of children including newborns up to 12 years of age with clinical features of CNS infection, and age-/sex-matched outpatient controls with fever yet not severely ill. Participants are recruited at 2 Pediatric clinics in Mbarara, Uganda. Cerebrospinal fluid (for cases only), blood, and nasopharyngeal (NP) swabs (for both cases and controls) sampled at both clinics are analyzed at the Epicentre Research Laboratory through gold-standard methods for CNS infection diagnosis (microscopy, biochemistry, and culture) and a commercially available ME panel for multiplex PCR analyses of the cerebrospinal fluid. An additional blood sample from cases is collected on day 3 after admission. After initial

clinical analyses in Mbarara, samples will be transported to Stockholm, Sweden for (1) validation analyses of a novel nucleic acid–based POC test, (2) biomarker research, and (3) serotyping and molecular characterization of *S. pneumoniae* and *N. meningitidis*.

Results: A pilot study was performed from January to April 2019. The PI-POC trial enrollment of patients begun in April 2019 and will continue until September 2020, to include up to 300 cases and controls. Preliminary results from the PI-POC study are expected by the end of 2020.

Conclusions: The findings from the PI-POC study can potentially facilitate rapid etiological diagnosis of CNS infections in low-resource settings and allow for novel methods for determination of the severity of CNS infection in such environment.

Trial Registration: ClinicalTrials.gov NCT03900091; https://clinicaltrials.gov/ct2/show/NCT03900091

International Registered Report Identifier (IRRID): DERR1-10.2196/21430

(JMIR Res Protoc 2020;9(11):e21430) doi:10.2196/21430

KEYWORDS

global health; central nervous system infections; pediatrics; diagnostics; low-resource settings; meningitis; Uganda; children

Introduction

Pediatric Central Nervous System Infections and Their Etiology

Infections of the central nervous system (CNS) are life-threatening conditions affecting thousands of children worldwide, resulting in significant morbidity and mortality, and contributing to the current burden of disease in low-income countries [1,2]. When correctly treated, mortality falls significantly. However, many survivors are often left with neurological sequelae [3-5]. In most African countries, the etiology of CNS infections among children is often unknown due to the lack of advanced laboratory tests [6,7]. Although CNS infections can be caused by different infective agents, such as bacteria, viruses, and parasites, the symptoms of the infection, such as fever, are similar [8,9]. The common symptoms of CNS infection make it difficult to distinguish between different causes of infection clinically, posing challenges to clinical fever case management. Globally, the most common pathogens causing bacterial CNS infections beyond the neonatal period are *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B (Hib) [10]. When managing bacterial infections, it is important and sometimes crucial that antibiotics, if available, are administered without delay [11]. At the same time, the irrational use of antibiotics for the treatment of nonbacterial infections is a global public health concern that leads to increased development of antibiotic resistance [12]. In order to minimize preventable deaths and severe outcomes in children, it is crucial to direct research toward better and robust diagnosis of CNS infections.

Etiology of Childhood CNS Infections in Southwestern Uganda

Uganda is a low-income country with a high prevalence of malaria, HIV, and other infectious diseases. In the Mbarara district of Southwestern Uganda, a child presenting with fever at a health facility is typically suspected of having either malaria or an unidentified bacterial/viral infection. Such patients are routinely tested for malaria using antigen-based rapid diagnostic point-of-care (POC) tests, commonly known as malaria rapid diagnostic tests (RDTs); if the test result is positive, the patient is treated for malaria. However, if the test result is negative, then empiric antibiotics are often prescribed without confirmation of the bacterial cause of infection [12]. One of the major reasons for this routine is the lack of adequate diagnostic methods [13]. A study conducted in the Mbarara district in Uganda from 2009 to 2012 showed that the bacterial etiologies of childhood CNS infection to primarily be *S. pneumoniae*, nontyphoid Salmonella, and Hib [14]. Vaccination against Hib and *S. pneumoniae*, 2 major causative bacterial agents in childhood CNS infection, has been added to the child immunization program in Uganda in 2003 and 2013, respectively. As described elsewhere, immunization programs have changed etiologies of invasive infectious diseases, allowing for previously infrequent pathogens to rise and take leading roles in infection etiology [15]. Whether this epidemiological shift is also happening in Uganda is important to study.

A Need for Novel Rapid Microbiological POC Tests Integrated Into the Laboratory

Development of POC tests for CNS infections

The current gold-standard laboratory methods to confirm suspected cases of CNS infection are bacterial culture and PCR analyses of cerebrospinal fluid (CSF) and blood [16]. However, a vast number of cases in sub-Saharan Africa occur in areas with little or no access to laboratory diagnostics, resulting in mistreatment and poor clinical outcomes [6]. To improve clinical management of patients with suspected CNS infections in resource-limited settings, new field-friendly, easy-to-use, low-cost, and reliable diagnostic POC assays are greatly needed. To maximize the POC benefit, we have previously shown that design and development of tests must be conducted with a focus on needs and capacities of intended end users [17].

Multi-POC for Bacterial Meningitis Developed for Resource-Limited Settings

We have currently developed protein-, immuno-, and DNA-based platforms amenable for the POC multiplex format [18,19]. The DNA technologies are paper based, using printed microarrays to capture specific DNA targets by vertical flow and displaying the results colorimetrically [20]. These methods make use of traditional PCR as well as recombinase polymerase amplification, a nucleic acid amplification technique which

does not require thermal cycling. Recombinase polymerase amplification combines the advantage of sensitivity and short turnaround time for analyses, making it well suited for laboratories without capacity for performing advanced molecular-based assays [21]. Paper-based POC tools offer not only a superior advantage in terms of costs and simplicity of use, but also when it comes to logistics, as they are easy to transport, store, and ultimately dispose safely via incineration.

A Commercially Available Multiplex PCR Instrument for Meningitis/Encephalitis Diagnostics

Concurrently, a new PCR meningitis/encephalitis (ME) panel is being marketed as a multiplex and fast instrument for integrated analysis of CSF specimens [22]. An increasing number of clinics in high-income countries (HICs) are now implementing its use as it has shown good performance for the diagnosis of CNS infections [23]; however, no studies have so far, to our knowledge, evaluated its clinical performance, influence on patient management, or clinical usability for the diagnosis of pediatric CNS infections in low-income settings.

Novel Biomarkers for Future POCs

A promising biomarker related to viral infections is Myxovirus resistance protein A (MxA). MxA is an intracellular protein that is upregulated upon activation of the antiviral defense. Because of its potential to function as a biomarker for viral infective agents, MxA is possibly an important complement to current inflammatory biomarkers that mostly focus on bacterial infection [24-26]. The correlation between MxA and the presence of viral encephalitis has previously been reported; however, this is only through histological analyses of brain tissue samples [27].

The mapping of the proteomic characteristics of febrile children with varying clinical signs of severe disease using an established, highly multiplexed antibody suspension bead protein microarray platform (Luminex) will be carried out [28,29]. Multivariate and machine-learning methods can be employed for the extraction of protein expression profiles that robustly correlate or predict clinical patterns such as disease severity, hospitalization, organ failure, and other complications.

Molecular Mechanisms of Potential Virulence Traits

The pathogen *N. meningitidis* is known to cause rapid onset of severe sepsis and meningitis. Several virulence factors are well known but how the pathogen progresses from an asymptomatic colonizer to an invasive infection remains unclear. Previous research has identified a specific capsule RNA thermosensor that is able to sense environmental temperature [30]. This temperature-sensing mechanism enables the bacterium to increase capsule production to evade host complement-mediated killing [31]. Specific sequence polymorphisms of the RNA thermosensor have also been linked to invasive *N. meningitidis* isolates [32]. Identification and surveillance of these RNA elements within naturally occurring populations of *N. meningitis* could aid the further development of tailored diagnostics and treatment.

Aim

The overarching aim of the Pediatric Infection-Point-of-Care (PI-POC) clinical trial is to strengthen the capacity for differential diagnosis and management of childhood CNS infections in low-income health systems.

The specific objectives of the trial are the following (Table 1):

- To evaluate the diagnostic accuracy of novel nucleic acid-based assays for etiological diagnosis of bacterial CNS infection.
- To evaluate clinical performance, influence on patient management, and clinical usability of a commercially available multiplex PCR-based ME panel in managing pediatric CNS infection in a low-income setting.
- To compare differences in the etiology of confirmed childhood CNS infection before and after the introduction of the pneumococcal conjugate vaccine.
- To study the putative biomarker MxA in plasma in cases with viral CNS infection in comparison with that in cases of nonviral CNS infection.
- To study the proteomic profile, in CSF and in plasma, of children with severe versus uncomplicated infections.
- To study the prevalence, serogroup distribution, and molecular characteristics of *N. meningitidis* virulence traits.

Table 1. Summary of objectives, samples, and aims of the PI-POC[a] study.

Objective	Aim	Specimen analyses	Specimen utilized
I	Validating a novel nucleic acid-based multi-POC[b] method developed for the identification of CSF[c] pathogens.	Sweden	CSF and cases
II	Evaluating the clinical utilization of a commercially available multiplex ME[d] PCR panel in a low-income setting.	Uganda	CSF and cases
III	Updating current etiology of pediatric CNS[e] infections in Mbarara and comparing it to the pre-pneumococcal conjugate vaccine era.	Uganda/Sweden	CSF and cases
IV	Validating MxA[f] as a blood biomarker for differentiation of viral/nonviral cause of CNS infection.	Sweden	Plasma and cases and controls
V	Comparing proteomic characteristics of severe/nonsevere childhood infection and identification of novel biomarkers for severe pediatric infections.	Sweden	CSF, cases, plasma, and cases and controls
VI	Identifying mechanisms of virulence traits of *Neisseria meningitidis* isolated from pediatric patients.	Sweden	Nasopharyngeal swabs and cases and controls

[a]PI-POC: Pediatric Infection-Point-of-Care (trial).

[b]POC: point of care.

[c]CSF: cerebrospinal fluid.

[d]ME: meningitis/encephalitis.

[e]CNS: central nervous system.

[f]MxA: Myxovirus resistance protein A.

Methods

Study Site and Design

The PI-POC trial is a prospective observational study of children aged 0 months to 12 years presenting with symptoms of CNS infection. It also includes outpatient controls with a fever that are clinically assessed as not severely ill. The study is being conducted at the Pediatric Departments of Mbarara Regional Referral Hospital (MRRH) and Holy Innocents Children's Hospital (HICH), Mbarara District, Uganda. MRRH is the main health facility and regional referral hospital in the southwestern region of Uganda and even receives patients from Tanzania, Rwanda, and the Democratic Republic of Congo. It is a teaching hospital for the medical faculty of the Mbarara University of Science and Technology (MUST) and has an admission capacity of 460 beds, outpatient and inpatient services, and a pediatric 70-bed ward that admits about 5000 children annually, mainly newborns and children with infectious diseases. HICH is a private pediatric nonprofit hospital established in 2009 and has a capacity of 60 beds. It offers inpatient and outpatient services, basic clinical laboratory (biosafety level 1), and counseling services. The Epicentre Laboratory is a biosafety level 3 facility, located within the campus of MUST and adjacent to MRRH. It includes parasitology, mycobacteriology, microbiology, and molecular biology (PCR, real-time qPCR, GeneXpert, BioFire FilmArray) laboratories and has biochemistry, hematology, and serology capacities. The laboratory is currently in the process of undergoing quality accreditation and operates on the principles of Good Clinical Laboratory Practice. Biobanking of samples in liquid nitrogen, –80°C and –20°C, is available on-site. Shipment of samples is conducted according to International Air Transport Association regulations.

Recruitment of patients commenced in January 2019 and was to end in June 2020. However, due to the current COVID-19 pandemic, the country underwent a total lockdown from March to June 2020, during which the study activity was paused. The study resumed mid-June and will continue until September 2020. The trial is registered at ClinicalTrials.gov (registration number NCT03900091).

Study Participants

Children aged 0 months to 12 years who meet the case or control definition criteria, and for whom informed consent was obtained from the parent or guardian were recruited at the pediatric wards of both MRRH and HICH by the attending medical officer.

Case Definition

Children are suspected to have a CNS infection if they have fever or a history of fever in the past 48 hours (except for children younger than 9 months who may present with fever, normal body temperature, or hypothermia) and recent onset of any of the following at inclusion:

- Nontraumatic reduced level of consciousness (in preverbal children, this corresponds to Blantyre coma score <4 for those aged <9 months, and <5 for those older than 9 months (up to 12 years of age); in verbal children, this corresponds to Glasgow Coma Scale score <15);
- Prostration, hypotonia/hypertonia, unexplained irritability;
- Severe headache (severe enough to require hospitalization);
- Photophobia;
- Neck stiffness or bulging fontanel;
- Prolonged, partial, or multiple seizure(s);
- Focal neurological signs;
- In children older than 18 months: Kernig sign (flexion of the hip 90° with subsequent pain in legs extension) or

Brudzinski sign (involuntary flexion of the knees and hips after passive flexion of the neck);
- Skin petechiae; and
- Cheyne–Stokes breathing.

Cases are recruited from the emergency department and inpatient ward of HICH and MRRH, when clinical presentation instigates suspicion of CNS infection and when the aforesaid inclusion criteria have been met. However, due to the often-ambiguous presentation of CNS infection symptoms, attending medical officers may include suspected cases even if the stated criteria are not met. The inclusion criteria of those children will be clearly mentioned in the case report form (CRF), and inclusion has to be validated by the principal investigator (EK) in Mbarara.

Control Definition

Controls included children aged 0 months to 12 years with a fever and not meeting the case definition, seeking care at the outpatient departments of MRRH or HICH. For every case, 1 sex- and age-matched control is included. When age matching, we allow flexibility to match up to 1 month of age for newborns, within 6 months for infants, and within a year for children from 1 to 12 years. The control definition is chosen to cater for all stated objectives of the trial, without subjecting healthy children to unnecessary and often painful diagnostic procedures.

Biological Samples

Biosamples are collected from participants of the study, preferably before the initiation of antibiotic therapy (Table 2). In any instance, emergency care for the patients has priority over study procedures and sample collection.

Cerebrospinal Fluid (Cases Only)

CSF is collected through lumbar puncture (LP) by study clinicians at MRRH or HICH. LP is delayed or not performed in the presence of contraindications (signs of elevated intracranial pressure, focal neurological signs, local infection in the area of the puncture, signs of bleeding disorders, and cardiorespiratory compromise). The collected CSF is prioritized for patient care and routine primary laboratory diagnostics at the Epicentre Research Laboratory. Residual CSF is biobanked for further analyses.

To control for possible contamination, a sample of sterile water was poured into test tubes that are used for CSF collection. This was done at regular intervals during the trial, following the same procedure as when CSF is being collected from patients.

Blood (Cases and Controls)

Cases

Up to 6 mL of venous blood is collected from cases and prioritized for routine primary diagnostics upon study inclusion. Any residue is put aside for study purposes. On day 3 of the hospital stay, an additional study sample of 1-2 mL of blood is collected and cryopreserved for the longitudinal studies.

Controls

Capillary or venous samples are collected for routine primary diagnostics, and additionally, up to 1 mL is sampled and cryopreserved for study purposes.

Nasopharyngeal Swab (Cases and Controls)

One NP swab is collected from each suspected case or control. Swabs are frozen in a medium containing skim milk, tryptone, glucose, and glycerin and will be sent to the Karolinska Institutet.

Microbiological and Biochemical Analyses

All clinical analyses are performed on-site at the Epicentre Research Laboratory. Primary clinical analyses of CSF, such as microscopy, cytology, Gram staining (when white blood cell count is 10 cells/mm^3 or if sample is hematic), microbiology culture, and biochemistry assay (glucose, protein, lactate) are performed. One aliquot of 200 µL of CSF is used for the multiplex ME panel (BioFire FilmArray ME Panel; BioFire Diagnostics) according to the manufacturer protocol. Blood analyses include Malaria RDT (SD Bioline Malaria Ag Pf/Pan RDT; Standard Diagnostics), HIV RDT using a sequential algorithm of Determine HIV 1/2 (Alere), followed by HIV 1/2 STAT-PAK (Chembio) for reactive samples, and SD Bioline HIV-1/2 (version 3.0; Standard Diagnostics) as a tie-breaker for discordant results, according to Uganda's national guidelines. Other analyses included blood culture (BD BACTEC Peds Plus; Beckton Dickinson & Company), hematology (XN-550, Sysmex), biochemistry (Cobas C111; Roche), and malaria microscopy if RDT is positive. NP swabs are cryopreserved at –80°C for whole-genome sequencing and typing of relevant strains; such analyses will be conducted at the Science for Life Laboratory (SciLifeLab) and Karolinska Institutet.

Table 2. Summary of samples and analyses in Uganda and Sweden.[a]

Specimens (type and tests)	Inclusion (Day 0)	Day 3	Clinical analyses (when/where)	Type of research analyses (when/where)
Cases				
Blood: Hematology, biochemistry, HIV serology (and confirmation), malaria RDT[b], culture, plasma biobank	6 mL	1-2 mL	Routine clinical analyses (same day at the Epicentre Laboratory).	Proteomics analyses for profiling of biomarkers including MxA[e] (later at the SciLifeLab[f]).
CSF[c]: Biochemistry, microscopy and cytology, culture, ME[d]-PCR panel, PCR, biobank	2 mL	—	Routine clinical analyses including ME-PCR panel (same day at the Epicentre Laboratory).	Proteomics analyses for profiling of biomarkers including MxA (later at the SciLifeLab).
Nasopharyngeal swabs: Biobank	1 swab	—	—	Typing of bacteria and bacterial whole-genome sequencing (later at the Karolinska Institutet and SciLifeLab).
Controls				
Blood: Hematology, HIV serology (and confirmation), malaria RDT, biobank	1-2 mL	—	Routine clinical analyses (same day at the Epicentre Laboratory).	Proteomics analyses for profiling of biomarkers including MxA (later at the SciLifeLab).
Nasopharyngeal swabs: Biobank	1 swab	—	—	Typing of bacteria and bacterial whole-genome sequencing (later at the Karolinska Institutet and SciLifeLab).

[a]Additional testing for clinical care, such as TB GeneXpert or TB ZN, was performed according to clinical needs and at the discretion of the medical officer.

[b]RDT: rapid diagnostic test

[c]CSF: cerebrospinal fluid.

[d]ME: meningitis/encephalitis.

[e]MxA: Myxovirus resistance protein A

[f]SciLifeLab: Science for Life Laboratory.

Study Variables

A CRF for cases and controls is filled upon study enrollment. CRF includes demography, medical history, vaccination status, and use of anti-infective medicines prior to inclusion. The following information is registered by the study doctor recruiting cases: respiratory rate, consciousness according to the Glasgow Coma Scale, pulse, peripheral oxygen saturation, weight, body temperature, administered antipyretic medication (<4 hours), vomiting, neck stiffness, bulging fontanelle, unexplainable screaming, opisthotonos, central cyanosis, jaundice, inability to feed, and capillary refill time. Information regarding admission, length of stay, radiological routine clinical examination, microbiology and chemistry analyses, treatment, discharge diagnosis, and complications will be retrospectively collected from the medical records.

Laboratory data are collected by the biologist responsible for the study laboratory activities. Data entry and management are performed by the data management team in Mbarara. Deidentified data are double-entered in the REDCap (Research Electronic Data Capture) database, a web-based software for electronic capture of clinical research data [33].

Study Size, Power Calculation, and Statistical Methods

With the primary aim of this exploratory study being the evaluation of new diagnostic assays in development, a proper power calculation cannot be done. In a previous study, 459 cases with suspected CNS infection were included [14]. In half of them, a causative pathogen was identified in the CSF. Based on previous reports, we can assume that the introduction of pneumococcal conjugate immunization to the Mbarara district has halved the incidence of bacterial CNS infections caused by *S. pneumoniae* [14]. However, other causative bacterial agents of CNS infection are unlikely to have decreased in the region. We thus believe that we should be able to include approximately 160 cases in which a causative pathogen can be identified if we include the same number of cases with suspected CNS infection as in the previous study. This means that around 300 cases with suspected CNS infection will be included in this study. These numbers will be adequate for the validation of the assays.

Statistical Methods and Data Analysis

Standards for Reporting of Diagnostic Accuracy Studies (STARD) will be followed to report results [34]. For continuous variables, mean, median (IQR), SD, and maximum and minimum values will be given. Variables will be described by their percentages and CI. Clinically relevant differences in protein levels of samples versus controls will be reported using appropriate statistical methods in accordance with sample size, number, and distribution of the data. Data will be presented with 95% CI and a *P*-value of <.05 will be considered significant.

Ethics Approval and Consent to Participate

The final protocol has received ethical approval from the Institutional Ethical Review Board of MUST in Uganda (ref. 22/05-18) and the Regional Ethical Review Board in Stockholm, Sweden (ref. 2018/1676-31/1). Approval for the study was granted by the Uganda National Council for Science and Technology (UNCST Reference No HS 2508). All substudies are conducted in accordance with the Helsinki Declaration and follow guidelines for Good Clinical Practice and Good Laboratory Practice. Guardians of potential participants will receive written information on the study and can decide freely whether or not to participate. Their choice to participate or not will not have any influence on the continued clinical management of their child. No identifying data are recorded in the database or used in the analysis. The children are identified by a numeric identifier. Documents including the name of the child, name of the guardian, inclusion number, and contact address are kept locked and accessible only to investigators for the purpose of active follow up. All procedures included in this study, except for the NP swabs, are standard procedures in the management of cases of CNS infections. Good clinical practice and good laboratory practice will be followed. This study might have some direct benefits for the patient, as in the standard routine practice only bacterial culture is performed on the CSF samples. The results from additional tests are communicated directly to the ward as soon as they are obtained, and the treatment is adapted based on these results.

Results

The Regional Ethical Review Board in Stockholm approved the study (ref. 2018/1676-31/1) in September 2018. A pilot study was performed from January 2019 to April 2019, to evaluate the study protocol, the sample transfer logistics from the hospitals to the Epicentre Research Laboratory, and the turnover of patients with suspected CNS infections at both facilities. Helpful information about patient screening and recruitment procedures, including matching control patients, was retrieved during the pilot study. Improvements to the recruitment process, handling of logistics, and transfer of study data between Mbarara and Stockholm were made. We identified a cultural barrier and misconception for LP procedure in the local population, as seen in other sub-Saharan countries [35], and it was promptly addressed by the medical officers by providing additional counseling to the children's guardians. Enrollments of the patients started in April 2019. The FilmArray instrument was installed at the Epicentre Research Laboratory in May 2019.

Discussion

Protocol Overview

CNS infections in children remain a leading cause of death and life-long disability. Thus, early diagnostics are playing a pivotal role in ensuring the right treatment is delivered in a timely manner. The findings from the PI-POC study aim to increase knowledge about CNS infection etiology in Southwestern Uganda using a nucleic acid–based assay amenable for POC use and an ME panel to evaluate the performance of this assay in a burdened health system. Further, it aims at describing the current epidemiological landscape of CNS infection in the area and whether any changes have occurred with the introduction of pneumococcal conjugate and Hib vaccines. Interestingly, not many cases of *N. meningitidis* have been reported in the area [14] although Mbarara is in the proximity of the African meningitis belt. Therefore, the PI-POC study aims at characterizing the serogroup, sequence type, and strain characteristics of all the identified cases of meningococcal meningitis. MxA is a putative blood biomarker that could discern viral and bacterial infection, and it will be investigated in this cohort via a massive proteomics profiling of CSF and plasma.

POC-Amenable Solutions for CNS Infection Detection in a Low-Income Context

Unknown fever etiology in children is a barrier to successful treatment and rapid recovery [36,37]. Findings from the PI-POC study aim at improving near-patient differential diagnosis of CNS infection etiology using POC diagnostics for CSF infections. Because many of the cases occur in rural areas, where access to a physician and advanced diagnostics is limited, the PI-POC trial employs high-throughput affinity proteomics approaches to investigate plasma protein profiles of children having either bacterial or viral CNS infections. Such an approach could aid in the further development of novel POC diagnostics for CNS infection in blood.

Limitations of the Study

Patients are recruited from 2 different hospital sites in the same area which might limit the findings to that region. Often, antibiotics are administered before LP; hence, most cases have negative results in microbiological culture. Another limitation of the study is the potential selection bias of patients during recruitment. According to the clinical picture, the medical officer may suspect a CNS infection even when not all criteria have been met. In such a scenario, cases are always validated/discussed with the principal investigator (EK) of the study in Mbarara and if included, described in detail in the CRF.

The Epicentre Research Laboratory is an advanced biosafety level 3 facility and might not be a representation of other diagnostic laboratories in Uganda. Finally, the ME multiplex PCR panel includes 14 different pathogens known to cause meningitis; however, this panel is not epidemiologically targeted to Uganda, and other agents, such as nontyphoid Salmonella, which are known to cause meningitis in children in the area [14], are not included in the panel.

Requirements for Future RDTs in Low-to-Middle-Income Countries

POC tests should be designed with good knowledge of the health system in which they will be used. The mere availability of rapid or simple tests does not automatically ensure their adoption or scale-up [38]. Several barriers are preventing the successful uptake of POC testing. One barrier is usability; several tests are designed in high-income countries without incorporating the user's perception into the process. Rapid tests designed for a context might fail in another. We successfully addressed this by first conducting a qualitative study and continuously

interacting with the end users of our POC prototype [17]. Other cultural barriers might prevent the test from being used, such as the cultural acceptability of LP [35]. During the PI-POC trial pilot, it was evident that effort was needed by the physician to address the importance of LP to diagnose CNS infections. Logistics also plays a big part in the design of rapid POC tests and should incorporate knowledge of distribution (temperature-sensitive reagents might fail), usage, and finally of the disposal, as safe laboratory waste disposal is a pressing issue in many contexts. An economic effort is also needed to make sure tests have an advantageous package cost for low- to middle-income countries, as many tests remain too expansive for use outside high-income countries or special settings in low- to middle-income countries.

POC tests should not replace advanced laboratory facilities and should not be seen as an antagonist to the central laboratory; in fact, strong knowledge of clinical diagnostics is a requirement for successful POC testing in all settings [39]. As we have learnt from the current COVID-19 pandemic, diagnostic capacity plays a significant role in successful disease surveillance, detection, and response [40] and should not be overlooked by the global health community.

Acknowledgments

The authors thank all colleagues in Uganda and Sweden who have contributed to the clinical trial. Our gratitude also goes to the following external financial contributors who made this trial possible: the Einhorn Foundation, the Swedish Research Council (Vetenskapsrådet, grant 2015-03217, and international post-doc grant 2019-05170 to GG), the European Research Council (consolidator grant 615458), EIT-Health 18373 (to GG), Region Stockholm (clinical research appointment to RR), the Swedish Society for Medical Research (SSMF travel grant to RR), the Swedish Society of Medicine (SLS travel grant to RR), the Swedish Foundation for Strategic Research, and the Knut and Alice Wallenberg Foundation. The funding bodies have not had any influence on trial design, execution, data analyses, or decisions regarding publication of results.

Authors' Contributions

GG, EK, RR, and TA had leading roles in trial design, execution, and drafting of this manuscript. DeN, DN, and JM-A participated in the laboratory study design, supervised the pilot study, and optimized the sample logistics. MN, JM, and SB participated in the study design with a focus on the enrollment, collection, and handling of biosamples at both hospitals. YB and AM took part in the study design from the early stages. JG, HA-S, and PR participated in the study design with a focus on POC development. JK, EL, and PN participated in the study design for the analyses conducted at the SciLifeLab. Revision and critical commenting of this manuscript were done by all authors. The final version of the article was approved by all authors.

Conflicts of Interest

We declare that we have no competing financial or nonfinancial interests. RR had, prior to the commencement of the PI-POC trial, owned a smaller amount of shares (<1500 Euros) in bioMérieux, the parent company of BioFire. All shares were sold in December 2018.

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Abbreviations

CNS: central nervous system
CRF: case report form
CSF: cerebrospinal fluid
Hib: Haemophilus influenzae type B
LP: lumbar puncture
ME: meningitis/encephalitis
MxA: Myxovirus resistance protein A
NP: nasopharyngeal
PI-POC: Pediatric Infection-Point-of-Care (trial)
POC: point of care
RDT: rapid diagnostic test

Edited by G Eysenbach; submitted 15.06.20; peer-reviewed by KNB Nor Aripin, B Nievas Soriano; comments to author 20.07.20; revised version received 09.09.20; accepted 13.09.20; published 04.11.20.

Please cite as:
Gaudenzi G, Kumbakumba E, Rasti R, Nanjebe D, Réu P, Nyehangane D, Mårtensson A, Nassejje M, Karlsson J, Mzee J, Nilsson P, Businge S, Loh E, Boum II Y, Andersson-Svahn H, Gantelius J, Mwanga-Amumpaire J, Alfvén T
Point-of-Care Approaches for Meningitis Diagnosis in a Low-Resource Setting (Southwestern Uganda): Observational Cohort Study Protocol of the "PI-POC" Trial
JMIR Res Protoc 2020;9(11):e21430
URL: https://www.researchprotocols.org/2020/11/e21430
doi:10.2196/21430
PMID:33146628

Protocol

Improving Physical Activity in Adults Admitted to a Hospital With Interventions Developed and Implemented Through Cocreation: Protocol for a Pre-Post Embedded Mixed Methods Study

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Abstract

Background: Admission to a hospital is often related with hospital-associated disabilities. Improving physical activity during hospitalization is considered effective to counteract hospital-associated disabilities, whereas many studies report on very low physical activity levels. Gradually developing and implementing interventions in cocreation with patients and health care professionals rather than implementing predefined interventions may be more effective in creating sustainable changes in everyday clinical practice. However, no studies have reported on the use of cocreation in the development and implementation of interventions aimed at improving physical activity.

Objective: This protocol presents a study that aims to investigate if interventions, which will be developed and implemented in cocreation, improve physical activity among patients in surgery, internal medicine, and cardiology hospital wards. The secondary aims are to investigate effectiveness in terms of the reduction in the time patients spend in bed, the length of hospital stay, and the proportion of patients going home after discharge.

Methods: The Better By Moving study takes place for 12 months at the following five different wards of a university hospital: two gastrointestinal and oncology surgery wards, one internal medicine hematology ward, one internal medicine infectious diseases ward, and one cardiology ward. The step-by-step implementation model of Grol and Wensing is used, and all interventions are developed and implemented in cocreation with health care professionals and patients. Outcome evaluation is performed across the different hospital wards and for each hospital ward individually. The primary outcome is the amount of physical activity in minutes assessed with the Physical Activity Monitor AM400 accelerometer in two individual groups of patients (preimplementation [n=110], and 13 months after the start of the implementation [n=110]). The secondary outcomes are time spent in bed measured using behavioral mapping protocols, and length of stay and discharge destination assessed using organizational data. A process evaluation using semistructured interviews and surveys is adopted to evaluate the implementation, mechanisms of impact, context, and perceived barriers and enablers.

Results: This study is ongoing. The first participant was enrolled in January 2018. The last outcome evaluation and process evaluation are planned for May and June 2020, respectively. Results are expected in April 2021.

Conclusions: This study will provide information about the effectiveness of developing and implementing interventions in cocreation with regard to improving physical activity in different subgroups of hospitalized patients in a university hospital. By following step-by-step implementation and by performing process evaluation, we will identify the barriers and enablers for implementation and describe the effect of new interventions on improving physical activity among hospitalized patients.

Trial Registration: Netherlands Trial Register NL8480; https://www.trialregister.nl/trial/8480
International Registered Report Identifier (IRRID): DERR1-10.2196/19000

(JMIR Res Protoc 2020;9(11):e19000) doi:10.2196/19000

KEYWORDS

implementation science; quality improvement; physical activity; mobility; outcome and process assessment; health care

Introduction

Admission to a hospital is often related with the occurrence of hospital-associated disabilities, such as a reduced muscle mass, reduced muscle strength, malnutrition, and new limitations in activities of daily living (ADLs) [1-3]. In turn, hospital-associated disabilities are related with a prolonged length of stay, increased risk of institutionalization, permanent loss of ADLs, and mortality [4-6]. As hospital-associated disabilities are frequently registered in hospitalized older patients [7] and the age of the general population increases by the year, it is important to develop intervention strategies to reduce hospital-associated disabilities.

Improving physical activity during hospitalization is considered to be effective for counteracting hospital-associated disabilities [1,8-10]. Several studies showed that early mobilization and increasing physical activity in surgical and nonsurgical patients reduces hospital length of stay and improves independence in daily activities and discharge destination [11-13]. Yet, despite the knowledge that increasing physical activity contributes to the prevention of in-hospital functional decline, many studies continue to report on very low physical activity levels among hospitalized patients [14,15].

Previous research showed that physical activity in specific subgroups (ie, gastrointestinal surgery, internal medicine, and stroke) of hospitalized patients can be improved with a single intervention involving a one size fits all approach [10,16,17]. Gradually developing and implementing interventions in cocreation rather than implementing predefined interventions is believed to be more effective in creating sustainable changes in everyday clinical practice [18-20]. However, no studies have recently reported on the use of cocreation in the development and implementation of interventions aimed at the improvement of in-hospital physical activity. Therefore, the Better By Moving study in our university hospital is the first study that has been developed to investigate whether interventions, which will be developed and implemented in cocreation with patients and health care professionals, improve physical activity in patients admitted to surgery, internal medicine, or cardiology hospital wards. Moreover, by improving physical activity, we aim to reduce the time patients spend in bed, reduce hospital length of stay, and improve the number of patients going home after discharge. A systematic process evaluation provides important information on barriers and facilitators for future quality improvement projects aiming to improve physical activity in hospitalized patients.

Methods

Study Design

An uncontrolled pre-post embedded mixed-methods study is designed to evaluate whether we can improve physical activity in hospitalized patients by using interventions that we develop and implement in cocreation. The development and implementation describe the iterative (cyclical) process of planning, conducting, reflecting, and refining, which is being used in close collaboration with local stakeholders, such as patients, health care professionals, and managers [19]. The study has been approved by the Medical Research Ethics Committee of the Amsterdam University Medical Centers (Amsterdam UMC), Academic Medical Center (W17_479 #18.003 and W19_213 #19.258). Written informed consent will be obtained from all participants in both the outcome and process evaluations.

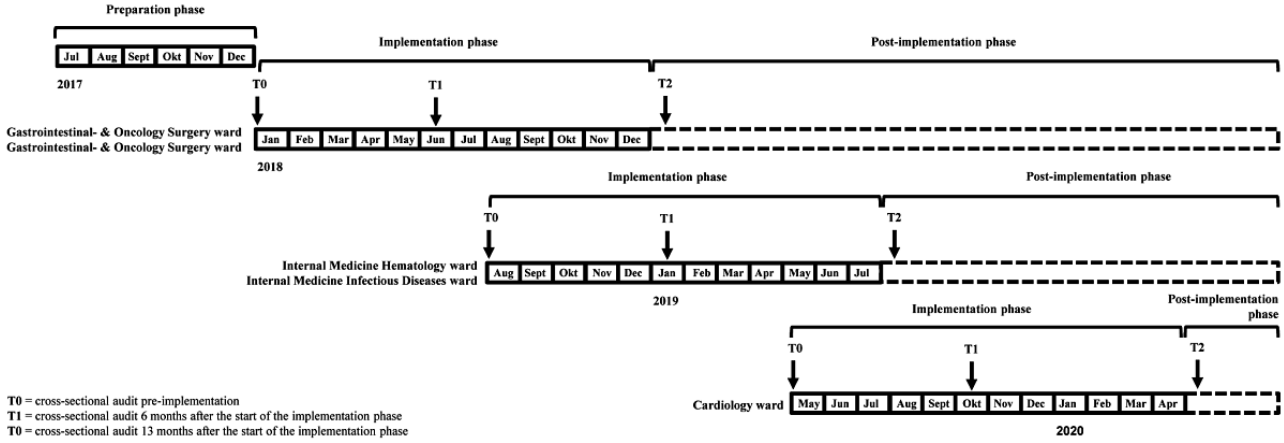
Setting

This study will be conducted at five different hospital wards (two gastrointestinal and oncology surgery wards, one internal medicine hematology ward, one internal medicine infectious diseases ward, and one cardiology ward) in a 1000-bed tertiary university teaching hospital Amsterdam UMC, Academic Medical Center, the Netherlands. Each hospital ward has 29 beds and a nursing-to-patient ratio of either 1:3 or 1:4, depending on the patient acuity. Allied health staffing involves 0.5 to 1 physical therapists for each hospital ward.

Development and Implementation of Interventions

The Better By Moving study consists of a 6-month preparation phase and a 12-month hospital ward-specific implementation phase, starting in January 2018. The entire project timeline has been described in Figure 1. At each hospital ward, the step-by-step implementation model of Grol and Wensing will be used [21]. A summary of the different steps according to Grol and Wensing has been described below. Stakeholders participate in cocreation at the following different levels as described by Cornwall: “co-option,” “compliance,” “consultation,” “co-operation,” “colearning,” and “collective action” [22,23].

Figure 1. Project timeline.



Step 1: Defining the Proposal for Change

The purpose of step one is to finalize the Better By Moving project plan. Therefore, hospital-wide attention is attracted on the benefits of physical activity with presentations and workshops during the 6 months prior to the start in the first hospital ward. Patient representatives, local stakeholders (ie, nurses, physicians, rehabilitation professionals, managers, and team leaders), and experts working on this topic in different hospitals will be asked to participate in discussions to develop the project plan.

Step 2: Analysis of Actual Performance

The purpose of step two is to quantify the outcome measures at baseline. Therefore, a cross-sectional audit will be performed at each hospital ward prior to assess the total amount of physical activity using accelerometers (Physical Activity Monitor [PAM] AM400, PAM BV) [24,25]. In addition, behavioral mapping protocols [26-28] will be used during the same cross-sectional audits to assess the time patients spend in bed, as well as on other physical activities. While the PAM AM400 accelerometer assesses the activity duration and intensity by measuring accelerations, the behavioral mapping protocols indicate how much time patients spend on each type of activity (ie, lying in bed, sitting, standing, or walking) by observing the patient every 10 minutes. Both outcomes complement each other in the understanding of in-hospital physical activity behavior. Further details on both assessments and the included patient population can be found in "Outcome and Process Evaluation."

Step 3: Analysis of Barriers and Enablers Among Patients and Health Care Professionals

The purpose of step three is to gain insights into the barriers and enablers to improve physical activity during hospital stay. Barriers and enablers for physical activity as perceived by patients and health care professionals will be assessed by a mixed-methods design using surveys, interviews, observations, and focus group discussions.

The patient surveys identify the perceived barriers and enablers to physical activity using two open-ended questions, the level of encouragement patients perceive from health care professionals and context using six questions with a 5-point scale based on the questions of van Delft et al [29], and their perceived self-efficacy in performing basic mobility activities independently using seven standardized questions with a 5-point scale based on the Short Falls Efficacy Scale-International [30]. Patients participating in the baseline cross-sectional audit will be asked to complete the survey. In addition, to further assess the perceived barriers and enablers to physical activity, patients will be asked to participate in an additional short face-to-face interview using the following purposeful sampling criteria: survey responses and age.

To identify the barriers and enablers as perceived by health care professionals, we developed a survey based on the theoretical domains framework (TDF) [31]. The TDF encompasses 12 domains, providing a theoretical lens to view all cognitive, affective, social, and environmental influences on behavior and behavior change. Using the 12-domain TDF as a basis, a multidisciplinary team of physical therapists, senior researchers, nurses, and a medical psychologist developed a survey consisting of 39 items and a 5-point Likert scale (totally disagree, disagree, neutral, agree, and totally agree), with two items assessing the health care professional's "knowledge" with regard to improving physical activity in hospitalized patients, one item assessing the health care professional's "skills," one item assessing "social/professional role and identity," two items assessing "beliefs about capabilities," five items assessing "beliefs about consequences," two items assessing "motivation and goals," one item assessing "memory, attention, and decision processes," 17 items assessing "environmental context and resources," two items assessing "social influences," two items assessing "emotion," three items assessing "behavioral regulation," and one item assessing "nature of behaviors." The TDF ensures that all cognitive, affective, social, and environmental influences on behavior will be considered. Further elaboration on the 12 domains of the TDF can be found in the study of Atkins et al [31]. The survey will be distributed among all health care professionals working in each of the hospital wards. Subsequently, at each hospital ward, focus groups will be held to further substantiate the most relevant items. Participants will be asked to participate in the focus groups based on the following purposeful sampling criteria: survey responses, age, working experience, and profession. Finally, health care professionals will be observed at random intervals during the 12-month implementation phase to better understand the daily hospital care, culture, environment, and

context (ie, social and environmental influences) in each of the hospital wards.

Step 4: Development and Selection of Interventions and Strategies

The purpose of step four is to develop interventions and strategies in cocreation while taking into account the barriers and enablers raised by hospitalized patients and health care professionals. Therefore, a working group will be formed at each hospital ward with the project manager (SJGG), nurses, physicians, and a physical therapist. In periodic working group meetings, interventions most suitable to the local context will be developed based on information from the previous steps. Through the use of an iterative (cyclical) process of planning, conducting, reflecting, and refining, the working group will develop various interventions [19]. The behavioral change wheel (BCW) framework will be used to guide the development of interventions [32]. In the BCW, behavior is explained as part of an interacting system between capability, opportunity, motivation, and behavior, also known as the COM-B model. These BCW components will help the working groups to better understand the patients' and health care professionals' behaviors. Moreover, the use the BCW framework will help the working groups to identify optimal behavioral change techniques, which they can incorporate in the detailed intervention proposals [32]. Working group progress will be closely coordinated and supported by the project manager, and the project manager will keep track of the cocreation process using an audit trail. When needed for the iterative (cyclical) development process, the working groups will consult caregivers, family members, patient representatives, local stakeholders, hospital managers, or experts regarding in-hospital physical activity in different hospitals for additional input. At random intervals, a group of patients from the hospital ward will be asked for feedback on the interventions.

Step 5: Development, Testing, and Execution of an Action Plan With Multiple Interventions

The purpose of step five is to gradually implement the intervention proposals in the local context. For each intervention proposal, a testing and implementation plan will be developed in collaboration with the local hospital ward team leader and carried out by the hospital ward specific working group. Hospital managers will be involved and will provide input on a regularly basis. Experience with potentially effective interventions will be translated to the subsequent participating hospital wards.

Step 6: Including Integration of Changes in Routine Care

The purpose of step 6 is to ensure implemented interventions are integrated in routine hospital care. All implemented interventions considered potentially effective will therefore be further refined by the working group and project manager during the 12-month implementation phase. In consultation with hospital managers, local team leaders, and the working group, integration in daily hospital practice will be ensured. In addition, tools will be developed for each hospital ward to systematically evaluate the implementation of the interventions.

Outcome and Process Evaluation

Target Population

A cross-sectional audit will be conducted at baseline, 6 months, and 13 months after the start of the implementation phase. During each cross-sectional audit, a random sample of hospitalized patients will be approached to participate during one day from 8 AM to 8 PM. Eligible patients are 18 years or older, have sufficient Dutch or English speaking ability and reading skills, and are admitted for at least 24 hours. The following exclusion criteria will be used: inability to perform independent transfers prior to hospital admission, delirium, obligatory bed rest as indicated by the attending physician, expectation to be discharged before 12 AM on the day of observation, and receiving end-of-life care. Random selection of potential participants will be performed using a computer-generated list based on the room numbers of the hospital ward, and potential participants will be approached one or two days prior to the day of observation. In the case of refusal or when the patient does not meet the study criteria, the investigator will approach the patient in the next hospital room on the computer-generated list. Each participant can only be enrolled once. No a priori sample size calculations are performed. Resources allow us to spend 1 year at the iterative (cyclical) process at each hospital ward; therefore, we determined a pragmatic sample size. Considering the duration of the different steps, including three cross-sectional audits, the inclusion of 65 participants is deemed feasible at each hospital ward. Given this sample size (n=110 at baseline and n=110 at 13 months) and assuming normality of the outcome parameter, we will be able to detect an effect size of 0.38 or higher for the primary outcome (two groups *t* test of equal means; α=.05; 1−β=.80; nQuery 8, Statistical Solutions Ltd).

Primary Outcome

The primary outcome is the total amount of physical activity in minutes (>1.4 metabolic equivalent tasks [METs] [33]), which will be measured during each cross-sectional audit from 8 AM to 8 PM using the PAM AM400 wireless accelerometer. The PAM AM400 is a 2-cm-wide coin and is waterproof, and it will be attached to the ankle. The PAM AM400 measures accelerations 10 times per second in three dimensions and converts these accelerations to the total amount of time of physical activity in minutes >1.4 METs. METs is a concept that is used to assign an intensity value to specific activities. In healthy participants, light-intensity physical activity involves <3.0 METs, moderate physical activity involves 3.0-6.0 METs, and vigorous physical activity involves >6.0 METs [33]. Sedentary behavior is defined as ≤1.5 METs [34]. In addition to the total amount of physical activity in minutes >1.4 METs, the PAM AM400 compares each second of physical activity with the following three predefined intensity zones: light physical activity (1.4-3.0 METs), moderate physical activity (3.0-7.0 METs), and vigorous physical activity (>7.0 METs), and measures the derivative of METs for 24-h physical activity (PAM score = [METs − 1] × 100 averaged over the day). The validity and reliability of the PAM in healthy adults is moderate to good for assessing the estimate of energy expenditure [24,25].

Secondary Outcomes

Secondary outcomes include the time patients spend in bed, length of stay, and discharge destination. Data on the time patients spend in bed will be measured during each of the cross-sectional audits using the behavioral mapping method [26-28]. In detail, structured observations will be undertaken by trained physical therapy graduate students for a 1-minute period every 10 minutes between 8 AM and 8 PM, using a predetermined set of mutually exclusive types of activities (lying in bed, sitting on the edge of a bed or sitting in a chair, making a transfer from bed to chair, or standing, walking, and using the ergometer). For each minute of observation, the activity with the highest intensity is recorded. Patients are not followed off the ward and not intruded on if behind closed curtains. In addition, the following patient characteristics will be collected during each of the cross-sectional audits: sex, age, comorbidities, number of functional restraints (eg, intravenous lines and drains), functional ability with the Katz-ADL 2 weeks before admission [35], and independence in mobility using the Activity Measure for Post-Acute Care "six clicks" Basic Mobility Short Form [36]. Data will be directly recorded in the online Castor Electronic Data Capture database (Ciwit BV).

Data on length of stay and discharge destination will be obtained from the hospital administrative data for all patients admitted to the surgery, internal medicine, and cardiology hospital wards. Discharge destination will be categorized as follows: going home or going to a temporary institution (ie, nursing home, geriatric rehabilitation center, or medical rehabilitation center). Data on patients who are discharged to a permanent nursing home or other hospitals, those who receive end-of-life care (at home or at a facility), or those who die during hospitalization will be omitted because other influences (such as illness, prognosis, and cognitive function) determine the outcome.

Process Evaluation

Process evaluations are advised to monitor the implementation processes of complex interventions. In this study, the framework of the Medical Research Council guideline is followed to guide the process evaluation [31,37]. The three key functions of this framework include "implementation," "mechanisms of impact," and "context." "Implementation" contains the goals and interventions that have been delivered, and how the implementation is achieved. The "mechanisms of impact" include the response to the interventions, the mediators, and all (unexpected) results and consequences. "Context" includes all other factors that may affect the implementation, interventions, and outcomes, such as barriers (eg, openness to changes, motivation, workload, and costs) and enablers [31]. In this study, we will assess these three key functions by using semistructured interviews by purposefully selecting health care professionals, team leaders, and managers 13 months after the start of the implementation. A topic guide in Dutch will be developed specifically for each hospital ward, which will consist of items covering all three key functions. In addition, 13 months after the start of the implementation, we will re-evaluate the perceived barriers and enablers to physical activity, the level of encouragement patients perceive from health care professionals and context, and their perceived self-efficacy in performing basic mobility activities independently using the survey described in step 3. We will assess the experience with our implemented interventions and various aspects of implementation fidelity (ie, adherence, exposure, and participant responsiveness) by adding both questions with a 5-point scale and open-ended questions to the patient survey (eg, "Did you receive …?" and "If so, did you find … of added value?"). We will also assess health care professionals' perception and experience with the project and our implemented interventions by using an additional survey with open-ended questions (eg, "The following intervention does/does not add to more in-hospital physical activity …" and "Were you made aware of …?") and by adding specific questions to our process evaluation topic guide.

Data Analysis

All analyses will be conducted using IBM SPSS Statistics version 25 (IBM Corp). Patients' characteristics in each cross-sectional audit will be described using descriptive statistics. Primary outcome evaluation will be performed between month 0 and month 13 across all hospital wards, and only the data of patients wearing the PAM during the entire observation period (8 AM-8 PM) will be used. The total amount of physical activity in minutes will be tested on normality with the Kolmogorov-Smirnov test and will be visually inspected using Q-Q plots. A logarithmic transformation will be considered in case of nonnormality. Analysis of covariance will be used to assess the difference in the total number of minutes of physical activity (>1.4 METs), whereby the covariates include independence in mobility and the presence of a urinary catheter. Both covariates are based on unpublished results of multivariable regression models considering various patient factors in relation to physical activity. In case nonnormality persists after logarithmic transformation, a Poisson regression model will be considered using the same covariates.

Additionally, data of behavioral mapping observations will be categorized into different activity types, from which time spent lying in bed between 8 AM and 8 PM in percentage will be derived. The difference in time patients spend lying in bed will be assessed among months 0, 6, and 13. An interrupted time series (ITS) will be used to evaluate the changes in length of stay and discharge destination among the following three predefined periods: 12 months prior to the implementation phase, 12 months implementation phase, and 6 months after finishing the implementation phase [38].

For the process evaluation, MAXQDA Analytics Plus 2018 (VERBI Software) will be used to facilitate the data analysis. All semistructured interviews will be thematically analyzed following the methods of Braun and Clarke [39]. The analytic process will be performed by two independent researchers (BMG and SJGG) and supervised by MvdS. Consensus meetings will be used to discuss and refine each theme. Member checking will be used to ensure the credibility of the data analysis. Triangulation of data will be performed by using the open-ended survey data during the qualitative data collection and analysis. Patient and health care professional survey results will be compared using chi-square tests and analysis of variance tests, depending on the type of data.

Results

This study is ongoing. The first participant was enrolled in January 2018 at the gastrointestinal and oncology surgery ward. The last outcome evaluation and process evaluation are planned for May and June 2020, respectively. Results are expected in April 2021. A summary of all participation types within this study can be found in Multimedia Appendix 1.

Discussion

While the amount of evidence on the negative consequences of physical inactivity during hospitalization continues to grow, few studies have evaluated the effectiveness of interventions that have been specifically tailored (ie, developed and implemented) in collaboration with the target population. So far, several studies revealed that increasing physical activity in general or encouraging early mobilization (after admission or operation) has a positive influence on physical functioning in daily activities, the duration of admission, and discharge home [11,13]. However, these studies often focus on unilateral interventions and have been performed in a specific context, while physical inactivity seems to affect patients in all hospital wards and patients of all ages [27]. The integration of multiple interventions in daily hospital care entails various challenges, as also described in the quality improvement projects of Mudge et al and Hoyer et al [9,16]. The Eat Walk Engage program of Mudge et al describes an approach using multiple interventions, which demonstrated a reduced length of stay after implementation in older hospitalized patients [9]. In addition, the currently ongoing Hospital in Motion study of van Delft et al describes the usage of multiple interventions tailored to tackle the numerous described barriers perceived by health care professionals and hospitalized patients [29]. The Better By Moving study will contribute to this research by providing more insight into the effectiveness of interventions that are developed bottom-up and in cocreation with the target population and by thoroughly analyzing the process of cocreation.

The strength of the Better By Moving study is the thorough problem analysis of actual performance, and barriers and enablers, which will be carried out prior to the development of the first intervention. More specifically, the barriers and enablers perceived by patients or health care professionals will be assessed through different mixed methods, such as surveys, physical measurements, observations, interviews, and focus groups. In addition, we hypothesize that the extensive analysis will create support among health care professionals, manifest ownership among local stakeholders, and facilitate the development of a local testing and implementation plan. Second, colearning in the development and implementation of new interventions together with local stakeholders from five different hospital wards can offer both an in-depth and a broad perspective on what works and what does not work when trying to improve physical activity in hospitalized patients. Third, the use of evidence-based behavioral change theories, such as the TDF [31] and BCW [32], makes it more likely that the underlying reasons for physical inactivity in hospitalized patients will be identified and countered [31,32]. Finally, the ITS analysis, which will be used, is considered one of the strongest quasiexperimental designs to evaluate outcomes such as length of stay and discharge destination. So far, none of the previously published studies investigating physical activity–improving interventions incorporated ITS analysis.

Diverse factors could challenge the success of the Better By Moving study. First, several “system” factors may affect the implementation process, such as a change in the environmental context (ie, staff turnover, competing trials, and workload) and the hospital ward culture (ie, attitude to change, commitment, and motivation) [40]. For instance, the planned renovation of the participating hospital wards and the recent merger with the Vrije Universiteit Medical Center may create a lack of focus and provide additional workload. Second, because it is not known in advance which interventions will be developed and implemented, the achieved effect may differ in each hospital ward owing to differences in the interventions used. To counter this as much as possible, we will provide for both an overall and a ward-specific analysis. Third, changing the health care professionals’ and patients’ behaviors toward in-hospital physical activity through the development and implementation of multiple interventions in cocreation takes time. While we have 12 months for each hospital ward to cocreate interventions, important changes in hospital culture, environmental context, and outcomes may arise after the last cross-sectional audit. Lastly, a pre-post mixed-methods design is used to investigate if interventions developed and implemented in cocreation improve physical activity among patients. To evaluate the effect of an intervention, a randomized controlled trial is considered the gold standard. With respect to cocreational bottom-up intervention development and implementation, in which the process, to a large extent, determines the outcome, it is considered not feasible to use a control group. Instead, we aim to evaluate the impact of our interventions on physical activity as representative as possible by approaching a random sample of at least 110 hospital patients using a computer-generated list based on hospital room numbers before and after the implementation of interventions.

By using cocreation to develop and implement interventions and by performing a process evaluation, useful insights will be provided on the effect and underlying processes of bottom-up intervention development and implementation in close collaboration with the target population and local stakeholders. Using this information, health care professionals, managers, and researchers will be able to better assess the elements that do and do not work with regard to improving physical activity in daily hospital care.

Acknowledgments

BMG and SJGG declare equal contribution, as both provided equal contribution in drafting the protocol. BMG, SJGG, and MvdS designed the framework and methodology, and drafted the protocol. SJGG and MvdS developed the research protocol, database, and data collection tools. FN and RHHE participated in designing the protocol and participated in writing the manuscript. MvdS critically revised the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data sources and participation types used for intervention development.
[PDF File (Adobe PDF File), 94 KB - resprot_v9i11e19000_app1.pdf]

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Abbreviations

ADLs: activities of daily living
BCW: behavioral change wheel
ITS: interrupted time series
MET: metabolic equivalent task
PAM: Physical Activity Monitor
TDF: theoretical domains framework
UMC: University Medical Centers

Edited by G Eysenbach; submitted 31.03.20; peer-reviewed by Q Fang, YH Kwan, P Abril; comments to author 21.08.20; revised version received 25.09.20; accepted 13.10.20; published 13.11.20.

Please cite as:
Geelen SJG, Giele BM, Nollet F, Engelbert RHH, van der Schaaf M
Improving Physical Activity in Adults Admitted to a Hospital With Interventions Developed and Implemented Through Cocreation: Protocol for a Pre-Post Embedded Mixed Methods Study
JMIR Res Protoc 2020;9(11):e19000
URL: http://www.researchprotocols.org/2020/11/e19000/
doi:10.2196/19000
PMID:33185561

Protocol

Risk Perception of Health Professionals in Intrapartum Care Decisions: Protocol for a Mixed Methods Study

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Abstract

Background: Risk perception plays an important role in decision-making processes. Differences in obstetric intervention rates suggest that, in addition to medical indications, the risk perception of obstetric health professionals might have a major influence on their decision-making process during childbirth. Although studies have investigated whether risk perception affects the role of midwifery or influences decision making during childbirth, little is known about what obstetric health professionals actually perceive as risk or risky situations and whether different risk perceptions lead to more interventions during intrapartum care.

Objective: The objective of this study is to understand the association of risk perception and the decision-making processes of obstetric health professionals (midwives and obstetricians) in Germany during intrapartum care. The study has 3 specific aims: (1) gain insight into what obstetric health professionals perceive as risk in the German clinical setting, (2) assess the extent to which personal and systemic factors have an impact on obstetric health professionals' risk perception, and (3) investigate whether different perceptions of risk are associated with different decisions being made by obstetric health professionals.

Methods: This is an exploratory sequential mixed methods study with 2 phases, a qualitative followed by a quantitative phase. In the first phase, qualitative data are collected and analyzed by conducting focus group discussions and applying qualitative content analysis to address aim 1. In the second phase, for aims 2 and 3 and to help explain the qualitative results, quantitative data are collected and analyzed by conducting an observational study using case vignettes within a survey constructed on the basis of the qualitative results.

Results: Enrollment in the first (qualitative) phase began in July 2019, and data collection and analysis have been completed. The second (quantitative) phase is currently planned, and data collection is expected to start in December 2020. First results of the qualitative phase are expected to be submitted for publication in 2020, with completion of the second phase scheduled for 2021.

Conclusions: This mixed methods study will examine the perception of risk and its association with the decision-making processes of obstetric health professionals during their care of women in childbirth. The rationale for this approach is that the qualitative data and their analysis explore participants' views in more depth, while the quantitative data will help to provide and explore a general understanding of the research problem. The results are expected to be relevant to health care professionals, policymakers, and educational institutions in order to minimize underuse, overuse, and misuse of interventions during intrapartum care.

Trial Registration: German Clinical Trials Register DRKS00017172; https://tinyurl.com/y2zoowkx

International Registered Report Identifier (IRRID): DERR1-10.2196/21443

(JMIR Res Protoc 2020;9(11):e21443) doi:10.2196/21443

KEYWORDS

risk perception; decision making; obstetric health professionals; midwives; obstetricians; mixed methods; focus group discussion

Introduction

Background

Professionals in the field of childbirth have to make many decisions daily regarding the births they are involved in. These decisions can have far-reaching consequences for the women and children involved. They concern in particular the application and implementation of interventions during intrapartum care which have become routine in developed countries, although their effectiveness is often unproven [1]. A large number of women experience some form of intervention during labor, for example, an epidural, administration of oxytocin, an episiotomy, or a caesarean section [2,3]. However, there are remarkable major cross-national and regional differences [3-7]. For example, in 2017 the caesarean section rates in Europe ranged from 15% to 37% [8], and an even larger range of 5%-70% was found for episiotomy [8]. Clear reasons for these differences are not known [9,10]. Aside from the lack of knowledge about the effectiveness of many interventions [1,11], forensic reasons are assumed to influence the decision regarding whether or not to intervene [5,12]. Maternity care is labeled as "risk oriented" and different risk assessments are considered to be the reason for the differences in intervention rates [5]. The fear of litigation "has led to a rising level of intervention in labour" [13] and it influences health professionals' decisions to perform interventions, for example, a caesarean section [12]. Therefore, this explains why the concept of risk and risk management has become a central principle in the care of women during childbirth [7].

MacKenzie Bryers and van Teijlingen [14] emphasize the importance of the "cultural influences, or the way risk is perceived" in provision of maternity care and refer to Downe [15], who argues that social and environmental issues such as institution, experience, and environmental impact are also important. In general, risk perception refers to subjectively perceived risk, that is, the subjectively perceived probability of the occurrence of a normally negative event [16]. Therefore, risk perception is "highly subjective" and a complex process [17]. Studies on risk perception and decision making show that nonlinear weighting of probabilities, heuristics (eg, availability or anchoring heuristics), and systematic biases play a role in risk perception [18,19]. Simplified rules of thinking and decision making lead to hasty judgments and systematic deviations between perception and reality. In addition, medium and high probabilities are often underestimated, while the occurrence of events with a lower probability are often overestimated [18,19]. Nevertheless, adequate risk perception of health professionals in maternity care is important, so that both trivialization and overestimation of risks do not lead to an inappropriate care, that is, to overuse, underuse, or misuse of interventions in labor. The significant differences in intervention rates may indicate that this is currently the case without it being possible to judge whether there is too little, too much, or adequate willingness to intervene in some regions and areas [3].

Mead and Kornbrot [20] investigated the influence of maternity units' intrapartum intervention rates and the risk perception of midwives. The authors stated that there is a relationship between practice and perception of midwives, and that midwives working in a unit with high levels of intrapartum intervention generally had a higher perception of risk than those working in a unit with a lower intervention rate. Healy et al [21] used semistructured interviews to investigate whether midwives' and obstetricians' perceptions of risk affected care practices for normal birth and low-risk women in labor. They state that birth is viewed through the lens of medicalization and they consider this the reason for the routine use of interventions and technology. Researchers from the Netherlands [13,22] examined the association between a midwife's personality, place of work, years of experience, and the timing of their decisions to make referrals from primary midwifery care to secondary obstetric care using case scenarios (vignettes). The authors found no significant correlations and stated that other factors must explain the variations in referral decisions. Nevertheless, they claim that "risk perceptions or beliefs about the course of labour influence midwives' decisions" (p. e76). However, the transfer of these results to the German health care context is limited due to the different models of care available for women in labor.

In Germany, in general, midwives and obstetricians are involved in the care of women giving birth. According to the legal regulations, a midwife must be present at every birth and therefore all women in labor, regardless of having a low- or high-risk pregnancy, are cared for by midwives. In a low-risk birth without complications the midwife is responsible for the birth process on her own; nevertheless, in hospitals a doctor usually is also present at the actual birth. In a high-risk birth or when abnormalities occur, a doctor must be called and takes charge of the birth, but a midwife still takes care of the woman. There are some midwife-led units where women in labor with a low-risk pregnancy are cared for exclusively by midwives as long as no abnormalities occur [23], but this is rather the exception. However, most births occur in consultant-led obstetric units [2]. Therefore, women giving birth in hospitals are usually interdisciplinary cared for by midwives and obstetricians. Decisions to or not to intervene are made by a midwife alone, by a doctor alone, or together, which depend on the model of care and the circumstances. In Germany, there also are regional variations in the use of interventions. For example, the overall caesarean section rate was 30.2% in 2015 [24], but varied from 19% to 47% in western and eastern districts of Germany [5,6]. Epidurals and augmentation of labor differed significantly in hospitals with lower or higher annual number of births [25]. The high intervention rates and the regional differences lead to the assumption that, in addition to medical indications, other factors influence the decision to intervene. As other researchers showed, these might be the clinicians' personal beliefs, including the risk perception, which was an influencing factor for the choice of the mode of birth, of performing a cesarean section [12]. The association between risk perception and the decision-making processes of health professionals during

intrapartum care has not yet been investigated in the German clinical setting. To gain insights into the decision making to use interventions during childbirth is of importance to study because interventions such as administering an epidural agent, intrapartum use of oxytocin, performing an episiotomy or a caesarean section are associated with short- and long term effects such as higher maternal mortality and morbidity (eg, increased risk of uterine rupture, abnormal placentation, sexual dysfunction), less satisfaction with the birthing process, a longer and more costly hospital stay, a longer recovery including the experience of pain and reduced mobility, or stillbirth, preterm birth, and greater incidence of late childhood obesity [7,26-30]. This has led to the tremendous increase in the relative cost of birth within the last century; besides, obstetric interventions during labor for women with a low-risk pregnancy, in general, are costly to the health system [31].

It is therefore crucial to gain insight into the risk perception of obstetric health professionals working in Germany so as to investigate the association between risk perception and decision-making processes in the German clinical setting in order to improve intrapartum care in Germany. Overall, in a simplified view, midwives and obstetricians are often assigned to different models of care, with midwives being assigned to the social model focusing on normality and obstetricians to the medical model focusing on technology and pathology. Although more of a continuum, this could be an indication of different approaches and perspectives due to socialization [14]. Therefore, this work focuses on the risk perception of obstetric health professionals in general, but differentiates between midwives and obstetricians to obtain more specific insights.

Aims and Research Question

The overall aim of this study is to understand the association between risk perception and the decision-making processes of obstetric health professionals in Germany during intrapartum care. This study has 3 aims: (1) to gain insight into what midwives and obstetricians perceive as risk in the German clinical setting in order to construct valid case vignettes of risky situations; (2) to assess the extent to which personal factors (eg, age, gender, professional experience, qualification level) or systemic factors (eg, annual number of births or level of care provided, ie, secondary or tertiary) have an impact on midwives' and obstetricians' risk perception; and (3) to investigate whether differing perceptions of risk are associated with different decisions by midwives and obstetricians.

To this end, the research questions are as follows:

1. What do obstetric health professionals understand by risk in labor in a clinical setting, and which situations are perceived as risky intrapartum?

2. Do personal, systemic, or both factors affect the risk perception of obstetric health professionals?

3. Does risk perception affect the decisions of the obstetric health professionals or the care of women in labor?

The decisions were predefined as administering an epidural agent, intrapartum use of oxytocin, or performing an episiotomy or an unplanned caesarean section. However, adding other decisions based on the results of the first research question remained open.

Methods

Study Design

An exploratory sequential mixed methods design will be used to study the risk perception of midwives and obstetricians. It will first be explored via qualitative data collection and analysis. Second, a quantitative phase will be conducted involving a survey. This design has been chosen to combine the strengths of both quantitative and qualitative research [32].

In phase I the qualitative approach will be applied and narrative data collected via focus group discussions to gain an in-depth understanding of the individual risk perceptions of midwives and obstetricians in the German clinical setting and what they perceive as risky situations. The results of the focus group discussions will assist in determining case vignettes to be used in the second phase to investigate the association of different variables on risk perception and its influence on decision making. In this way, the perceptions and actions of obstetric staff will be documented and evaluated with the help of applicable and everyday case vignettes which reflect the views and personal experiences of the target population and fit the participants being studied [32]. The survey will provide the opportunity for generalization, precision, and investigation of the influence of the obstetric staffs' risk perception on their intrapartum decision making.

The results will be reported with the Good Reporting of A Mixed Methods Study (GRAMMS) Checklist [33]. Furthermore, the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [34] is also taken into account.

Phase I: Focus Group Discussions

A qualitative approach in the form of focus group discussions was chosen in order to conduct a preliminary exploration with midwives and obstetricians and gain insight into their views. Focus groups are not intended to "generalize […] and not to make statements about the population but to provide insights about how people in the group perceive a situation" [35]. Furthermore, focus groups are very well suited when a "range of opinions, ideas or feelings" is looked for or "when opinions or attitudes are conditional or when the area of concern relates to behaviour" [35]. Focus group discussions thus have the advantage of gaining insight into participants' views in order to capture their voices [32,35]. The evoked discussions create synergies that could not have been achieved to this extent in a one-to-one interview [35]. In addition, group discussions are inexpensive and efficient [35].

Recruitment and Sampling

Midwives and obstetricians working in Germany can take part in the focus group discussions. The group composition of the contrasting or comparative groups is based on a sampling plan and on theoretically justified predefined criteria [35]. These predefined criteria have been investigated and described in several studies as possible nonclinical factors influencing clinical performance in general [36] or in the context of childbirth

[12,37-41]: age, gender, number of years of experience, type of professional qualification (vocational or tertiary education), and work setting (annual number of births, level of care, care models, eg, midwife-led care/obstetrician-led care). A pool of prospective participants (stratified purposeful sample) will be generated using purposeful sampling strategies, such as typical case sampling and maximum heterogeneity sampling in order to find out which participants "can best help to understand the central phenomena" [32]. The aim will be "to capture major variations rather than to identify a common core, although the latter may also emerge in the analysis" [42]. This approach "represents less than the full maximum variation sample, but more than simple typical case sampling" [42]. Based on the topic under investigation, the predefined criteria will be taken into account to reflect the heterogeneous characteristics of obstetric professionals and, where possible, to assign participants to the different groups. Self-activation and direct contact at specialist congresses, snowball sampling, press releases, and announcements in mailing lists and on the bulletin boards of professional associations in Germany, gatekeepers, and social media platforms, such as Facebook, Twitter, and Instagram, will be used. Inclusion criteria were age (18+) and recent clinical activity: midwives employed by or affiliated with a hospital as an independent midwife; obstetrician/gynecologists employed in an obstetric department; having 1 or more years of professional experience since qualifying; and having good knowledge and understanding of the German language. Freelance midwives with no hospital affiliation or midwives who have not worked in a delivery room within the last 2 years will be excluded. According to Krueger and Casey [35], the ideal size of a focus group is between 5 and 8 participants, so 3-4 focus groups of 5-8 participants are planned.

Data Collection and Analysis

Krueger and Casey's [35] recommendations will be followed such that each focus group discussion will last approximately 60 minutes (maximum 90 minutes). Further, the moderator conducting the focus group discussion will use a questioning route, developed for consistency and including opening, introductory, transition, key, and ending questions [35]. Participants will be asked to answer the following question: "What do you understand by the term 'risk' during labor and birth?" and "Which situation(s) in the delivery room do you consider risky?" or "Describe a situation in the delivery room that you associate risk with."

The focus group discussions will be digitally audio recorded and the recordings transcribed using the software program f4transkript (Dr. Dresing & Pehl GmbH) [43]. Before the beginning of the discussion, participants will be asked to fill in a short questionnaire to specify demographic data (eg, age, gender, years of professional experience, annual number of births, and level of care of the past and present places of work) for the analysis process. The transcribed data will be analyzed using the software MAXQDA (version 2018.2; VERBI GmbH) according to qualitative content analysis and an analysis plan. This systematic approach includes initial examination of the data, highlighting text passages, writing notes and memos, developing codes, subcodes, and identifying an emerging code system [44,45]. The main author (NP) will be the main person responsible for the analysis process and coding, nevertheless the entire analysis process will be discussed and reflected in the research team meetings; additionally, a peer audit is planned. Discrepancies will be resolved through team discussions and reflection. The results of the focus group interviews will be used to construct case vignettes of risky situations in the delivery room. The case vignettes are intended to highlight the subjective sense of action in which the social reality of the obstetric professionals is produced. The vignettes will be checked by clinicians and experts (clinicians, psychologists, researchers) to assess their face validity in a subsequent evaluation phase and adjusted if necessary. The experts will be recruited from the professional network of the authors. The valid case vignettes will be used in phase II. In this way, qualitative findings will be used to construct the second, quantitative phase of this research project.

Phase II: Survey

In phase II, a survey (either web-based or paper and pencil) using the case vignettes constructed in phase 1 will be used to study whether different factors such as age, gender, years of experience, annual number of births, or level of care of the clinic have an influence on the risk perception. Furthermore, the association of between the risk perceptions of obstetric health professionals and the decision-making process during intrapartum care will be investigated.

Recruitment and Population

Almost the same recruitment strategies and inclusion/exclusion criteria as those outlined above for phase I will be used to invite midwives and obstetricians employed in Germany to participate in the survey. The sample will be a convenience sample. Using the recruitment strategies, it is planned to invite as many midwives and obstetricians to participate as possible.

Data Collection and Statistical Analysis

Participants will be asked to fill out a version of either the web-based or paper-and-pencil self-constructed survey containing the vignettes of different birth scenarios. The primary endpoint is the risk perception of obstetric health professionals (midwives and obstetricians) caring for women giving birth measured on a 6-point Likert scale. The primary endpoint is thus ordinally scaled with 6 parameter values (from 0=hardly or no risk to 5=very high/highest possible risk).

As the aim is to invite as many midwives and obstetricians to participate as possible, no formal statistical sample size calculation will be carried out.

The secondary endpoint is the decision to intervene (binary with the variables "intervene yes" and "intervene no") whereby the decisions are partly predefined as described earlier. On the basis of a 5-point Likert scale (from 1=very unlikely to 5=very likely to choose the intervention), if the score is over 3, the characteristic "intervene yes" will be assumed.

Descriptive presentation of the results of the primary endpoint (categorical; 6 categories) will be displayed through bar charts and associated absolute and relative frequencies. Other additionally recorded variables will be analyzed according to the data situation (continuous, categorical, or binary) using

statistical methods appropriate to the data structure (categorial/binary: absolute and relative frequencies; continuous: medians, quartiles, means, standard deviation, minimum, maximum). Exploratory analyses for the primary endpoint (generating hypotheses) will be performed via ordinal regression using SPSS (IBM Inc) or R (R Foundation for Statistical Computing) with the following potential influencing factors: age, gender, type of professional qualification, years of experience, annual number of births or level of care of the current work location, and personality inventories. The choice of the link function to be used for this purpose will depend on the distribution of the observed cases among the different categories of the dependent variable. The quality of the model will be checked by Nagelkerke R^2. Results of the ordinal regression will be summarized via regression coefficients, corresponding odds ratios, and by determining 95% confidence intervals for the odds ratio.

Descriptive evaluation of the secondary endpoint depending on the risk perception will be carried out using a frequency table with absolute and relative frequencies. Depending on the obtained date, either a table form with a risk perception dichotomized at cut point over 3 or a table form with a risk perception as described in the primary endpoint with 6 variables will be used.

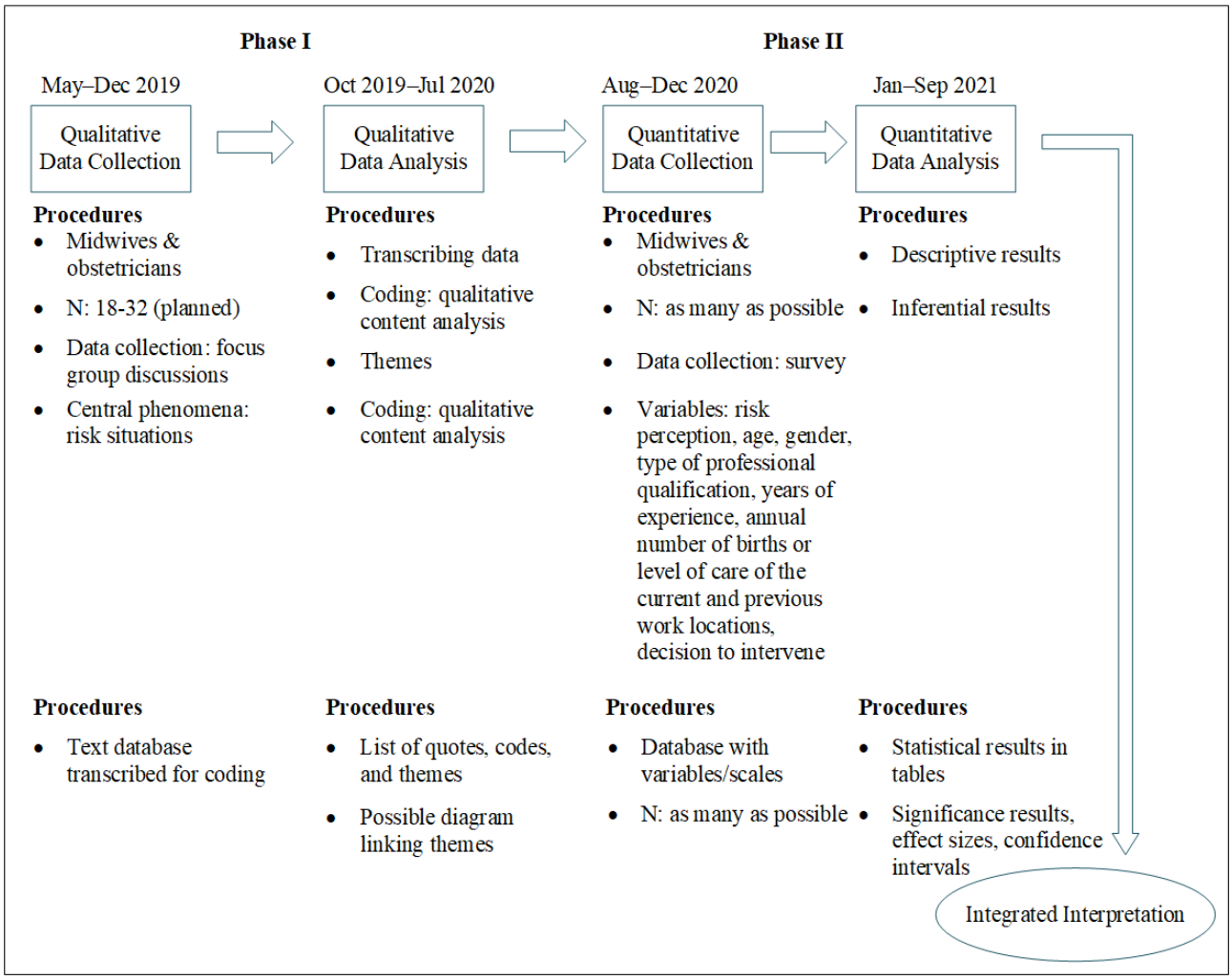
In an additional analysis, the influence of risk perception on the decision to intervene (yes or no) will be done using logistic regression adjusted for the following variables: age, gender, type of professional qualification, years of experience, annual number of births or level of care of the current work location, and personality inventories. The choice of model is made by forward selection using a likelihood ratio test. The quality of the model will be analyzed with Nagelkerke R^2. Results of the logistic regression are summarized with regression coefficients, corresponding odds ratios, and by determining 95% confidence intervals for the odds ratio.

Continuous data are descriptively evaluated by calculating measures of central tendency (minimum, maximum, quartiles, median, mean) and measures of variation (standard deviation, interquartile ranges, span). Graphical presentation will be made by suitable methods (eg, boxplot, scatter plot).

Categorical and binary data will be represented by calculating absolute and relative frequencies within frequency tables (potentially supported by bar charts). In addition, the risk measures (odds ratio, absolute risk) for group comparisons of interest will be calculated. An optional analysis of the actual power of the resulting models is desired via G*Power [46].

Statistical analysis will be supported by the Institute for Medical Biometry and Epidemiology at the University of Witten/Herdecke. The design and scope of the survey in phase II depend on the results of phase I, so it will be possible to adapt the content and design of the survey as appropriate. A pretest of the survey will be undertaken before fielding the questionnaire with a heterogeneous group of clinicians and research associates using a think aloud protocol and written feedback. In Figure 1 the exploratory sequential mixed methods design of this study is summarized according to Creswell [32].

Figure 1. An exploratory sequential mixed methods design of this study evaluating risk perception of obstetric health professionals.



Ethics Approval and Informed Consent

The Ethics Committee of the Hochschule für Gesundheit, University of Applied Sciences, has granted ethical approval (file number 190128). Interested participants for phase I will be provided with an information sheet on the study prior to the focus group discussion and again directly before the start. Participants will have the opportunity to ask questions before they give informed consent and sign the relevant form. All participants will be informed they can withdraw from the study at any time but data can only be deleted before they have been anonymized. Privacy and confidentiality will be ensured by assigning codenames to participants and any identifying data will be changed or removed from the transcripts. Participants interested in phase II will receive information about the study, length of time of the survey, data protection regulations, and the purpose and scope of use of the data collected before starting the survey. Participants need to agree to be aware of the data protection regulations; to consent to the collection, processing, and storage of the data for the specified purpose; and to the publication of the anonymized data in written or electronic form in both versions by ticking an "I agree to participate box" at the bottom of that page or by providing written consent. Phase II responses will be collected anonymously with a certified web-based survey tool that complies with the local data protection regulations, or a printed questionnaire. All data will be securely stored/transferred to a password-encrypted computer in a locked office and will be stored securely for 10 years. Participants will not receive any incentive to participate in this study.

Results

Participants were enrolled in the focus groups between July and September 2019. Data collection for phase I and the analysis were completed by May 2020. The results of the focus group discussions will be used to construct case vignettes of risk situations for use in phase II and for the enrollment of participants which is planned for August 2020. It is anticipated that the data collection and analysis will be completed by September 2021, and therefore results should be published by April 2022 in peer-reviewed publications.

Discussion

Relevance and Strength

The mixed methods design in this study is expected to provide an in-depth understanding of the risk perception of obstetric health care professionals, the extent to which risk perception is influenced by personal or systemic factors, and whether there is an association between risk perception and decision making. The mixed methods approach therefore allows researchers "to

obtain a more comprehensive view" [32] about the risk perception of obstetric health care professionals than either the quantitative or qualitative perspective by capturing voices of the health professionals working in the field and investigating the association between risk perception and decision making. To the knowledge of the authors, this topic has not yet been researched in the German maternity setting, so this study may be the first to do so. The value of the mixed methods design is a "contribution of a better understanding of the problem than what might be provided by quantitative or qualitative research alone" [32].

One of the German Health Objectives (agreements between the responsible parties in the health care system) concerning childbirth is to promote physiological, low-intervention birth [47]. Thus, addressing the risk perception of midwives and obstetricians as a potential determinant influencing intrapartum decision-making processes can support the implementation and achievement of this objective. Insights into intrapartum decision-making processes and the extent to which these are affected by personal and systemic factors can help to minimize underuse, overuse, and misuse of interventions during intrapartum care. The findings might be used by care providers to give careful consideration to their decision-making process in order to modify their practice [12]. Avoiding unnecessary medical decisions can have health advantages for the women and economic advantages. The results possibly provide insight into gaps in the training of obstetric health care professionals, so that these gaps can be addressed through new training, evaluation, and reflection programs. In this way the research project outlined above supports the improvement of maternity care, and the results of this study are likely to be relevant for health care professionals, policymakers, and educational institutions in Germany and potentially internationally.

Limitations

Case vignettes should be "a stimulating initial situation," and encourage the participants "to make assessments or take further action" [48]. The purpose of the case vignette is to create the subjective sense of action by establishing the social reality of the obstetric staff [48]. However, a major disadvantage of vignettes "is that judgments or decisions are only hypothetical" and real assessments and actions may differ from the answers given by participants [49]. The use of case vignettes is a simplifying approach and cannot fully reflect the complexity of situations in maternity care which are influenced by verbal, visual, and intuitive information [14,49]. Nevertheless, because observations in the setting would be unethical and associated with personnel and financial challenges, case vignettes are still considered an appropriate tool in some contexts.

Distortion/bias is possible due to the recruitment methods. Self-activation using the methods described earlier may lead to the participation of particular motivated people with a special interest in the decision-making process whose response behavior differs from the overall population. This would lead to a lower variance of opinions being surveyed and there would be a possibility that the results would be influenced by the respondents and nonrespondents, respectively. Furthermore, mixed methods designs generally require more time, resources, and detailed skills in different research methods [32]. Because this research project is part of a doctoral thesis, the availability of personnel and financial resources is limited, but different strategies have been applied to address this challenge. The principal investigator (NP) is able to rely on a team of supervisors with skills and experience in different research methods. In addition, the integration into a PhD program involves continuous reflection and discussion of the methodological approaches and the consulting services of the university's own Institute for Medical Biometry and Epidemiology. As a result, skills in quantitative and qualitative approaches are bundled together into this research project. Furthermore, this collaboration and peer audits help to deepen the researcher's reflexivity. Because the principal investigator (NP) used to work as a midwife, her own role and experiences are continuously reflected and discussed in peer audits, both before and during data collection and analyses, in order to avoid subjective biases in interpretation.

Conclusion

This paper outlines the methods applied in the study described above to investigate the risk perception of midwives and obstetricians and the association between risk perception and intrapartum decision making of obstetric health care professionals. The results of this study are expected to be relevant to policymakers, health care professionals, and educational institutions in order to minimize underuse, overuse, and misuse of interventions during intrapartum care.

Conflicts of Interest

None declared.

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys
GRAMMS: Good Reporting of A Mixed Methods Study

Edited by G Eysenbach; submitted 26.06.20; peer-reviewed by T Krishnamurti, T Wieringa; comments to author 24.08.20; revised version received 14.10.20; accepted 03.11.20; published 23.11.20.

Please cite as:
Peterwerth NH, Halek M, Tulka S, Schäfers R
Risk Perception of Health Professionals in Intrapartum Care Decisions: Protocol for a Mixed Methods Study
JMIR Res Protoc 2020;9(11):e21443
URL: http://www.researchprotocols.org/2020/11/e21443/
doi:10.2196/21443
PMID:33226353

Protocol

Methodological Challenges in Investigating Supracondylar Fractures of the Humerus From a Child's Viewpoint: Evolution of Study Protocol

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Abstract

Background: Outdoor play and risk-taking behaviors, including play at heights, are important to children's physical, social, and cognitive development. These aspects of play are important to consider when informing prevention policies for serious injuries that commonly occur on play structures. Supracondylar fractures of the humerus (SCH) are the most common type of elbow fractures that result from falls on an outstretched hand among healthy children. Despite being one of the leading causes of admission to the hospital and surgical intervention, the details surrounding the cause of these injuries are often not recorded. Previous research has correlated decreased overall playground safety with higher rates of SCH fractures. Play structure height and the type of undersurface have been identified as potential risk factors for severe injuries, including SCH fractures, in part due to low compliance with safety standards. This paper explores the challenges we encountered designing the study and the resulting insights and methodological modifications we made.

Objective: The aim of this paper is to discuss the challenges related specifically to clinical research in pediatrics and strategies developed to conduct a study that prioritizes the engagement and perspective of children and their families.

Methods: To explore the link between the severity of SCH fractures and children's behavioral, environmental, and mechanistic factors, we conducted a mixed-methods study.

Results: During phase 1 (the original methodology) from April 2017 to July 2018, there were 58 eligible study participants and 17 were recruited. For phase 2 (the revised methodology) between October 2018 and October 2019, there were 116 eligible participants and 47 were recruited.

Conclusions: The changes in methodology made following the first phase of data collection were effective in our ability to recruit participants. By identifying and addressing challenges pertaining to recruitment and resource limitations, we were able to collect data in a concise manner while not compromising the quality of the data and make for an easily adoptable methodology for other sites interested in participating in the study. We hope that future studies that plan to employ a similar methodology can gain insight through the methodological challenges we have encountered and the way we adapted the methodology to build a more pragmatic approach.

International Registered Report Identifier (IRRID): DERR1-10.2196/21816

(JMIR Res Protoc 2020;9(11):e21816) doi:10.2196/21816

KEYWORDS

supracondylar fracture; pediatrics; trauma; protocol; injury prevention; child's viewpoint

Introduction

Supracondylar fractures of the humerus (SCH) are the most common type of elbow fractures that result from falls on an outstretched hand among healthy children [1,2]. In Canada, the incidence varies by province but has increased over time, accounting for 75% of total pediatric elbow injuries, with a peak incidence among children aged 5 to 8 years [3,4]. SCH vary from simple fractures that heal well with good outcomes by being treated with a cast to those that result in significant disability due to irreparable damage to the neurovascular structures in the forearm. With increased severity of injury, treatments may include surgery, and the potential for complications increases. Early surgical intervention is important in displaced fractures [5,6]. Complications that result from injury include infection, nerve injury, and vascular compromise, which can result in the devastating complication of the Volkman ischemic contracture, leading to lifelong disability [7]. Despite being one of the leading causes of admission to the hospital and surgical intervention [8-11], details surrounding the cause of these injuries are often not recorded. Furthermore, existing literature has not detailed the mechanical and behavioral causes and circumstances leading to injury [12].

Previous research has correlated decreased overall playground safety with higher rates of SCH fractures [13]. Play structure height and the type of undersurface have been identified as potential risk factors for severe injuries, including SCH fractures, in part due to low compliance with safety standards [12,14]. A study comparing falls from playground equipment versus standing height found that falls from playground equipment represented 85% of major fractures [15]. However, these studies did not specifically address SCH fractures but rather a wide range of upper limb fracture types.

Outdoor play and risk-taking behaviors, including play at heights, are important to children's physical, social, and cognitive development [16-20]. These aspects of play are important to consider when informing prevention policies for serious injuries that commonly occur on play structures. The majority of injuries that result in an SCH fracture in children are thought to occur on playground structures; however, there is limited data supporting this assumption [11,21]. Although falls from monkey bars have been reported as the cause of over 60% of injuries resulting in an SCH fracture, there are limited Canadian data to support this [10,15,22]. It is important to note that despite playgrounds being a common location for injuries among young children, the frequency and severity are relatively low [23]. To inform evidence-based injury prevention policies that take into consideration the aspects of play most important to a child's development, more research on SCH fractures is needed to gain a better understanding of the specific mechanisms and child-related factors surrounding injuries.

To explore the link between the severity of SCH fractures and children's behavioral, environmental, and mechanistic factors, we conducted a mixed-method study among children presenting to the Department of Orthopaedics at the senior author's center from June 2017 to the present. We used qualitative interviews with children combined with the use of visual aids, such as photographs, and quantitative analysis of playground structures comparing them to the safety standards [24-27]. This combination of methods has been shown to assist children who have experienced elbow fractures in sharing their viewpoints in a clinical setting [28].

An important and increasingly relevant perspective in clinical research is that of the child's viewpoint. For instance, efforts to understand a traumatic event from a child's perspective are important in clinical research so as to capture relevant aspects of the events leading up to the injury that may be overlooked or missed in the relay of the incident by parents and caregivers [29,30]. Important ethical considerations need to be made to the methodology when conducting patient-oriented research, particularly with children. For example, the appropriate age at which a child can give consent or refuse assent must be considered in the recruitment process. Additionally, we need to be careful around questions that may elicit negative emotions in children [30]. Through purposeful integration of children's perspectives and child-friendly methodologies into research, relevant factors pertaining to the injury may be identified that are often overshadowed in routine, adult-focused elicitation [25,28,31].

This paper explores the challenges we encountered and the resulting insights and methodological modifications we made. We will discuss the challenges related specifically to clinical research in pediatrics and the strategies developed to conduct a study that prioritizes the engagement and perspective of children and their families. The aim of this manuscript is to describe the progression of the mixed-methods study protocol from a detailed qualitative approach to a more pragmatic approach.

Methods

Phase 1. Original Methodology

Data collection for the study was designed to coincide with children's routine 3-week, 6-week, and 12-week postinjury appointments at the orthopedic clinic at British Columbia Children's Hospital. Once the study received ethics approval (#H17-00561), eligible study participants were identified by the senior author. A designated research assistant assented child participants while consent was obtained from the parents/legal guardians at the first visit to the orthopedic clinic. Consented participants were given a GPS camera and a prepaid mailing envelope for the return of the camera. They were instructed to take photographs of the play structure where the injury occurred. This required the families to go back to the site of the injury to

take the photographs. They were provided with training on basic photography skills and made aware of privacy concerns during photography. At this point demographic and basic injury data were collected by asking the participants' parents in an informal interview setting. Fracture classification and treatment plan were collected through a medical chart review.

At the 6-week follow-up, a photo elicitation interview (PEI) was conducted using the participant-generated photographs to discuss the mechanism of injury, site of injury, and injury experience. The children were encouraged to describe how they fell and other details around their injury and recovery, aided by the photographs they took. Interviews were audio recorded and transcribed verbatim using a professional transcription service. The transcripts were reviewed using a framework analysis that involved interpretation, thematic identification, charting, and consensus codes from two reviewers [32,33]. Treatment updates and complications were also recorded from medical chart review after every clinical follow-up. At the 12-week follow-up, participant medical charts were used to log final injury-related outcomes and complications. No participant interaction was necessary.

Using the GPS cameras, the exact location of the injury was extracted from geo-tagged photographs taken by the injured children. A research assistant identified the exact playground equipment where the injury took place using the images taken by the participants combined with the information collected in the interview. This research assistant visited each of these injury sites and took measurements of the play structures involved in the injury. Several measurements were taken including the surface depth of the terrain, height of the play structure platforms, and handlebars. Measurements were taken using basic tools including a ruler, tape measure, and soil probe. The results were compared with the standards provided by the Canadian Standards Association, which provides detailed information about materials, installation, and strength of the equipment; surfacing, inspection, maintenance, performance requirements, and access to the playground; play space layout; and specifications for each type of equipment [34].

Identified Challenges

Participant Recruitment

The main concerns voiced by participants and families that declined participation were related to the time investment required by the families. In particular, returning to the site of the injury to take photographs and partaking in the PEI were identified as demanding. To improve participation, changes were made to the methodology based on these concerns.

Resource Limitations

Constraints in resources were also barriers in following the methodology of this study. This methodology required purchasing GPS cameras to take photos of the playground sites. Additionally, special training was required for staff to conduct the PEIs. Likewise, analyzing the qualitative data was time intensive. The interviews were scheduled to take place at the time of the participant's regular clinic follow-ups to save families from an additional visit, but a trained interviewer was not always available at that time. In those cases, participants and their families were asked to return to the hospital to complete the interview.

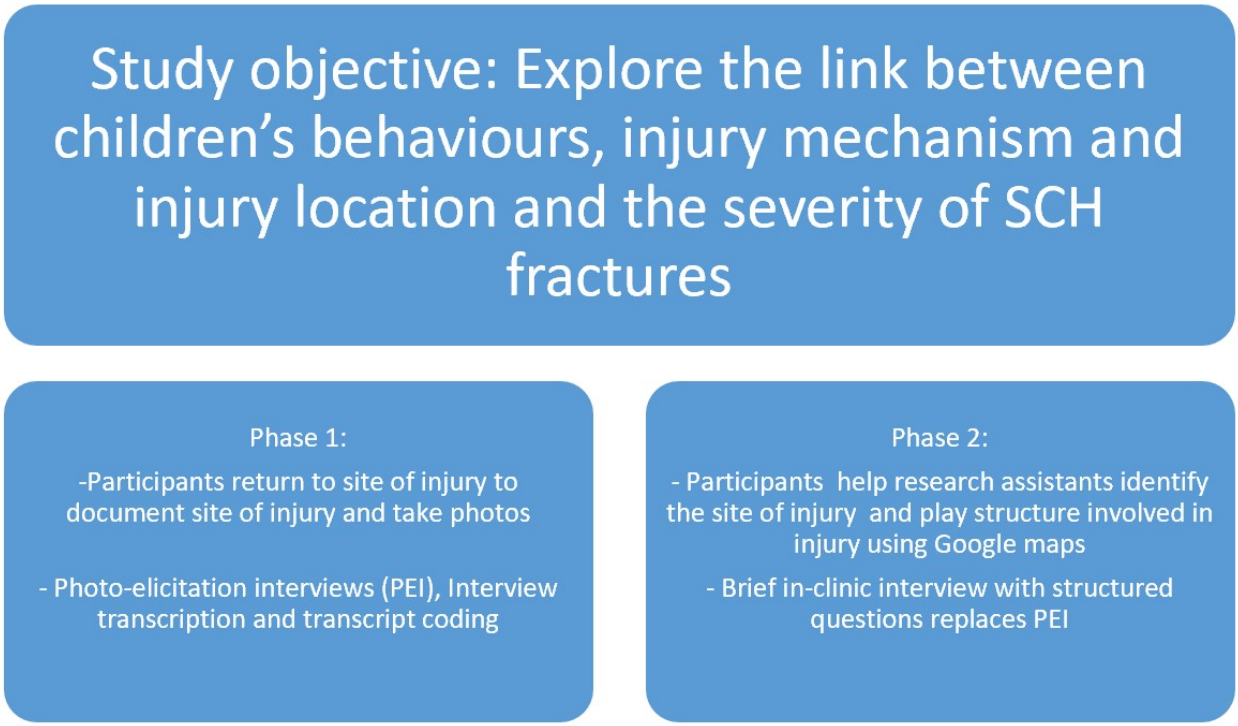
Phase 2. Revised Methodology

The study methodology was revised to overcome challenges identified during phase 1 while addressing the same research questions. Figure 1 demonstrates the relationship between the two phases of the study. A summary of modifications can be seen in Table 1 and Multimedia Appendix 1. At the first visit to the orthopedic clinic, children who consented to participate were asked a series of questions pertaining to their injury. Data collection except for the measurement of the play structure was completed at the time of recruitment. The participant was asked to describe the location of the injury event and the play structure involved. The family provided the address, at which point the research assistant typed that into Google Maps. Using satellite view, the participant indicated the exact play structure where the injury occurred. The research assistant then took a screenshot image of the structure and the street view of the location to make the identification of the play structure easy when going to the site to complete the measurements. This ultimately allowed for the elimination of GPS cameras and the need for the participant to return to the site of injury. This change in methodology increased efficiency, reduced resource requirements, and maintained feasibility for both the research study and the participants and families. Families were not pressured to return to the site of injury between clinic follow-up appointments to take photos of the site. This action reduced the financial requirements for having expensive cameras.

If the site of injury or play structure was not visible using Google Maps, the participant and their parent or legal guardian were asked to return to the site and take photographs using their personal photo-taking device in order to identify the exact play structure for measurement. The participants were informed of privacy concerns during photography, and instructions on what to capture in the photos were described. Participants were then asked to describe the mechanism of injury through a short in-clinic interview transcribed by the research staff. At the first visit, demographic data, fracture classification, treatment plan, and basic injury data were also collected. At the 6-week or 12-week clinic follow-up, recruited participants who were injured on a play structure not visible using Google Maps were asked to send photographs of the play structure involved in the injury via email.

In phase 1, specific training was required for the research assistant to be able to conduct and review the PEI. Phase 2 alleviated the need for extensive preparation and training to conduct the interviews because of the more structured setting. The extensive amount of time required to transcribe, code, and analyze the qualitative data was eliminated.

Figure 1. Study objective with the key components from each phase of the study.



Given that the aim of the interviews remained the same in both phases of the methodology and the questions were focused on uncovering specific aspects of the child's memory of the injury, the research assistant asked questions and provided prompts as necessary to help the participant with elicitation of the injury. Based on the preliminary analysis of the data collected in phase 1, we were able to select the questions in the PEI based on the questions that elicited the most complete responses during the PEI. Multimedia Appendix 1 includes more details on the changes made to the questions through the evolution of the protocol.

Some children had difficulty articulating the events that lead to the injury or simply said they did not remember. To aid the elicitation of the injury events in these cases, the research staff demonstrated different arm motions and asked participants to identify which motion was most like their experience. Research staff were intentional in clarifying these memories while remaining impartial to avoid influencing the responses.

Table 1. Overview of modifications to the methodology.

Phase 1: Identified challenges	Phase 2: Modifications to the methodology
Recruitment	Condensing data collection into one clinic visit to reduce the need for research follow-up at every clinic visit
Time investment	Use of Google Maps to identify play structure where injury occurred to eliminated need for participants and their families to return to the site of injury
Resource limitations	Replacing the detailed PEI[a] with a short in-clinic interview with structured questions and therefore no longer needing GPS cameras

[a]PEI: photo elicitation interview.

Results

During phase 1 (the original methodology) from April 2017 to July 2018, there were 58 eligible study participants and 17 were recruited. For phase 2 (the revised methodology) between October 2018 and October 2019, there were 116 eligible participants and 47 were recruited. The results from this study will be published in a separate manuscript.

Discussion

Summary

The progression of the study methodology has been integral to advancing this research because patient engagement and input is valuable in clinical research settings [29]. The identification of challenges such as recruitment, time investment, and resource limitation enabled us to see the need to modify the methodology. Through identifying the most relevant aspects of data collection and modifying methodology to collect these data, we have taken a more pragmatic approach and shifted some data collection methods from qualitative to quantitative.

In the first phase of data collection, qualitative data pertaining to the injury experience from the child's perspective were prioritized. However, as phase 1 was completed, it became apparent that amendments to this methodology could reduce resource investment in data collection and analysis while still answering the research question. In doing so, we have lost some of the qualitative data that were collected through the photo elicitation interviews. This could represent a potential limitation to the modified research methodology as we were not be able to go as in depth on the behavioral, emotional, and mechanistic factors influencing the events surrounding the injury from the child's perspective.

Challenges in clinical research can provide opportunities to explore new methodological approaches for data collection, recruitment, and participant interaction. Steps toward addressing resource investment and increasing patient participation and hence the recruitment rate were undertaken in this study. Through the pediatric elbow fracture study, we have shown the feasibility of making modifications to methodology to an ongoing study to reduce patient and resource burden. Our modification of methodology did not compromise the quality of our data.

Recruitment

The increase in recruitment rate from 0.29 to 0.41 is an indication that the modifications to the methodology were effective in addressing the concerns of eligible participants and their families.

To address the concerns voiced by participants and their families that participated and declined participation, a more pragmatic methodology was devised that allowed for data collection while reducing demand on the participating families. Consideration of the time commitment that the study demanded of participants and their families was important, as it led to our understanding that this requirement of the study impacted recruitment.

Google Maps

The use of Google Maps satellite view enabled the research assistant to identify the exact location of the injury event with the participant and the family at their clinic visit. However, a limitation to the use of Google Maps was if the play structure was not visible using street view, then the participant would need to return to the site to take pictures of the exact structure where the injury occurred. In these cases, we asked the participants' families to take photos on their personal devices and send the photos to the research team by email.

Time Investment

Condensing data collection into one clinic follow-up appointment was an effective change to the methodology because this enabled the recruitment of eligible participants at any of their clinical appointments and alleviated some of the time investment that the original methodology required.

Resource Limitation

The PEIs used photographs taken by participants to help overcome age-related linguistic and cognitive barriers for young participants [31]. However, it required participants and their families to return to the site of injury to take photos in addition to the time commitment of the interview itself. This was time consuming for participants and their families, and it was felt that the necessary information could be collected through a shorter and more structured interview as opposed to a semistructured interview. There were concerns that the change in methodology would affect the quality of data. However, the data from the original and revised methodology were found to be comparable.

Therefore, we began performing brief in-clinic interviews that captured the child's account of events leading to injury. Using focused questions informed by our phase 1 interviews, we were able to obtain detailed accounts of the injury from the child's perspective. The questions were centralized around the mechanism of the injury and a description of the play structure or location of where the injury took place. From this, we were able to modify our questions that specifically addressed our research inquiry without having to do a more detailed interview. By replacing the PEI with a more condensed and structured set of questions that could be answered during the participants' regular clinic follow-ups, we were able to collect important information on the mechanism of injury from a child's perspective while alleviating resource limitations associated with transcribing and coding the interview and training for staff to conduct the interview.

In clinical research, it is important to address barriers affecting recruitment and patient involvement and formulate pragmatic solutions to retain participation. By accommodating the needs of participants and their families, the recruitment rate was improved for the ongoing elbow fracture study. This experience has emphasized the importance of taking into consideration what participants and their families value most when being involved in research studies. Participant and family participation and input in the development of guidelines and methodology can provide insight to clinicians that could be otherwise overlooked [35]. This insight is valuable during the design phase but is still important to consider at all stages of the study, as demonstrated in the methodology outlined in this manuscript.

More Canadian research is needed to identify and evaluate the safety of playground structures including specific mechanisms and child-related factors surrounding elbow fractures to inform prevention policy. Addressing resource constraints was important to ensure that the methodology was not only feasible and sustainable for our site but also to facilitate this as a multicenter study resulting in a larger sample size.

Conclusion

The changes in methodology made following the first phase of data collection enhanced our ability to recruit participants, collect data in a concise manner while not compromising the quality of the data, and design an easily adoptable methodology for other sites interested in participating in the study. We hope that future studies that plan to employ a similar methodology can gain insight through the methodological challenges we have encountered and the way we adapted the methodology to build a more pragmatic approach.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Iterations of the questions asked in clinic.
[DOCX File , 17 KB - resprot_v9i11e21816_app1.docx]

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Abbreviations

SCH: supracondylar fractures of the humerus
PEI: photo elicitation interview

Edited by G Eysenbach; submitted 26.06.20; peer-reviewed by G Testa, G Hu; comments to author 21.07.20; revised version received 09.09.20; accepted 29.09.20; published 02.11.20.

Please cite as:
Lim BT, Chhina H, Pike I, Brussoni M, Cooper A
Methodological Challenges in Investigating Supracondylar Fractures of the Humerus From a Child’s Viewpoint: Evolution of Study Protocol
JMIR Res Protoc 2020;9(11):e21816
URL: https://www.researchprotocols.org/2020/11/e21816
doi:10.2196/21816
PMID:33136061

Protocol

Building a Digital Bridge to Support Patient-Centered Care Transitions From Hospital to Home for Older Adults With Complex Care Needs: Protocol for a Co-Design, Implementation, and Evaluation Study

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Abstract

Background: Older adults with multimorbidity and complex care needs (CCN) are among those most likely to experience frequent care transitions between settings, particularly from hospital to home. Transition periods mark vulnerable moments in care for individuals with CCN. Poor communication and incomplete information transfer between clinicians and organizations involved in the transition from hospital to home can impede access to needed support and resources. Establishing digitally supported communication that enables person-centered care and supported self-management may offer significant advantages as we support older adults with CCN transitioning from hospital to home.

Objective: This protocol outlines the plan for the development, implementation, and evaluation of a Digital Bridge co-designed to support person-centered health care transitions for older adults with CCN. The Digital Bridge builds on the foundation of two validated technologies: Care Connector, designed to improve interprofessional communication in hospital, and the electronic Patient-Reported Outcomes (ePRO) tool, designed to support goal-oriented care planning and self-management in primary care settings. This project poses three overarching research questions that focus on adapting the technology to local contexts, evaluating the impact of the Digital Bridge in relation to the quadruple aim, and exploring the potential to scale and spread the technology.

Methods: The study includes two phases: workflow co-design (phase 1), followed by implementation and evaluation (phase 2). Phase 1 will include iterative co-design working groups with patients, caregivers, hospital providers, and primary care providers to develop a transition workflow that will leverage the use of Care Connector and ePRO to support communication through the transition process. Phase 2 will include implementation and evaluation of the Digital Bridge within two hospital systems in Ontario in acute and rehab settings (600 patients: 300 baseline and 300 implementation). The primary outcome measure for this study is the Care Transitions Measure–3 to assess transition quality. An embedded ethnography will be included to capture context and process data to inform the implementation assessment and development of a scale and spread strategy. An Integrated Knowledge Translation approach is taken to inform the study. An advisory group will be established to provide insight and feedback regarding the project design and implementation, leading the development of the project knowledge translation strategy and associated outputs.

Results: This project is underway and expected to be complete by Spring 2024.

Conclusions: Given the real-world implementation of Digital Bridge, practice changes in the research sites and variable adherence to the implementation protocols are likely. Capturing and understanding these considerations through a mixed-methods approach will help identify the range of factors that may influence study results. Should a favorable evaluation suggest wide adoption of the proposed intervention, this project could lead to positive impact at patient, clinician, organizational, and health system levels.

Trial Registration: ClinicalTrials.gov NCT04287192; https://clinicaltrials.gov/ct2/show/NCT04287192

International Registered Report Identifier (IRRID): PRR1-10.2196/20220

(JMIR Res Protoc 2020;9(11):e20220) doi:10.2196/20220

KEYWORDS

digital health technology; care transitions; multimorbidity; pragmatic trial; co-design; hospital; primary care

Introduction

Background

Older adults with multimorbidity and complex care needs (CCN) are among those most likely to experience frequent care transitions between settings, particularly from hospital to home [1,2]. Many of these community-dwelling older adults fall into the category of high-cost users [3], who account for the majority of year over year health care spending internationally [4-7]. The complexity of these individuals stems not only from their multimorbidity disease profiles but also the social, environmental, and contextual issues that make it difficult for them to manage their physical and mental health needs [8]. It is often the interaction of these challenges that results in frequent visits to the hospital.

When patients leave the hospital, they face challenges as they attempt to cope and adjust at home. Krumholz [9] coined the term posthospital syndrome to describe this acquired, transient period of vulnerability post-discharge due to impaired physiological systems and depleted reserves. This depletion limits patients' ability to adjust and manage their health issues, often leading to hospital readmission within 30 days with an acute medical illness unrelated to the original diagnosis. Poor communication and incomplete information transfer between the various clinicians and organizations providing care to CCN patients as they transition from hospital to home can lead to medication errors, readmissions, decreased patient satisfaction, further morbidity, and even mortality [10]. These issues can be exacerbated in smaller communities where resources and services may be lacking, transportation limitations may exist, providers may be limited, or wait times may be increased [11,12]. Studies have demonstrated that insufficient communication during the transition process can lead to poor patient outcomes and higher rates of readmission for older adults with CCN [13,14].

While improving clinician communication is important, the quality and content of that communication with patients also matters. Patients with CCN benefit most from person-centered delivery models that can adapt to their unique needs and engage them as partners in their care [15,16]. Person-centered approaches have been shown to improve discharge from hospital to home by emphasizing partnership between patient and provider, improving patient self-efficacy, and improving communication between patients and providers and within care teams [17-19]. For patients with CCN, incorporating ongoing support for self-care after they return home as part of that communication can offer additional support and benefit [20]. In sum, communication that enables person-centered care and supported self-management may offer the greatest advantages as we support older adults with CCN transitioning from hospital to home.

Digital health technologies offer a promising solution to support person-centered communication across interprofessional teams working within and across health care organizations [21-26]. A systematic review of interprofessional communication in transitional care models found that information systems and multiprofessional care coordination support higher satisfaction and subjective quality of life for older adults [27]. A key strength of digital solutions is their ability to potentially foster shared situational awareness to support clinical decision making across care teams [28,29] of interprofessional teams. An essential component of interdisciplinary communication [30], shared situational awareness is a group or team's ability to understand the big picture and work together toward a common goal [31,32], like transitioning a patient from hospital to home. Digital solutions have the ability to both synchronously and

asynchronously enable information sharing regarding a team's common goal.

While these examples demonstrate the potential of digital communication platforms to improve team communication and functioning, a number of issues remain that limit the value of current systems. First, the majority of communication systems exist within single teams or organizations and rarely span those boundaries [33]. Second, many available communication systems do not inherently support person-centered care delivery, as few are co-designed with patients and providers [34]. Third, digital health solutions have been criticized for limiting other forms of information communication needed to foster shared situational awareness [35]. As such, many of the available systems are not well suited to supporting the communication needs of care teams, patients, and families during the time of transition from hospital back to the community. Finally, many existing systems have only been evaluated over short periods with insufficient attention to implementation as a means to support both evidence of effectiveness and transferability of findings [36].

Our project will address these gaps by implementing and evaluating a Digital Bridge to support person-centered health care transitions for older adults with CCN. The Digital Bridge will (1) span organizational and professional boundaries by enabling communication between interdisciplinary teams working in hospital and primary care with patients and caregivers, (2) support person-centered delivery through adoption of co-design methods to establish a workflow, and (3) be evaluated through an implementation science lens.

The Digital Bridge will integrate two previously and separately tested and validated technologies that are currently in use in hospital and community settings: (1) Care Connector and (2) the electronic Patient-Reported Outcomes (ePRO) tool. Care Connector is an interprofessional communication and collaboration platform initially designed in the hospital setting to support clinical teams caring for patients with CCN [37]. The tool includes discharge communication supports like Patient-Oriented Discharge Summaries (PODS) [38] to support clinician communication and collaboration in the community and across care settings. The ePRO tool is a primary care–facing technology co-designed with patients with CCN, their primary care providers, and family caregivers to enable communication of patient-oriented goals [39].

While ePRO and Care Connector have been designed and tested in their single settings (primary care and hospital, respectively), bringing the solutions together to create the Digital Bridge will build in new functionality and workflows that are, as yet, untested. This protocol outlines a development (co-designing the integration of the solutions), implementation (putting the new Digital Bridge into practice), and evaluation (testing impact of the Digital Bridge) study. We hypothesize that these two technologies will work synergistically by supporting communication and collaboration needs of clinicians and patients at the critical time of care transitions (Care Connector) and engaging patients to set goals and monitor progress throughout transitions from hospital to living in the community over the longer term (ePRO).

Objective and Research Questions

This project poses three overarching research questions aimed at adapting the technology to local contexts (RQ1), evaluating the impact of the Digital Bridge (RQ2), and exploring the potential to scale and spread the technology (RQ3).

1. What are the workflow design considerations in adopting digital solutions that bridge care settings to support transitions from hospital to home for patients with CCN, from patient/caregiver, clinician, and organizational perspectives?
2. Does the digital solution achieve quadruple aim goals by offering a cost-effective means of supporting care transitions to achieve improved provider experience (improved communication around transitions and improved teaming), patient experience with transitions (improved person-centered care transitions), and patient-reported outcomes (health-related quality of life)?
3. What are the implementation enablers and barriers to adopting technology in this process from patient, caregiver, provider, organizational, and system perspectives?

Our proposed project will advance learning in three areas, each of which has strong potential for downstream impacts for patients, providers, and health systems. First, this project will further our understanding of person-centered transition models of care through the co-design of the workflow and evaluation of its impacts. Second, we will be among the first to integrate hospital-based and primary care–based digital health technologies to support care transitions, addressing a critical integration challenge identified by health system decision makers. We will learn how to build stable and secure integrated data architectures, establish productive partnerships across multiple stakeholders, and determine the costs and values of this type of integration. Finally, the project will develop a template for adopting innovative models and digital technologies to support older adults with CCN that cross organizational and professional boundaries. Drawing on implementation science theory to guide our work allows us to produce recommendations on how to adopt similar boundary-spanning technologies in different health care settings.

Setting and Context

To ensure the designed intervention is potentially scalable, we will carry out this project in two distinct health care organizations in Ontario, Canada. Sinai Health System (SHS) is a hospital system located in Toronto, Ontario, comprising two hospitals (Mount Sinai and Bridgepoint), two family health teams, and a community agency (Circle of Care). The hospitals have a total of 831 beds in-service, 29,062 admissions to Mount Sinai, 19,611 outpatient visits to Bridgepoint, with Circle of Care providing over 1.4 million hours of personal support and rehabilitation to people in their homes [34]. Located in Mississauga, Ontario, Trillium Health Partners (THP) is one of Canada's largest community-based teaching hospitals, affiliated with the University of Toronto. In 2018-2019, it operated 1306 in-patient beds across 3 sites and had more than 1.7 million patient visits including 64,907 inpatient admissions and 276,003 emergency and urgent care visits. Due to their complexity, patients with CCN are often admitted to acute medicine services

at both organizations and may require rehabilitation prior to returning home. We therefore focus our project in the general medicine and rehabilitation services at both organizations.

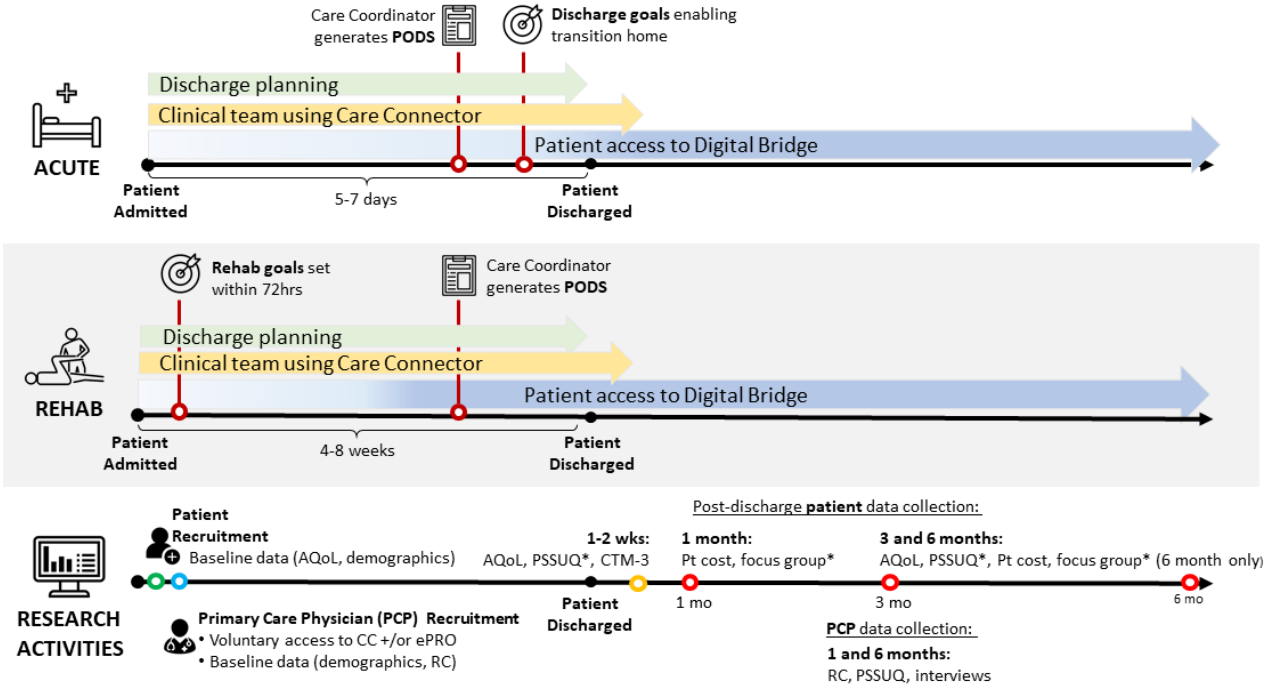
Intervention

The Digital Bridge will be an integration of the Care Connector and ePRO technology solutions. Multimedia Appendices 1 and 2 offer descriptions of feature sets and wireframes of both solutions. Both technologies have been designed and developed through user-centered co-design approaches and have undergone usability and feasibility testing and evaluations [34,39-48].

The Digital Bridge will support care transitions by (1) inviting primary care physicians (PCPs) to access Care Connector while the patient is in hospital, allowing for asynchronous communication via the messaging feature for proactive discharge planning; (2) facilitating the inclusion of interprofessional recommendations in the discharge module (e.g., diet and mobility) typically missing from traditional physician-generated discharge summaries; (3) fostering electronic generation of PODS for use in patient-centered discharge teaching; (4) providing patients electronic access to PODS postdischarge to facilitate use of information at home; (5) adopting a digital enabled goal-oriented process to engage patients and families in the discharge process; and (6) providing ongoing self-management support for patients using ePRO for the vulnerable period 6 months postdischarge.

While both systems have been tested and validated in their independent settings, we will co-design the workflow with end users to establish a feasible model for use in care transitions, modifying the technologies as needed. We will pay particular attention to integration with each hospital's existing hospital information system (HIS) to support workflow and adoption. Of note, our hospital partners will use 3 distinct vendor HISs during the implementation phase. These HISs provide native support for the 6 functionalities to varying degrees. In our co-design, we will focus particularly on achieving the 6 functionalities above using the best technology (including those embedded in the local HIS) in each context to support workflow. We will use the term Care Connector to refer to technology functionalities 1 to 4, and ePRO to refer to technology functionalities 5 and 6. Although the transition workflow will be co-designed in phase 1, we anticipate the intervention will involve the process seen in Figure 1 and described in more detail in Multimedia Appendix 3.

Figure 1. Proposed Digital Bridge workflow and trial data collection timelines.



Methods

Multiphased Evaluation Approach

The study includes two phases: workflow co-design (phase 1), followed by implementation and evaluation (phase 2). Research question 1 will be the main focus of phase 1, while phase 2 will address research questions 2 and 3. Table 1 offers an overview of the data collection strategy aligned to research questions and relevant theories and constructs.

Table 1. Data collection tools and timeline.

Research question, participant/level of analysis, and theories and constructs	Tool/method	Collection timeline
Phase 1		
What are the workflow design considerations in adopting digital solutions that bridge care settings to support transitions from hospital to home for patients with CCN[a] from patient/caregiver, clinician, and organizational perspectives?		
Patients, caregivers, and hospital and primary care providers		
User-centered co-design, usability and feasibility testing, FITT[b] framework	4 working groups (2 hours each), cognitive walk-throughs, and PSSUQ[c]	12 weeks in year 1: 1 month for first 3 groups, 1 month for refining workflow, 1 month for final group, 1 group session including 5 to 10 walk-throughs, 2 to 3 weeks to finalize workflow (total 1 month)
Phase 2		
Does the digital solution achieve quadruple aim goals by offering a cost-effective means of supporting care transitions to achieve improved provider experience (improved communication around transitions and improved teaming), patient experience with transitions (improved person-centered care transitions), and patient-reported outcomes (health-related quality of life)?		
Patient (outcomes)		
Transition quality	CTM3[d]	1 to 2 weeks post-discharge
Health-related quality of life	AQoL-4D[e]	At 1 and 6 months post-discharge
Goal attainment	GAS[f]	As captured by ePRO[g] (intervention only)
Provider (processes): hospital and primary care		
Relational coordination	Relational coordination measure	Baseline, 1 and 6 months post-deployment (hospital providers) or first patient onboarded (primary care)
Quality of discharge summaries	Document analysis of PODS[h] in Care Connector	Random sample via chart review
Value for money		
Health system utilization and costs	ICES[i]	Utilization 1 year after discharge
Patient-reported costs	Patient cost survey	At 1 and 6 months post-discharge
What are the implementation enablers and barriers to adopting technology in this process from patient, caregiver, provider, organizational, and system perspectives?		
Patients and caregivers		
CFIR[j] characteristics of individuals: demographics, level of complexity, social supports, comfort with technology	Patient information sheet	At recruitment
Self-efficacy, other relevant characteristics (eg, health literacy)	Focus groups (patients)	1 and 6 months post-discharge
CFIR process: patient-provider relationship, service frequency (what services from whom at what time points?)		
	Observation (discourse analysis)	Interactions in hospital and in community
	Focus groups (patients)	1 and 6 months post-discharge
Providers		
CFIR characteristics of individuals: demographics, profession, location, comfort with technology	Provider information sheet	At recruitment
CFIR process: provider workflows, provider-team communication	Observation	Training, onboarding, site visits
All users (during implementation): CFIR characteristics of the intervention		
Usability of the tool	PSSUQ (survey)	1 and 6 months post-discharge

Research question, participant/level of analysis, and theories and constructs	Tool/method	Collection timeline
Data use	Digital Bridge system data use	Monthly
Perceived value and tool experience	Interviews (providers) and focus groups (patients)	1 and 6 months post-discharge
User interactions with tool	Observation and interviews	Training, patient and provider on-boarding on technologies, and use during the study
Organization(s)		
CFIR inner setting: hospital units, size, structure, resources, support, training, leadership, culture, and readiness to adopt		
	Document analysis	—
	Interviews (providers)	Post-intervention
CFIR inner setting: primary care practices, size, structure, resources, support, training, leadership, culture, and readiness to adopt		
	Document analysis	—
	Interviews (providers)	Post-intervention
CFIR process: change management	Interviews (providers)	1 and 6 months post-discharge
System		
CFIR outer setting: system structure, standardization of data systems, legal requirements, funding, local resources, preexisting interorganizational linkages (particularly to primary care)	Interviews (providers)	Post-intervention

[a]CCN: complex care needs.

[b]FITT: Fit between Individuals, Task, and Technology.

[c]PSSUQ: Post-Study System Usability Questionnaire.

[d]CTM-3: Care Transitions Measure–3.

[e]AQoL-4D: Assessment of Quality of Life–4 Dimensions.

[f]GAS: Goal Attainment Scale.

[g]ePRO: electronic Patient-Reported Outcome.

[h]PODS: Patient-Oriented Discharge Summary.

[i]ICES: Institute for Clinical Evaluative Sciences.

[j]CFIR: Consolidated Framework for Implementation Research.

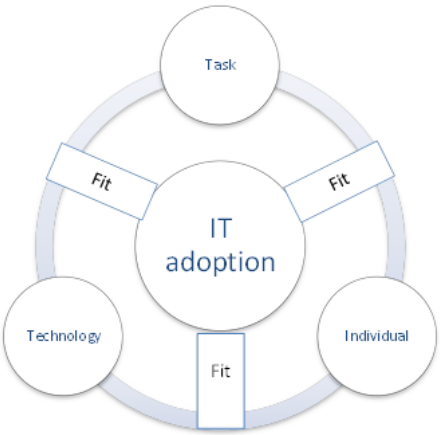
Phase 1: Engaging in Co-Design Research to Adapt Validated Technologies Into New Contexts

Building on our previously successful co-design methods [34], we will establish patient/family, hospital provider, and primary care provider working groups (6-10 participants in each) to design the digitally enabled transition workflow. Starting with the intervention steps outlined above, each working group will work with the research team to modify the workflow. The research team will integrate modifications across the 3 groups and present this to a final working group consisting of a mix of representatives from the first 3 to finalize the workflow from all stakeholder perspectives. Each session will last approximately 2 to 3 hours. Care Connector and ePRO technologies will then be adapted and integrated into the Digital Bridge.

The co-design approach is consistent with other approaches that have sought to design new workflows that can be enhanced using existing technologies [49,50]. While this may reduce the ability to address all ideas that are arrived at through the co-design process, this approach does improve feasibility of the study as we do not have to build new technologies from scratch. We view this stage as part of the ongoing approach to co-design used by each technology in their respective design and building phases. As such, this project marks another important iterative step in the evolution of ePRO and Care Connector.

A feasibility and usability assessment will be conducted with working group members. Consistent with previous studies [39], we will adopt the Fit between Individuals, Task, and Technology (FITT) framework [51] to guide the data collection on feasibility (the ability for a technology to be adopted into a setting [52]) and usability (how well a technology meets user needs) [53-55] (see Figure 2 [56] for a visual of the FITT framework). Working group members will convene a final time and work in triads (hospital physician, PCP, and patient/family) to engage in a cognitive walk-through [57] of the Digital Bridge workflow. Triads will complete the 19-item Post-Study System Usability Questionnaire (PSSUQ) used to assess similar mobile health technologies [53] with demonstrated reliability and validity [58].

Figure 2. Fit between Individual Task and Technology framework (adapted from Ammenwerth [56]).



Phase 2: Implementation, Economic, and Developmental Evaluation

The evaluation is a pragmatic, real-world implementation and developmental evaluation design to support feasibility. A developmental evaluation approach, in which evaluation questions are used to support decision making and modifications to improve interventions and programs [59], allows for iterative modification of the intervention based on collected data. This method has been successfully adopted to evaluate the ePRO tool [46].

Study Design

We will conduct a nonrandomized controlled trial to understand the impact of the intervention. For each site (SHS and THP) and each service (acute medicine and rehab), half of the participating wards will be designated as control while the other half will be designated as intervention (4 wards per hospital for a total of 8 wards). Quasi-experimental (or nonrandomized) design is often used in medical informatics evaluation due to insufficient sample size for cluster-randomized design [60] and complexity of intervention [61]. We have chosen to designate intervention wards together with operational leaders at each organization rather than randomize wards to increase the chance of successful implementation. While this could introduce selection bias into the study, it is felt this risk is worthwhile given that one important barrier to adoption of information communication technologies in hospitals is lack of readiness for implementation [62-64]. If clinical units that are not ready to take on a new technology implementation are randomized into the intervention group, we may experience a feasibility barrier that could derail the study before it begins. Our mixed-methods approach has been designed to capture important characteristics of the included clinical wards so that any potential selection bias can be understood.

General medicine units at both organizations serve a complex and clinically diverse population, with a median age of 73 (IQR 57-84) years and a median of 6 (IQR 3-9) coexisting medical conditions [65]. They care for patients with a wide variety of diagnoses (more than 200 distinct diagnoses) with the top 10 diagnoses comprising 36.2% of hospitalizations [66]. Rehabilitation services across the two organizations admit patients due to stroke, musculoskeletal concerns, and complex medical needs. At THP, services are not diagnosis-based; at SHS, however, patients are clustered on wards with specialized services.

We will collect baseline data from all wards (control and intervention) during phase 1 while co-design is ongoing and the intervention has not been deployed. During phase 2, after co-design is complete, the co-designed technology intervention and workflow will be rolled out to only the intervention wards. We will then collect data (identical to what was collected at baseline) from all wards (control and intervention) to understand the impact of technology by examining the differential change in control and intervention wards between baseline and intervention periods (difference in differences approach).

Population and Recruitment

Patients will be recruited at the time of admission to one of the services (acute medicine or rehab) in the study. Patients aged 60 years and over, with CCN defined as presenting with 3 or more chronic conditions from the 16 most prominent in the population: arthritis (except rheumatoid arthritis), chronic coronary syndrome, dementia, hypertension, cardiac arrhythmia, rheumatoid arthritis, asthma, osteoporosis, stroke, depression, chronic obstructive pulmonary disease, acute myocardial infarction, diabetes, congestive heart failure, cancer, and renal failure.

This method is aligned with current and established methods to identify patients with CCN [67-69]. Patients must be slated to be discharged home. As the technology is only currently available in English, patients (or a caregiver) must be able to speak and read English. Patients with mild cognitive impairment will not be excluded if able to provide informed consent and engage with the intervention (independently or with caregiver aid). During phase 1, all recruited patients will receive usual care. During phase 2, recruited patients from the intervention wards will receive the Digital Bridge intervention while those from control wards will receive usual care. Family/caregivers of recruited patients may be invited to participate in qualitative interviews.

As workflow integration is a foundation for implementing technology, all hospital providers on the general medicine and rehabilitation services will be invited to participate. PCPs of recruited patients will be contacted and invited to participate

while the patient is still in hospital. Recruited patients may still participate in the study if their PCP does not wish to participate or if they do not have a PCP at the time of study enrollment. Should the PCP choose to join, they will be consented and trained to adopt the technology to support their patients post-discharge if their patients were recruited from the intervention wards during phase 2.

Study Measures

Developmental and Economic Evaluation Measures

Our primary outcome is the Care Transitions Measure–3 (CTM-3), a patient-reported measure of transition quality focusing on person-centeredness and communication. The CTM-3 has been validated in similar patient populations transitioning from hospital to home and primary care and in a systematic review of transitions measures was deemed to be the most acceptable measure of quality transitions [70]. To capture likely downstream impact, we will collect secondary outcomes including number of days at home (as a measure of readmissions), goals achieved (captured through the ePRO Goal Attainment Scale), and health-related quality of life (Assessment of Quality of Life–4 Dimensions [AQoL-4D], a brief survey validated in similar populations with demonstrated responsiveness and predictive validity with regard to entrance to long-term care [71,72]).

Team and provider level processes most relevant to this study are measures of communication and relational aspects of teamwork. Relational coordination is "a mutually reinforcing process of communicating and relating for the purpose of task integration" and is measured with a validated instrument consisting of 4 communication domains (frequency, timeliness, accuracy, problem solving) and 3 relational domains (shared goals, shared knowledge, respect) [73]. High relational coordination has been associated with improved patient functioning and quality of care and reduced pain and length of stay [74,75]. Relational coordination will be measured across 4 groups (hospital physicians, nursing, all allied health involved, and PCP) with care transition as the work process. We will administer the relational coordination survey to hospital clinicians at baseline and 1 and 6 months postdeployment. PCPs will be surveyed at enrollment and 1 and 6 months. We recognize using the Digital Bridge for care transitions may be rare events for individual PCPs; their views on communication and relationship with inpatient clinicians will be explicitly captured during interviews in addition to relational coordination surveys.

To determine cost-effectiveness in relation to outcome and process measures, an economic evaluation will be conducted to compare costs and outcomes among patients who transitioned out of hospital using Digital Bridge with the control patient group. Control and intervention patients will be followed for 1 year. Costs will be estimated from a societal perspective. Health services utilization and health system costs will be measured for 1 year using province-wide health system administrative data. Over 85% of total direct costs can be measured using a cost methodology for health administrative data implemented at ICES [76]. System utilization measures will include hospital admission, emergency department visits, days in acute care, 30-day readmissions, primary and specialty care visits, labs, diagnostic imaging, and 7-day post-discharge primary care follow-up. Out-of-pocket costs will be estimated using a patient survey. Caregiver time costs will be estimated using the average industrial wage. Total costs will include the sum of health system costs and out-of-pocket costs. Resources and costs required to design and implement Digital Bridge will be estimated through a project budget review.

Sample Size Calculation

Patient participants will be grouped into 1 of 4 arms (as determined by the unit they were discharged from) in both the baseline (pre-intervention) and postintervention periods. Our primary outcome, CTM-3, is scored as a continuous variable (0 to 100%) based on a published algorithm [77]. THP pilot data with 107 patients showed a baseline CTM-3 score of 74% (SD 21.4; unpublished). Our sample size calculation is based on an anticipated 13% to 14% increase in CTM-3 score and a standard deviation of 21.4 (derived from our previous studies of Care Connector). To ensure analysis for each of the 8 subgroups to be significant, we required a higher sample size than would be required in typical drug trials where randomization occurs at the individual level. As such we will recruit 33 to 38 patients per group; 8 groups in baseline (264 to 304) and 8 groups in intervention (264 to 304) for a total of 528 to 608 (based on P=.05 and power of .80).

Intervention Fidelity, Controlling for Bias, and Optimizing Internal Validity

We aim to optimize internal validity by asking providers about their involvement in other care transition interventions during the evaluation and in the 12 months prior to the study. We will also track readmitted patients who already used the Digital Bridge, as patients with CCN can have frequent hospital visits, without altering data collection time frame from index admission.

Our previous work identifies a need to balance real-world implementation and maintaining methodological rigor [78,79]. To accomplish this, we will distinguish core components of the intervention (what is determined to be central to success) from adaptable components [79]. This is an established approach to intervention fidelity in highly complex interventions such as this one [80,81]. Complex interventions often need to be continually adapted to local contexts and changing environments [82]. Attending to our third research question will support this work.

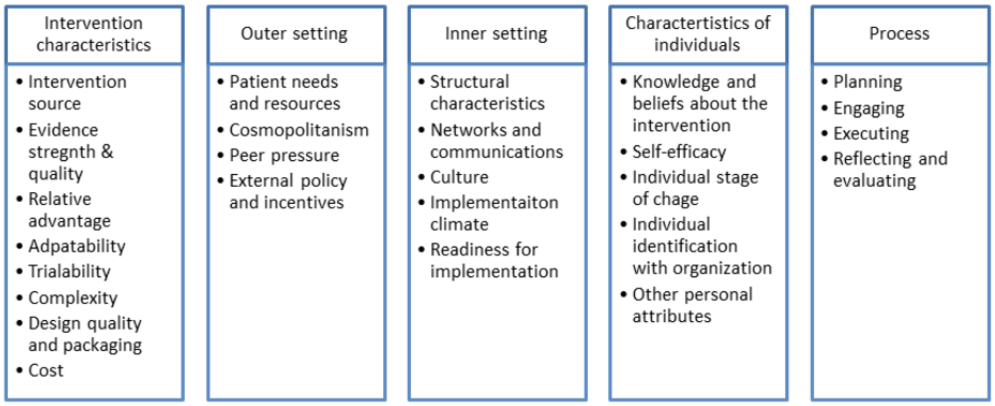
Implementation Measures

Implementation relates to the processes required to put an intervention or new model of care into use [79]. An implementation lens identifies context and process variables likely to influence intervention outcomes, known to be important in studies of digital health interventions [83]. Context and process data will additionally support the development of a scale and spread strategy [84] and is consistent with a developmental evaluation approach [59]. We will adopt the Consolidated Framework for Implementation Research (CFIR) [79], which compiles constructs that have been associated with

effective implementation of complex interventions (see Figure 3 [79]).

An embedded ethnographic comparative case study methodology will be adopted, aligned with the case study approach of Yin [85] and the ethnographic approach to evaluating technology of Greehalgh [86]. Each site/service combination is considered a single case (8 cases total). Interviews with patients and caregivers (subset of 5 patients and caregivers from each unit, 40 patients and 40 caregivers total) and focus groups with providers and managers (6 to 8 participants per group [87]) will be conducted, along with a review of relevant organizational documents (eg, annual reports and vision statements) and observations of provider interactions and patient-provider interactions (eg, rounds, care planning meetings, clinic visits).

Figure 3. Consolidated framework for implementation research constructs (adapted from Damschroder [79]).



Data Analysis Strategy

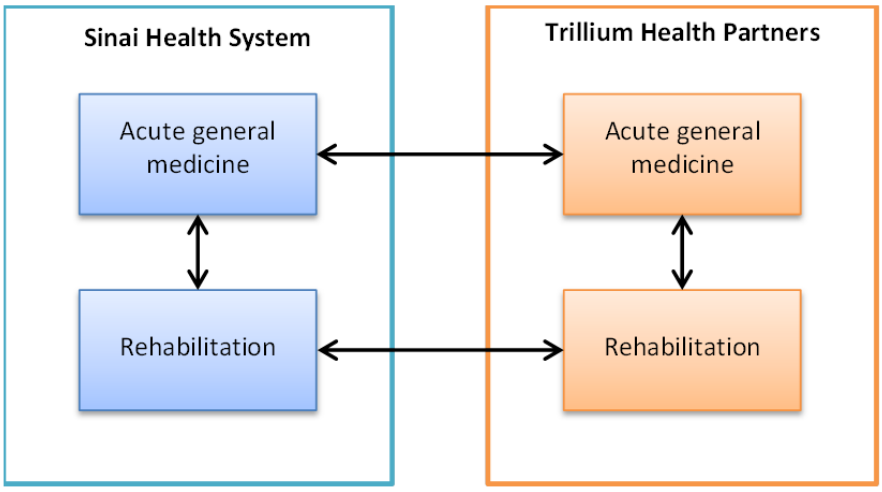
Phase 1: Workflow Analysis

Consistent with established user-centered co-design methods, we will adopt an interpretive descriptive approach to analyze focus group data and iteratively design the workflow [88]. Analysis will guide modifications and integration of the Care Connector and ePRO technologies into the Digital Bridge. Feasibility and usability will be assessed using standard descriptive statistics across 3 domains of the PSSUQ. Demographic information collected from participants will inform analysis and support transferability to other settings.

Phase 2: Developmental Evaluation and Implementation Analysis

We will adopt a multimethod case study analysis approach [85], looking at within and between group assessments (Figure 4), accounting for hospital/service specific context variables. Single case and cross-case comparative analyses will be used to assess context, process, and outcome measures.

Figure 4. Within and between group pre-post analysis.



For quantitative outcome measures (eg, CTM-3, relational coordination, AQoL-4D), statistical comparisons between the pre- (baseline) and post- (intervention) data will be made using mixed-effects regression models to account for potential clustering effect of patients from the same service. As this is a complex intervention and local context/implementation factors may affect outcomes, we will perform sensitivity analysis and examine each of the participating services separately. For repeated measures within the same individual, we will use a difference in differences approach (eg, AQoL-4D measured at 0, 2 weeks, 1 month, and 6 months post-discharge). Patients may experience decline in QoL over time in both control and intervention groups for reasons unrelated to the intervention; a lesser magnitude of decline in intervention versus control group may suggest a benefit of the intervention.

For patients who do not complete a study follow-up, we will analyze all available data points. Additionally, understanding the characteristics (via collected demographic and administrative data of this study) of those who do not complete follow-up may inform us of under what conditions and for whom the technology works best.

Qualitative data will be analyzed using an ethnographic case study approach [86], adopting techniques such as interpretive descriptive coding methods and word tables [85] to support the within and cross case analysis as used in previous evaluations and similar case comparisons [33,48]. Two researchers trained in qualitative research will read interview and focus group transcripts and field notes, record key themes, compare, and discuss findings. Both inductive and deductive analysis techniques will be used to identify themes and then conceptually map with the CFIR theoretical framework. NVivo software (QSR International) will be used for qualitative data management.

Phase 2: Economic Evaluation Analysis

A cost utility analysis will be conducted comparing total costs and quality-adjusted life years (QALYs) of Digital Bridge to usual care from the perspective of Canada's health care system. Costs and utility values will be assessed over the study follow-up period. Analysis will conform to most recent Canadian guidelines for economic evaluation [89]. Responses to the AQoL-4D will be scored using preference weights, converting the 5 responses into a single summary index, where a score of 1 reflects perfect health and 0 is equivalent to dead [90]. QALYs will be estimated using total area under the curve methods [91]. Statistical analysis will be conducted in accordance with current guidelines for clinical and cost-effectiveness analysis alongside randomized controlled trials [92], accounting for the repeated nature of the cost and outcome data. The incremental cost and QALYs will be estimated using generalized estimating equations, a flexible multivariate regression framework that explicitly allows for the modeling of nonnormal distributional forms of repeated measure data. As we will have individual level data on costs and QALYs for the period of study follow-up, we will evaluate uncertainty of the cost utility estimates using nonparametric bootstrapping, obtaining 5000 estimates of costs and QALYs for each strategy. Bootstrapping results will also be used to estimate 95% confidence intervals and depict cost-effectiveness acceptability curves. These analyses represent the probability of an intervention being cost-effective to a range of potential threshold values that the health system may be willing to pay for an additional unit of effect. As a scenario analysis, we will also conduct a cost utility analysis from a societal perspective by including patient-related costs. Economic analysis will be conducted using Stata version 15.1 (StataCorp LLC) and Excel Visual Basic for Applications (Microsoft Corporation). Analyses will support a proposed model of scale and spread in the Ontario context and/or similar health system contexts in Canada based on patient volumes.

Ethical Considerations and Dissemination

The study will undergo research ethics board review and receive approval at each study site. All participants will provide signed informed consent prior to participation. The study was registered at ClinicalTrials.gov [NCT04287192].

An integrated knowledge translation strategy will be implemented; engaging stakeholders and knowledge users in the design, implementation and interpretation of study results. A Knowledge Translation Advisory Group will be established to provide insight and feedback regarding the project design and implementation, leading the development of the project knowledge translation strategy and associated outputs. The advisory group will comprise our project team, collaborators, patient representatives, and decision-making partners. Knowledge translation activities will ensure that the results are made available to those who need them and are packaged in a manner for sustained knowledge use; presentations at relevant conferences and in peer-reviewed publications and a symposium at project end are planned. A key knowledge translation activity is the development of a scale and spread strategy which will identify spread sites for the intervention in other hospitals in Ontario and other provinces across Canada.

Results

The project began August 2019 and received ethics approval from all necessary institutions September 2020. Due to challenges related to the COVID-19 pandemic, we have adjusted our timelines and anticipate the project will be completed by Spring 2024. This study was funded by the Canadian Institute for Health Research through a Team Grant in Transitions in Care (FRN 165733). Results from different phases will be published in peer-review journals. Phase 1 results are expected to be published in 2022, with phase 2 findings published in 2025.

Discussion

Summary

This protocol describes a novel approach to developing, implementing, and evaluating a digital health technology to support transitions of complex patients returning home from hospital. By incorporating a mixed-methods and pragmatic approach we will be able to purposefully develop, feasibly implement, and rigorously evaluate the Digital Bridge solution. The study seeks to determine if the Digital Bridge will support improved communication across providers in the hospital and community and the patient and family caregivers, leading to greater shared situational awareness during care transitions.

Strengths and Limitations

Given the real-world implementation of Digital Bridge, practice changes at the research sites and variable adherence to the implementation protocols are likely. Additionally, contamination between control and intervention wards may occur as clinicians rotate between units and modify their behaviors in control settings based on using Digital Bridge in intervention settings. Capturing and understanding these considerations is essential in order to identity the range of factors that may have influenced study results. In addition, the health system within which the study is being conducted is undergoing transformational change,

and the research team must track any policy and organizational changes that may affect the implementation.

Other important limitations to track and potentially mitigate with regard to the intervention focus on integration of the solution into practice-based electronic medical record (EMR) systems. While Care Connector is integrated with the hospital-based EMR, we may not be able to fully integrate the Digital Bridge (which includes the ePRO tool) into primary care EMRs. A lack of interoperability can lead to tools not aligning to clinical processes and additional burden on providers, a challenge that has been well documented in the implementation literature [93]. We will probe the impact on workflow as part of our interviews with providers using the tool to determine the degree of impact. We will also use implementation findings to assess generalizability of findings to other nonurban settings. Given the intervention will be running in large urban health care organizations, findings may not be fully transferable to other small nonurban settings.

One important limitation of this study is in the separation of groups (patients, families, clinicians) in the first round of co-design working groups. Based on previous experience co-designing with mixed groups, we have found that bringing groups together too early in the process can lead to conversations being dominated by those perceived as holding the most power and knowledge, often physicians. We decided to forgo the opportunity to create shared understanding early in the process in favor of creating safe spaces in which participants feel able to speak freely and openly about what works and what doesn't for them. It is our hope that bringing the groups together after an initial engagement will help participants feel more comfortable with the process and able to speak freely in mixed groups where shared understanding can be built.

The protocol has a number of strengths. First, the use of a pragmatic trial will allow for adaptability required in real-world complex interventions, while the ethnography will uncover core and adaptable factors. Second, using co-design approaches will help adapt the model to local contexts and ensure that study results meet the needs of stakeholders. Third, broad inclusion criteria and minimal exclusion criteria will enable researchers to capture as much variation in the patient population as possible. And finally, the multisite nature of the study will support broader application of study results. A potential challenge will be ensuring we have adequate representation of the wider patient population in co-design activities. Working with patient and family representatives as well as the patient engagement offices at each research site will help mitigate this concern. With platforms currently only available in English, a language barrier to access may be created. The Knowledge Translation Advisory Committee (which will include patients and family representatives) will help determine the extent of that barrier and mitigate as best possible throughout the implementation.

Potential Impact

With wider adoption of the proposed intervention, this project could have impact at patient, clinician, organizational, and health system levels. Patients and families may have improved experience with transitions and health-related quality of life. Clinicians may experience greater efficiency in their coordination of care efforts and likely fewer errors and missed information. For organizations, the Digital Bridge could help standardize care transition practices across organizational boundaries. Finally, at the health system level, the Digital Bridge could address the growing challenge of transitioning older adults with CCN from hospital to home, potentially reducing unnecessary readmission or emergency department visits by patients post-discharge, leading to cost savings.

Should the intervention evaluation come out favorably, future work will also seek to test the Digital Bridge's ability to support transitions for patients to other settings such as long-term care, assistive living, or long-term rehabilitation.

Acknowledgments

The authors would like to acknowledge the support of our research administrative, technology, and support staff at the Bridgepoint Collaboratory for Research and Innovation at the Lunenfeld-Tanenbaum Research Institute and the Institute for Better Health at Trillium Health Partners for their help with the Canadian Institutes of Health Research application process. We would also like to acknowledge the large and growing number of senior staff, managers, and frontline staff in our THP and SHS implementation teams who are key decision-making partners in our project and will be integral to the success of this project. This study has been funded by the Canadian Institute for Health Research through a Team Grant in Transitions in Care (FRN-165733).

Authors' Contributions

All authors were involved in developing the study design and methods in preparation for the original grant from the Canadian Institutes of Health Research as well as for this protocol paper. CSG, TT, and MN co-lead the project. CSG was responsible for writing the first draft of the manuscript based on the grant submission. All authors contributed to and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Care Connector features and wireframes.
[PDF File (Adobe PDF File), 1782 KB - resprot_v9i11e20220_app1.pdf]

Multimedia Appendix 2
Electronic Patient-Reported Outcome features and wireframes.
[PDF File (Adobe PDF File), 1699 KB - resprot_v9i11e20220_app2.pdf]

Multimedia Appendix 3
Description of Digital Bridge workflow.
[DOCX File , 15 KB - resprot_v9i11e20220_app3.docx]

Multimedia Appendix 4
Peer Review Comments.
[PDF File (Adobe PDF File), 560 KB - resprot_v9i11e20220_app4.pdf]

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Abbreviations

AQoL-4D: Assessment of Quality of Life–4 Dimensions
CCN: complex care needs
CFIR: consolidated framework for implementation research
CTM-3: Care Transitions Measure–3
EMR: electronic medical record
ePRO: electronic Patient-Reported Outcome
FITT: Fit between Individuals, Task, and Technology
HIS: hospital information system
ICES: Institute for Clinical Evaluative Sciences
PODS: Patient-Oriented Discharge Summaries
PCP: primary care physician
PSSUQ: Post-Study System Usability Questionnaire
QALY: quality-adjusted life year
SHS: Sinai Health System
THP: Trillium Health Partners

Edited by G Eysenbach; submitted 13.05.20; peer-reviewed by J Sont, R Mickelson, P Stolee; comments to author 29.06.20; revised version received 10.08.20; accepted 13.09.20; published 25.11.20.

Please cite as:
Steele Gray C, Tang T, Armas A, Backo-Shannon M, Harvey S, Kuluski K, Loganathan M, Nie JX, Petrie J, Ramsay T, Reid R, Thavorn K, Upshur R, Wodchis WP, Nelson M
Building a Digital Bridge to Support Patient-Centered Care Transitions From Hospital to Home for Older Adults With Complex Care Needs: Protocol for a Co-Design, Implementation, and Evaluation Study
JMIR Res Protoc 2020;9(11):e20220
URL: https://www.researchprotocols.org/2020/11/e20220
doi:10.2196/20220
PMID:33237037

Protocol

Use and Evaluation of Computerized Clinical Decision Support Systems for Early Detection of Sepsis in Hospitals: Protocol for a Scoping Review

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Abstract

Background: Sepsis is a leading cause of death in hospitals, with high associated costs for both patients and health care systems worldwide. Early detection followed by timely intervention is critical for successful sepsis management and, hence, can save lives. Health care institutions are increasingly leveraging clinical data captured in electronic health records for the development of *computerized clinical decision support* (CCDS) systems aimed at enhancing the early detection of sepsis. However, a comprehensive evidence base regarding sepsis CCDS systems to inform clinical practice, research, and policy is currently lacking.

Objective: This scoping review aims to systematically describe studies reporting on the use and evaluation of CCDS systems for early detection of sepsis in hospitals.

Methods: The methodology for conducting scoping reviews presented by the Joanna Briggs Institute Reviewer's Manual and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) will be used and adapted as guides. A comprehensive literature search of 10 electronic databases will be conducted to identify all empirical quantitative and qualitative studies that investigate the use of CCDS systems for early detection of sepsis in hospitals. Detailed inclusion and exclusion criteria have been developed. Two reviewers will independently screen all articles based on these criteria. Any discrepancies will be resolved through discussion and further review by a third researcher if required.

Results: Electronic database searches have retrieved 12,139 references after removing 10,051 duplicates. As of the submission date of this protocol, we have completed the title and abstract screening. A total of 372 references will be included for full-text screening. Only 15.9% (59/372) of these studies were focused on children: 11.0% (41/372) for pediatric and 4.8% (18/372) for neonatal patients. The scoping review and the manuscript will be completed by December 2020.

Conclusions: Results of this review will guide researchers in determining gaps and shortcomings in the current evidence base for CCDS system use and evaluation in the early detection of sepsis. The findings will be shared with key stakeholders in clinical care, research, policy, and patient advocacy.

International Registered Report Identifier (IRRID): PRR1-10.2196/24899

(JMIR Res Protoc 2020;9(11):e24899) doi:10.2196/24899

KEYWORDS

sepsis; early detection of disease; computerized clinical decision support systems; patient safety; electronic health records; sepsis care pathway

Introduction

Sepsis and Early Detection

Sepsis, defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" [1], is estimated to affect 50 million people each year worldwide, of which more than 40% are among children younger than 5 years [2]. Despite advances in vaccines, antibiotics, and acute care, sepsis remains the leading cause of death from infection [1]. About 20% of patients with sepsis die, with global estimates recording 11 million deaths due to sepsis in 2017 alone [2]. Surviving sepsis is associated with increased mortality across an individual's lifespan and significant reductions in quality of life, including higher rates of chronic illness, physical disability, cognitive impairment, and mental health issues [3-9]. Additionally, sepsis treatment is extremely expensive [10]. In the United States it has been listed as the most expensive condition in US hospitals (>US $20 billion annually) [11]. The World Health Organization has declared sepsis a global medical emergency and adopted a resolution in 2017 to reduce the global burden of sepsis by improving sepsis diagnosis, treatment, and management [12].

Early detection of sepsis allows for prompt treatment, which is associated with reduced mortality and lower costs [13,14]. The 2016 Surviving Sepsis Campaign (SSC) guidelines, a set of clinical guidelines designed by a panel of international sepsis experts, strongly recommend treatment begin immediately, with the administration of intravenous antimicrobials within 1 hour of sepsis or septic shock recognition [15]. To enhance the effectiveness of rapid treatment, it is critical that septic patients are identified as early as possible [15-17]. Interventions such as regular monitoring of vital signs and elevated lactate levels can aid early recognition [18]. However, studies show that delays in both disease diagnosis and treatment are not uncommon in hospitals [19-21]. One of the main barriers to early sepsis diagnosis is the lack of effective diagnostic tools, further compounded by the fact that sepsis is a heterogeneous and enigmatic syndrome with no diagnostic gold standard [22]. Consequently, clinicians face a challenge in differentiating sepsis from other acute conditions with similar signs or symptoms.

Sepsis detection and recognition pathways can play an important role in facilitating early sepsis diagnosis and initiation of treatment. A number of sepsis-risk warning tools have been developed, for example, the Quick Sepsis-Related Organ Failure Assessment, the National Early Warning Score in the United Kingdom, and the Adult Sepsis Pathway in Australia [23-25]. Many hospitals currently rely upon paper-based sepsis recognition tools, which are susceptible to transcription and interpretation errors and highly reliant upon vigilant and timely patient monitoring by clinicians. In contrast, appropriately designed automated systems have the potential to decrease delays and increase the accuracy of sepsis detection [26].

Computerized Clinical Decision Support Systems

Given the difficulties associated with timely sepsis recognition, health care institutions are increasingly leveraging clinical data captured in electronic health records (EHRs), which have been rolled out extensively in recent years around the world. EHR-based computerized clinical decision support (CCDS) systems, built into hospital electronic systems, present a great opportunity to facilitate sepsis early detection and prompt treatment. CCDS systems automate sepsis-risk warning tools to alert clinicians to the possible presence of sepsis [16,27], while reducing the mental load on clinicians and nurses [28,29]. Following an alert, a protocol is followed that usually involves a patient being evaluated by senior medical staff to confirm diagnosis and initiate the appropriate sepsis treatment [27].

Over the past 10 years, two distinct CCDS approaches to sepsis identification have emerged: knowledge-based electronic CCDS following predefined *rules* of an established diagnosis pathway, and nonknowledge-based CCDS utilizing artificial intelligence and machine learning techniques [28,30]. Our primary focus in this scoping review is the use of knowledge-based electronic CCDSs in sepsis detection.

Research Questions and Aims

Implementation of sepsis CCDS in hospital clinical information systems is a novel and rapidly expanding area [28]. Furthermore, the use of technological innovations in health care is rife with complexity [31]. This is particularly true for the use and evaluation of sepsis CCDS in real-world clinical settings. Sepsis itself is a complex and multifaceted condition, and various clinical criteria for sepsis early detection have been developed over the years and implemented in an evolving range of sepsis CCDS systems [32]. These systems have been evaluated in numerous clinical settings in hospitals, such as emergency departments, intensive care units (ICUs), and various wards [32,33]. In addition, there is extensive heterogeneity in the design of studies evaluating the effectiveness of these CCDS systems, such as differing outcome measures (eg, mortality, cost, and clinical workflow) and evaluation methods [28,32]. We intend to explore the complexity present in the use and evaluation of sepsis CCDS by systematically mapping the breadth of the literature in a scoping review to identify knowledge gaps and inform future research. The research question we have formulated for this review is as follows: *What is the evidence base for the use of knowledge-based CCDS systems in hospitals for sepsis early detection and how have they been evaluated?*

In this scoping review, we will aim to (1) scope the study contexts, designs, and research methods employed, (2) summarize study outcomes investigated and outcome measures utilized, and (3) map out the range of CCDS designs and implementation features, such as sepsis clinical criteria and related sepsis care and management protocols.

Methods

Scoping Review Method

The methodology for conducting scoping reviews presented by the Joanna Briggs Institute (JBI) Reviewer's Manual [34] and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [35] will be used and adapted as guides. In particular, the five-stage scoping review framework presented by Arksey and O'Malley [36] will be followed as recommended by JBI [35]:

(1) identifying the research question, (2) identifying relevant studies, (3) selecting studies, (4) charting the data, and (5) summarizing and reporting the results.

A search for current reviews and protocols on this topic was undertaken on MEDLINE, the JBI database, and Google Scholar, confirming the absence of scoping reviews in this research area. Only one similar scoping review protocol was identified [37]; however, the authors are focusing only on the use of machine learning or artificial intelligence–based CCDS, whereas our review is instead focused on only knowledge-based (ie, nonmachine learning) CCDS.

Scoping Review Stages

Identifying the Research Question

An ideal question for a scoping review is broad, with clear links to the rationale and intended purpose of the review [38,39]. The research question, aims, rationale, and purpose of this review are detailed above. The research question was formulated following preliminary reading and exploratory searches of the literature on CCDS systems for early detection of sepsis and subsequent discussions with the review team. The question, as described above in the Introduction section, was developed in an iterative manner, following contemplation of the rationale and the intended purpose of the research.

Identifying Relevant Studies

The search used in a scoping review should be as broad as feasibly possible to ensure a comprehensive overview of the field [36]. To achieve this, we employed a three-step search strategy. The design and refinement of the search strategy was undertaken with consultation from an experienced librarian. During step 1, MEDLINE and CINAHL were searched using a preliminary search strategy derived from the initial exploratory literature searches. The index terms and text words in the abstract and title of the preliminary search results were then analyzed to identify relevant text words and subheading terms. These identified text words and index terms were added to the preliminary search. MEDLINE and Embase were then used to pilot and refine the search strategy to ensure the final search would be as comprehensive as possible, without becoming too time-consuming and impractical. The search strategies of previous relevant systematic reviews were also retrieved and analyzed for additional relevant terms and text words [16,27,28,33,40]. An example of the final search strategy, used to search MEDLINE, is presented in Multimedia Appendix 1. In step 2, all included databases were then searched using the final search strategy. Both peer-reviewed and grey literature databases were searched. During step 3, the reference lists of relevant systematic reviews and of salient papers selected for data charting were hand-searched to identify additional relevant articles.

The databases we intend to search are as follows: MEDLINE; Embase; CINAHL; the Cochrane database, including CENTRAL (Cochrane Central Register of Controlled Trials); LILACS (Latin American and Caribbean Health Sciences Literature); Scopus; Web of Science; OpenGrey; ClinicalTrials.gov; and ProQuest Dissertations and Theses Global. These databases were chosen to ensure that a broad overview of both the black and grey literature relevant to our topic was retrieved by our search. There will be no limits set on publication date and, thus, we will include studies from the inception of each database, up until the date of our search.

Selecting Studies

All identified articles will be exported into an EndNote X9 (Clarivate) library, which will be used to manage reference data throughout the review, and duplicates will be removed. Two reviewers will then independently screen the titles and abstracts for relevant articles as determined by the eligibility criteria, with any disagreements resolved through discussion or further review by a third researcher if necessary. The full texts of included articles will then be retrieved and similarly screened by the same two independent reviewers using the eligibility criteria to select the final articles for inclusion. Any disagreements will be resolved though discussion or consultation with a third reviewer. The reference lists of relevant systematic reviews as well as of salient articles selected for inclusion will be hand-searched to identify any further articles. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram will be used to visually illustrate this process.

Title and abstract screening using the eligibility criteria (see Textbox 1 [1,27,30]) will be trialed with a random selection of 25 articles by both reviewers, and discussed with a third reviewer, to ensure that there is consensus within the review team surrounding what is considered to meet the inclusion or exclusion criteria. Once consensus and clarification have been reached, then the search selection will begin. Similarly, once title and abstract screening is completed, full-text screening will be piloted with a random selection of 10 articles to ensure consensus. The study selection process will be an iterative process, with any potential changes to the eligibility criteria or study selection detailed in the final report.

Textbox 1. Eligibility criteria for articles.

Inclusion criteria (if they met all of the following criteria):

1. Investigated or evaluated a knowledge-based computerized clinical decision support (CCDS) system used for early detection of sepsis. Knowledge-based CCDS systems are those where the algorithm receives, collects, and integrates data to evaluate a predefined rule and then executes the appropriate action [30]. In practice, this means they are programmed with a set of sepsis detection criteria predetermined by humans [27]. Once a patient is calculated to meet these criteria, an action will commence, normally in the form of a sepsis alert [27]. Due to the evolving nature of the official sepsis definition, the most recent of which was only released in 2016 [1], and the intentionally broad scope of this review, we will include all studies that include CCDS systems designed for systemic inflammatory response syndrome (SIRS), sepsis, or septic shock, by any definition.
2. Investigated in any hospital setting. We will include all articles that investigate the use of CCDS in a hospital setting, including but not limited to CCDSs implemented in the emergency department, intensive care units, or in general wards.
3. Any human patient population with sepsis. Studies investigating the use of CCDS for sepsis in any human patient population will be eligible, regardless of age, sex, ethnicity, or comorbidities.
4. Original research investigated the use of an implemented CCDS system. We will include all study designs, provided the studies involve original research evaluating a CCDS that has been implemented in clinical settings.
5. Published in the English language. We will limit our search to only studies published in the English language due to time and resource constraints.

Exclusion criteria (if they met one or more of the following criteria):

1. Investigated the use of a nonknowledge-based CCDS system. A nonknowledge-based CCDS system is one that utilizes machine learning, artificial intelligence, or statistical-based pattern recognition [30]. In this case, rather than relying on set criteria programmed by a human, normally a clinician or researcher, the algorithm is programmed to use advanced computational techniques to independently determine the appropriate action following training on a model data set [30].
2. Only investigated CCDS systems or sepsis, not both. Throughout hospitals, CCDS systems are used for an extensive variety of purposes, including but not limited to disease detection, checking order sets, and improving documentation and communication [30]. Studies will be excluded if the primary focus is not on the detection of sepsis, septic shock, or SIRS, by any definition. There is an extensive body of literature on sepsis itself, relating to a diverse range of subtopics. We will exclude any articles that do not investigate the use of a CCDS system.
3. Simulations of CCDS use, or CCDS use outside of hospitals. We will exclude any studies in which the CCDS system is not implemented in hospitals in the real world, including but not limited to studies in which the CCDS system is only evaluated through a data-driven simulation or is implemented outside of a hospital, such as in prehospital care.
4. Studies that did not include original research on CCDS system use. We will exclude any studies that do not investigate original research on CCDS system use, such as commentaries, editorials, opinion pieces, and reviews. However, while reviews will not be used for data charting or analysis, they may be retained for the purpose of reference list searching for relevant articles.
5. Studies performed in animals or other nonhuman organisms. We will exclude any studies that are not exclusively performed in human populations, such as mouse, dog, or guinea pig studies.

Charting the Data

Data charting will be performed by one reviewer using a predesigned charting form, and a second reviewer will double-check the accuracy of a random sample. Any disagreements will be resolved through discussion or consultation with a third reviewer. The data-charting form will be designed in Microsoft Access and initially piloted by the review team to ensure that appropriate and sufficient data are extracted. As discussed by Levac et al [39], data charting is often an iterative and continually updated process; thus, our data-charting form will be altered during extraction as needed, with all changes recorded and explained. The following data will be charted to address the study aims:

1. Study context, design, and research methods (Aim 1). We will extract relevant contextual information, such as authors, the year of publication, CCDS implementation if available, the study title and objectives, and the country of the CCDS implementation. In addition, we will also collect the study setting, defined as the specific situation in which the CCDS is implemented (eg, ICU), and demographic and clinical information of the study population, such as age category (ie, adult, pediatric, neonatal, or all), the numerical age range if given, gender, and any underlying conditions reported to be common to the study population. We will also extract all relevant information about the study design, including the study type, using typical categories as described by Ranganathan and Aggarwal [41-45]; how sepsis patients were identified (eg, chart review or EHR data); and study power, if relevant.
2. Study outcomes and outcome measurements (Aim 2). We will extract all relevant information about all outcomes investigated, including outcome category, which is predecided by the research team (ie, patient outcomes, sepsis treatment and management, CCDS usability, and cost); the specific outcome itself; and the outcome measures used. The patient outcome category is defined as outcomes that directly measure the change in patient health care endpoints, such as mortality, ICU admission, and hospital length of stay. The prognostic accuracy of the CCDS systems in predicting these outcomes could be reported using measurements such as sensitivity, specificity, positive predictive value, negative predictive value, and area under receiver operating characteristic curve. The sepsis treatment and management category is defined as outcomes that

measure the change in sepsis management following CCDS implementation, such as time to diagnosis, time to treatment, and SSC guideline adherence. The usability category is defined as outcomes that are related to the usability or user experience of CCDS, such as clinician perceptions. The cost category is defined as outcomes that are related to the cost or cost-effectiveness of CCDS implementation and use.

3. CCDS design and implementation features (Aim 3). We will extract all relevant information regarding the design of the CCDS, such as CCDS type (ie, either commercial or homegrown), and details regarding the implementation of the CCDS, such as the type of responding personnel, the type of alert, and clinical integration method. Commercial CCDS systems are defined as CCDS systems that have been purchased from an external supplier. Some commercial CCDS systems may have been subsequently modified; however, for the purpose of this review, we will still consider them as commercial. Homegrown CCDS systems are defined as CCDS systems that have been designed in-house by the institution implementing it. The method of clinical integration of CCDS will include information regarding where the CCDS has been implemented, how it works, whether response teams and specific care and management protocols or bundles were simultaneously introduced, and what the vital sign criteria are if available.

Summarizing and Reporting the Results

The results will be analyzed through both a narrative review and quantitative analysis. A narrative summary of the data will be presented, organized by our three aims. Each aim may be further divided into sections, which will be determined iteratively following data charting. Basic summary statistics, primarily frequency counts and percentages, will also be used to give a numerical overview of the data. The data will be presented in tabular and graphical forms to support the narrative review, and numerical analysis and will be designed iteratively following data charting with consideration for the intended purpose of the review.

The results may be divided and published over multiple papers, depending on the quantity of data charted. If this is considered, the split will be a well-documented iterative process. It is likely that we will either publish two papers divided by population age category, in which we may publish the results for adult populations and pediatric populations separately, or we may publish a second paper focusing only on mapping CCDS type and design across the literature. This will be determined following data charting.

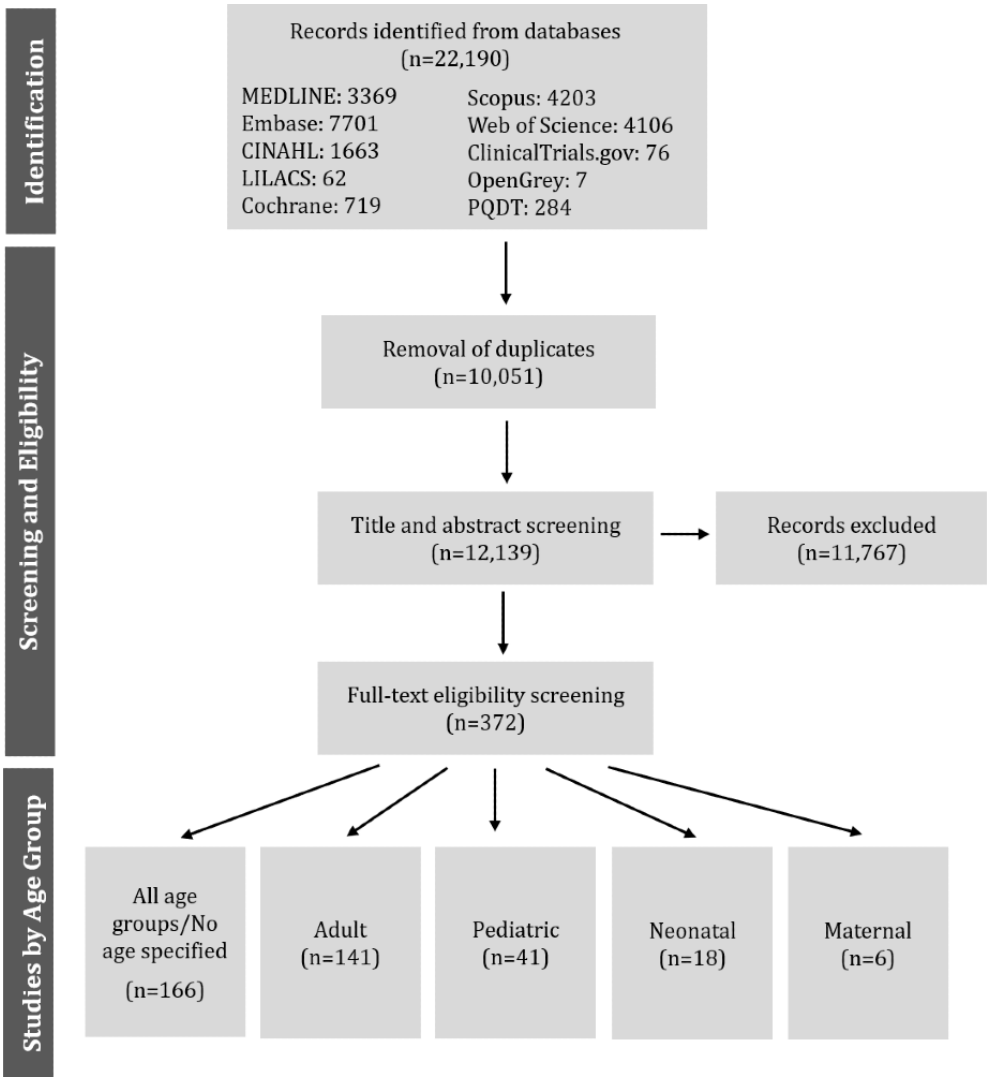
Ethics

Ethical approval or consent to participate is not required for this protocol and scoping review. The data will be extracted from published articles, and no individual information will be included.

Results

As of the submission date of this protocol, title and abstract screening has been completed. Figure 1 illustrates the search results and screening process. The search was run in September 2020 and resulted in 22,190 references. After removing 10,051 duplicates, 12,139 references were included for title and abstract screening by two reviewers. The full texts of 372 references will be screened for inclusion in the final review. A total of 44.6% (166/372) of these references included all age groups or did not specify age, another 37.9% (141/372) were focused on adult patients, and the rest were for pediatric (41/372, 11.0%), neonatal (18/372, 4.8%), and maternal patients (6/372, 1.6%). Data charting and analysis will follow with the aim to submit a manuscript describing initial results by the end of December 2020.

Figure 1. Flowchart of the preliminary search results and screening process. LILACS: Latin American and Caribbean Health Sciences Literature; PQDT: ProQuest Dissertations and Theses.



Discussion

Overview

The increasing digitization of health care has promoted the use of CCDS systems in hospitals for sepsis early detection and treatment [27]. However, there is poor consensus on the effectiveness of these systems in improving the health outcomes of patients with sepsis [28]. This can be partly attributed to the complex and heterogenic nature of studies investigating this topic [16,28]. Additionally, as the field is rapidly emerging, there are increasingly varied methods of CCDS evaluation seen in the literature. In this paper, we have presented a protocol for a scoping review based on well-established methodology, as explained in the Methods section. A strength of our review, and of scoping reviews in general, is their broad search strategy and eligibility criteria, which will allow us to scope the breadth of the field more comprehensively. To our knowledge, this scoping review is the first review to comprehensively map the breadth of the literature investigating the use of CCDS for the early detection of sepsis in hospitals. Mapping the literature will provide a broad outline of the current studies within the field, promoting a more comprehensive understanding of current research efforts. We will, therefore, be better able to identify research gaps, which in turn can inform future studies and clinical practice.

Due to feasibility and time constraints, we limited our search to studies published in English, or that had English translations readily available. Therefore, we must acknowledge that our scoping review may miss some studies published only in non-English languages.

Conclusions

The review will provide a comprehensive summary on the use of knowledge-based CCDS systems in the early detection of sepsis in hospitals, providing researchers, clinicians, policy makers, and developers with a relevant and important evidence base. Our findings will highlight research gaps and shortcomings in existing evaluations and implementations of sepsis CCDS and, hence, guide future research efforts. The results will be shared with key stakeholders in clinical care, research, policy, and patient advocacy to inform clinical practice and policy.

Acknowledgments

We would like to thank Mr Jeremy Cullis, an experienced clinical librarian, for his advice and expertise on designing the final search strategy and translating it for other databases.

Conflicts of Interest

None declared.

Multimedia Appendix 1
MEDLINE search strategy.
[PDF File (Adobe PDF File), 84 KB - resprot_v9i11e24899_app1.pdf]

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Abbreviations

CCDS: computerized clinical decision support
CENTRAL: Cochrane Central Register of Controlled Trials
EHR: electronic health record
ICU: intensive care unit
JBI: Joanna Briggs Institute
LILACS: Latin American and Caribbean Health Sciences Literature
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
SSC: Surviving Sepsis Campaign

Edited by G Eysenbach; submitted 09.10.20; peer-reviewed by S Sarbadhikari; comments to author 02.11.20; revised version received 02.11.20; accepted 03.11.20; published 20.11.20.

Please cite as:
Li L, Ackermann K, Baker J, Westbrook J
Use and Evaluation of Computerized Clinical Decision Support Systems for Early Detection of Sepsis in Hospitals: Protocol for a Scoping Review
JMIR Res Protoc 2020;9(11):e24899
URL: http://www.researchprotocols.org/2020/11/e24899/
doi:10.2196/24899
PMID:33215998

Publisher:
JMIR Publications
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