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Impact of an Electronic Monitoring Intervention to Improve Adherence to Inhaled Medication in Patients with Asthma and Chronic Obstructive Pulmonary Disease: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Despite progress in pharmacological and non-pharmacological treatment in recent years, the burden of disease among patients with asthma and chronic obstructive pulmonary disease (COPD) is high and patients are frequently hospitalized due to exacerbations. Reasons for uncontrolled diseases are manifold, but are often associated with poor inhalation technique and non-adherence to the prescribed treatment plan. This causes substantial mortality, morbidity, and costs to the healthcare system. In this respect, the study of causes for non-adherence and the development of measures to increase and maintain treatment adherence in chronic diseases is of major clinical importance.

Objective: The primary objective of this study is to investigate the impact of using specific, validated electronic devices on adherence to inhaled medication in patients with chronic obstructive lung diseases such as asthma and COPD. Furthermore, it aims to assess the impact of a reminder and close supervision of the course of disease and quality of life.

Methods: In this ongoing prospective, single-blind, randomized controlled study, adherence to inhaled medication is analyzed over a 6-month period in at least 154 in- and outpatients with asthma or COPD who have experienced at least 1 exacerbation during the last year. Adherence is measured using electronic data capture devices, which save the date and time of each inhalative device actuation and transfer these data daily via a wireless connection to a Web-based database. Patients are randomly assigned to either the intervention or the control group. The clinical intervention consists of an automated and personal reminder. The intervention group receives an audio reminder and support calls in case medication has not been taken as prescribed or if rescue medication is used more frequently than pre-specified in the study protocol. During the study, participants are assessed every 2 months in the form of clinical visits.

Results: Recruitment started in January 2014. To date, a total of 169 patients have been recruited. Follow-up assessments are still ongoing. The study will be concluded in the first quarter of 2017. Data analysis will take place during 2017.

Conclusions: Few studies have investigated medication adherence in patients with chronic obstructive lung diseases. With this prospective study design and the use of state-of-the-art devices for measuring adherence, we expect scientifically relevant and clinically meaningful results that will have a substantial and positive impact on the provision of healthcare in chronically ill patients suffering from asthma or COPD.

Trial Registration: ClinicalTrials.gov: NCT02386722; https://clinicaltrials.gov/ct2/show/NCT02386722 (Archived by WebCite at http://www.webcitation.org/6oJq1fel0)

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KEYWORDS

asthma; pulmonary disease; chronic obstructive; medication adherence; randomized controlled trial

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are highly prevalent lung diseases requiring daily and often lifelong use of inhaled medication [1]. According to the World Health Organization (WHO), COPD currently represents the fourth leading cause of death worldwide and is predicted to become the third leading cause of death by 2030 [2]. The prevalence of COPD is increasing due to continuing exposure to COPD risk factors (e.g. tobacco smoke or air pollution) and the continuously aging world population) [3]. The prevalence of asthma is increasing as well [4]. In Swiss adults, the prevalence of asthma and COPD was found to be around 7% and 7% to 9%, respectively [5,6].

Treatment and Disease Control

Despite progress in pharmacological and non-pharmacological treatment in recent years, the burden of disease imposed by asthma and COPD remains high and patients may be frequently hospitalized due to exacerbation. Based on data from the Swiss COPD Cohort Study, COPD exacerbation rates are high at 23% per year [7]. Acute exacerbations are a risk factor for disease progression and are associated with increased mortality [8]. A survey published by Leuppi et al showed that the level of asthma control in Switzerland is very low with 15% of the investigated patients [9]. This has also been confirmed by a cross-sectional survey by Miedinger et al who found controlled asthma in 27% of all patients according to the international Global Initiative for Asthma (GINA) guidelines [10]. However, good adherence to therapy can increase the likelihood of achieving better disease control [11].

Reasons for insufficient disease control in asthma and COPD patients are manifold. They are frequently associated with poor inhalation technique and non-adherence to prescribed treatment plans, which may influence mortality and morbidity and pose a financial burden on healthcare systems [12].

Medication Adherence

According to the WHO, adherence is defined as “the extent to which a person’s behavior (including medication-taking) corresponds with agreed recommendations from a healthcare provider” [13]. Adherence represents the basis for effective drug therapy and complete disease control. It is a multidimensional issue with several influencing factors. The WHO classifies these factors into 5 dimensions: socioeconomic-related factors, healthcare team and system-related factors, condition-related factors, therapy-related factors, and patient-related factors [13]. Furthermore, 2 different patterns of non-adherence behaviors are observed in patients, namely intentional and unintentional non-adherence. Intentional non-adherence describes the deliberate discontinuation or reduction of the intake of medication in case of absence of symptoms [14], which may be due to a lack of understanding of the disease course and treatment aims. In addition, the occurrence of side effects can also lead to intentional non-adherence. Unintentional non-adherence, however, is observed when patients do not follow treatment plans due to reasons out of their control, such as forgetfulness, cognitive impairment, or physical disability [15]. In patients taking inhaled medication, impaired vision or musculoskeletal disorders can affect their ability to use the inhaler devices correctly [16]. Other reasons for unintentional non-adherence are complex medication regimes, poly-pharmacy, and the use of multiple inhalers [17,18]. Non-adherence not only leads to suboptimal treatment of individual patients, but may also cause disease prolongation and increased hospital readmission. Finally, it can increase costs for the healthcare system [19].

Based on a systematic literature review of medication adherence literature, Vrijens et al proposed a new taxonomy for describing and defining adherence to medication [20]. The Ascertaining Barriers to Compliance (ABC) taxonomy considers a sequence of events that have to occur for a patient to achieve an optimal benefit from their prescribed treatment regimen and to minimize the risk of harm. This process is divided into 3 essential components: initiation, implementation, and persistence. The process starts with initiation characterized by the intake of the first dose of a prescribed medication. It continues with implementation of the dosing regimen, which is defined as the extent to which a patient’s actual dosing corresponds to the prescribed medication during the time period from initiation to the last dose taken. The last step of the process is persistence, which refers to the time from initiation to eventual discontinuation. After discontinuation, a period of non-persistence may follow until the end of the prescription period.

As such, non-adherence to medications can occur in the following situations: late or non-initiation of a prescribed treatment, suboptimal implementation of the dosing regimen, or early discontinuation of the treatment. This classification is particularly helpful in framing focused research questions as well as finding measures and data to answer them.

Adherence to long-term therapy is estimated to be around 50%, as shown in a systematic review summarizing the results of randomized controlled trials (RCTs). It investigated interventions in order to help patients follow prescriptions for medications [21]. Among patients with asthma, rates of non-adherence ranged from 30% to 70% [22]. Levels of non-adherence are comparably high in patients with COPD, ranging from 43% to 58% [23,24]. Adherence to medication can be measured using direct or indirect methods. Direct methods encompass direct observation of drug intake or measurement of drug concentration, such as markers in the blood, urine, or other body fluids. Indirect methods include assessment of a patient’s clinical response, pill count, rates of refilling prescriptions, patients’ self-report, or the use of electronic monitoring devices [25,26]. While none of these methods are currently considered the gold standard for

measuring adherence to medications [27,28], the emerging method of choice is electronic monitoring devices [29].

Self-reporting by patients was shown to be the most cost-effective approach to the assessment of adherence in clinical and research settings [30]. However, being a subjective method, it also bears the highest risk of overestimating adherence compared to electronic measurements [31].

Observational retrospective studies based on dispensing data from pharmacy record databases analyzed refill adherence for different inhaled medication in patients with asthma and COPD [32-34]. The importance of refill adherence is limited, since this measurement cannot assess the timing of the ingested or inhaled doses that depend on the duration of drug action, which in turn has an important impact on the efficacy of treatment [35].

To investigate the variability in timing and medication adherence, measurements of dose and timing are necessary, which can be done with electronic medication monitors. Electronic monitoring provides precise data on timing and the pattern of inhaler actuation. In addition, it may detect multiple successive actuations (dumping) [36].

Electronic monitoring methods such as SmartInhaler devices (Adherium Ltd., Auckland, New Zealand) are non-invasive and represent one of the best ways to detect adherence patterns when using additional tools attached on the inhaler devices [37]. SmartInhaler devices have been validated for the assessment of adherence to inhaled medication on a daily basis [38]. They are able to track the time and date of each actuation of the inhaler device (incorporated switch activates by depression or rotation of the device) and transmit the data via a wireless connection to a secure Web database [38]. SmartInhaler devices have been used in several studies measuring adherence to inhaled medication [39,40]. In a study on patients with asthma using inhaled corticosteroids, the integrated audio-visual reminder function of these devices significantly improved adherence to inhaled medication [41].

Adherence to orally administered drugs or inhaled medications available, such as powder capsules, can be measured by applying a novel technology called Polymedication Electronic Monitoring System (POEMS). This technology is composed of a printed, self-adhesive polymer film carrying loops of conductive wires that can be affixed to multidose punch cards (Pharmis GmbH, Beinwil am See, Switzerland) with 28 cavities. Every time a powder capsule is taken out of the blister, a loop is broken leading to changes in electrical resistance that can be measured and recorded with date and time [42]. The reports generated by SmartInhalers and POEMS detect whether the patients have taken the medication at the right time and dose.

Interventions to Improve Medication Adherence

Maintenance of sufficient adherence to the prescribed medication is a critical factor in achieving therapeutic success, particularly in chronic diseases. Haynes et al [43] reviewed randomized controlled intervention trials to improve adherence to pharmacological regimens in patients with chronic diseases, including asthma. Both adherence and clinical outcomes were measured in these studies. The authors found that less than 50% of the interventions achieved a significant improvement of adherence while only 30% demonstrated an improvement in clinical outcome. The greatest success was attained with complex interventions combining several strategies (information, reminders, self-monitoring, reinforcement, counseling, telephone follow-up, supportive care, etc). [43]. Lu et al [44] showed that disease management interventions are associated with short- and long-term improvements with regards to the process and quality of care; in particular, when using structured, population-based and multidisciplinary approaches for the identification, treatment, and monitoring of patients with chronic illness. This review also suggested that coordinating pharmacist services as a component of the process of care can improve quality of life, medication adherence, and clinical outcomes in chronic patients [44]. However, particularly successful intervention components could not be determined specifically [45].

Study Objectives

The objectives of this study are (1) to investigate the impact of using specific, validated electronic devices on adherence to inhaled medication in patients with asthma and COPD; and (2) to assess the effect of an acoustic reminder and close supervision on the course of disease and quality of life.

Methods

Participants and Recruitment

In- and outpatients with a diagnosis of asthma bronchiale or COPD from several hospitals in the Basel region and patients treated by pulmonologists in private practice are screened for eligibility (Table 1). Advertisements are distributed in the form of posters, flyers, as well as on ad-screens (Cantonal Hospital Baselland Liestal and Bruderholz), communicating the most important information about the study. Advertisements are also placed in local newspapers.

Table 1. Recruitment locations and related recruitment types.

Hospital	Location	Recruitment
Cantonal Hospital Baselland	Liestal, Switzerland	Screening of hospitalized patients
		Screening of the emergency department
		Screening of DRG[a] lists
Cantonal Hospital Baselland	Bruderholz, Switzerland	Screening of DRG[a] lists
		Collaboration with the pulmonology department
Claraspital	Basel, Switzerland	Collaboration with the pulmonology department
Clinic Barmelweid	Barmelweid, Switzerland	Collaboration with pulmonology department
Gesundheitszentrum Fricktal AG	Rheinfelden, Switzerland	Collaboration with the pulmonology department

[a]DRG: diagnosis related group.

Initially, inclusion and exclusion criteria are checked via telephone, during hospitalizations, or practice visits. Eligible patients are invited for an introductory training course. Before the start of the study, the investigator provides written and verbal information about content and duration of the study. The investigator obtains written consent from patients confirming their willingness to participate in the study.

Inclusion and Exclusion Criteria

The study inclusion and exclusion criteria for male and female participants are shown in Textbox 1 [46]. Enrolment started January 2014 and will end when at least 154 individuals are included in the study.

Textbox 1. Inclusion and exclusion criteria.

Criteria

Inclusion

Aged 18 years or older

Have an established asthma-diagnosis according to the Global Initiative for Asthma (GINA) guidelines and/or

- Have an established COPD diagnosis according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (severity GOLD I-IV based on the international GOLD-Criteria) [46] and
- Are prescribed daily inhaled medication (controller medication for a daily maintenance treatment)
- Had at least one exacerbation in the previous 12 months before study start

Exclusion

- Suffering from malignancies and/or other severe diseases
- Insufficient in the German language
- Pregnant or lactating

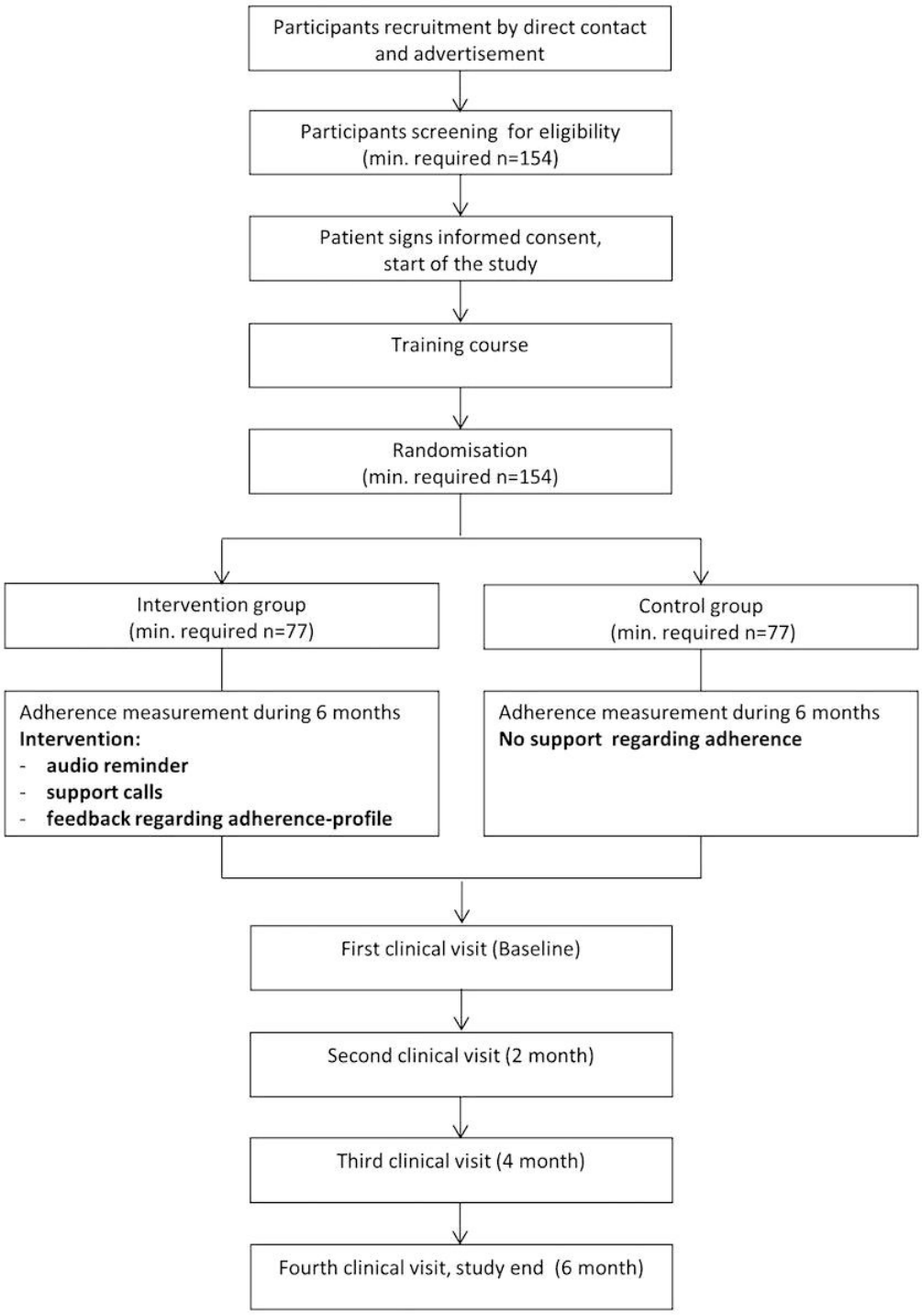
Study Design and Procedures

In this prospective, single-blinded RCT, 169 participants are followed for up to 6 months (Figure 1). Prior to study start, patients have to be in a stable phase of their obstructive lung disease. This is defined as an exacerbation-free period of at least 1 month prior to commencement of the study and no current hospitalization for any other medical condition. Study participants will continue to be cared by their usual treating physician(s) who decide on all prescriptions and treatments.

All participants take part in a training course before the baseline visit, which takes approximately 45 to 60 minutes to complete. The goal of the training course is to provide refresher training on inhalation techniques in order to ensure that all participants are at the same level of disease knowledge and use their medication correctly. The training begins with a brief introduction about asthma and COPD. Afterwards, the most frequently used devices are presented and briefly demonstrated. Correct technique depends on inhaler type and it is important that patients use their own inhaler correctly. Common mistakes and problems associated with the use of the devices are explained. The correct use of the individual devices is demonstrated in a short film (produced by the “Deutsche Atemwegsliga” Bad Lippspringe, Germany) [47], which presents the most important steps to follow in order to achieve an effective inhalation. Notably, it has been shown that the manufacturer’s instruction sheet is not effective enough to achieve correct techniques [48-50]. However, the combination of verbal and visual instructions seems to have a higher success rate in improving the application of inhaler devices [51]. At the end of the training, participants are given the opportunity to ask questions concerning the devices.

Visits take place at baseline (T0), after 2 (T1), 4 (T2), and 6 months (T3) and will take between 45 to 60 minutes, depending on the patient, regardless of the group they belong to. Each visit includes a spirometry test (EasyOne Pro, ndd Medizintechnik AG, Zurich, Switzerland), measurement of diffusion capacity (EasyOne Pro, ndd Medizintechnik AG, Zurich, Switzerland), and exhaled nitric oxide (NIOX MINO, Aerocrine AB, Sweden) and carbon monoxide (piCO^{+}Smokerlyzer, Bedfont Scientific Ltd., Kent, UK) levels. To detect false device applications, each patient is asked to demonstrate the inhalation technique with all prescribed devices to the investigator by using a placebo device (to avoid overdosing). Moreover, participants have to complete the COPD Assessment Test (CAT) [52], the Asthma Control Test (ACT) [53], the St. George's Respiratory Questionnaire (SGRQ), and the Short Form (SF)-36 [54,55] to assess quality of life at baseline, after 2, 4, and 6 months. To investigate patients' beliefs about the necessity of the prescribed medication as well as their concerns about the potential adverse consequences of taking it, the Beliefs About Medicines Questionnaire (BMQ) is used at baseline [56,57]. Throughout the 4 visits, information about exacerbations since the last visit are also obtained.

Figure 1. Study flow chart based on the Consolidated Standards of Reporting Trials (CONSORT) guidelines.



Randomization

Participants are randomly assigned either to the intervention or to the control group. The intervention group is provided with an acoustic reminder for inhalation and receives support calls when the medication is not taken as prescribed. The control group does not receive further support regarding their adherence. A randomization list with study group allocation is generated using R (RStudio, Boston, US). The randomization procedure is provided in a block size of 2. Therefore, examinations between study groups are sequent. This reduces the risk of a season effect between the 2 study groups. Furthermore, the patients are not aware of which group they have been randomized to (single-blinded).

Clinical Intervention

The clinical intervention consists of an automated and personal reminder. Patients assigned to the intervention group receive an audio-reminder, generated by a mobile phone with app capabilities (smartphone). For patients with SmartInhaler, the inhalation times are entered on the Smartinhalerlive website by the investigator. These are then generated by an app directly onto the participant's mobile phone. For patients using POEMS, the inhalation times are entered by the investigator directly in form of an alarm clock onto the mobile phone. Patients are allowed to choose the inhalation times themselves, depending on their personal habits and daily routine. This allows for times during the workday and weekend to be defined. Since the inhalation actuation does not stop the device alarms, the reminder generated by the SmartInhaler app and those generated by the mobile phone have to be quitted by the patients themselves. Moreover, these patients receive support calls carried out by the pharmacist when the use of rescue medication doubles or if the inhaled medication is not inhaled as prescribed for more than 2 consecutive days. In exceptional cases and in the absence of the pharmacist, the support calls are carried out by the responsible study nurse who has been trained accordingly. Participants also receive feedback from the pharmacist on their adherence at each visit, especially for the results of the POEMS.

Patients assigned to the control group have no reminder and will receive no further support regarding their adherence to their inhaled medication.

Sample Size

Power calculation is based on "time to next exacerbation". A previous study has shown that 30% of patients with COPD are readmitted within 6 months because of an exacerbation [58]. Exacerbation rate could be reduced by 30% with an educational program [59]. Since our intervention is not only based on an educational program but on close supervision during the study period, we expect a bigger effect of our intervention, resulting in an assumed endpoint reduction of 40% (12/30), with 11% (8/70) of patients experiencing an exacerbation in the intervention group. This corresponds to a hazard ratio (HR; intervention/control) of 0.36, taking into consideration the time-to-event-curve for the primary outcome (time to next exacerbation). Assuming a sample size of 70 participants for each study group, there is a power of 80% to detect a HR of 0.36 based on a 1-tailed test, since only a decrease of the exacerbation risk is of interest and expected. The calculation is based on the assumptions mentioned above and on a 1-tailed test with a significance level of 5%. Furthermore, 14 additional participants (7 for each study group) will be added to account for dropouts. Therefore, a total of 154 participants will be included in this study.

Measurement of Objective Adherence

In both groups, adherence is measured using SmartInhalers and POEMS as outlined above. Daily measurements are started after the baseline visit (T0) and are continued until the end of the study (T3). All participants are aware that their adherence is measured during the whole study period using the delivered devices. Hence, a possible "hawthorne effect" can result, which represents a change in patient's behavior as a consequence of being monitored during a study [60]. However, previous studies showed that there is no better adherence in patients who were informed that their drug intake was being monitored compared to those patients who were unaware of the monitoring [61,62].

Recorded data are uploaded daily at 00:00 to a Web-based database via a wireless connection. Participants are asked to take their medication at the first visit in order to ensure the correct handling and usage of the SmartInhaler. Once the devices are installed on the inhalers, patients can use their medication as usual.

Currently, no monitoring devices exist that are specifically developed for monitoring the adherence of the newly introduced inhalation-device Ellipta. To assess adherence in patients undergoing treatment with Ellipta, a SmartInhaler with a placebo-device is handed out and patients are instructed to trigger a puff of the placebo every time when they inhale their active treatment. This procedure allows an indirect recording of date and time actuation of the Ellipta inhaler.

POEMS are used for inhalation with powder capsules (Breezhaler and HandiHaler). The capsules are pre-filled for the following 2 weeks with a patient's individualized prescription plan (mostly one time daily inhalation of capsule contents). The multidose punch cards are filled manually by a pharmacist. Participants who apply Breezhaler and HandiHaler will receive 1 multidose punch card for every 2 weeks. Every time the patients break a loop for taking the capsules, the date and time are recorded on a microchip, which can be read out when patients bring back the empty punch card.

Data Collection and Outcome Measures

The primary outcome of this study is "time to next asthma or COPD exacerbation", defined as acute-onset worsening of the patient's condition beyond day-to-day variations requiring interaction with a health care provider [63]. Outcome is expressed as the number of exacerbations since the last visit with the exact period of exacerbation as well as the number of exacerbations followed by hospitalization. If patients are not able to provide information about the time of exacerbation, the treating physician will be contacted.

Sociodemographic variables such as gender, civil status, age, educational level, and employment status are obtained by a generic questionnaire during the baseline visit. Furthermore,

smoking status is assessed from medical history and expressed as pack years (py; number of smoking years times the number of smoked packs per day). Body height and weight are signified by body mass index (BMI; body weight/[body height]^2). In addition, disease-related questions such as allergies, comorbidities, current medication, and number of exacerbations in the previous 12 months are recorded, including hospitalizations and emergency department attendance.

This project focuses on the implementation of a prescribed dosing regimen. Objective adherence will be analyzed according to the definitions shown in Textbox 2 [64].

Textbox 2. Objective adherence definitions.

Definition

- Taking adherence: (number of puffs inhaled during 24 hours/number of puffs prescribed during 24 hours) x 100
- Timing adherence: (number of correct dosing intervals during 24 hours/number of dosing intervals during 24 hours) x 100; correct dosing intervals are prescribed intervals ± 25%:
  - For once daily dosing: 24 hours ± 25% = 18 hours to 30 hours
  - For twice daily dosing: 12 hours ± 25% = 9 hours to 15 hours
  - For three daily dosing: 8 hours ± 25 % = 6 hours to 10 hours
- Gaps: (number of days without inhalation during the whole study period/number of days in same time period) x 100
- Maximal gap length: number of consecutive days of the longest period of time without inhalation

Throughout all visits, the following lung function tests are performed to assess changes in lung function: spirometry (FEV_1, FVC, FEV_1/ FVC), diffusion capacity, and nitric oxide and carbon monoxide measurements.

During each visit (T0 to T3), participants are asked to demonstrate how they actually use their device at home to evaluate the inhalation technique. For this purpose, placebo devices are used to prevent overdosing. Correctness of inhaler use is assessed using pre-defined checklists for each inhaler type based on user guidelines and instruction package inserts from the manufacturers [65-70]. Correct inhaler usage is defined as correct performance of every step on the checklist. Incorrect inhaler usage is defined as 1 or more steps done incorrectly. A total score is calculated with 0 (incorrect application) and 1 (correct application) and applied to every step. Possible errors are corrected by verbal instruction and visual demonstration. For ethical reasons the correction was performed in both groups. Patients demonstrate their inhalation technique until it is performed correctly.

At baseline, the BMQ is used to assess patients' beliefs about the need of the prescribed medication and their concerns about the potential adverse consequences of taking it.

Changes in quality of life are investigated at baseline, after 2, 4, and 6 months using different disease-specific questionnaires: SGRQ, CAT, and ACT. To determine general quality of life, the SF-36-questionnaire is used.

Data collection will end as soon as all study participants have finished the 6-month observational period and have had the fourth clinical visit.

Statistical Analysis

Statistical analyses, including descriptive statistic and survival analyses, are carried out using the software R (RStudio, Boston, US) and SPSS (IBM Corporation, Armonk, US). Statistical significance is set at the 5% level. Time to next exacerbation is compared by applying the Kaplan-Meier method and Cox proportional hazard model. Results will be reported as a HR with a corresponding confidence interval (CI) of 95 % and *P* values. A HR smaller than 1 is expected. This implies that the intervention group will have a smaller risk for exacerbations. Associations between time to between exacerbation and independent predictors will be analyzed (taking adherence, timing adherence, and gaps without inhalation). Comparisons of secondary parameters are done using *t* tests or chi-square tests (or their nonparametric equivalents if data are not normally distributed).

Missing Data and Dropouts

Patients will be rated as dropout when they are excluded from the study at their own request or if they are no longer able to participate in the study until the final visit. Patients who are not able to undergo all clinical examination during the follow-up visits will remain in the study. Multiple imputation methods will be used to impute missing data with less than 25% missing values. This is typically more efficient than complete case analysis when covariates have missing values [71].

Ethics and Dissemination

This study is conducted according to the Helsinki Declaration and according to the good clinical practice guidelines. Study participation is voluntary and can be revoked at any time without specification of reasons and will have no disadvantages for their future medical care. The study was approved by the Ethics Committee Northwest/Central Switzerland (registry number: EK-269/13) and was registered with Clincialtrials.gov (NCT02386722). In case of any considerable deviations from the actual study protocol, the investigator will send an amendment for further approval from the ethical committees. The results of this study will be disseminated via seminar, conference presentations, and academic, peer-reviewed journals.

Data Security and Disclosure of Original Documents

Patient data are collected and stored under confidentiality rules. For reports, data collection, and administrative forms an anonymization will be done and participants will be assigned a study identification (ID) (PXXX). All study-related data and documents are stored on a protected server of the Cantonal Hospital Baselland. Data access is limited to members of the medical research group at the Cantonal Hospital Liestal. After study completion, all documents and informed consent forms will be retained in the archives of the University Department of Internal Medicine at the Cantonal Hospital Liestal for 10 years according to applicable Swiss regulatory requirements.

Results

This is a single-centre, randomized controlled study. It is performed at the Cantonal Hospital Baselland, Liestal, and Bruderholz, Switzerland. Recruitment started in January 2014, and to date, a total of 169 patients have been recruited. Follow-up assessments are still ongoing. The study will be concluded in the first quarter of 2017. Data analysis will take place during 2017.

Discussion

To date, only a few studies have investigated medication adherence in patients with chronic obstructive lung diseases. These studies were retrospectively analyzed, limited to refill adherence, and had several important limitations such as the lack of assessment of the relationship between the duration of drug action and the timing of the ingested doses, which impacts the efficacy of treatment [15]. Other disadvantages of this measurement are missing data when refills were obtained outside of the investigated system and incomplete records if the medication plan is verbally modified by the prescriber without informing the dispensing pharmacy. Moreover, assumptions have to be made on medication intake behavior, if it is taken according to the prescription, and corresponds to the prescribed refilling [72].

We expect that a regular adherence reminder and close supervision by a healthcare professional will have a beneficial effect on adherence to inhaled medication in patients with asthma or COPD, resulting in an increased time to next exacerbation. In addition, we assume that improved adherence will increase the quality of life of these patients.

With the prospective study design and the use of state-of-the-art devices for measuring adherence, we expect scientifically relevant and clinically meaningful results that will have a substantial and positive impact on the provision of healthcare in chronically ill patients suffering from asthma or COPD.

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The pharmaceutical companies that provided funding for this study have no bearing on the study design, data collection and analysis, or writing of the manuscript.

Ethical approval for this study was obtained from the Ethics Committee Northwest/Central Switzerland (EK-269/13).

Conflicts of Interest

None declared.

Authors' Contributions

CG, TD, and JDL are chief investigators of the project. CG, TD, SD, IA, KH, and JDL made contributions to the protocol in their specific areas of expertise. CG prepared the first draft of this manuscript and all authors revised the paper critically for intellectual content and gave approval for the final version.

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Abbreviations

ACT: Asthma Control Test
BMQ: Beliefs about Medicines Questionnaire

CAT: COPD Assessment Test
CI: confidence interval
COPD: chronic obstructive pulmonary disease
HR: hazard ratio
POEMS: Polymedication Electronic Monitoring System
RCT: randomized controlled trial
SF-36: Short Form 36
SGRQ: St. George's Respiratory Questionnaire
WHO: World Health Organization

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Protocol

Assessing the Value of Prehabilitation in Patients Undergoing Colorectal Surgery According to the Enhanced Recovery After Surgery (ERAS) Pathway for the Improvement of Postoperative Outcomes: Protocol for a Randomized Controlled Trial

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Abstract

Background: A key element in the postoperative phase of the standardized Enhanced Recovery After Surgery (ERAS) treatment pathways is mobilization. Currently, there are no recommendations in the ERAS guidelines for preoperative physical activity. Patients undergoing major surgery are prone to functional decline due to the impairment of muscle, cardiorespiratory, and neurological function as a response to surgical stress. It has been shown that preoperative physical training reduces postoperative complications. To date, there are limited studies that investigate preoperative physical training combined with ERAS.

Objective: The aim of this study is to assess the impact of tailored physical training prior to colorectal surgery conducted according to an ERAS protocol on overall morbidity. This study proposes the initial hypothesis that 3-6 weeks of prehabilitation before elective colorectal surgery may improve postoperative outcome and reduce complication rates, assessed using the Comprehensive Complication Index. The primary objective is to evaluate overall morbidity due to postoperative complications. Additionally, complications are assessed according to the Clavien-Dindo classification, length of stay, readmission rate, mortality rate, and treatment-related costs.

Methods: The prehabilitation Enhanced Recovery After colorectal Surgery (pERACS) study is a single-center, single-blinded prospective randomized controlled trial. Patients scheduled for colorectal resections are randomly assigned either to the prehabilitation group or the control group. All patients are treated with the ERAS pathway for colorectal resections according to a standardized study schedule. Sample size calculation performed by estimating a clinically relevant 25% reduction of postoperative complications (alpha=.05, power 80%, dropout rate of 10%) resulted in 56 randomized patients per group.

Results: Following ethical approval of the study protocol, the first patient was included in June 2016. At this time, a total of 40 patients have been included; 27 patients terminated the study by the end of March 2017. Results are expected to be published in 2018.

Conclusions: The pERACS trial is a single-center, single-blinded prospective randomized controlled trial to assess the impact of tailored physical training prior to colorectal surgery, conducted according to an ERAS protocol, in order to evaluate overall morbidity.

Trial Registration: Clinicaltrials.gov NCT02746731; https://clinicaltrials.gov/ct2/show/NCT02746731 (Archived by WebCite at http://www.webcitation.org/6tzblGwge)

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KEYWORDS

prehabilitation; enhanced recovery after surgery; ERAS

Introduction

During the 1990s, Henrik Kehlet, a Danish surgeon, developed the concept of fast-track surgery [1]. By optimizing perioperative care, recovery was accelerated. To advance this, the Enhanced Recovery After Surgery (ERAS) concept was developed by Scandinavian and British surgeons. ERAS is an evidence-based multimodal treatment concept to improve postoperative recovery. In contrast to the fast-track concept, the ERAS guidelines do not only focus on pace. Instead, the multifaceted ERAS approach aims to reduce perioperative stress, improve postoperative recovery, reduce morbidity and mortality rates, and shorten the length of hospital stay (LOS). The first ERAS guidelines for elective colorectal surgery were published in 2005 [2].

In the postoperative phase, one of the most important elements pertaining to physical activity is mobilization. According to the ERAS approach, the goal is to get patients out of bed on the same day as the surgery, for at least 4 hours on postoperative day (POD) 1 and for at least 6 hours from POD 2 onwards. However, there are no recommendations for physical activity prior to surgery.

Patients undergoing major surgery are prone to physical decline due to preexisting reduced general health and the impairment of muscle, cardiorespiratory, and neurological function in response to surgical stress. While physically healthy patients have the capacity to cope with this stress response, patients with poorer preoperative physical conditions might not have this capacity. Therefore, these patients are at a higher risk for postoperative complications [3].

In elective cardiac surgery, there is evidence that preoperative physiotherapy reduces postoperative pulmonary complications [4]. Similar effects are suggested for thoracic, abdominal, and major joint replacement surgery [3]. Dronkers at al reported an association between preoperative physical fitness/physical activity and outcome after scheduled major abdominal surgery [5].

To date, there have been only a few studies investigating preoperative physical training combined with ERAS [6]. In respect to existing evidence, which suggests potential benefits through preoperative physical training, one objective of this study is to investigate these findings in the setting of an ERAS approach for colorectal resections. The primary aim of the study is to examine whether moderate to intense physical training (partially supervised by a qualified person), implemented within a short timeframe prior to surgery, will reduce overall morbidity and mortality rates in the ERAS cohort. The hypothesis of the trial is that 3-6 weeks of prehabilitation before elective colorectal surgery improves postoperative outcome.

Methods

Study Design

The prehabilitation Enhanced Recovery After Colorectal Surgery (pERACS) trial is a single-center, single-blinded prospective randomized controlled trial to assess the impact of tailored physical training on overall morbidity, prior to colorectal surgery, conducted according to an ERAS approach. Patients with an indication for elective colorectal resection will be randomized into either the intervention group, with preoperative physical training, or the control group without preoperative physical training. Apart from the physiotherapeutic mobilization according to the protocol and ERAS guidelines, all patients will undergo their normal physical activities. All patients will be treated along the ERAS pathway for colorectal resections.

Patients and Setting

Patients with an indication for elective colorectal resection will be eligible for this study, which will be carried out in the Department of Surgery of the Cantonal Hospital in Winterthur, Switzerland. Patients will be recruited for the study by senior surgeons who will also perform the surgical intervention.

Inclusion Criteria

Patients will be included based on the following criteria: adult patients over age 18 with or without comorbidities (eg, diabetes, obesity, cardiovascular disease), patients suffering from colorectal diseases (eg, colorectal cancer, diverticulosis, benign tumors such as polyps or inflammatory bowel disease), patients needing an operative treatment (eg, rectosigmoid resection, anterior resection of rectum, ileocecal/right hemicolectomy, left hemicolectomy, abdominoperineal resection, or total/subtotal colectomy), patients treated according to ERAS, patients undergoing reversal of stoma and Hartmann procedures treated according to ERAS, and informed consent as documented by signature.

Exclusion Criteria

Patients will be excluded if they are under age 18, are not able to provide informed consent, have a physical impairment (eg, paresis) or severe cardiac or pulmonary comorbidities (NYHA III or IV), cannot perform the necessary physical training, are not able or willing to attend the physical training at the institute of physiotherapy, are not able to follow the procedures of the study (eg, due to language restrictions, psychological disorders), are participating in another study with investigational drugs 30 days preceding and during the study, or enrollment of the investigator, his/her family members, employees, and other dependent persons.

Sample Size Calculation

The sample size calculation was performed assuming a clinically relevant 25% reduction of postoperative complications as assessed by the Comprehensive Complication Index (CCI) favoring the treatment group (prehabilitation) when compared to the control group (no prehabilitation) [7,8]. Using a dataset of 47 patients who underwent ERAS colorectal surgery in our department, we determined the mean CCI was 10 (SD 5). Thus, the treatment group mean was set at 7.5, and the standard deviation was adjusted accordingly (SD 3.75) [9]. The alpha error was typically set at .05 and power at 80%. The initial total sample size of 102 patients was increased by 10% to adjust for potential of loss to follow-up resulting in a total sample size of 112 participants (ie, 56 participants per group respectively).

Intervention

Patients in the intervention group will train for 3-6 weeks prior to surgery, twice a week at the institute of physiotherapy under the guidance of a qualified physiotherapist and once unsupervised at home. Training will be tailored and constantly adapted according to the actual condition of the patient. The program comprises both strengthening and endurance components (see Table 1). In addition, patients will be informed about the importance of their physical condition with respect to the postoperative course and will be encouraged to adhere to the training program, as well as to remain as physically active as possible in addition to the physical exercise training program. Each supervised training session will last 90 minutes and will include the following elements:

- Warm-up: guided movements of all main articulations in order to prevent injuries and increasing activity in order to prepare the cardiovascular system for exercise
- Aerobic interval training on a bicycle: high-intensity interval training with a duration of 32 minutes (4x4mins with 85-90% of maximum training capacity)
- Resistance training: circuit training on six different devices allowing the strengthening of large muscle groups of the arms and legs
- Cool-down: guided stretching of the previously trained muscles

Patients assigned to the control group receive instructions about the importance of their physical condition with respect to the postoperative course and are encouraged to remain physically active. This is in accordance with the current standard procedure. All patients will be asked to record their physical activity in a diary. Regardless of the group allocation, all patients will be treated according to the ERAS approach.

The Steep Ramp Test

The steep ramp test is a validated short maximal exercise capacity test that does not require respiratory gas analysis measurements and has been described in the exercise rehabilitation of patients with chronic heart failure. The main outcome of the steep ramp test is the achieved work rate peak, which partially reflects anaerobic power and leg muscle strength [10]. The test has been proved to be safe, reproducible, and practical in use for prescribing the training load and for monitoring training progress in the rehabilitation of cancer patients [11].

2-Minute Walk Test

The 2-Minute Walk Test is a measurement of endurance by assessing walking distance over 2 minutes. It is a simple test that can be widely used in clinical practice as well as for research [12].

Five Times Sit to Stand Test

The Five Times Sit to Stand Test (FTSST) is a quick and easy test to perform. It measures the time (in seconds) that an individual needs to change between sitting (standard chair with arms and a seat height of 43 cm) and standing five times in a row. FTSST is a multidimensional task that is associated with lower extremity strength and balance.

Hand Grip Strength

Reduced grip strength has been shown to be a predictor of impaired short-term outcome, such as increased postoperative complications, increased length of hospitalization, higher readmission rate, and decreased physical status [13]. For the grip strength, the average value of three successive measurements of the dominant hand with a Jamar dynamometer [14,15] will be calculated.

Fatigue-Visual Analogue Scale

The Fatigue-Visual Analogue Scale (F-VAS) is a horizontal line, 100 mm in length, anchored by word descriptors at each end. Patient mark on the line the point representing their perception of their fatigue. The F-VAS score is determined by measuring in millimeters from the left end of the line to the point that the patient marks.

Pain (Numeric Rating Scale)

Level of pain will be assessed by asking patients prior to and after the physiotherapy session to rate their perceived pain intensity using a numeric rating scale (NRS). The NRS is an 11-point scale from 0-10, where “0” indicates no pain and “10” indicates the maximum pain imaginable [16].

International Physical Activity Questionnaire Short Form

The International Physical Activity Questionnaire short form (IPAQ-SF) will be used in this study because the ease of administration (ie, the burden on participants to report their activity) is small [17]. The IPAQ-SF (9 items) records the activity of four intensity levels: (1) vigorous-intensity activity such as aerobics, (2) moderate-intensity activity such as leisure cycling, (3) walking, and (4) sitting.

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 is a questionnaire developed to assess the quality of life of cancer patients. It is an instrument that has been translated and validated in over 90 languages and is used in more than 3000 studies worldwide.

Table 1. Administration of study intervention and control intervention.

	Body structure and function	Activity	Questionnaires and other tests
Preoperative (3-6 weeks before surgical intervention)	Steep ramp test	Five Times Sit to Stand	International Physical Activity Questionnaire short form
	Fatigue-Visual Analogue Scale	2-Minute Walk Test	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
	Pain Numeric Rating Scale		
	Hand grip strength		
Surgical intervention	Fatigue-Visual Analogue Scale		Adherence to exercise
	Pain Numeric Rating Scale		
	Pulse and oxygenation		
Postoperative during hospitalization	Fatigue-Visual Analogue Scale	Five Times Sit to Stand	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
	Pain Numeric Rating Scale	2-Minute Walk Test	
	Hand grip strength	Modified Iowa Levels of Assistance Scale	
Postoperative (6 weeks after surgical intervention)	Steep ramp test	Five Times Sit to Stand	International Physical Activity Questionnaire short form
	Fatigue-Visual Analogue Scale	2-Minute Walk Test	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
	Pain Numeric Rating Scale		
	Hand grip strength		

Assessment of Postoperative Functional Recovery During Hospital Stay: Modified Iowa Levels of Assistance Scale

For assessment of postoperative functional recovery, the modified version of the Iowa Levels of Assistance Scale (MILAS) [18] will be obtained daily. The MILAS assesses the ability of patients to safely perform four activities of daily life (supine to sit, sit to stand, walking, and stair climbing) and rates the amount of assistance needed. This measurement enables the physiotherapist to assess whether and when a patient can function independently and allows tailoring treatment goals.

Endpoints

As the primary endpoint, the complication rate will be assessed in-hospital and at the 30-day follow-up using the CCI [19,20]. Secondary endpoints are the complications assessed according to Clavien/Dindo [21], LOS, readmission rate, mortality rate, and costs as well as measures associated with physical performance. To compare the two groups and follow the progress in the intervention group, tests and questionnaires will be used (see Table 2).

Study Procedures

Patients are allocated to our consultation center by general practitioners or gastroenterologists. They will be recruited to the study during normal consultation through senior surgeons. We will include all consecutive patients electively treated for colorectal diseases in accordance with the ERAS approach, for colorectal resections from June 13, 2016, onwards. Patients will be randomly assigned either to the control or to the intervention group after entering their data into the Web-based database. All complications will be recorded and assessed according to the Clavien-Dindo classification at the time of discharge and follow-up, by the unblinded study nurse (Table 2). Results will be transformed to the CCI score. The LOS and readmission rate will be recorded at the time of discharge and follow-up. Cost analysis will be performed with the local department of finance.

Analyses

The statistical analysis will be performed on an intention-to-treat basis by the study's independent statistician. For each patient, basic demographic, prehabilitation, intraoperative, postoperative, and follow-up data will be generated and stored in a password-protected and encrypted database. These data will be compared separately for each randomization group. Both significant as well as nonsignificant results will be reported accordingly.

The primary endpoint (CCI) will be compared between the two randomized groups (prehabilitation/treatment group vs no prehabilitation/control group) using the Student *t* test. The CCI is known from other trials on postoperative complications to be normally distributed [19,20].

As for the secondary outcomes, the two randomized groups will be compared with the Pearson chi-square test with regards to the Clavien/Dindo classification [21]. This is typically an ordinal variable. Furthermore, the LOS, typically with a skewed distribution, will be compared between the two randomized groups with the Mann-Whitney U test. Readmission and mortality rates will be compared with the Fisher's exact test between the two groups. The overall total in-hospital costs between the two randomized groups will be compared either with the Student *t* or the Mann-Whitney U-test, depending on their normality of distribution. Cost-effectiveness between the two groups will be compared. All *P* values will be 2-sided and considered statistically significant, if $P<.05$. The statistical analysis will be performed on SPSS 22 for Mac.

A subgroup analysis to investigate whether disease entity (benign vs malignant disease) influences the impact of prehabilitation on the outcome will be performed. Due to the small sample size, further subgroup analysis (eg, for different procedures) will not be performed. There are no multivariable analyses planned for this study due to the nature of the study design (randomized controlled trial) as there will be no need for adjustment of the results.

An interim analysis will be performed as soon as the total sample size of the study reaches 56 patients for both groups. The purpose of the interim analysis is to assess whether the inclusion rate of patients is acceptable and as expected. Further, we analyze the possibility of unexpected rates of severe or life-threatening adverse events or the extraordinary favorable effectiveness of the intervention, which may indicate the premature closure of the trial. An ad hoc interim analysis will be performed after inclusion of 20 patients to assess practicability only.

Table 2. Physical tests and questionnaires.

	Intervention group		Control group	
	Preoperative	Postoperative	Preoperative	Postoperative
Steep Ramp Test	x	x	x	x
Borg Rating of Perceived Exertion Scale	x	x	x	x
Numeric Rating Scale Pain	x	x	x	x
Hand grip strength	x	x	x	x
Five Times Sit to Stand test	x	x	x	x
2-Minute Walk Test	x	x	x	x
International Physical Activity Questionnaire-short form	x	x	x	x
Modified Iowa Levels of Assistance		x		x
Comprehensive Complication Index		x		x
Clavien/Dindo Score		x		x
Length of stay		x		x
Readmission		x		x
Mortality rate		x		x
Costs		x		x

Results

Following ethical approval of the study protocol, the first patient was included in June 2016; 40 patients have now been included, and 27 patients had terminated the study by the end of March 2017. Results are expected to be published in 2018.

Discussion

Principal Considerations

Since the introduction of the evidence-based ERAS treatment pathway, the rate of complications has been markedly reduced [22-24]. Equal observations were made in the study center (ie, Cantonal Hospital Winterthur unpublished data). A defining characteristic of ERAS is its multimodal, multidisciplinary approach. One component of ERAS is physical activity, more specifically the early postoperative mobilization of patients. With our study, we aim to investigate the effectiveness of physical training prior to the operation. There is an indication from other areas that physical preconditioning improves the resistibility of patients. The consequence is better toleration of operation-associated stress. However, these findings need to be confirmed for patients with colorectal disorders requiring surgical intervention according to an ERAS approach.

Strengths and Limitations

An arbitrary choice in this study was the duration of the training and the number of training sessions. Practical aspects, the tolerated period of waiting time, and the risk for undesired progression of the underlying disease were taken into consideration as we defined a training period of 3-6 weeks. This was a consensus based on time needed to see any physical improvements and previous studies investigating the impact of treatment delay on outcome. To our best knowledge, there is no study showing that a delay of 3-6 weeks has an impact on the oncological outcome [25,26].

We believe that the strength of this study is the consideration of the whole treatment process as opposed to a single element. In addition the study can be considered a pragmatic trial since it represents daily clinical routine.

Conclusion

The pERACS trial is a single-center, single-blinded prospective randomized controlled trial to assess the impact of tailored physical training prior to colorectal surgery, conducted according to an ERAS protocol, in order to evaluate overall morbidity.

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Authors' Contributions

CMK drafted the manuscript. CMK, MKH, CT, GM and MW designed the protocol and cowrote the manuscript. DAR performed the sample calculations. All authors were involved in editing the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CCI: Comprehensive Complication Index
ERAS: Enhanced Recovery After Surgery
FTSST: Five Times Sit to Stand Test
F-VAS: Fatigue-Visual Analogue Scale
IPAQ-SF: International Physical Activity Questionnaire short-form
LOS: length of hospital stay
MILAS: Modified Iowa Levels of Assistance Scale
NRS: Numeric Rating Scale
pERACS: Prehabilitation Enhanced Recovery After Colorectal Surgery
POD: postoperative day

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Protocol

Efficacy of Seren@ctif, a Computer-Based Stress Management Program for Patients With Adjustment Disorder With Anxiety: Protocol for a Controlled Trial

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Abstract

Background: Adjustment disorder with anxiety (ADA) is the most frequent and best characterized stress-related psychiatric disorder. The rationale for prescription of benzodiazepine monotherapy is a public health issue. Cognitive behavioral stress management programs have been studied in many countries. Several reports have shown beyond reasonable doubt their efficiency at reducing perceived stress and anxiety symptoms and improving patient quality of life. Considering the number of people who could benefit from such programs but are unable to access them, self-help programs have been offered. First presented as books, these programs became enriched with computer-based and digital supports. Regrettably, programs for stress management based on cognitive behavioral therapy (CBT), both face-to-face and digital support, have been only minimally evaluated in France. To our knowledge, the Seren@ctif program is the first French language self-help program for stress management using digital supports.

Objective: The aim of this study is to assess the effectiveness of a 5-week standardized stress management program for reducing anxiety conducted via eLearning (iCBT) or through face-to-face interviews (CBT) with patients suffering from ADA compared with a wait list control group (WLC). These patients seek treatment in a psychiatric unit for anxiety disorders at a university hospital. The primary outcome is change in the State Trait Anxiety Inventory scale trait subscale (STAI-T) between baseline and 2-month visit.

Methods: This is a multicenter, prospective, open label, randomized controlled study in 3 parallel groups with balanced randomization (1:1:1): computer-based stress management with minimal contact (not fully automated) (group 1), stress management with face-to-face interviews (group 2), and a WLC group that receives usual health care from a general practitioner (group 3). Programs are based on standard CBT principles and include 5 modules in 5 weekly sessions that include the following topics: stress and stress reaction and assessment; deep respiration and relaxation techniques; cognitive restructuring, mindfulness, and acceptance; behavioral skills as problem solving; and time management, healthy behaviors, and emotion regulation. In the Internet-based group, patients have minimal contact with a medical professional before and after every session. In the first session, a flash memory drive is supplied containing videos, audio files, a self-help book portfolio in the form of an eGuide, and log books providing the exercises to be completed between 2 sessions. The patient is encouraged to practice a 20-minute daily exercise 5 or 6 times per week. In the face-to-face group, patients receive the same program from a therapist with 5 weekly sessions without digital support. Interviews and self-assessments were collected face-to-face with the investigator.

Results: The feasibility of this program is being tested, and results show good accessibility in terms of acceptance, understanding, and treatment credibility. Results are expected in 2018.

Conclusions: To our knowledge, this is the first French study to examine the effectiveness of a computer-based stress management program for patients with ADA. The Seren@ctif program may be useful within the framework of a psychoeducative approach. It could also be advised for people suffering from other diseases related to stress and for people with a clinical level of perceived stress.

Trial Registration: Clinicaltrials.gov NCT02621775; https://clinicaltrials.gov/ct2/show/NCT02621775 (Archived by WebCite at http://www.webcitation.org/6tQrkPs1u)

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KEYWORDS

computer-assisted therapy; eHealth; cognitive therapy; behavior therapy; psychological stress; adjustment disorders; randomized controlled trial

Introduction

Background

Numerous studies have shown that exposure to a stressor increases the risk of psychiatric symptoms and disorders, especially anxiety. When anxiety symptoms are at a higher level than a normal reaction to a stressful event, we consider the possibility of a diagnosis of adjustment disorders, which are classified as stress-related disorders. They are responsible for significant direct and indirect costs from treatment, work stoppages, and loss of productivity [1].

Adjustment Disorder With Anxiety

Definition

Adjustment disorder with anxiety (ADA) is the most frequent and best characterized stress-related psychiatric disorder [2]. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), a diagnosis of ADA is appropriate with the finding of anxiety occurring within 3 months of a psychosocial stressor or life event (eg, divorce, job loss, serious physical illness) [3] with symptoms generally abating by 6 months after the event. Considered a common disorder ranging from mild to moderate intensity, ADA is a true diagnostic entity. A general medical study showed that the level of anxiety is comparable to that of other anxiety disorders such as generalized anxiety disorder [4].

Current Recommendations for Adjustment Disorder With Anxiety

Patients are generally not treated with a tailored approach but with medication, mainly benzodiazepine monotherapy. Benzodiazepine misuse is a public health problem. Although stress management is considered the most appropriate psychological treatment for ADA, the evidence base for this approach is limited [5] **.** However, several studies compared cognitive behavioral therapy (CBT) with other treatments for generalized anxiety disorders and found greater improvements in stress and anxiety symptoms from CBT. In a study comparing CBT with relaxation, a posttreatment progression for State-Trait Anxiety Inventory scale (STAI-T trait subscale) scores from 53.04 to 46 and for Penn State Worry Questionnaire (PSWQ) scores from 61 to 51.13 were shown for the group that received CBT [6]. A study comparing psychodynamic psychotherapy with CBT found a greater improvement in the symptoms of stress and anxiety for the CBT intervention (a posttreatment progression of STAI-T trait subscale scores from 58.83 to 43.41 and of PSWQ scores from 63.48 to 49.86 in this group) [7]. In addition, eMental health options are considered uniquely suited for offering early intervention after patients experience stressful life events that can potentially trigger adjustment disorders [8].

Development of Preventive and Curative Measures for Adjustment Disorder With Anxiety

It seems legitimate, given the prevalence and the human, economic, and social costs of this pathology linked to stress, to develop preventive and curative measures for ADA. It is not always possible to intervene upstream to reduce the exposure to stress and prevent the occurrence of ADA (primary prevention). Secondary and tertiary prevention measures are therefore useful to limit their consequences.

Stress and Anxiety Management

Stress management is a set of educational and psychotherapeutic measures that combines several cognitive behavioral techniques. The aim is to allow the patient to reach a satisfactory level of emotional and cognitive control and cope with stressors in order to reduce the negative consequences. The common practice is to offer group sessions or individual interviews in the form of a structured module limited in time [9].

Cognitive Behavioral Therapy

CBT has been shown to be an effective treatment for reducing anxiety symptoms in various somatic pathologies such as cardiovascular disease [10,11], diabetes [12], chronic fatigue syndrome [13], and breast cancer [14] and in subjects with high levels of perceived stress or anxiety or burnout, particularly in the workplace [15]. A meta-analysis by Richardson and Rothstein [16] showed a moderate effect size (d=0.53) of stress management programs in the context of work, which is considered an average effect size according to the Cohen criteria [17]. For structured programs based on CBT, the effect is clearly greater (d=1) [9].

Self-Help Therapy

Given that many patients do not have any access to stress and anxiety management programs, therapeutic education modules based on guides and self-help books have been offered and have

shown positive results compared with classical CBT programs and control groups [18,19].

Digital Stress Management

In recent years, the development of new technologies has enriched self-help programs by integrating new tools (CD-ROM, flash memory drive, or directly accessible on the Internet), allowing better interactivity and use other than contact with the therapist for patients [20].

These computer-assisted programs are intended to limit the amount of contact time with a mental health professional [21-23]. They have been evaluated in many countries in general, student, and corporate populations [24-36]. Unfortunately, computer-assisted programs have not been evaluated in France.

Recently, a meta-analysis evaluating the effect sizes of 26 computer- and Internet-based interventions was conducted on psychological stress and found significant results in terms of reduction of symptoms of stress (Cohen *d*=0.43, 95% CI 0.31-0.54), depression (Cohen *d*=0.34, 95% CI 0.21-0.48), and anxiety (Cohen *d*=0.32, 95% CI 0.17-0.47) compared to other types of interventions. These results provide evidence that Web- and computer-based stress management interventions can be effective and have the potential to reduce stress-related mental health problems on a large scale [37].

Development of the Seren@ctif Program

It was in this context that Seren@ctif, a computer-based self-help management program, was developed at Lille University Hospital. It is the first French CBT program using digital support (iCBT). Seren@ctif is a neologism formed from 2 French words: seren for *serenité*, which means serenity, and actif, which means active and refers to self-help. The words are joined with an “at” sign to indicate the use of a digital format.

A pilot study was carried out between January and June 2014 to study the feasibility of this therapeutic program [38]. The results are satisfactory (average scores for satisfaction questionnaires were high, with scores ranging from 4 to 5 on a 5-point Likert scale). These results were the reason why it seemed appropriate to go further by evaluating this program in a controlled manner.

Aims of the Study

The primary objective of this study is to assess the effectiveness of our stress management program conducted via e-learning (iCBT) or through face-to-face sessions compared with a wait list control (WLC) to reduce the anxiety level after 2 months in patients with a diagnosis of ADA.

The primary outcome is the change in the STAI-T score between the baseline and the 2-month visits.

The secondary objectives of this study are as follows:

- Evaluate the maintenance of effectiveness of the 2 therapeutic stress management programs (iCBT and CBT) at 6 months
- Compare the change in stress, worry, anxiety, and depressive symptoms in the 2 therapeutic programs at 2 and 6 months
- Measure the impact of the 2 therapeutic programs on the consumption of tobacco, alcohol, and drugs
- Assess overall satisfaction with the 2 therapeutic programs at 2 and 6 months and with the WLC at 6 months

The secondary outcome measures include the following:

- Change in STAI-T scores at 6 months
- Hospital Anxiety Depression Scale (HADS) anxiety subscale scores at 2 and 6 months
- Worry symptoms evaluated by the PSWQ
- Stress level evaluated by the Perceived Stress Scale (PSS) and the Visual Analog Scale–stress (VAS-stress) at 2 and 6 months
- Depressive symptoms evaluated by the Beck Depression Inventory (BDI) and the HADS depression subscale at 2 and 6 months
- Overall satisfaction evaluated by the VAS-satisfaction at 2 and 6 months for the 2 therapeutic groups and at 6 months for the WLC group
- Change in consumption of tobacco, alcohol, and drugs evaluated at 2 and 6 months

Hypotheses

We hypothesize that (1) both therapeutic programs will have a greater clinical impact on the reduction of anxiety symptoms, perceived stress, and depressive symptoms compared with a WLC in the short term (2 months), and this effect will be maintained in the long term (6 months); (2) the 2 therapeutic programs will have the same effectiveness in reducing these symptoms; (3) both therapies will be more cost effective than will WLC; (4) these 2 programs both reduce the consumption of tobacco, alcohol, and drugs compared with WLC; and (5) participants will be satisfied with the 2 therapeutic programs.

Choice of Comparators

The comparison with the program implemented face-to-face is intended to highlight the value of eLearning, and the comparison with the control group, whose members receive general medical care, is intended for comparison with the current recommendations for therapeutic studies.

Prospect of the Project

The future goal of this project is to enrich the program with new information and communication technologies, such as the Internet (eCBT) [39-41] and mobile (mCBT) options [42-45], and propose the program to a large population for prevention of stress-related disorders.

Methods

Setting and Procedure

Type of Study

It is a multicenter, comparative, prospective, unblinded, randomized, controlled study in 3 parallel groups. As it is not possible to mask the different treatment groups, patients were not blinded from their intervention group.

Ethics

The project was approved by the local ethics committee, *Comité de Protection des Personnes Nord Ouest IV* (approval number CPP 15/12), as is required for medical intervention research in France. Data processing will be carried out in accordance with the requirements of the *Commission Nationale de l'Informatique et des Libertés* reference methodology, MR 06001 (Multimedia Appendix 1).

Recruitment

The study is being conducted at 3 university hospitals (Lille, Amiens, Caen) in the northwest area of France as part of the university communities (*InterRégional*). Patients are referred by their general practitioner to a psychiatric consultation service for psychological treatment of anxiety symptoms in a context of recent stress. To improve recruitment, general practitioners in the 3 areas were informed of the study by a local investigator during continuing medical education, during scientific meetings, and through all types of collaborative contacts between primary care and psychiatry services. We also directly informed the general practitioners who were involved in previous research on ADA and CBT and invited them to refer patients.

Agreement of the Subjects

During a medical interview, participants will receive oral and written information detailing the progress of the trial and be allowed a period of reflection. Informed consent will be collected from each subject before they enter the study (Multimedia Appendix 2).

Criteria for Discontinuing Participation in the Study

Participants are told they are free to leave the study at any time. Participants will be released from the study by the investigator in cases of adverse events such as diagnosis of an illness requiring hospitalization or surgery, beginning a new medication, or changing medication doses. The current research does not involve any risk, with the exception of the possible negative psychological impact of completing the psychological questionnaires.

Eligibility

Each newly referred patient is asked to answer the optional adjustment disorder section of the Mini International Neuropsychiatric Interview (MINI) [46], French version [47], to confirm he or she meets to the ADA criteria according the DSM-5. The MINI is administered during a face-to-face interview by clinical investigators who are trained in psychiatry. See Textbox 1 for selection criteria for study subjects.

Randomization

Immediately after inclusion and assessment, patients are randomly allocated in a 1:1:1 ratio into 3 groups using a Web-based central randomization: patients using a digital stress management module (group 1), patients following the stress management module guided by a therapist in attendance (group 2), and patients on a waiting list and benefiting from usual care through their attending physician (group 3).

The randomization sequence is provided by an independent statistician (who does not take part in assessing the patients at any point in the study) using computer-generated random numbers with block sizes of 6 and center stratification consistent with the Consolidated Standards of Reporting Trials (CONSORT) [48]. The randomization sequence is implemented in the electronic case report form (eCRF) system to ensure a centralized, real-time randomization procedure.

A document describing the randomization procedure is kept confidential in the Clinical Investigation Centre of Lille University Hospital.

Assessments

Assessments are conducted for the 3 groups at baseline, 2 months, and 6 months. At baseline, participants complete the self-administered questionnaires for anxiety and depressive symptoms, and care contacts and medications are recorded. At 2 and 6 months, an evaluation of overall satisfaction as well as adverse events is additionally carried out. Self-assessments are collected in the face-to-face sessions with the investigator.

It is the same psychiatrist investigator for each site who generated the random allocation sequence, enrolled the participants, assigned the participants to the interventions, and assessed the participants, so he is not blinded to the intervention group.

The flowchart in Figure 1 summarizes the experimental design.

Interventions

The content of the 2 programs is identical; one is delivered by computer and the other face-to-face. The details of the programs are presented in Table 1.

Computer-Based Stress Management Program

The program includes 5 weekly sessions lasting 1 hour that patients follow from a program accessible on a computer in our unit.

Participants have minimal contact with a clinician to encourage adherence and engagement with the program. This minimal contact of 5 minutes is performed before and after every session by a trained nurse, who investigates the adverse events and drug dose changes since the last session, answers any questions, discusses the progress of the session, and possibly guides participants in the navigation of the computer program.

To avoid connection problems, a flash memory drive is supplied to the participant at the first session that contains videos, audio files, self-help books, a portfolio in the form of an eGuide, and a log book with the program of exercises to be completed between 2 successive sessions of the program. The patient is encouraged to practice 1 or several daily exercises for 20 minutes each, 5 or 6 days per week (Multimedia Appendix 3).

Textbox 1. Selection criteria.

Inclusion criteria:

- Ambulatory patient (as inpatients are frequently a mixed anxiety depressive type of adjustment disorder)
- Male or female aged 18 to 60 years (we use a cutoff age of 60 years for inclusion to limit chronic somatic comorbidities)
- Diagnosis of adjustment disorder with anxiety (ADA) according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria
- Currently not supported by structured psychotherapeutic treatment for ADA or any other problem
- Taking no new psychotropic drug therapy or stabilized for at least 3 months (in the latter case, the patient will be informed of the need to keep the same dosages for the duration of the study)
- Minimum score on the Hospital Anxiety and Depression scale (HADS) anxiety subscale greater than or equal to 10 and a maximum score on the HADS depression subscale of less than 10
- Access to a computer

Exclusion criteria:

- Inability to read or use a computer with support (the platform is easy-to-use and a nurse is available to guide the patient in the navigation of the computer program)
- Pregnancy (as recommended by the French ethics committee; urine pregnancy test performed on female patients)
- Not capable of consenting, not having legal protection, or being deprived of liberty
- Diagnosis of another psychiatric disorder (according to the Mini International Neuropsychiatric Interview)

Figure 1. Flowchart of the study.

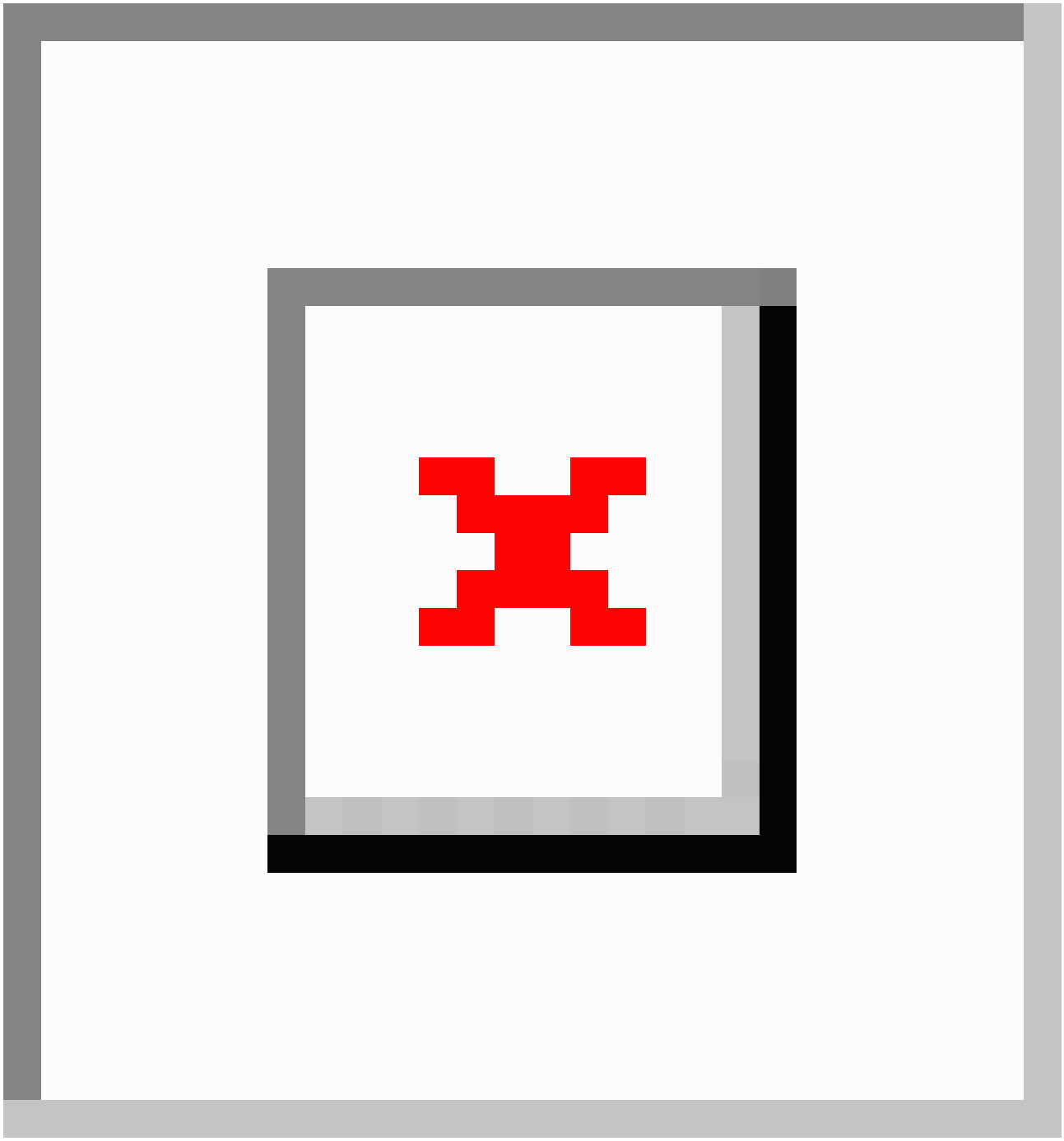

Table 1. Seren@ctif content.

Module theme	Aims of the module	Content of the module
Introduction and education regarding stress and anxiety	Provide psychoeducation about stress and anxiety and their treatment; identify anxiety symptoms and discuss treatment goals and expectations.	Psychoeducation about stress and anxiety (the model of the cognitive emotional stress spiral from a concrete example of stressful situations in everyday life); query about anxiety symptoms, treatment goal and expectations. Daily exercise: anxiety monitoring.
Body relaxation	Introduce different relaxation techniques and their respective targets and learn to practice them.	Different relaxation techniques: deep breathing, progressive muscle relaxation, and imagery and their relevance to stressful situations. Daily exercise: podcasts.
Cognitive therapy	Introduce the concept of changing thoughts; explain common thinking errors, alternative thoughts, and coping statements; practice.	Cognitive work on automatic thoughts based on concrete situations in everyday life; rationalization of the content of thoughts through cognitive restructuring and identification of repetitive negative ruminations. Daily exercise: identify dysfunctional automatic thoughts and search for other less stressful thoughts.
Mindfulness	Understand the interest in accepting rather than repressing emotions to focus attention on the present moment; focus on sensations to relieve negative thoughts and sensations.	Direct attention to breathing and bodily sensations to overcome stressful thoughts and accept the world and its surrounding thoughts. Daily exercise: podcasts.
Exposure and developing positive attitudes	Introduce the concept of changing behavior and practice it.	Principles of problem-solving, exposition, time management, planning pleasant activities, developing empathy, better assertiveness, exercise of full consciousness by concentration on the present moment.

Stress Management by Face-to-Face Interviews

The program includes 5 weekly sessions lasting 45 minutes or 1 hour with trained clinical psychologists (graduate of a master's program in cognitive and emotional therapy with a minimum of 1 year of practice in CBT and cognitive behavioral stress management). Information, exercises, and homework assignments are delivered by the therapist without self-help support. At the beginning of each session, the therapist asks the participant about adverse events and changes in drug doses since the last session.

Wait List Control

Control group patients received usual care consisting of contact with their general practitioner and nonspecific psychoeducation about stress and anxiety. Medication is prescribed as a stable dose during the period prior to assessment at 2 months.

Outcome Measures

We used the French version of self–report measures for which reliability and validity have been demonstrated.

Anxiety

- Spielberger State Trait Anxiety Inventory (STAI)–Form Y Trait version [49]. The French adaptation by Bruchon-Schweitzer and Paulhan [50] is a 20-item questionnaire with 4 levels of ratings from 1=not at all to 4=much (total score of 20 to 80) that captures how the subjects feel generally (9 reversed items).
- Hospital Anxiety and Depression Scale (HADS). This questionnaire queries anxiety and depressive disorders using 14 items rated on a 0 to 3 scale with 7 questions relate to anxiety (total A). A score between 8 and 10 on each of the subscales is considered a risk (possible or probable) of anxiety or depressive disorders [51]. The French version is used [52].
- Penn State Worry Questionnaire (PSWQ). This is a self-assessment questionnaire consisting of 16 items measuring the general tendency to worry with answers based on a 5-point Likert scale ranging from 1=not at all characteristic to 5=extremely characteristic (scores range from 16 to 80) [53]. A French version of the PSWQ is used [54].

Stress

- Perceived Stress Scale (PSS) comes from the stress transactional model and contains 14 items. The total score ranges from 0 to 56, and higher scores represent higher stress levels. Two dimensions emerge from this scale: perceived threat and perceived personal effectiveness [55]. The French version is used [56].
- Visual analog scale of stress (VAS-stress) is often used to measure the intensity of various symptoms, especially pain. It was used for the first time in 1996 for a subjective assessment of stress. The simplest VAS scale is a horizontal segment whose ends are defined as the limits of the parameter to be measured, oriented from the best to the worst. A study found external validity for the French version of VAS-stress by comparing its scores with the PSS, and it has a good sensitivity/specificity ratio [57].

Depression

- Abbreviated Beck Depression Inventory (BDI) is a self-assessment questionnaire measuring the severity of depression with 13 items rated from 0 to 3 [58,59].
- Hospital Anxiety and Depression Scale (HADS) assesses anxiety and depressive disorders using 14 items rated 0 to 3 with 7 questions relative to depressive symptoms (total

D). A score between 8 and 10 on each of the subscales is considered a risk (possible or probable) of anxiety or depressive disorders [52].

Interview for Diagnosis of Psychiatric Disorders

The Mini International Neuropsychiatric Interview Version 5.0.0 (MINI) is a fully structured diagnostic interview that assesses a major axis for the diagnosis of disorders [46]. Each newly referred patient was asked to answer the optional adjustment disorder section of the MINI from the French version [47]. The MINI was administered by research assistants who were trained to established reliability criteria. Any participant who met diagnostic criteria for a DSM-5 Axis I diagnosis was excluded from the study. There was no major change between DSM-IV and DSM-5 for anxiety and depressive disorders.

Satisfaction

The visual analog scale of satisfaction (VAS-satisfaction) measures the overall satisfaction with the program.

Main Criterion

The change in the STAI scale between baseline and the 2-month visit was the main criterion. We chose this criterion because it is a self-report measure, and self-report is commonly used in CBT and seems particularly indicated for Internet-based interventions [60]. In addition, the trait of anxiety is the core of a diagnosis of ADA, and the STAI-T measures the trait of anxiety, which is distinguished from a state of anxiety. The HADS scale and the Hamilton Anxiety Rating scale do not make this distinction.

Secondary Criteria

- Change in the STAI scale between baseline and the 6-month visit
- Changes in other validated self-report measures of anxiety and worry at 2 and 6 months (HADS anxiety subscale, PSWQ)
- Changes in validated self-report measures of stress at 2 and 6 months (VAS-stress, PSS)
- Changes in validated self-report measures of depression at 2 and 6 months (BDI, HADS depression subscale)
- Consumption of tobacco (number of cigarettes smoked per day), alcohol (number of drinks of alcohol per week—in France, the standard drink contains 10 grams of alcohol) and drug use (days per week for each product) at 2 and 6 months
- VAS-satisfaction at 2 and 6 months for the 2 therapeutic groups and at 6 months for the WLC group

Sample Size

In a study on the clinical and psychometric characteristics of ADA, the mean (standard deviation) of the STAI baseline score was 52.1 (SD 14.6) [4]. Two clinical studies with patients with generalized anxiety disorder, 1 comparing CBT with relaxation [61] and the other comparing CBT with brief psychodynamic psychotherapy [62], showed changes in the STAI-T scores of 7 and 16, respectively. In view of these results, we hypothesize that an average difference between each experimental arm and the control arm of 11.5 (the mean of 7 and 16). To demonstrate this difference in variation with a standard deviation of the STAI score change of 14.6 (assuming a conservative correlation coefficient of 0.5 between the baseline and 2-month STAI measures), a 2.5% type I error (using a Bonferroni correction for the 2 prespecified comparisons), and a power of 80%, it is necessary to include 32 patients per group. Although analysis of the primary outcome will be adjusted for baseline values, the sample size calculation does not take into account this adjustment to maximize the power. Finally, considering 20% missing data, 120 patients (40 per group) are planned in this clinical trial.

Data Collection and Management

Data are recorded in an eCRF developed using Clinsight (Ennov Inc). The eCRF is used for data entry at each investigator site, and every center is responsible for patient anonymization. The eCRF was created, tested, and validated before the start of data entry. The data necessary for monitoring the primary and secondary endpoints are identified and managed at regular intervals throughout the trial. Data are monitored by the data management team of the data management department of University Hospital of Lille using predefined data management rules, and queries are automatically edited. Finally, overall automated monitoring is performed by the data manager at the end of data entry. In case of discrepancies, queries are edited to resolve the problems encountered. After validation, the database is frozen and exported for analysis.

Statistical Analysis

Overview

Statistical analysis will be conducted in a blinded fashion with a blinded code for the intervention. All statistical analyses will be carried out independently in the Department of Biostatistics of the University Hospital of Lille. SAS 9.3 (SAS Institute Inc) software or later will be used. *P* values will be reported as the actual values, unless $P<.001$. No interim analyses are planned. A detailed statistical analysis plan (SAP) will be drafted and validated before the database is frozen. Patient characteristics at baseline will be described for each of the 3 arms; the quantitative variables will be described either by the mean and standard deviation in case of a Gaussian distribution or by the median and interquartile range if not. The normality of the distributions will be verified graphically by histograms and by the Shapiro-Wilk test. The qualitative variables will be described by the numbers and percentages of each category. All analyses for the primary and secondary objectives will be performed on all randomized patients in their original group of randomization according to intention-to-treat (ITT) principles. No subgroup analysis will be performed.

Main Objective

Comparison of the primary endpoint (2-month change in STAI scale) between each experimental group and the control group will be performed separately using an analysis of covariance with an adjustment for the STAI baseline value and the center. Since 2 comparisons will be made for the primary analysis, each of them will be performed at the 2.5% significance level (Bonferroni correction). The absolute mean differences and effect sizes (standardized mean difference) will be reported with the 95% confidence interval. In case of deviation from normality

of model residuals, nonparametric analysis will be used; absolute changes between baseline and 2-month visits will be calculated and compared between the experimental arm and control arm using nonparametric analysis of covariance adjusted for baseline values [63,64]. The primary analysis will be conducted according to the ITT principle. Missing values will be handled by multiple imputation procedures. Missing data will be imputed under the missing at random assumption using a regression switching approach (chained equation with m=20 imputations) with predictive mean matching method for continuous variables and logistic regression (binary, ordinal, or polynomial) for qualitative variables [65]. The imputation procedure will be performed using the main baseline characteristics, outcome, and variable group of randomization, and multiple imputed data sets will be combined using Rubin's rules [66,67]. Sensitivity analyses will first be conducted using all available STAI measurements (complete cases analysis) and second in patients without major deviation from protocol (per protocol analysis); major deviations will be specified in the SAP.

Secondary Objectives

For the secondary endpoints of the HADS anxiety subscale, PSWQ, VAS-stress, PSS, BDI, and HADS depression subscale scores, comparisons of the changes between the baseline and the 2-month visit between each experimental group and the control group will be performed separately with the same methodology used for the primary endpoint.

Comparison of the change between the baseline and the 6-month visit for the primary endpoint and secondary endpoints between each experimental group and the control group will be performed separately using a linear mixed model. In this model, we will include the 2 measurements (at 2 and 6 months) for the time effect, the group effect (experimental/control), an adjustment for baseline values and center, and a time × group interaction. A contrast with a 2.5% type I error will be used to compare the 6-month change between the experimental and the control group.

The efficacy of the 2 therapeutic programs (face-to-face versus digital support) at 2 and 6 months will be compared using an analysis of covariance at the 5% significance level to compare the variations in the STAI score between the groups, adjusting for the baseline value.

VAS satisfaction and consumption of tobacco, alcohol, and drug use will be analyzed in each group using descriptive statistics.

The full version of the protocol can be viewed in Multimedia Appendix 4.

Results

Recruitment started in January 2016. The duration of the inclusion period is 24 months, and the duration of research is 3 years (including 6 months for conducting the study with the last patients included and 6 months for data analysis). The final report will be written based on the CONSORT statement [48] and its adaptation for an eHealth trial [68] (Multimedia Appendix 5).

As of this writing, there have been no major changes during the study (eg, staff turnover, equipment breakdowns). We have lost a subject during the protocol. We are currently making an attrition or engagement diagram of the subjects over time that we will include in the final article once we have the results of the study.

To our knowledge, this is the first French study to examine the effectiveness of a computer-based stress management program (CBT) for patients with ADA.

Discussion

The aim of this study is to demonstrate the efficacy of 2 therapeutic programs with 120 patients suffering from ADA and to compare these programs. To date, we have 50 of the required 120 participants (42%).

We can already cite as a limitation that because this is an eHealth study, the participants are not blinded to the treatment group.

Some elements of this randomized controlled trial would be different if it were conducted in routine clinical practice. Indeed, currently, patients come to do their eLearning sessions in consultation, so one can easily control adherence, which we would not be able to do if it were in clinical practice. This adherence is reinforced by minimal contact time with a nurse before each session (which is very short).

In clinical practice, a way to assess and reinforce adherence should be found. This issue is why we plan to improve this program by integrating tools from new information and communication technologies (eCBT, mCBT, eCoaching, telemedicine) and rely on a recent literature review concerning adherence to self-help treatment with digital media [37].

We would propose that the program is not just for the psychiatric population (tertiary prevention) but for a wider population exposed to stress who may suffer from stress-related disorders (primary and secondary prevention).

This program would make it easier to access treatment with the aim of preventing stress, which is not available in France at the present time.

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Authors' Contributions

DS conceived of the study. OB, LR, and GV initiated the study design. AD conducted the statistical analysis. ACL participated in the initial protocol development. ACL, AD, and DS participated in writing the manuscript. All authors read and approved the final manuscript. All authors will be involved in data analysis, interpretation, and future manuscript preparation.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Declaration to Commission Nationale de l'Informatique et des Libertés.

[PDF File (Adobe PDF File), 154KB - resprot_v6i10e190_app1.pdf]

Multimedia Appendix 2

Patient information and informed consent.

[PDF File (Adobe PDF File), 139KB - resprot_v6i10e190_app2.pdf]

Multimedia Appendix 3

Screenshots of the Seren@ctif program.

[PDF File (Adobe PDF File), 3MB - resprot_v6i10e190_app3.pdf]

Multimedia Appendix 4

Full version of the protocol.

[PDF File (Adobe PDF File), 1MB - resprot_v6i10e190_app4.pdf]

Multimedia Appendix 5

CONSORT-HEALTH check list.

[PDF File (Adobe PDF File), 733KB - resprot_v6i10e190_app5.pdf]

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Abbreviations

ADA: adjustment disorder with anxiety
BDI: Beck Depression Inventory
CBT: cognitive behavioral therapy
eCRF: electronic case report form
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
HADS: Hospital Anxiety and Depression Scale
iCBT: CBT program using digital support
ITT: intention-to-treat
MINI: Mini International Neuropsychiatric Interview
PSS: Perceived Stress Scale
PSWQ: Penn State Worry Questionnaire
SAP: statistical analysis plan
STAI-T: State-Trait Anxiety Inventory scale, trait subscale
VAS-stress: visual analog scale–stress
WLC: wait list control

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Protocol

A Telerehabilitation Approach to Enhance Quality of Life Through Exercise Among Adults With Paraplegia: Study Protocol

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Abstract

Background: Despite compelling evidence linking physical activity and quality of life among adults with spinal cord injury (SCI), exercise participation rates are extremely low in this population. Unfortunately, a lack of behavioral exercise interventions, in particular theory-based randomized controlled trials (RCT), exists within the SCI literature. A pilot RCT is needed to first examine the feasibility to conduct such interventions and determine the appropriate effect size to inform future full-scale interventions.

Objective: The overall goal of this pilot RCT is to test an 8-week innovative, video-based telerehabilitation intervention based on self-determination theory and aimed at enhancing the basic psychological needs, motivation, exercise participation, and quality of life related outcomes of adults with paraplegia. The objectives are to (1) determine if individuals in the intervention group have greater increases in their basic psychological needs and autonomous motivation and a decrease in controlled motivation compared to the control group, (2) determine whether the intervention group reports greater increases in exercise participation and quality of life related variables (eg, life satisfaction, participation in daily/social activities, depressive symptoms) compared to the control group, and (3) examine if adults with paraplegia who received the intervention report improved scores on psychosocial predictors of exercise (eg, action planning) and well-being (eg, positive affect) compared to the control group. We also aimed to examine the implementation characteristics of the intervention (eg, satisfaction with the technology, counselor's ability to foster the psychological needs).

Methods: Adults with paraplegia (N=24) living in the community will be recruited. All participants will be invited to complete assessments of their psychological needs, motivation, exercise, and quality of life related variables at three time points (baseline, 6, and 10 weeks). Following the baseline assessment, participants will be randomly assigned to the intervention or control group. Participants in the intervention group will participate in 8 weekly, 1-hour video-based telerehabilitation sessions with a trained physical activity counselor, while participants in the control group will be asked to continue with their regular routine.

Results: We expect higher ratings of the basic psychological needs and autonomous motivation and lower scores for controlled motivation for the intervention group compared to the control group (Objective 1). We also expect that our video-based intervention will have moderate effects on exercise participation, as well as small-to-moderate positive effects on the quality of life related

variables (Objective 2). Finally, we expect the intervention to have a small positive effect on psychosocial predictors of physical activity and well-being (Objective 3).

Conclusions: We anticipate that the results will show that the intervention is appropriate for adults with paraplegia and feasible to test in a full-scale RCT.

Trial Registration: ClinicalTrials.gov NCT02833935; https://clinicaltrials.gov/ct2/show/NCT02833935 (Archived by WebCite at http://www.webcitation.org/6u8U9x2yt)

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KEYWORDS

telehealth; spinal cord injuries; exercise; motivation; telerehabilitation

Introduction

Quality of life (QOL) and participation in daily/social activities have become important research topics in spinal cord injury (SCI) [1]. One health behavior that has shown potential to positively influence these psychosocial outcomes is exercise. Exercise consists of any physical activities that are structured and planned and have the objective of improving or maintaining physical fitness [2]. Systematic reviews have demonstrated the important relationship between exercise and QOL among adults with SCI [3]. These reviews provide empirical support for exercise as a viable intervention strategy to enhance QOL in the SCI population.

Despite the compelling evidence linking exercise and QOL among adults with SCI, participation rates are extremely low in this population. One large epidemiological study (N=695) showed that 50% (n=348) of adults with SCI participated in 0 minutes of exercise [4] and that this inactive group was mostly represented by male participants over age 33 who had 11 or more years since injury. Exercise participation among adults with SCI remains bleak when we look at the percentage of individuals who are meeting the SCI-specific physical activity (ie, exercise activity) recommendations that were published in 2011 [5]. According to these guidelines, adults with SCI should participate in at least two 20-minute bouts of aerobic activity per week and two strength training activities per week, both at a moderate-to-vigorous intensity [5]. Using this benchmark, only 12% (n=9) of a sample of 73 adults with SCI met these guidelines [6]. Given the low participation rates, a clear need exists among the SCI population to find strategies to promote physical activity.

Exercise Interventions Among Adults With Spinal Cord Injury

Unfortunately, few behavioral exercise interventions have been tested among adults with SCI [7]. The majority of the six SCI behavioral exercise intervention studies outlined by Nery et al were delivered in person [7]. Given that transportation is an important barrier among adults with SCI who may want to participate in trials [8] and that transportation-related costs are an obstacle to exercise participation as a whole [9], the reach of in-person interventions is limited to individuals who live in proximity to the research sites or who can easily pay to commute to the sites.

Recent technological advances within the rehabilitation context [10] allow for other alternative and viable options for delivering cost-effective and equitable exercise interventions to community-dwelling adults with SCI. One such example is telerehabilitation, which consists of delivering rehabilitative and health-related services from a distance with the use of telecommunications [11]. A systematic review found that telerehabilitation was as successful as traditional, in-person rehabilitation across various settings and populations [10]. Of importance to exercise promotion, telerehabilitation has the advantage of delivering the intervention in the person's natural environment and is an effective tool in the self-management of chronic conditions, which includes increasing exercise participation [12]. Thus, telerehabilitation has the potential to be a viable alternative for community dwelling adults with SCI.

Telerehabilitation has also been shown to be effective at managing mental health outcomes among adults with SCI [13-15]. For instance, Dorstyn et al [13] conducted a systematic review of telerehabilitation and found, across seven studies (N=272), that telerehabilitation was effective at improving short-term psychological (eg, depression) and functional outcomes and was time- and cost-effective. Furthermore, physicians, nurses, psychologists, and physical/occupational therapists have effectively applied telerehabilitation to consult on a wide range of outcomes such as pressure ulcers, depression, and functional motor skills [14-17].

In terms of exercise participation, a telerehabilitation phone-based intervention was conducted among adults with SCI, which consisted of a 6-month national telephone-based exercise counseling service (called Get in Motion) for Canadian adults with SCI [18]. This service was derived from two previous randomized controlled trials (RCT) [19,20]. Results from this telephone counseling service demonstrated that individuals' intentions to be active remained high throughout the 6 months. The percentage of adults with SCI who participated in regular exercise (defined as ≥30 minutes of moderate-to-vigorous intensity activity on ≥3 days/week) increased from 35% (n=16) at baseline to 52% (n=24) at 6 months. This study provided initial evidence that telephone-based telerehabilitation interventions could be an effective strategy for increasing exercise participation among community-dwelling adults with SCI. Moving to video-based telerehabilitation will allow the counselor to capture nonverbal messages, demonstrate exercises, and see the person's natural environment in order to better adapt the counseling (a need that has been previously mentioned by clients using the Get In

Motion service [21]). To our knowledge, no study has conducted a video-based telerehabilitation intervention to promote exercise participation among adults with SCI. Because no such intervention exists, we propose to develop and evaluate the effectiveness of this type of telerehabilitation intervention, which will also fill the current gap in SCI-specific exercise intervention research [7].

Self-Determination Theory

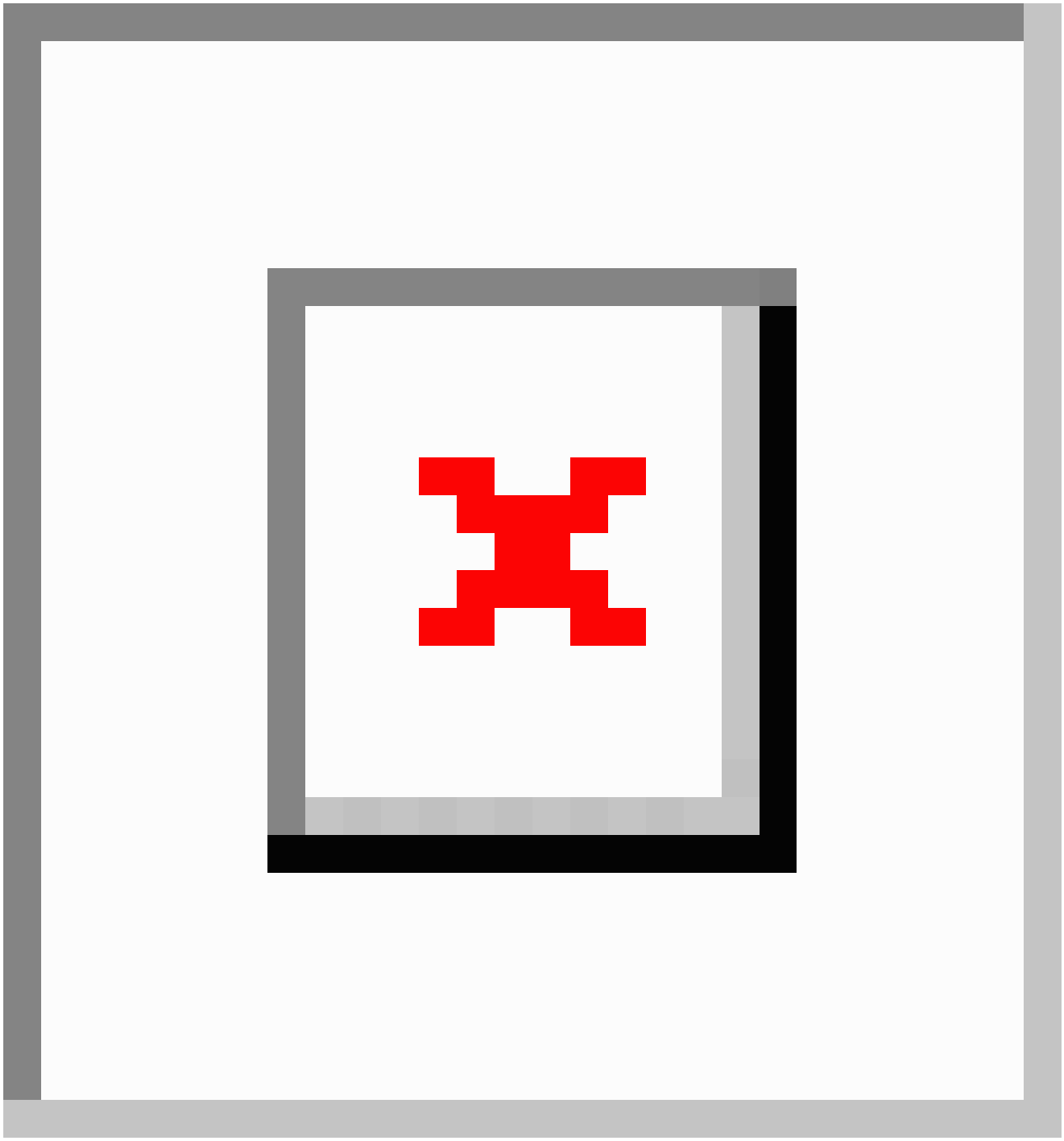
Experts have strongly recommended that exercise interventions be grounded in psychological theory to enhance their effectiveness [22,23]. Self-determination theory (SDT [24,25]; see Figure 1) is a motivational theory based on a humanistic perspective that acknowledges every human being has an innate tendency towards growth, integration, and well-being. According to SDT, satisfaction of the three psychological needs is essential for promoting motivation and well-being [26]. The three basic psychological needs of autonomy (ie, volition in one's actions), competence (ie, belief in one's actions), and relatedness (ie, sense of belongingness). In SDT, motivation is conceptualized as either autonomous, where people engage in behaviors because they want to, or controlled, where they engage in behaviors because they perceive they have to [27,28].

As elaborated in SDT, the social environment is central to facilitating the satisfaction of the three basic psychological needs. Exercise counselors who adopt an interaction style that is consistent with SDT principles (ie, a need supportive style) would create such an environment by fostering and helping satisfy the basic psychological needs of autonomy, competence, and relatedness. A key element to support the need for autonomy is to elicit and acknowledge individuals' perspectives and life aspirations. Support for competence is intended to enhance participants' perceptions that they have the ability to attain their behavior change goals. An empathic, nonjudgmental approach aimed at understanding participants' viewpoint would facilitate the need for relatedness.

Previous research supports the tenet that satisfaction of the psychological needs predicts greater autonomous motivation which, in turn, predicts greater exercise behavior [29,30]. SDT-based interventions have also shown success with positively influencing psychological needs fulfillment, autonomous motivation, exercise behavior, and QOL [31-33]. Despite the success of SDT-based physical activity interventions, no such intervention has been applied among adults with SCI.

To our knowledge, only a few published studies have examined SDT-based concepts in adults with a physical disability and they used primarily correlational designs [34,35]. A recently published study demonstrated that autonomous motivation had both direct and indirect relationships with exercise activity among adults with SCI [6]. Specifically, the results showed that autonomous motivation was positively related to the likelihood of meeting the physical activity guidelines for adults with SCI. Taken together, these results suggest that the principles of SDT are applicable to adults with a disability, including SCI.

Figure 1. Overview of self-determination theory.



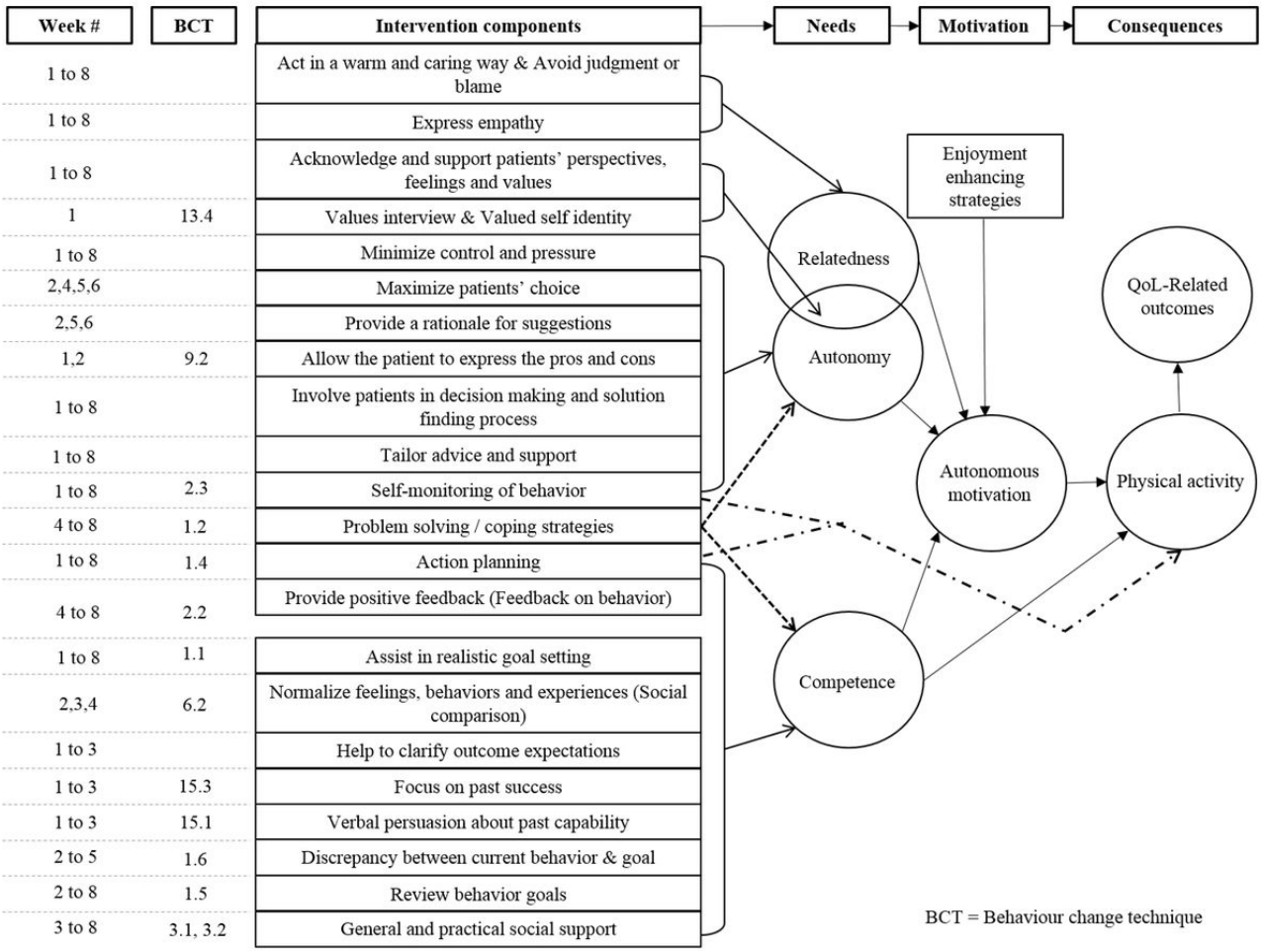
Proposed Research

Given the compelling evidence linking exercise participation and QOL, the low rates of exercise participation among adults with SCI, and a lack of exercise participation interventions, in particular SDT-based, telerehabilitation RCTs, a pilot RCT is needed. The advantage of a pilot RCT is that it allows us to determine the feasibility and acceptability of the intervention, design, and procedures prior to running a full-scale RCT. Furthermore, the effect sizes derived from this pilot RCT can help estimate an appropriate effect size for the full-scale RCT [36].

The development of effective interventions should also be grounded in sound theory given the conceptual and methodological advantages of theory-based interventions outlined earlier. Although most interventions claim to be guided by theory, the majority does not link the intervention components to the theoretical constructs being tested [37,38]. To avoid this common flaw, we have implemented the Theory Coding Scheme [38] into the design of this pilot RCT, as recommended by Gourlan et al [37]. By following this coding scheme, we are ensuring that our intervention is theory-based. The proposed intervention is also novel for the SCI field as, to date, no exercise interventions have used SDT as the guiding framework. We will therefore be the first to extend the generalizability of SDT to adults with SCI, which is an important and often disregarded step of theory testing. Figure 2 illustrates

the conceptual and process model that guides this proposed intervention [39].

Figure 2. Conceptual model with intervention components of the proposed pilot RCT (with permission from Canadian Science Publishing to use a modified version of the figure appearing in Fortier et al [39]).



Specific Aims

The overall goal of this pilot RCT is to test an 8-week innovative, SDT- and video-based telerehabilitation intervention aimed to enhance the basic psychological needs, motivation, exercise participation, and QOL-related outcomes of adults with paraplegia. The primary purpose of this pilot RCT is to determine if individuals in the intervention group have greater increases in their basic psychological needs and autonomous motivation and a decrease in controlled motivation, compared to the control group. We expect moderate effects on these SDT variables based on the results from previous SDT exercise interventions among the general population [40].

The secondary purpose of this study is to determine if the intervention group reports greater increases in exercise behavior compared to the control group. Additionally, we will examine if adults with paraplegia who received the intervention report improved scores on QOL-related variables (eg, life satisfaction, participation in daily/social activities, depressive symptoms) compared to the control group. Given that moderate effects were found for exercise behavior in the previously mentioned Get In Motion service and theory-based exercise interventions [18,37], we hypothesize, for Objective 2, that our video-based intervention will have moderate effects on exercise participation. We anticipate small-to-moderate positive effects of the intervention group compared to the control group on the QOL-related outcomes of life satisfaction, participation in daily/social activities, and depressive symptoms given the results of a leisure activity (including exercise participation) intervention [41] and cross-sectional research [3,42] in adults with SCI. We are expecting smaller effects for these variables given the relatively short duration of the proposed pilot RCT.

Our tertiary purpose is to investigate group differences in additional and common psychosocial predictors of exercise participation (eg, action planning), as well as indicators of well-being (eg, positive affect), to obtain a broader perspective of the impact of the intervention. Similarly, we expect moderate differences between the intervention and control groups on these variables.

Finally, we are conducting an implementation evaluation to determine satisfaction with the technology and extent to which the counselor delivered the intervention as intended. No hypotheses are derived for this evaluation given its description nature.

Methods

Participants

We will recruit 24 adults with paraplegia from three rehabilitation centers, one adapted fitness center, provincial SCI organizations, and through social media. We will randomize 12 participants to the intervention group and 12 to the control group. Based on previous interventions [18], we expect a 15% dropout rate resulting in 20 individuals who will complete the proposed pilot RCT.

Eligible participants will be adults with paraplegia who (1) have sustained their injury at least 1 year prior, (2) are over the age of 18 years, (3) have access to a computer, and (4) speak and understand English or French. Eligible participants will either have the intention to become physically active in the next 2 months (ie, not amotivated as per SDT) or have been minimally active (<2 times a week [5]) in the past 2 months. Participants will be excluded if they are receiving in-patient rehabilitation services, been diagnosed with memory impairments, severe communication difficulties and/or severe visual impairments, do not require a mobility device (eg, wheelchair, cane), or have answered yes to one of the questions on the Physical Activity Readiness Questionnaire (PAR-Q) and the SCI questions on the PAR-QX. Participants who have answered yes to the PAR-Q could be eligible if they provide a note from their physician stating that it is safe for them to participate in exercise activities. We have elected to focus on adults with paraplegia who use a mobility device because we want to pilot test the intervention in a more homogeneous sample than if we included both adults with tetraplegia and paraplegia.

Procedures

Registration

This trial is funded by the Craig H. Neilsen Foundation through their psychosocial research grants funding program. As a first step, this trial was officially registered at ClinicalTrials.gov (#NCT02833935). This is an online official protocol registration and results system.

Study Protocol

Interested participants will meet over the phone with a research assistant to assess their eligibility for the study, provide their informed consent, and confirm that they meet the requirements for installing the Remote Education, Augmented Communication, Training, and Supervision (REACTS) software (Innovative Imaging Technologies), which is the video-based telerehabilitation software and that they know how to use the software. REACTS is an interactive audio-video software that enables secure live communication and interaction between two or more individuals over an encrypted network. REACTS also allows for multifeed streaming where multiple webcams can be connected and for multimedia sharing. All sessions can also be videorecorded if the participant accepts the recording. In addition to using the video-audio and secure features, the exercise counselor also enables the multimedia sharing platform where both she and the participants can edit a shared document (eg, action plans). Both the participant and the exercise counselor use a Windows-based computer meeting the software requirements.

Next, participants will be invited to complete the baseline questionnaire either verbally over the phone (with an emailed or mailed copy of the questionnaire to follow along with) or electronically using an online survey platform (SurveyGizmo). If the questionnaire package is mailed, a 1-day courier service will be used to minimize the delay. Once the baseline questionnaire is completed, the research assistant will randomly assign participants to the intervention or control group by opening a blinded, prelabeled (1-24), randomly ordered envelope to assign participants to one of two groups. The randomization is also stratified by gender (16 men, 8 women) in attempt to have a representative sample by gender [43]. The envelopes will be prepared by another member of the research team not directly involved in the data collection. The random allocation will be determined by a randomization tool (randomizer.org). Participants will be informed of their group assignment and told that another research assistant, blinded to their group allocation, will contact them to complete the same questionnaire at two other time points (6 weeks and 10 weeks from baseline). These follow-up data collection time points (6 weeks and 10 weeks) are set to represent the mid and end of the 8-week intervention, which will start 2 weeks after baseline. Participants will receive up to Can $100 for completing the study. Specifically, they will receive $30, $35, and $35 if they complete the baseline, 6-week, and 10-week questionnaires, respectively.

Intervention Group

For participants assigned to the intervention group, the research assistant will schedule the participants' first intervention session with the exercise counselor 2 weeks after their baseline assessment. The 2-week delay will allow us to send intervention-related materials (eg, webcams) and train participants on the REACTS software.

Intervention Format

The exercise intervention will be delivered by a kinesiologist trained in behavioral counseling and the adapted exercise in a Web-based face-to-face format through the REACTS interactive audio-video software. Intervention participants will receive 1 weekly exercise session for 8 weeks. An 8-week intervention was chosen (1) because the 8-week mark was associated with the greatest increases in Get in Motion clients' exercise participation behavior [18] and represented the time point with the highest number of dropouts [21], and (2) to ensure feasibility for completion of the pilot RCT. The exercise counselor will receive behavior change skills training to ensure she is capable of fostering the psychological needs within SDT and apply behavior change techniques. The counselor will also participate in a motivational interviewing workshop to fine-tune her counseling skills. The use of motivational counseling intervention methods do not have any detrimental effects on exercise participation levels as motivationally focused interventions have been shown to be as effective as structured exercise interventions [44]. Across all of the eight intervention sessions, the counselor will create a social environment that is congruent with SDT.

Intervention Components

The exercise counselor will individually tailor her approach to each participant by understanding and taking into consideration the participant's past and current exercise experiences (including a discussion of any prescribed exercise programs after completing an outpatient rehabilitation program), motives to be physically active (eg, improve functional ability, enhance participation in daily/social activities), salient concerns and barriers regarding exercise participation, and their physical home environment. Throughout the intervention, the exercise counselor and participants will co-construct and collaboratively adapt the participants' exercise goals. SDT is at the core of this proposed intervention and a Theory Coding Scheme [38] will be used to evaluate the extent to which the theory is used, applied, and tested within the intervention. In line with the Theory Coding Scheme, we have linked each of our intervention components to either the three basic psychological needs, autonomous motivation, and/or exercise participation as illustrated in Figure 2. The specific weeks that each intervention component is planned to be implemented is shown in the first column of Figure 2 (Week #). Although the intervention components have been attributed to specific counseling sessions/weeks, the timing of the intervention components may differ between participants. The intervention is not standardized because, to be in line with SDT, the intervention will be tailored to the participants. As such, the participants' interests and goals will be at the forefront of each session, and some components may be used earlier or later than outlined in Figure 2. Thus, the exercise counselor will be trained to use the model as a guide rather than a set protocol.

Control Group

Participants assigned to the control group will be asked to continue with their regular routine for the next 2 months. We recognize that a compensatory rivalry bias [45] may occur as participants in the control group may seek out their own exercise program, which may then reduce the intervention's effect. To help minimize this bias, the research assistant will remind control participants, after they complete the baseline questionnaire, of the importance of keeping their regular routine for the following 10 weeks. The control group will also be offered an exercise counseling session following the completion of the 10-week data collection time point.

Measures

Participants will be invited to complete each of the primary, secondary, and tertiary outcome measures at all three time points (baseline, 6, and 10 weeks). Participants in the intervention group will also complete the relevant measures under implementation outcomes.

Primary Outcomes

Basic Psychological Needs

The Psychological Need Satisfaction in Exercise Scale will be used to assess the satisfaction of the psychological needs for exercise [46]. On a 6-point Likert scale ranging from 1 (false) to 6 (true), participants will respond to 18 items reflecting how they might feel when physically active. A mean will be calculated for autonomy (6 items; "I feel free to exercise in my own way"), competence (6 items; "I feel that I am able to complete exercises that are personally challenging"), and relatedness (6 items; "I feel close to my exercise companions who appreciate how difficult exercise can be"). A higher value on each need will indicate greater satisfaction for that need [46].

Autonomous and Controlled Motivation

Two scales will be used to assess participants' motivation. The Behavioral Regulation Exercise Questionnaire-3 will be used to assess participants' motivation for why they usually engage in exercise activities [47,48]. Participants will respond to 23 items, on a 5-point Likert scale ranging from 0 (not true for me) to 4 (very true for me), covering the types of motivational regulations on the self-determination continuum. The mean score of participants' autonomous and controlled motivation will be calculated. This questionnaire has been shown to be reliable and valid [47,48]. Additionally, the Treatment Self-Regulation for Exercise Scale [49] will be used to assess changes in autonomous and controlled motivation for reasons why one would engage in exercise activities. Participants will respond to 15 items, using a 7-point Likert scale ranging from 1 (not at all true) to 7 (very true). Again, a mean score of participants' autonomous and controlled motivation will be calculated.

Secondary Outcomes

Moderate-to-Vigorous Exercise

This will be assessed using the self-report 7-day Leisure-Time Physical Activity Questionnaire for Adults with SCI [50]. This scale was validated among adults with SCI. Participants will be asked to indicate the frequency (days) and duration (in minutes) they engage in mild (ie, activities that require little effort), moderate (ie, activities that require some physical effort that make you feel like you are working somewhat hard, but you feel like you can keep going for a long time), and vigorous intensity (ie, activities that require a lot of physical effort that make you feel like you are working really hard, almost at your maximum, and you can do the activity only for a short period of time before getting tired) activities over the last 7 days. Weekly minutes of total activity (mild, moderate, and vigorous) and of moderate and vigorous activity will be summed.

Life Satisfaction

The Life Satisfaction Questionnaire-11 [51] is a standardized and validated QOL measure that asks 11 questions about satisfaction in various areas of life, including life in general, vocation, financial situation, leisure, social/friends/family, sexual life, family life, and physical and mental health (1=very dissatisfying to 6=very satisfying). The mean score of the 11 items will be calculated for this measure. We have previously used this scale among adults with SCI [52].

Participation in Daily/Social Activities

The Patient-Perceived Participation in Daily Activities Questionnaire will be used to assess participation as it was developed for the SCI population [53]. Participants will be presented with a list of 26 activities. For each activity, they are asked, "Do you participate in this activity?" Response options are "Yes, as much as I want" (4); "Yes, but less than I want"

(3); "No, but I would like to" (2); and "No, but I don't want to" (1). An overall participation in daily/social activities score will be calculated as well as six subscale scores reflecting broad categories of participation (the reliability indices from a previous study are also noted for each subscales [54]):

- autonomous participation – indoors (7 items, eg, performing bladder care; Cronbach alpha=.88)
- autonomous participation – outdoors (6 items, eg, carrying out productive activities that are unpaid, like volunteering; alpha=.74)
- family roles (4 items, eg, carrying out family responsibilities; alpha=.66)
- health (2 items, eg, maintaining your physical health; r=.25)
- social relationships (4 items, eg, maintaining relationships with others; alpha=.62)
- work-education (3 items, eg, participating in activities that prepare you to start working in a paid job; alpha=.71)

Depressive Symptoms

The 9-item Patient Health Questionnaire (PHQ-9) [55] will be used to assess self-reported depressive symptoms. Participants will be asked, "Over the past 4 weeks, how often have you been bothered by any of the following problems?" and rate each symptom (eg, little interest or pleasure in doing things, poor appetite or overeating) on a 4-point scale (0=not at all; 3=nearly every day). The PHQ-9 has been suggested as a valid and reliable tool for the SCI population [56] and demonstrated to have strong psychometric properties in people with SCI [42,57]. A mean score of the items will be computed.

Tertiary Outcomes

Psychosocial Predictors of Exercise

Participants will complete the Social Cognitive Predictors of Leisure Time Physical Activity among adults with SCI [58]. This measure consists of a battery of short questionnaires assessing additional psychosocial predictors of leisure time exercise activity such as self-efficacy, intentions, and action planning among adults with SCI.

Well-Being

Participants will also complete the Positive and Negative Affect Schedule Questionnaire [59], a 10-item mood scale. This is a measure of affective experience capturing broader aspects of well-being/QOL. Finally, participants will complete the Meaning Questionnaire [60], which is a questionnaire designed to measure meaningful life experiences. This 5-item scale asks participants to rate their responses from 1 (absolutely untrue) to 7 (absolutely true) and demonstrates strong reliability (Cronbach alpha=.88).

Implementation Outcomes

Participants' perceptions of the exercise counselor will be assessed with a modified Health Care Climate Questionnaire [61]. This questionnaire assesses participants' perceived need support from their exercise counselor. Participants will respond to six items (eg, "My exercise counselor listened to how I would like to do things regarding my exercise") on a 7-point Likert scale ranging from strongly disagree (1) to strongly agree (7). High alpha levels (.88-.95) have been demonstrated in previous studies [62,63]. They will also respond to an adapted Short Feedback Questionnaire to obtain information about the participants' experience in using technology, in this case the REACTS telerehabilitation system. Participants will rate eight questions addressing the sense of presence, enjoyment, control, ease of use and discomfort using a 5-point Likert scale ranging from not at all (1) to a lot (5). This measure has been shown to have good internal consistency and moderate concurrent validity [64].

To ensure that our intervention was delivered as intended, we have included implementation and feasibility evaluation procedures. First, we will ask the exercise counselor to fill out a checklist for each session with each participant. The checklist will include questions regarding the logistics of the session (eg, time, components of the REACTS software used), and a list of the intervention components. We will also assess the exercise counselors' satisfaction with the REACTS technology with the validated Technical Quality Subjective Appreciation questionnaire. The questionnaire is divided in two sections: 1) five items relate to the technical quality of the sessions (audio, video); and (2) three questions relate to the counseling objectives, relationship with the patient, and overall satisfaction. The exercise counselor will rate each item on a score from 0 ("Bad") to 3 ("Good"). The mean score of each section will be calculated. Second, we will videorecord all eight counseling sessions of consenting participants. These sessions will be evaluated by the research assistant and principal investigator by using the aforementioned checklist to determine the consistency of the reporting by the exercise counsellor. In addition, we will evaluate the extent to which the counselor was able to provide a social environment that supported the psychological needs within SDT. By conducting this implementation and feasibility evaluation, we will gain valuable information as to the implementation of the intervention, which will help inform the intervention for the subsequent larger trial.

Results

Anticipated Timelines

Prior to starting the RCT, the exercise counselor will be trained in SDT-based counseling, motivational interviewing, and adapted exercise activity. The exercise counselor will also pilot the intervention with an experienced counselor and 2 inactive participants in order to troubleshoot any potential issues. The exercise counselor and research assistants will be also trained on the REACTS software system.

At the time of submission of this protocol, data collection was ongoing with 10 participants who had completed the study (5 intervention, 5 control) and 6 who were enrolled in the study (3 intervention, 3 control). At the time of publication, all 24 participants have been randomized.

Planned Data Analyses

Data will be screened for statistical outliers and assumptions for each statistical test will be examined [65]. Participant attrition is a common problem in trial studies and case-wise deletion can bias results [66]. As such, missing data will be examined to determine the pattern of missing data and imputed with multiple imputations methods that are appropriate for small

samples [67]. Further, we will collect reasons for missing data/attrition. These approaches will help inform the expected attrition rate, reasons why people did not continue with the trial, and required sample size to conduct a subsequent larger RCT. Once data are cleaned and imputed, demographic and injury-related covariates will be examined for each outcome through a correlation matrix. Any identified covariates will be controlled for in the subsequent analyses. The same analysis will be used to determine if the intervention group improved on the variables assessed for hypothesis 1 (basic psychological needs and autonomous motivation), 2 (exercise, life satisfaction, participation in daily/social activities, depressive symptoms), and 3 (well-being, and psychosocial predictors of exercise). A regression analysis approach is recommended for analyzing RCT data as this approach can address specific questions arising from the study design, above what could be expected from analysis of variance or other similar types of analyses [68]. As such, two hierarchical multiple regressions will be used to predict changes in participants' scores between baseline, 6 weeks, and 10 weeks. Specifically, participants' demographic and injury-related covariates will be entered in the first block, followed by their baseline scores on all study variables in the second block, and finally their group (ie, intervention or control) in the third block. This analysis will be conducted twice: once predicting participants' scores at 6 weeks, and again predicting their scores at 10 weeks. The differences in variance explained by the model (r^2) and the weight of the regressions (standardized betas) will be used to evaluate whether the model fit improves between Blocks 2 and 3, as well as to evaluate the success of the pilot RCT. In line with the Theoretical Coding Scheme, exploratory analyses will also be conducted to investigate the strength and direction of the relationships between the SDT variables and exercise participation, looking for moderate-to-strong relationships. Correlations of .1, .3, and .5 represent small, moderate, and strong relationships between the variables [69]. If the intervention has a moderate effect on the SDT variables and if the SDT variables have moderate-to-strong relationships with exercise participation, we can then hint at a potential mediation (ie, intervention is having an effect on exercise participation through the SDT variables). Because of the sample size, we do not have sufficient power to run full mediation analyses and it is for this reason it remains exploratory in nature. Descriptive statistics will be conducted for the implementation and feasibility evaluation.

Discussion

Principal Considerations

Our results will have higher credibility due to our design. By using an experimental design, specifically an RCT, cause and effect conclusions are more plausible, which are superior to cross-sectional or longitudinal designs. In addition, all our measures have been validated and found to be reliable in past research, increasing the credibility of our findings. We have also clearly outlined our primary, secondary, and tertiary purposes and associated hypotheses, giving transparency to our proposed project. Our specific outcome-based hypotheses are based on theory or past research, which allows for ease of duplicability of the results. The pilot RCT will also aid in identifying any changes that are required to our design, measures, or procedures before running a full-scale RCT. The implementation and feasibility purpose will enable us to determine if any changes to the intervention protocol should be implemented when designing the subsequent full-scale RCT.

Because we are testing a pilot RCT and focusing on the effect size rather than *P* values, we believe that our results will be able to be transferred to a future, larger, interprovincial exercise telerehabilitation intervention. It is only with this pilot RCT that we can reliably estimate the sample size needed for this larger trial. Our intervention components are predetermined as they are based on sound theory (ie, SDT) and from a taxonomy of behavior change and relational techniques [70,71]. We have also used the Theory Coding Scheme to develop our intervention to ensure that it is truly a theory-based intervention.

We have set procedures to control for some biases. For one, the randomization procedure will help to reduce some biases as the control and intervention group should be equivalent. The research assistant will randomize the participants by opening a blinded, prelabeled envelope. Therefore, the research assistant cannot bias group allocation. The second research assistant will also be blinded to the participants' group allocation when collecting the follow-up data, which should further reduce biases. We are also recruiting from multiple sources, which would allow us to reduce bias that might stem if participants were recruited from only one source and subsequently enhance the generalizability of our results. With the control group having access to the exercise counselor after the study, we hope to reduce the compensatory rivalry bias. We are also avoiding focus on *P* values due to their reliance on sample size [72]. Because of our sample size, if we solely focus on the *P* value we might be making a type II error.

In line with the general limitation of telerehabilitation, our intervention is limited to individuals who are comfortable using a computer and capable of running the Web-based audio-video REACTS software. Given the small sample of this pilot RCT, we will be unable to conduct subsample analyses to investigate whether the intervention had effects for individuals with specific demographic (eg, age, education level) and SCI-related factors (eg, years since injury, adapted home). However, we do plan to control for these variables in our regression models through a correlation matrix. These correlations will enable us to be mindful of these factors when designing the full-scale RCT.

Knowledge Translation

Results of this study will be translated through three main avenues. First, we plan to share our results with the academic community by presenting the results at SCI, disability, and/or exercise-related scientific meetings, and publishing our results in scientific peer-reviewed journals. Second, we will translate our findings to local adapted exercise centers to inform programs and kinesiologists of our study's results and approach. Finally, we will share our results with various community organizations who may want to distribute to their larger membership to reach adults with SCI. Our results will therefore be disseminated to academics, the broader SCI community, and relevant professionals.

Conclusions

This study will be the first to test SDT in an exercise intervention among adults with paraplegia. It is also the first to examine the use of an online video-based telerehabilitation approach in this context. We anticipate that the results of this pilot RCT will support that the intervention is appropriate for adults with SCI and feasible to test in a full-scale RCT.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Comments by the grant reviewers from the Craig H. Neilsen Foundation.

[PDF File (Adobe PDF File), 133KB - resprot_v6i10e202_app1.pdf]

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Abbreviations

QOL: quality of life
RCT: randomized controlled trial
REACTS: Remote Education, Augmented Communication, Training, and Supervision
SCI: spinal cord injury
SDT: Self-Determination Theory

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Protocol

Internet-Delivered Dialectical Behavioral Therapy Skills Training for Suicidal and Heavy Episodic Drinkers: Protocol and Preliminary Results of a Randomized Controlled Trial

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Abstract

Background: The need to develop effective and accessible interventions for suicidal individuals engaging in heavy episodic drinking (HED) cannot be understated. While the link between alcohol use and suicidality is a complex one that remains to be elucidated, emotion dysregulation may play a key role in alcohol-related suicide risk in these individuals.

Objective: In the current study, an 8-week Internet-delivered dialectical behavior therapy (DBT) skills training intervention was developed and preliminarily evaluated for suicidal individuals who engage in HED to regulate emotions. The aim of the study is to evaluate the feasibility and effectiveness of the therapist-assisted and Internet-delivered intervention, and to inform the design of a subsequent full-scale study.

Methods: The study was a pilot randomized controlled trial comparing participants receiving immediate-treatment (n=30) to waitlist controls (n=29) over a period of 16 weeks. Intervention effects will be assessed longitudinally using hierarchical linear modeling and generalized estimating equations, along with analyses of effect sizes and clinically significant change. The primary outcomes are suicidal ideation, alcohol problems, and emotion dysregulation. Secondary outcomes include alcohol-related consequences, reasons for living, skills use, and depression.

Results: The trial is ongoing. A total of 60 individuals returned their informed consent and were randomized, of whom 59 individuals were intended to treat. A total of 50 participants in the study were retained through the 16-week enrollment.

Conclusions: There is a dearth of evidence-based treatment for individuals presenting with high risk and complex behaviors. Furthermore, computerized interventions may provide a beneficial alternative to traditional therapies. The particular clinical features and treatment needs of suicidal individuals who also engage in HED constitute key domains for further investigation that are needed to consolidate the design of appropriate interventions for this high-risk population.

Trial Registration: Clinicaltrials.gov NCT02932241; https://clinicaltrials.gov/ct2/show/NCT02932241 (Archived by WebCite at http://www.webcitation.org/6uJHdQsC2)

(JMIR Res Protoc 2017;6(10):e207) doi:10.2196/resprot.7767

KEYWORDS

dialectical behavioral therapy; randomized controlled trial; eMental health; suicide; heavy episodic drinking; emotion dysregulation

Introduction

Suicide is the tenth leading cause of death across all age groups and is among the top four causes of death for Americans aged 10 to 54 years [1]. Furthermore, approximately 40% of suicides were found to be preceded by acute alcohol use [2]. Alcohol intoxication, both acute and chronic, has been identified as a uniquely salient risk factor for suicide among individuals with suicidal ideation [3-6]. These findings bring attention to the importance of attending to problematic alcohol use, and binge drinking in particular, in the management of suicide risk.

One possible explanation for the prevalence of suicide attempts preceded by binge drinking (ie, heavy episodic drinking; HED) is that suicidal heavy drinkers lack emotion regulation capabilities [7-10]. Emotion dysregulation is associated with risk for both suicide and problematic drinking [11-13]. Furthermore, suicide risk may be particularly elevated in individuals who engage in HED to reduce acute negative affect [9]. Given the behavioral complexity of suicidal individuals who drink alcohol to regulate emotions, an alcohol-focused treatment may not be sufficient to increase coping skills and/or distress tolerance techniques. This problem suggests the need for novel treatment approaches for HED and suicide that focus on increasing emotion regulation capabilities.

Dialectical behavior therapy (DBT) [14-16] is a behavioral intervention with strong empirical evidence in reducing suicidal behavior [17]. DBT was specifically designed for high risk, complex individuals, and consists of a combination of individual psychotherapy, group skills training, telephone coaching, and a therapist consultation team. Recent evidence has found that the DBT skill-training component alone is efficacious at reducing dysfunctional behaviors associated with emotion dysregulation [18,19], and that DBT skills usage mediates reductions in a variety of outcomes (including suicidal acts) [20]. Taken together, a DBT skills training intervention is a potent and efficient treatment package.

Unfortunately, despite the existence of evidence-based interventions such as DBT, there remains a vast discrepancy between the need and availability of treatment for suicidal individuals with cooccurring addictive disorders. For example, the majority of those who engage in suicidal behaviors never engage in treatment [1,21]. In addition, a rare study on alcohol-dependent suicide attempters who were hospitalized following a suicide attempt found that only 6% of participants had been enrolled in psychotherapy prior to hospitalization, and only 9% went on to receive psychotherapy in the month after discharge [22]. Interestingly, while severity of suicidal ideation has been associated with low endorsement of formal treatment engagement, suicidal individuals may be more apt to utilize such nontraditional modalities, including online and Web-based interventions [23]. For these individuals, technological mediation may offer a convenient and viable means to access needed treatment.

Technologically-assisted interventions for psychological disorders constitute the focus of a growing body of research [24-26]. Internet-delivered or computerized interventions are available to anyone with an Internet connection, and can be accessed at relatively low costs. Moreover, attitudinal barriers (eg, stigma associated with psychiatric diagnoses and attending face-to-face therapy) can be circumvented by treatment delivered anonymously in one's home. However, although computerized interventions have shown preliminary promise in accessing and treating suicidal ideation [27,28], as well as strong evidence in reducing problematic alcohol use [29-30], they are rarely tested on high risk individuals presenting with complex and multiple disorders [31].

To address this treatment gap, an Internet-delivered DBT skills intervention targeting the underlying mechanism of emotion dysregulation was adapted for individuals who endorse suicidal thoughts and engage in HED. The current pilot study is a proof of concept study that seeks to evaluate the feasibility, acceptability, and preliminary efficacy of a DBT skills training intervention delivered via technology (ie, Web-based portal). The following aims are: (1) to determine the feasibility of recruiting clients, administering the treatment, and retaining clients in the treatment; (2) to evaluate the safety of the treatment with respect to potential adverse events; (3) to assess the feasibility of the research methodology (eg, reliability of the measures used, feasibility of random assignment to treatment, appropriateness of the control condition); and (4) to evaluate the feasibility of using a wait-list control group in this line of research, and changes over time among individuals in such a comparison group.

Methods

This study is a pilot randomized controlled trial (RCT) comparing an Internet-delivered Dialectical Behavioral Therapy Skills Training (iDBT-ST) to a waitlist control condition. Participants were randomized to begin the 8-week intervention either immediately or after an 8-week waiting period. Assessments included monthly batteries, weekly surveys, brief daily reports, and acceptability questionnaires, all of which were all self-assessed. The project's primary aim is to determine whether further revisions of the iDBT-ST intervention are needed, and to inform the design of a subsequent full-scale RCT.

Participants

Participants were recruited from ads placed online (eg, Craigslist, Reddit) and in a local newspaper containing a brief description of the study. Interested participants were phone screened for eligibility on alcohol use severity, frequency of binge drinking episodes, suicidal ideation, emotion dysregulation, mental health treatment history, and demographic characteristics. Inclusion criteria included: (1) being 18 years or older, (2) endorsing suicidal ideation in the past month (defined as endorsing a wish to die at least once in the past 30 days), (3) engaging in at least two episodes of heavy drinking in the past month, (4) high emotion dysregulation (defined as scoring one standard deviation above the normative mean on the 16-item Difficulties in Emotion Regulation Scale [32]), and (5) residing in the United States. Exclusion criteria included: (1) currently receiving psychotherapy; (2) diagnosis of bipolar I, schizophrenia, or schizoaffective disorder; (3) non-English speaking; (4) unable to read or write; and (5) having no access to a computer connected to the Internet. Of 398 individuals who

expressed initial interest, 60 of 91 eligible individuals returned the informed consent forms and were randomized into the immediate-treatment (n=31) and waitlist (n=29) groups. One person randomized to the immediate-treatment group did not complete any of the assessments, leaving 59 people included in the analyses. The phone screening process helped us prevent participants from enrolling with multiple identities.

Ethics and Consent

The study has been approved by the Human Subjects Division of the Institutional Review Board at the University of Washington (IRB# 50295). Through the initial phone screening, all interested individuals were briefed on the aims of the study and their rights as participants. Participants were informed that their answers to the questions were voluntary, and that they could withdraw from the study at any time. Informed consent forms (see Multimedia Appendix 1) containing details about the study, procedures, and possible risks and benefits involved were provided to all eligible participants. Prior to randomization, participants were required to indicate on the consent forms their preferred mode of communication for receiving study materials, and to return their signed consent forms to the study site. Referral resources for treatment and crisis services were sent by email to interested callers who were deemed ineligible for the study. All participants consented to have their nonidentifiable data published. Access to the dataset is restricted to the principal investigator and authorized research assistants only. Complete data from this study can be obtained by contacting the first author once data analysis has been completed. iDBT-ST is not currently available online.

This study focuses on sensitive topics such as alcohol use and suicidal behavior, and the phone screen and outcome assessments contain questions that could potentially be distressing to participants. As a safety measure, participants were encouraged to consult with research staff whenever they felt distressed during screening and later participation. Suicide risk was also monitored and addressed in ways that are discussed later in this paper.

Procedure

Semistructured phone screening interviews were conducted with individuals who initiated contact via phone or email and remained interested after receiving information about the study. Phone screens were either prescheduled or conducted during the first call of contact, depending on caller preference, and were administered by trained research assistants. Eligible individuals received informed consent forms to sign and return, and were randomized once their signed forms were received at the study site.

Following randomization into the immediate-treatment and waitlist groups, participants in both conditions received a baseline assessment, followed by identical monthly assessments in the ensuing four months. Primary monthly outcomes included suicide ideation (Scale for Suicidal Ideation [33]), severity and frequency of alcohol consumption (Alcohol Use Disorders Identification Test; AUDIT [34], and Self-Administered Web-Based Timeline Followback [35,36]), and emotion dysregulation (Difficulties in Emotion Regulation Scale [37]). Secondary outcome measures included the Reasons for Living Inventory [38], Short Inventory of (Alcohol) Problems (SIP) [39], Patient Health Questionnaire [40], and Dialectical Behavior Therapy - Ways of Coping Checklist [41]. All participants also received brief online weekly assessments on suicide ideation and alcohol consumption. Suicide risk was monitored via weekly assessments.

Prior to treatment, participants also responded to their expectancy of outcome along with the credibility of the intervention (Credibility/Expectancies Questionnaire [42]). At the end of the treatment period, participants reported on their treatment satisfaction (Client Satisfaction Inventory-Short Form [43]) and therapeutic alliance (California Psychotherapeutic Alliance Scale [44]). Participants actively receiving treatment also received brief daily surveys about their urges to quit treatment, use of DBT skills, and engagement level.

All assessments were administered through an online survey platform (Qualtrics [45]) made accessible to participants via Uniform Resource Locator links in scripted emails sent at scheduled timepoints. As compensation for their participation, participants received up to US $120 in Amazon gift cards upon completing each monthly survey (baseline=$15, 4-week=$20, 8-week=$25, 12-week=$30, and 16-week=$30).

Randomization

Eligible and consenting participants were randomized into the immediate-treatment (n=31) and waitlist groups (n=29). To control for potential covariates that may spuriously affect analytic results, an open source desktop application called MinimPy [46] was used to match participants for equal distribution between conditions on three variables. The three variables were: sex assigned at birth (Demographic Data Schedule), severity of suicide ideation (Suicide Behavior Questionnaire-Revised) and degree of disordered drinking (AUDIT).

Managing Risk

Suicide risk was carefully monitored in the current study. Participants were assessed at the start and end of the recruitment phone screen, as well as throughout the course of their participation. High risk of suicide during phone-screening was indicated by endorsing 4 or more points on a 7-point Likert scale, or an increase of 3 or more points from the start of screening on urge to die by suicide. Throughout the 16-week trial period, weekly questionnaires assessing suicide risk were emailed to all participants. These emails included prompts on: (1) frequency of suicidal urges in the past week, (2) intensity of suicidal urges in the past week, (3) seriousness of acting out on suicidal urges in the past week, and (4) current suicidal urge, all using 5-point Likert scales. Participants endorsing a rating of 3 or higher on any item, or a 2-point increase from the previous week, would be called by phone and assessed for suicide risk. Additionally, the number for the National Suicide Prevention Lifeline was situated next to prompts on suicidality received by all participants.

The principal investigator was on call to intervene by phone at any time. Evidence-based procedures based on the University of Washington Risk Assessment Protocol (UWRAP) [47] were

implemented by the principal investigator whenever further assessments of risk were warranted. The UWRAP guides the assessor through a suicide risk assessment procedure that evaluates the presence of a plan, access to means, likelihood of following through with a plan, being interrupted by others, et cetera. If a participant was determined to be at high risk based on this interview and the clinical judgment of the principal investigator, a safety plan was to be developed with the cooperation of the participant and the principal investigator. If a participant was unavailable by phone, a nonjudgmental *caring email* (see Multimedia Appendix 2) was sent, which expressed concern and encouraged participants to reach out to a suicide hotline or textline provided in the email.

Intervention

One primary aim of iDBT-ST is to replace maladaptive behavioral strategies with alternative strategies for coping and emotion regulation. The current intervention comprises the skill-training component alone, which is administered in a computerized format. The intervention was modified from an online DBT skills training intervention for emotion dysregulation [48].

Participants randomized into the iDBT-ST group were immediately enrolled into the online treatment program, and received weekly sessions over a period of 8 weeks. After completing the eighth session, participants in active treatment were transitioned into a follow-up phase that entailed monthly and weekly assessments without treatment. Participants randomized into the waitlist group received repeated monthly assessments as well as weekly surveys for 8 weeks prior to receiving treatment.

The iDBT-ST intervention was administered through an online electronic learning server (Articulate Online [49]) which consists of 8 sessions (Table 1) accessible through an access portal individualized for each participant, with one new session activated each week. The sessions begin with a weekly assessment, followed by (1) a review of the last session at weeks 2-8, (2) an introduction of the current session, (3) skills teaching, and (4) summary and consolidation. The skills were taught via videos and graphics describing the skills and examples, along with interactive activities. The intervention completion rate of each participant was also monitored through the server. If consented by participants, reminders to complete sessions were sent via their preferred method before the next session became available. Individualized assignments of skill practice were provided following the completion of each session. See Figure 1, Figure 2, and Figure 3 for screenshots of the intervention.

Table 1. Description and function of session contents.

Session	DBT module	Skills	Function
1	Mindfulness	Observing, Describing, Participating	To introduce the foundational skills to develop nonjudgmental awareness of the present
2	Mindfulness	Nonjudgmentally, One-Mindfully, Effectively	To teach how to practice mindfulness with skillful effectiveness
3	Addiction	Dialectical Drinking, Clear Mind	To help learners find a middle path between oppressive sobriety and unrestrained freedom of drinking, and develop a clear mind
4	Addiction	Community Reinforcement, Burning Bridges	To teach strategies to identify relationships and activities that aim to stop or reduce problematic drinking
5	Emotions Regulation	Understanding Emotions	To teach the functions of emotions, and how to describe them
6	Emotions Regulation	Handling Unwanted Emotions	To teach skills to reduce frequency and quantity of unwanted emotions
7	Emotions Regulation	Building Mastery and Copy Ahead	To teach skills to build future resilience against intense emotion
8	Distress Tolerance	TIP (Temperature of face, intense exercise, paced breathing), Distract	To teach skills that help weather crises and intense negative emotions

Sessions 3 and 4 were designed to target problematic drinking, and included the new skill *Dialectical Drinking*. The skill of dialectical drinking describes the abstinence violation effect (see Figure 4), goal setting, pros and cons of maintaining or changing their drinking behavior, as well as an assessment of motivation and confidence to follow-through on their drinking goal. Dialectical drinking incorporates aspects of motivational interviewing [50] and harm reduction [51] as ways to nonjudgmentally reinforce a change toward goal-oriented drinking behavior. Problematic drinking is also targeted through the DBT skills of *Community Reinforcement*, whereby participants identify people, activities, and places that can reinforce their drinking goal, as well as *Burning Bridges*, whereby participants eliminate people, activities, and places that would reinforce their problematic drinking. In burning bridges, participants learned a variety of methods to manage alcohol cravings [15,16]. See Table 2 for common alcohol reduction strategies and their DBT counterparts.

Table 2. DBT skills that target problematic drinking.

Alcohol Reduction Strategy	Skill
Deciding to make a change	
Goal setting	Dialectical Drinking
Decisional balance	Dialectical Drinking
Assessment of motivation and interest	Dialectical Drinking
Abstinence violation effect	Dialectical Drinking and Clear Mind
Tracking behavior	Daily diary card
Making a change	
Contingency management	Contingency Management and Burning Bridges
Craving management	Burning Bridges
Drink refusal strategies	Dialectical Drinking

Figure 1. Screenshot of the session overview.

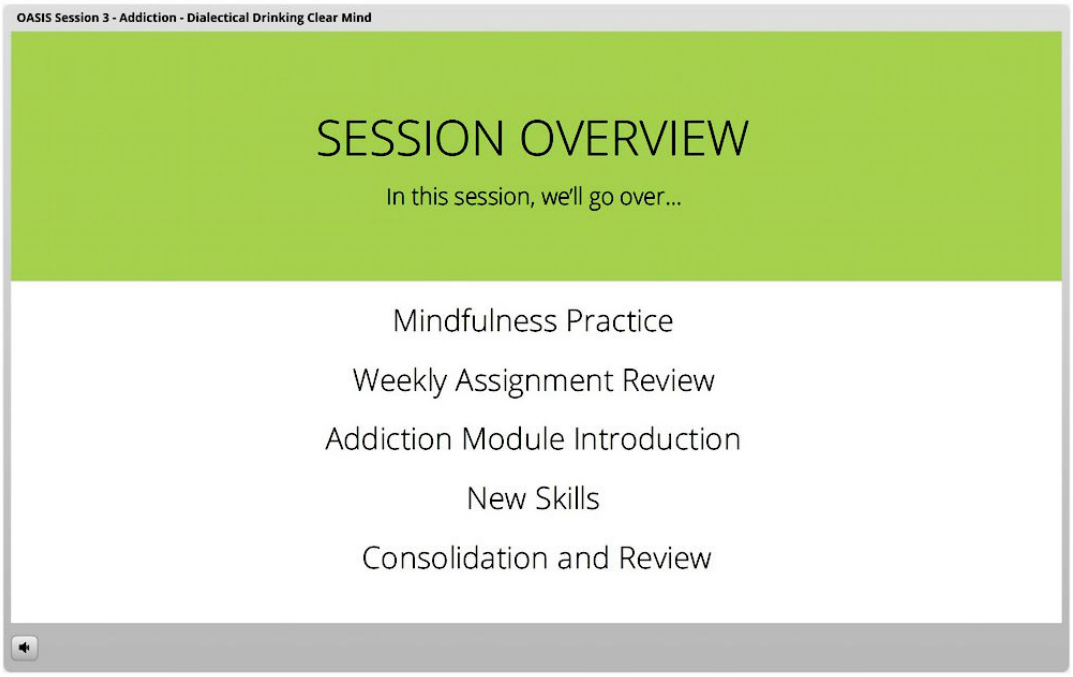


Figure 2. Screenshot of interactive activity (selecting drinking goal).

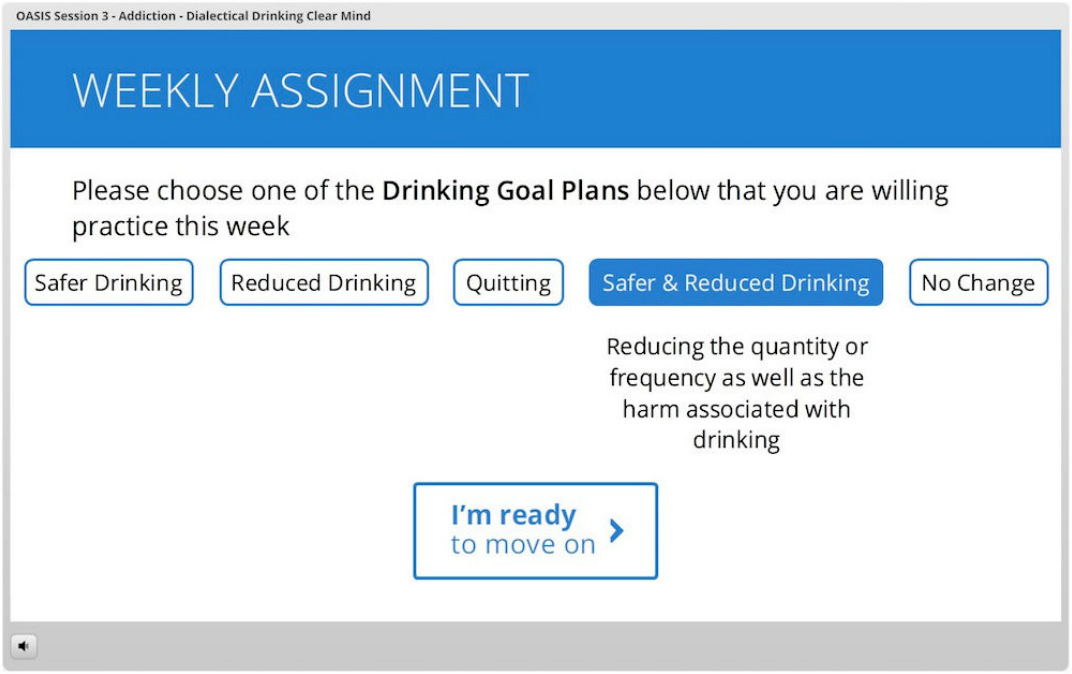


Figure 3. Screenshot of interactive activity (changing emotions).

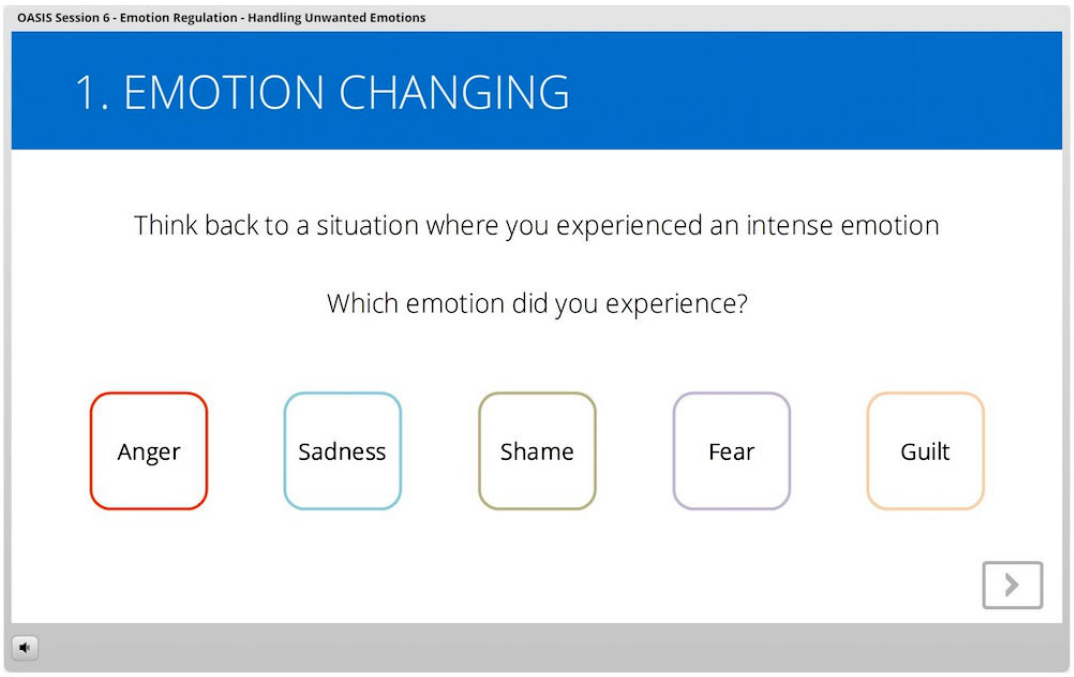
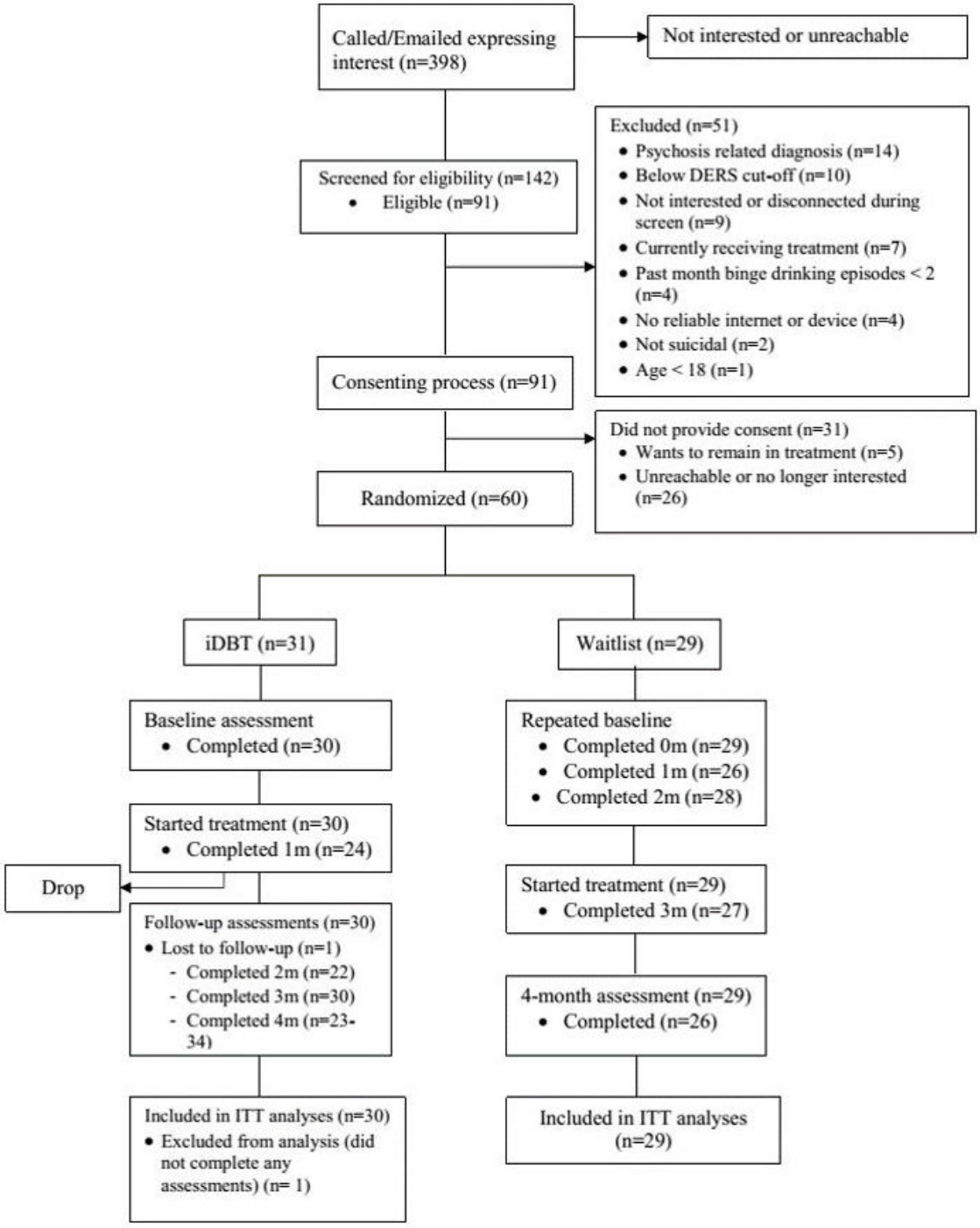


Figure 4. New Dialectical Behavioral Therapy skill: dialectical drinking.

Figure 5. CONSORT diagram. DERS: Difficulties in Emotion Regulation Scale; iDBT: Internet-delivered Dialectical Behavioral Therapy; ITT: intention-to-treat.



Confidentiality

All information provided by participants will be strictly confidential. Answers to phone screens and online assessments that will be kept indefinitely for research purposes were coded in a nonidentifying way, and stored in password-protected files on an encrypted server accessible only to the principle investigator and trained research assistants. Confidential records linking participant names with their respective research identification number will be deleted no later than September 30th, 2018. All identifying information from ineligible individuals was deleted immediately after phone screening. Additionally, the study site is a secure research clinic equipped with noise-cancelling devices to prevent conversations with participants from being overheard. Voice messages left for participants were devoid of details about the study and other sensitive information that may compromise confidentiality. Any paper documents that contained confidential Patient Health Information are kept in a locked area in the study site where access is restricted, and will be shredded before disposal. These documents may be examined in strictly confidential checks conducted by government or university staff for legal and safety insurance.

Participants were informed of one scenario in which confidentially may be breached. That is, if a participant reveals an imminent high risk of danger to their own or someone else's life, research staff may address that risk to police or emergency resources.

Power Calculation

A power analysis was not conducted because the primary purpose of the data analyses is to describe the effect of iDBT-ST protocol treatment over time using repeated observation data in a preliminary manner. The results will be used to help determine if further research on the treatment program for suicidal heavy drinkers is necessary in larger samples.

Analyses

Intervention effects will be evaluated by examining change outcomes as a function of treatment condition using both hierarchical linear modeling (HLM) [52] for outcomes with a normal distribution and generalized estimating equations (GEEs) [53,54] for count outcomes. Both HLM and GEEs accommodate observations that are missing at random, thus increasing the power of analyses. Analyses will be conducted using an intent-to-treat framework, in which all randomized and available participants will be included in the analyses. To examine changes over time for the entire sample, analyses will be conducted among all participants during all assessment waves (baseline to 16-week). A set of analyses will also be conducted using the first three assessment waves (baseline to 8-week) comparing immediate-treatment to no treatment, and at each condition's relative pretreatment, midtreatment (4-week for iDBT-ST; 12-week for waitlist), and posttreatment (8-week for iDBT-ST; 16-week for waitlist) assessment phases.

Given the pilot nature of the study, all outcomes will be evaluated in terms of effect sizes as well as clinically significant change using Jacobson and Truax's specifications [55]. Treatment effect sizes will be analyzed using Cohen's *d* and Relative risk ratios for continuous and count outcomes, respectively. Cohen's *d* will calculate within-condition effect sizes across all assessment waves. Descriptive analyses will also be conducted to examine acceptability.

Results

Recruitment to the study began June 17, 2016 and ended September 14, 2016. Data were collected using direct entry of online surveys tools (Qualtrics [45], Articulate Online [49]) by February 2017, and are currently undergoing analyses. The CONSORT diagram (Figure 5) presents the flow of participants during recruitment, enrollment, and participation. Of the 398 individuals who expressed interest in participating, 91 were determined to be eligible through the screening process. A total of 60 individuals returned their informed consent and were randomized, of whom 59 individuals were intended-to-treat. A total of 50 participants in the study were retained through the 16-week enrollment.

Discussion

The primary aim of this trial is to preliminarily evaluate an Internet-delivered DBT skills training intervention for suicidal and heavy episodic drinkers. Research on suicidal individuals who engage in HED is paramount to understanding and managing suicide risk, particularly as it pertains to high-risk populations who are less inclined to seek formal treatment. The set of protocols used in DBT to manage acute and chronic suicidality was translated relatively seamlessly for use in this pilot study's Web-based approach, demonstrating their potential utility as tools for remote risk-management in computerized interventions. A concern of this treatment is the 8-week waiting period; however, waiting times are often a reality for individuals seeking assessment and treatment (eg, mean=65.4 days) [56] due to resource or staff shortages [57-60], and we believe we can answer an important question about placing high risk individuals on waiting lists. Participants were fully informed about the possibility of being randomized to an 8-week waiting list, as well as their rights to withdraw from the study at any time. Referrals to treatment and crisis services were provided whenever participation was declined or withdrawn.

One major aim of the study was to investigate the feasibility of recruiting and retaining participants from this population. Sixty eligible individuals were recruited within three months, demonstrating the feasibility and effectiveness of the online recruitment strategy. Retention rates, particularly for waitlisted participants, were anticipated as a potential challenge, with findings in the literature suggesting an association between longer wait periods and reduced treatment motivation and retention [61,62]. To address this problem, customized reminders were sent to all participants to encourage treatment engagement and assessment completion [63]. Finally, 83.3% (50/60) of all participants were retained in the study by the end of their enrollment, suggesting that customized reminders may be an effective strategy to mitigate study dropout rates.

The level of risk commonly attributed to such studies may be inhibitive to research. Nevertheless, grounds for the safeguarding

of participant safety can be established with careful implementation of validated risk-management protocols, which equip researchers with contingencies against anticipated harm in conducting much-needed studies. In addition, the feasibility of recruiting, retaining, and monitoring participants demonstrated in this pilot study provides preliminary suggestions for the developing field of research on technologically-assisted interventions that may become beneficial alternatives to traditional therapy, or mediate adaptive help-seeking in at-risk and underserved populations.

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Authors' Contributions

CW is the principal investigator of the study and contributed to the design of the study, the study protocol, and preparation of this manuscript. QY and SA are research assistants on the study and contributed to data collection and preparation of this manuscript. BM is a research assistant on the study and contributed to data collection. AL contributed to the research design. ML is the faculty sponsor for the NIAAA grant that provided funding for this study and contributed to the design of the study.

Conflicts of Interest

iDBT-ST was developed by the principle investigator Chelsey Wilks, and it is owned by the University of Washington. Chelsey Wilks has received compensation for DBT training. Coauthor Dr. Linehan receives royalties from Guilford Press for books she has written on DBT, and from Behavioral Tech, LLC for DBT training materials she has developed. The remaining authors declare that they have no competing interests.

Multimedia Appendix 1

Informed consent.

[PDF File (Adobe PDF File), 67KB - resprot_v6i10e207_app1.pdf]

Multimedia Appendix 2

Caring email sent to those unreachable by phone.

[PDF File (Adobe PDF File), 21KB - resprot_v6i10e207_app2.pdf]

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Abbreviations

AUDIT: Alcohol Use Disorders Identification Test
DBT: dialectical behavior therapy
GEE: generalized estimating equation
HED: heavy episodic drinking
HLM: hierarchical linear modeling
iDBT-ST: Internet-delivered Dialectical Behavioral Therapy Skills Training
NIAAA: National Institute on Alcohol Abuse and Alcoholism
RCT: randomized controlled trial
UWRAP: University of Washington Risk Assessment Protocol

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Protocol

Combined Dietary Nitrate and Exercise Intervention in Peripheral Artery Disease: Protocol Rationale and Design

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Abstract

Background: Peripheral artery disease (PAD) is caused by atherosclerotic occlusions in the legs. It affects approximately 8-12 million people in the United States alone, one-third of whom suffer from intermittent claudication (IC), defined as ischemic leg pain that occurs with walking and improves with rest. Patients with IC suffer a markedly impaired quality of life and a high perception of disability. Improving pain-free walking time is a primary goal of rehabilitation in this population.

Objective: The nitric oxide (NO)-PAD trial is designed to compare the effects that 12 weeks of supervised exercise training, in combination with a high inorganic nitrate-content (beetroot [BR] juice) beverage or placebo (PL) beverage, has on clinical outcomes of exercise and functional capacity in two groups of PAD+IC patients: exercise training plus beetroot (EX+BR) and exercise training plus placebo (EX+PL). The primary aims of this randomized controlled, double-blind pilot study are to determine group differences following 12 weeks of EX+BR versus EX+PL in the changes for (1) exercise capacity: pain-free walking time (claudication onset time, COT), peak walk time (PWT), and maximal exercise capacity (peak oxygen uptake, VO_{2peak}) during a maximal-graded cardiopulmonary exercise test (max CPX) and (2) functional capacity: 6-minute walk (6MW) distance. The secondary aims will provide mechanistic insights into the exercise outcome measures and will include (1) gastrocnemius muscle oxygenation during exercise via near-infrared spectroscopy (NIRS); (2) gastrocnemius muscle angiogenesis: capillaries per unit area and per muscle fiber, and relative fraction of type I, IIa, IIb, and IId/x fibers; and (3) vascular health/function via brachial artery flow-mediated dilation, lower-limb blood flow via plethysmography, and pulse wave velocity and reflection.

Methods: A total of 30 subjects between 40 and 80 years of age with PAD who are limited by IC will undergo exercise training 3 days per week for 12 weeks (ie, 36 sessions). They will be randomized to either the EX+BR or EX+PL group where participants will consume a beverage high in inorganic nitrate (4.2 mmol) or a low-nitrate placebo, respectively, 3 hours prior to each training session.

Results: Data collection from this study has been completed and is in the process of analysis and write-up. While the study is too underpowered—EX+BR, n=11; EX+PL, n=13—to determine between-group differences in the primary outcomes of COT, PWT, and 6MW, preliminary observations are promising with Cohen *d* effect sizes of medium to large.

Conclusions: Exercise training is currently the most effective therapy to increase functional capacity in PAD+IC. If the addition of inorganic nitrate to an exercise regimen elicits greater benefits, it may redefine the current standard of care for PAD+IC.

Trial Registration: ClinicalTrials.gov NCT01684930; https://clinicaltrials.gov/ct2/show/NCT01684930 (Archived by WebCite at http://www.webcitation.org/6raXFyEcP)

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KEYWORDS

nitrate; nitrite; nitric oxide; exercise; peripheral arterial disease; intermittent claudication

Introduction

Peripheral artery disease (PAD) is caused by stenosis of the arteries in the lower limbs, leading to a reduction in blood flow to the legs [1]. It affects approximately 8-12 million people within the United States alone, one-third of whom suffer from intermittent claudication (IC), defined as ischemic leg pain that occurs with walking and improves with rest [2]. Patients with IC suffer a markedly impaired quality of life and a high perception of disability [3]. Consequently, improving pain-free walking time is an important clinical goal for these patients [4].

Thus far, interventions aimed at improving clinical outcomes in patients with PAD have been either surgical, pharmacological, or exercise based, with supervised exercise training identified as the current best intervention for improving functional outcomes such as peak walking time and pain-free walking time [5-7]. Exercise training has proven efficacy in improving vascular health and function for atherosclerosis-associated comorbidities such as obesity, hypertension, dyslipidemia, and type 2 diabetes mellitus [8-14]. Patients with PAD have marked impairments in the oxygen delivery and uptake pathway due to deficiencies in both vascular function—increased arterial stiffness, endothelial dysfunction, and decreased peripheral blood flow—and skeletal muscle composition and architecture—capillary density rarefaction, mitochondrial dysfunction, and a loss of oxidative (ie, slow-twitch) fibers [15-18]. As they result in a more glycolytic phenotype leading to earlier onset of fatigue and exhaustion, the skeletal muscle abnormalities have a detrimental effect on the delivery, uptake, and utilization of oxygen. While supervised exercise training can improve both the skeletal abnormalities [19] and vascular function [20] in these patients, improving the patient's ability to acutely tolerate an exercise bout could lead to even greater efficacy in the exercise training intervention by allowing them to exercise at a greater intensity at each session. Thus, to identify the next best treatment for patients with PAD, there is a continued need to advance our current understanding of both the disease and optimal interventional therapies.

Dysfunction of the vascular endothelium is a hallmark of cardiovascular diseases, including PAD [21]. A key facet of this dysfunction is abnormal vessel reactivity, which is mediated in part by a reduction in nitric oxide (NO) production [22]. NO is diatomic free radical that plays an important role in modulating vascular tone and regulating blood flow. In healthy individuals, NO is produced endogenously by endothelial nitric oxide synthase in response to elevated shear stress at the arterial wall. Patients with cardiovascular disease, in particular those with PAD, lack the ability to endogenously increase vascular NO bioavailability, leading to significant dysfunctions within the vasculature.

Plasma nitrite (NO_2^-), while once considered to be a biologically inert marker of NO, has recently been identified as an alternative NO source that can be reduced to NO under low oxygen conditions, such as hypoxia or ischemia [23]. One established noninvasive mechanism for increasing plasma NO_2^- is via oral consumption of inorganic nitrate (NO_3^-). Inorganic NO_3^- is found in relatively high concentrations in green leafy vegetables and beetroot. When swallowed, inorganic NO_3^- is rapidly absorbed in the small intestine and while a majority is excreted by the kidneys, up to 25% is retained and becomes concentrated in the salivary glands. When the saliva is secreted, commensal oral bacteria on the dorsal surface of the tongue reduce the NO_3^- to NO_2^-, which is then swallowed and absorbed back into the circulation. NO_2^- concentration peaks approximately 2.5-4 hours after inorganic NO_3^- consumption [24,25]. The circulating NO_2^- is further reduced to NO in hypoxic conditions; the NO_3^--NO_2^--NO reduction pathway increases peripheral blood flow during exercise and leads to improvements in exercise tolerance.

NO_3^- supplementation has shown mixed effects on exercise performance [26-30]. In healthy and athletic populations, NO_3^- supplementation has decreased the oxygen cost of exercise [28,31], increased time to exhaustion [28], and improved time trial performance [26]. However, studies utilizing similar participant demographics have reported no effect of NO_3^- supplementation on power output [32], time trial time [33], or submaximal exercise efficiency [34]. One proposed explanation for these mixed findings is the discovery that an individual's level of aerobic fitness could impact the effectiveness of nitrate supplementation, with one study demonstrating reductions in the oxygen cost of exercise and improvements in time trial performance only in participants with a low-moderate level of aerobic fitness [35]. While this research into responders and nonresponders to nitrate supplementation is still in the early stages, this particular finding perhaps lends more support for nitrate supplementation's potential efficacy in clinical populations with low aerobic capacity. Indeed, in clinical populations, most of the results have been positive: improvements in submaximal endurance, muscle contractile function, and exercise capacity in heart failure [36-38], as well as submaximal exercise endurance in chronic obstructive pulmonary disease [39]. Only a few studies showed no effect [40]. In patients with PAD, following a single acute dose of a high-nitrate-containing beetroot (BR) juice (18 mmol), which led to a five-fold increase in plasma nitrite in comparison to placebo (PL) [27], we have previously shown an 18% and 17% increase in treadmill walking claudication onset time (COT) and peak walk time (PWT), respectively. While initial results show promise, most of the studies have utilized acute dosing strategies and have been limited in both sample size and demographic diversity.

While exercise training is the current best intervention for patients with PAD, by allowing the patients to acutely train at higher intensities—due to improvements in oxygen delivery/uptake—resulting in a greater cumulative effect than exercise alone, the acute benefits of nitrate supplementation on exercise tolerance suggest a potential opportunity to further enhance the effects of exercise training [6].

The hypothesis of this study is that subjects with peripheral artery disease with intermittent claudication (PAD+IC) who undertake regular consumption of a high-inorganic nitrate (4.2 mmol) supplement in conjunction with 12 weeks of supervised exercise training (exercise training plus beetroot juice [EX+BR]) will experience a greater clinical benefit in pain-free walking time (COT, 6-minute walk [6MW]) and PWT than those undertaking exercise and a placebo beverage (exercise training plus placebo juice [EX+PL]) alone. Specifically, the primary aim of this study is to determine group differences (EX+BR vs EX+PL) in the changes in the following:

1. Exercise capacity: pain-free walking time (COT), PWT, and maximal exercise capacity/peak oxygen uptake (VO_{2peak}) during a maximal-graded cardiopulmonary exercise test (max CPX).
2. Functional capacity: 6MW distance.

Secondary aims designed to provide mechanistic insight into the exercise outcomes include the following:

1. Gastrocnemius tissue oxygenation during max CPX testing via near-infrared spectroscopy (NIRS).
2. Gastrocnemius muscle angiogenesis: capillaries per unit area and per muscle fiber, and relative fraction of type I, IIa, IIb, and IId/x fibers.
3. Vascular health/function via brachial artery flow-mediated dilation, lower-limb blood flow via plethysmography, and pulse wave velocity (PWV) and reflection.

Methods

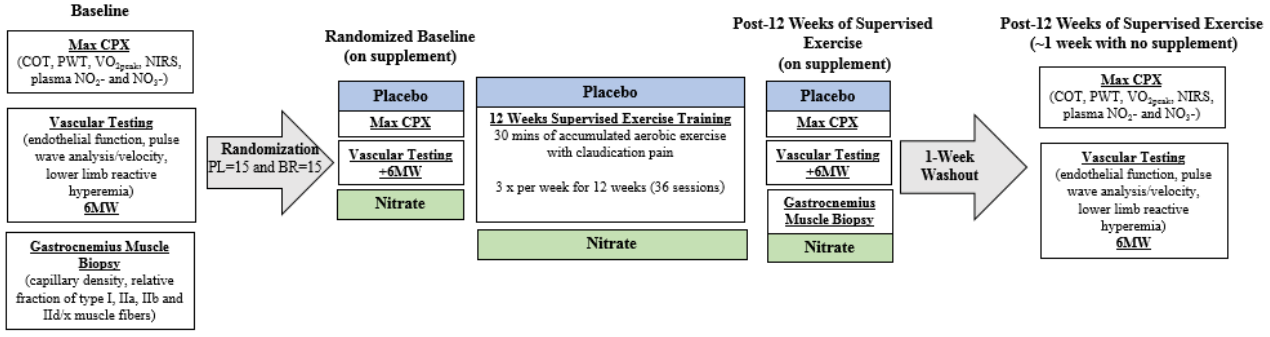
Study Design

The NO-PAD trial is a pilot, randomized, double-blind, per-protocol design with four different assessment time points (see Figure 1). This study is registered with ClinicalTrials.gov (NCT01785524).

The first round of assessment will act as a baseline with no exercise intervention or supplementation. Following this, all participants will be randomized to groups consuming either a 70 mL (4.2 mmol nitrate) beetroot juice (Beet It, James White Drinks Ltd, Ipswich, UK) or an identical nitrate-depleted placebo. Participants will then repeat the baseline assessments, except for the muscle biopsy, but will consume their assigned beverage 3 hours prior to each visit.

Participants will continue consuming their beverage 3 hours prior to each of their 36 exercise training sessions. Periodically, subjects will be selected for unannounced blood draws at training visits to check plasma nitrate and nitrite concentrations. Post-exercise training, participants will complete the same assessments as the baseline visit while still acutely consuming their beverage before visits. Both groups will then stop consuming the beverage for at least 1 week prior to the final visit. The half-life of nitrate is 5-8 hours and as the supplementation protocol is three acute doses per week, a 1-week washout period should be sufficient to minimize any possible residual effect of the nitrate [41]. To maximize internal validity, study personnel, time of day, equipment, and order of testing will be consistent for each of the assessment time points.

Figure 1. Study design with visit timeline and corresponding assessments. 6MW: 6-minute walk; BR: beetroot juice; COT: claudication onset time; max CPX: maximal-graded cardiopulmonary exercise test; NIRS: near-infrared spectroscopy; PL: placebo juice; PWT: peak walk time; VO2peak: peak oxygen uptake.



Recruitment Strategies and Eligibility

We aim to recruit a total of 30 participants—equal numbers of men and women—between the ages of 40 and 80 years with diagnosed PAD from the clinics and community at Duke University Medical Center. We anticipate a dropout rate of approximately 15%-20% and, therefore, 24 patients out of the 30 (EX+BR, n=12; EX+PL, n=12) are expected to complete the study. This study will have continuous rolling enrollment until the recruitment goals are met. Subjects will be recruited primarily through collaboration with Duke University Medical Center cardiovascular physicians and vascular surgeons. Clinic medical records will be reviewed to prescreen patients for inclusion and exclusion criteria (see Textbox 1).

Textbox 1. Inclusion and exclusion criteria for study screening visit.

Inclusion criteria:

1. Aged between 40 and 80 years.

2. Diagnosed peripheral artery disease (ankle-brachial index <0.90) with intermittent claudication.

3. No major changes in medications for at least 3 months.

Exclusion criteria:

1. Foot ulcers, advanced neuropathy, gangrene, or other musculoskeletal condition that could limit exercise performance.

2. Type 1 diabetes or glycated hemoglobin >8.5%.

3. A major cardiovascular event within the previous 6 weeks or a planned hospitalization within the next 2 months.

4. Any cardiovascular condition that impacts safety of completing a cardiopulmonary exercise test, including history of significant left main or three-vessel coronary artery disease (>70% stenosis), recent myocardial infarction (6 weeks), chest pain during cardiopulmonary exercise test, or >2 mm ST depression during exercise; foot ulcers/advanced neuropathy or other musculoskeletal condition that could limit exercise performance.

5. Allergy to beets or proton pump inhibitors.

6. Refusal or inability to abstain from the use of proton pump inhibitors for 24 hours prior to testing.

Records of those criteria will be noted and the appropriate medical doctor will introduce the study to the patient. Patients who consent to being contacted by the research team will undergo a telephone screening questionnaire to determine if the study eligibility criteria are met. Eligible and interested patients will then attend an orientation visit and a consent meeting. During this initial visit, the study details will be explained verbally and the individuals will have the opportunity to read over the approved informed consent document and ask any questions they may have about the trial. The patients can then choose to sign the informed consent form or decline participation. Following the consent visit, enrolled subjects will return on a separate day to undergo a physical examination and a review of their medical history and medications by the study physician. Participants will then be scheduled for their baseline assessment visits. Details of the testing occurring at each time point is outlined in Figure 1 and is described in detail in the Testing Methodology section.

Supplementation

Following initial screening and baseline testing, subjects will be randomized to consume either a high-nitrate-containing beetroot beverage or a low-nitrate placebo throughout the duration of the exercise training. Randomization should ensure the groups are initially equal within either the EX+BR or EX+PL intervention. Both groups will be instructed to consume one 70 mL bottle of beetroot juice (containing 4.2 mmol inorganic nitrate) 2.5-3 hours prior to every testing visit and training session between time point 2 and time point 3. The beetroot juice bottles will be identical in appearance and taste. The bottles will be color coded by a third party to ensure that the research staff remain blinded while providing the correct supplement to each participant.

Scheduled but unannounced blood draws will be performed throughout the study to confirm participants are conforming to their appropriate beverage allocations.

Exercise Intervention

Overall Program and Attendance Requirements

All subjects will attend supervised exercise training sessions three times per week for a total of 12 weeks at the Duke Health and Fitness Center at the Duke University Medical Center for Living. Each session is structured to last approximately 45-60 minutes, including taking vital signs—heart rate and blood pressure (BP)—before and after the training session. To meet minimum exercise session attendance requirements, participants will need to complete 34 of the 36 exercise training sessions and should not miss more than 1 week of training (ie, 3 sessions) consecutively. Additional sessions will be added if necessary to ensure that an adequate exercise stimulus is given to each subject so that any decreases in fitness or function during unintended breaks are mitigated. The study will be analyzed under per-protocol criteria. Subjects who withdraw from the study prior to completion will be excluded from the final analysis. However, attrition rates will be reported and documented.

Participants will not be excluded due to current exercise habits, but all participants will be instructed to maintain their normal activity levels throughout the exercise intervention.

Training Details

The exercise session will consist of approximately 5 minutes of warm-up, 30 minutes of accumulated exercise (not including rest periods), and cooldown (if necessary). The walking treadmill exercise prescription is individualized to each participant's exercise capacity during baseline testing and their rate of progression. The protocol requires participants to accumulate a total of 30 minutes of walking with claudication pain. Neither rest time nor time spent exercising before pain onset will count toward the 30-minute goal. The patient will be encouraged to continue walking as far as they can, but will self-select when they require a rest break. Exercise and rest periods are repeated during each session until the minimum total of 30 minutes of walking time is reached each session. When a patient can walk 8-10 minutes at the initial workload,

the grade will be increased by 0.5%, or the speed increased by 0.1 mph as tolerated, to ensure workload progression.

Subjects will be supervised by a trained exercise physiologist and will have continuous telemetry heart rate monitoring using the Polar heart rate monitor (Polar Electro). Fatigue will be assessed through rating of perceived exertion via the Borg 6-20 scale; blood pressure will be checked both before and after exercise as well as periodically during each exercise.

Each exercise training session will be documented with preexercise and postexercise vital signs, time of day beverage was consumed, total exercise time, and workload (ie, treadmill speed and grade) recorded. Body weight and dietary intake will be assessed on a weekly basis. All research team members working with the subjects will be blinded to the treatment intervention and every attempt will be made keep encouragement and workload adjustment standardized between subjects.

Testing Methodology

Overview

The subjects and research staff conducting the testing will be unaware of group assignments. The primary investigator will know to which treatment group the subjects are randomized, since changes in plasma nitrate and nitrite will be used to determine beverage volumes and tolerance. Because of the potential for bias, however, the primary investigator will not be directly involved in collecting or analyzing any of the exercise performance or training data.

For all testing visits, participants will be advised to avoid exercise and consuming alcohol for 24 hours prior to the examination day. They will also be asked to avoid tobacco and caffeine for 3 hours prior to any testing or exercise visit.

Maximal Cardiopulmonary Exercise Test

Overview

The maximal cardiopulmonary exercise test (CPX) with a 12-lead electrocardiogram and expired gas analysis will be conducted using a modified Gardner protocol. This protocol starts at 2.0 mph and 0.0% grade and increases by 2.0% grade every 2 minutes at each stage [42].

Prior to commencing the protocol, participants will be familiarized with the Borg rating of perceived exertion scale as well as the claudication pain scale. Resting measures of gastrocnemius tissue oxygenation, via NIRS, and oxygen consumption, via a metabolic cart, will be recorded.

Throughout the test, heart rate, blood pressure, NIRS, and rating of perceived exertion will be monitored. Assuming there are no adverse events, participants will walk on the treadmill until volitional exhaustion. These participants will likely be limited by leg claudication pain and, therefore, we expect to attain a VO_{2peak}, rather than a maximum.

Measures of Pain-Free Walking Time and Maximal Exercise Capacity

The measure of pain-free walking time will be recorded as the total time walked prior to the onset of claudication pain. During the max CPX, participants will be instructed to inform a research team member when they first feel pain in their leg during exercise—this will be recorded as COT. PWT will be recorded as the total time (in seconds) that the participant walked on the treadmill. VO_{2peak} will be the average of the last 30 seconds of exercise.

Nitric Oxide Bioavailability Measurement (Plasma Nitrite Changes)

Prior to beginning the max CPX, a 20-gauge intravenous catheter will be placed in an antecubital vein. Approximately 5 mL of blood will be taken prior to the max CPX testing (Pre) and at 10 minutes following exercise termination (Post). Samples will then be separated into five 1 mL Eppendorf tubes containing 5 µL heparin (1-1000 U/mL) and centrifuged at 5000 g for 3-4 minutes [26]. Afterward, the plasma will be removed into five separate tubes, snap-frozen in liquid nitrogen, and stored at -80°C until analysis.

All NO metabolite concentrations will be measured within 30 minutes of defrosting by chemiluminescence using the NOA 280 nitric oxide analyzer (Sievers Instruments) as per the manufacturer's instructions. The reductant used for nitrite analysis will be potassium iodide in acetic acid, which has the reduction potential to convert nitrite to NO; this reductant is insufficient to reduce any higher oxides of nitrogen such as nitrate and, thus, is relatively specific for nitrite. To obtain concentrations of total plasma nitrogen oxides, we will use the same apparatus with a stronger reductant, vanadium chloride in 1 M HCl, at 94°C. This reduces the sum of all nitrogen oxides with an oxidation state of +2 or higher, which is predominantly nitrate (µM), but also includes both nitrite (nM) and nitrosothiols (nM).

Tissue Oxygenation Measurement (Near-Infrared Spectroscopy)

NIRS has been shown to be a reproducible and reliable method to determine tissue oxygen stores in human skeletal muscle tissue [38]. The NIRS PortaMon device (Artinis Medical Systems) is a noninvasive portable tool for measuring tissue oxygenation. It works by emitting near-infrared light wavelengths of 760 nm and 850 nm that correspond to the absorption spectra of hemoglobin (Hb) and deoxygenated Hb, respectively. Depending on the oxygenation status of the tissues (ie, how much oxygenated vs deoxygenated Hb is present), the resultant spectra will change and the light fraction will be captured by a detector on the device itself [39]. This technique provides continuous snapshots of the muscle tissue oxygenation as well as percent oxygen saturation.

The tissue oxygenation will be assessed utilizing the NIRS device to obtain an index of fractional oxygen extraction—[deoxy(Hb + myoglobin)]—and percent oxygen saturation at rest at the beginning of the exercise test and continuously monitored throughout the max CPX and recovery period [26].

Vascular Function

Overview

For the vascular testing visit, subjects will be instructed to withhold all medications and consume no food for 8 hours prior to the exam. All vascular testing will be performed between 8 am and 11 am in a temperature-controlled room following 10-15 minutes of quiet relaxation.

Endothelial Function (Brachial Artery Flow-Mediated Dilation)

Endothelial dysfunction is a precursor to the development of atherosclerosis and an independent predictor of cardiovascular events and clinical outcomes [43]. Brachial artery flow-mediated dilation is the most commonly used noninvasive measure for the assessment of endothelial function [44]. This technique relies on the reactive hyperemic response where there is an increase in arterial blood flow following a period of ischemia (ie, occlusion). The dilation of the artery—typically the brachial artery is imaged—represents, in part, the NO-mediated arterial response to sheer stress [43,45]. All imaging will be performed at the brachial artery of the left arm with the subject in a supine position, with the forearm extended and slightly supinated. All image captures will be r-wave triggered. Two 10-second video-captures of the brachial artery will be obtained at baseline (resting), and then 2 minutes of continuous imaging will be recorded following 5 minutes of distal forearm occlusion (reactive hyperemia). Absolute and relative changes in brachial artery diameter will be calculated as follows:

Absolute and relative changes in brachial artery diameter = (peak posthyperemia diastolic diameter − baseline diastolic diameter)/baseline diastolic diameter × 100 (1)

Vascular Stiffness

Central blood pressures—the pressures by which the internal organs are perfused—have been shown to be strongly related to clinical outcomes [46]. A specially designed brachial cuff will be utilized to capture brachial systolic and diastolic pressure as well as the pulse waveform. The SphygmoCor software version 8.0 (AtCor Medical) will then use a validated generalized transfer function to derive central diastolic and systolic blood pressure, mean arterial pressure and pressure product along with the pressure augmentation (ΔP) due to wave reflection, and the pressure augmentation index (AIx):

AIx = ΔP/pulse pressure × 100 (2)

To capture PWV, sequential measurements of arterial pressure waves will be taken at the carotid artery, using applanation tonometry, and femoral artery, using a specialized thigh cuff. The surface distances from the sternal notch to the carotid and femoral sites will be measured and input into the software for calculation of the PWV. Pressure wave transit times to each site will be measured using the foot-of-the-wave method:

Distance of pulse wave (DPW) = sternal notch distance to femoral artery − carotid artery distance to sternal notch (3)

Carotid − femoral PWV = DPW/transit time(s) (4)

Ankle-Brachial Index

The ankle-brachial index (ABI) is the ratio of blood pressure in the feet in comparison to the arms and is linked with mortality and morbidity rates [47,48]. Measurements will be obtained on both the left and right side of each subject. A 5-7 MHz handheld Doppler probe coupled with a BP cuff—positioned proximal to the probe—will be used to detect blood flow through the arteries. On each arm, the brachial artery will be occluded at the biceps using an appropriately sized BP cuff, while the Doppler probe will be placed over the brachial artery to detect blood flow. An additional cuff will be placed approximately 3 cm above the medial malleolus in order to occlude the anterior tibial (AT) artery. The AT artery bifurcates in the foot into the dorsalis pedis (DP) and the posterior tibialis (PT) arteries, so both the DP and PT arteries will be measured separately via Doppler after occlusion of the AT artery using the BP cuff. The average of the least two separate measurements will be taken at each artery. The ABI value will be calculated by dividing the higher average DP or PT value from each side by the highest average radial artery value obtained from either side [27].

Lower-Limb Blood Flow

Following the ABI procedure, the participant will be kept supine throughout the plethysmography measurements. Lower-limb blood flow will be assessed both at rest and following reactive hyperemia via the use of a Hokanson A16 mercury-in-silastic strain gauge plethysmograph (Hokanson Inc). Initial setup requires the patient to lie supine, with the legs elevated slightly above the level of the heart to facilitate venous emptying. Two BP cuffs will be placed on the upper thigh of the leg to be assessed: one will be used for arterial occlusion and one for venous occlusion. A mercury-in-silastic strain gauge will be placed around the widest part of the calf to allow for the indirect measurement of blood flow via changes in lower-limb diameter. Resting measures will be acquired by inflating and deflating the venous occlusion thigh cuffs to approximately 50 mmHg (ie, just above venous pressure) every 10 seconds for five cycles. During inflation, the mercury-in-silastic strain gauge will be placed under stress, which will then be graphically represented as a pressure response curve on the Hokanson A16 machine. The average of three resting measures will be used as the baseline arterial inflow measure. Following 5 minutes of rest, the thigh cuff will be inflated to 30 mmHg above systolic pressure to induce arterial occlusion for 5 minutes. Upon release of the occlusion cuff, the same procedure used for resting measures will be initiated whereby the venous occlusion cuff will be inflated and deflated to create a pressure response curve for blood flow following reactive hyperemia [17].

Gastrocnemius Muscle Biopsy

Prior to muscle biopsies, all subjects will be asked to refrain from anticoagulant medications. Samples from the gastrocnemius muscle will be obtained using the Bergstrom percutaneous needle biopsy technique. Biopsy sites will be anesthetized with a 2% Xylocaine solution and a 0.5 cm incision will be made through the skin and fascia. Separate samples will be taken with approximately five passes of the needle into the muscle. All samples will then be prepared immediately by weighing and then dividing the samples for later analysis. A

tissue sample of approximately 100 mg is consistently obtained with a triple pass from a single insertion; we have demonstrated that this amount of tissue is sufficient for analyzing muscle fiber composition and angiogenesis. Visible blood and connective tissue will be removed and the specimens divided longitudinally. Portions for RNA (40 mg) analyses will be frozen in liquid nitrogen and stored at -70°C. Another portion to be used for histochemical analysis (~30 mg) will be oriented such that the fibers run longitudinally, mounted on cork-embedding medium (OCT compound), and frozen in isopentane cooled with liquid nitrogen.

For the analysis of the muscle tissue, after thawing the tissue, measurements will be taken for markers of angiogenesis including the following: capillaries per unit area and per muscle fiber, endothelial cells with surrounding pericytes, and relative fraction of type I, IIa, IIb, and IId/x fibers. Additionally, oxidative capacity of the fibers will be quantified via mitochondrial volume with citrate synthase activity.

Regulatory Issues

Informed consent has been obtained from each patient and the study has been approved by the Duke University School of Medicine Institutional Review Board. The study is being run under an Investigational New Drug application filed with the US Food and Drug Administration.

Statistical Analysis Plan

This is a repeated-measures design, with the purpose of assessing change over time for the two intervention groups. Since this is a pilot study, the overarching goal of the analyses is to derive effect sizes (ie, effectiveness) for this intervention for a future larger, confirmatory study. We will conduct the analyses chronologically in three phases: (1) descriptive analyses of dependent and independent variables; (2) bivariate analyses of the association between group membership and the outcome measures; and (3) controlled multivariable analyses, which assess the association between groups and the outcomes controlling for important covariates. Randomization should ensure the groups are initially equal; however, we will control for important baseline variables, including the two outcomes of interest. We will not control for any variables observed postrandomization [46]. Our general analytic strategy will be to employ these models to assess differences between groups and, most importantly, assess the differences in change over time between the groups. Our general baseline model will have the following form:

$$Y_{it} = \beta_0 + \beta_1 (\text{Group}) + \beta_2 (\text{Time}_t) + \beta_3 (\text{Group} \times \text{Time}_t) + \beta_4 (\text{Covariates}_{it}) + \varepsilon_{it} \quad (5)$$

where Y_{it} is the change in the outcome over the time points, t is an indicator of change period (t=2,4) depending on the wave of measurement, and i is an indicator of the individual (i=1,24). β_1 is an indicator variable indicating group membership. β_2 is an indicator variable indicating the time of testing: baseline, baseline on supplement, postintervention on supplement, and postintervention off supplement. β_3 is a Group × Time_t interaction. As listed, β_4 is a vector of regression weights linking the design matrix of covariates—time varying and time invariant—to the outcome of interest. We will center Time_t=0 at the final 12-week time point, which will allow us to test if there are differences at the end of the trial, β_1=0. Follow-up analyses will assess the impact of Group × Time_t interaction and the functional form of the change over time. Inclusion of covariates into the model, including baseline measures, may add precision to the estimates and allow us to assess the generalizability of the effects across the covariates. The list of covariates (eg, age, gender, health events, comorbidity, and medications) will be developed prior to any analysis. This is a small sample (n=24); hence, the number of covariates we can utilize in any regression is minimal: ≈10 cases per variable [47]. We will assess the impact of each potential covariate individually without respect to group and, if significant (*P*=.10), it will be retained in models with Group, Time_t, and Group × Time_t (see above).

This is a pilot study and we do not expect to declare statistical significance for any of the variables assessed under this analytic structure. However, if the target 12 subjects per group is attained—EX+BR and EX+PL; 24 total subjects—and if a power of 80% with alpha set to .05 (two-tailed) is used, then we will be able to detect a 0.826 standardized difference in the difference in the change labeled as “large” in the statistical power literature [49]. We will not control for the type I error risk inherent in testing multiple outcomes. Rather, should any outcome be declared significant, the reader will be alerted to the number of tests performed and the risk in drawing definitive conclusions with multiple outcomes and a small sample size.

As noted previously, the results from this pilot study will be used to power a subsequent, larger, adequately powered confirmatory clinical trial of the impact of beetroot juice on the outcomes listed above. The results, along with theory and clinical significance, will guide the choice of the primary outcome(s) for that trial, with appropriate control for type I error. While the results of this pilot study will prove useful in the calculation of power, we are aware of the many risks of “playing the winner” in choosing to power a subsequent trial from pilot study results only [50,51].

Results

Data collection from this study has been completed and is in the process of analysis and write-up. While the study is too underpowered—EX+BR, n=11; EX+PL, n=13—to determine between-group differences in the primary outcomes of COT, PWT, and 6MW, preliminary observations are promising with Cohen *d* effect sizes of medium to large.

Discussion

Principal Findings

Improving pain-free walking and exercise capacity are key goals for the treatment and rehabilitation of patients with peripheral arterial disease [1]. This study aims to determine if the combined intervention of the current best treatment for PAD (ie, supervised exercise training) in conjunction with inorganic nitrate supplementation using beetroot juice can increase exercise

tolerance more than exercise training alone (ie, placebo supplement).

The physiological basis for this trial relies on the fact that supplementation with inorganic nitrate will lead to increased plasma nitrite that can be transported throughout the circulation and is reduced to NO in tissue with a low partial pressure of oxygen. This hypoxic tissue-targeting effect may be particularly pertinent for patients with PAD+IC experiencing tissue ischemia during exercise participation. While it is well established that consuming inorganic nitrate increases circulating levels of plasma nitrite [28,52], research on the corresponding effect on key clinical outcomes such as exercise performance in clinical patients, while promising, is still limited [27,38,39].

There are three mechanisms that lend support to nitrate supplementations' clinical utility in improving exercise performance in patients with PAD. First, acute supplementation data suggest that increasing plasma nitrite via beetroot juice improves ischemic tissue perfusion leading to increases in pain-free walking time and aerobic function [27]. Second, increased exercise time or intensity will facilitate greater training responses and tissue adaptations. Third, increased bioavailability of NO could lead to a greater tissue angiogenic response. These mechanisms are complementary to each other and may result in a greater overall exercise tolerance

Study Limitations

The small sample size and the focus on patients with PAD+IC only limit the ability to broadly apply the results of the study to the larger PAD population and to generalize these results to subsequent studies. This study also uses a per-protocol design with the intent that data may provide the physiological proof of concept for the intervention and allow us to derive variance data and effect sizes within and between groups to inform future studies, which will utilize an intent-to-treat criterion in the analytic structure.

Potential Impact

This study has been designed to investigate a new therapeutic approach for the treatment of PAD+IC. If successful, the results could influence current medical practice for these patients, while also providing mechanistic insights into potential physiologic targets for other interventions. Research clearly identifies supervised exercise training as being one of the most effective interventions for improving exercise tolerance in patients with PAD [1,53,54]. We hypothesize the combination of supplementation with exercise will create greater adaptations than the sum of the individual exposures alone. If true, the findings would lead to a paradigm shift in the treatment recommendations for patients with PAD.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

NIH Clinical and Integrative Cardiovascular Sciences Study Section: Peer review report.

[PDF File (Adobe PDF File), 60KB - resprot_v6i10e139_app1.pdf]

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Abbreviations

6MW: 6-minute walk
ABI: ankle-brachial index
AIx: augmentation index
AT: anterior tibial
BP: blood pressure
BR: beetroot
COT: claudication onset time
CPX: cardiopulmonary exercise test
ΔP: pressure augmentation
DP: dorsalis pedis
DPW: distance of pulse wave
EX+BR: exercise training plus beetroot juice
EX+PL: exercise training plus placebo juice
Hb: hemoglobin
IC: intermittent claudication
max CPX: maximal-graded cardiopulmonary exercise test
NIRS: near-infrared spectroscopy
NO: nitric oxide
NO2-: nitrite
NO3-: nitrate
PAD: peripheral artery disease
PAD+IC: peripheral artery disease with intermittent claudication
PL: placebo
PT: posterior tibialis
PWT: peak walk time
PWV: pulse wave velocity
VO_{2peak}: peak oxygen uptake

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Protocol

Epidemiology of Hepatitis C Virus Among People Who Inject Drugs: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Hepatitis C virus (HCV) is a persistent epidemic among people who inject drugs (PWID), and PWID remain as the population experiencing the most significant impact of HCV-related morbidity and mortality worldwide.

Objective: The purpose of this systematic review and meta-analysis is to synthesize data on the epidemiology of HCV infection among PWID. Our main objectives are to characterize the global and regional distribution and determinants of HCV infection among PWID.

Methods: A search strategy is conducted that involves both the electronic and manual retrievals of literature. Reports are included in this review if they present data published between 2006 and 2015 on prevalent or incident HCV infection among current or former PWID. Standard meta-analytic techniques are performed to synthesize the pooled data and identify correlates of HCV infection.

Results: The search strategy has been performed, and data collection is in progress. Data analysis will follow, and the final results of this systematic review/meta-analysis are expected by December 2017.

Conclusions: This article describes the protocol for the systematic review and meta-analysis of epidemiology of HCV among PWID. We aim to provide synthesized data on HCV incidence and prevalence as well as to identify factors associated with HCV transmission. Our research contributes empirical evidence that informs scholarly, medical, and policy discussions concerning HCV.

Trial Registration: PROSPERO CRD42016035687; https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016035687 (Archived by WebCite at http://www.webcitation.org/6ttYLn65N)

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KEYWORDS

hepatitis C virus; PWID; systematic review; meta-analysis; epidemiology; HCV incidence; HCV prevalence; HCV reinfection

Introduction

Hepatitis C virus (HCV) is a persistent epidemic among people who inject drugs (PWID), and PWID remain as the population experiencing the most significant impact of HCV-related morbidity and mortality worldwide [1]. In countries where infection control procedures (which include the systematic screening of blood and blood products) have been implemented, injection drug use is the primary means of HCV transmission [1-2]. Conversely, in countries where procedures to prevent the spread of bloodborne pathogens in health care settings have been less systematically adopted, the spread of HCV has been largely due to nosocomial and iatrogenic causes [3]. Both means of HCV acquisition contribute to an increasing global burden of HCV, and the World Health Organization now estimates that 3% of the world's population is infected with HCV [4].

Systematic reviews and meta-analyses (SR/MAs) are increasingly being used to inform public health policy and guide

allocation of resources to improve population health outcomes. Previous SR/MAs of HCV epidemiology in PWID generated country-specific estimates of prevalent HCV infection (ranging between 10% and 91%) and summarized HCV incidence rates among PWID in Europe (3 to 66/100 person-years) [5-6].

In general, the public health response has not yet matched the pace at which HCV is spreading with respect to primary prevention; HCV prevalence remains high despite the availability of more tolerable and efficacious treatment [7-8]. Additional research and resources are necessary to improve treatment and prevention strategies that address the HCV epidemic among PWID globally. Indeed, individual-level risk behavior during drug injection also has implications for controlling coinfection, especially with human immunodeficiency virus (HIV) and/or hepatitis B virus (HBV).

This article describes the protocol for an SR/MA of the epidemiology of HCV infection among PWID. Our main objectives in the SR/MA are to synthesize global and regional HCV incidence and prevalence and synthesize determinants of HCV infection among PWID.

The SR/MA examines a range of topics on the epidemiology of HCV among PWID. In particular, we assess the following: time to HCV seroconversion subsequent to the onset of drug injection, updating estimates from a previous SR/MA [9]; trends in incidence and prevalence by geographic region; the effect of harm reduction (ie, substance use treatment and syringe/drug injection equipment access programs) on disease burden; and associations between HCV infection and PWID characteristics. Findings in these areas will be interpreted in relation to public health policy.

Methods

This protocol is consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol 2015 statement (see Multimedia Appendix 1) [10-11].

Selection Criteria

Reports are included in this review if they satisfy the following criteria:

- Evaluated participants who reported current or previous injection drug use (ie, PWID)
- Presented original data on HCV prevalence or incidence based on laboratory-confirmed HCV infection in a sample composed of at least 90% PWID
- Published between January 1, 2006, and December 1, 2015

We will exclude reports that are SR/MAs, present self-reported HCV data, or use simulated data.

Participants

The study population is PWID. We define active PWID as individuals who have injected within the past year, while former PWID are those whose most recent injection drug use occurred over 1 year prior to study admission. Reports that do not provide a detailed description of what constitutes a PWID will be analyzed as a separate group (thus producing 3 categories of PWID: active, former, and status nonspecified). If reports explicitly state that PWID are current or active (or use similar language to convey that PWID have recently injected drugs or are currently injecting drugs) but do not specify a time frame, then we will consider these PWID as active PWID.

Outcome Measures

The primary outcome is the frequency of HCV infection. We use 4 measures to capture disease distribution:

1. Prevalence of HCV infection
2. Incidence of HCV infection
3. Incidence of HCV reinfection following spontaneous clearance
4. Incidence of HCV reinfection following sustained virologic response to HCV treatment

Prevalence and incidence are measured as proportions and rates, respectively, where possible.

The preferred criteria for measuring prevalent HCV infection are both positive HCV antibody and HCV RNA test results. The alternative criterion is a single positive antibody marker.

Detection of HCV antibody or RNA in a previously seronegative individual are the preferred criteria for determining incident HCV infection. The alternate criterion is RNA positivity in an antibody-negative individual [12].

Measuring incident reinfection subsequent to spontaneous clearance or sustained virologic response is similar. The preferred criterion is a change in the HCV genotype from the cleared infection (either spontaneously or through treatment) to the recently acquired infection over consecutive tests. In the absence of genotype testing, conversion from RNA negative to RNA positive over multiple tests is the alternative criterion.

Secondary outcomes examined are associations between exposures and HCV incidence or prevalence. Exposures include biological and environmental factors such as HIV coinfection, sex, and geographic location.

Search Strategy

Literature is searched electronically and manually. Electronic searches using a string consisting of terms related to HCV, epidemiology, and PWID are undertaken in 4 databases: Cumulative Index to Nursing and Allied Health Literature, Excerpta Medica database, ProQuest, and PubMed (see Multimedia Appendices 2-5). Results are filtered by date of publication (01/01/2006), record type (peer-reviewed journal), and language (English). Manual searches are performed on reference lists of eligible reports and other relevant papers, conference materials, and research study websites.

Report Selection

Reports are assessed for inclusion through 3 stages. First, each unique record in the deduplicated set of literature, all of which is retrieved from the search strategy, is screened by title and abstract to determine if it meets the eligibility criteria. Second, for every report that is considered eligible, the full text is subsequently screened. Reports that did not meet the criteria at either of these 2 stages are excluded from further consideration.

Third, following data extraction, a final assessment is made on the admissibility of each report.

Report Appraisal

The quality of reports is determined through the use of an adapted version of the Quality In Prognosis Studies instrument developed by Hayden et al [13-14]. The instrument, which was modified for 2 previous SR/MAs [15-16], evaluates potential sources of bias, such as selection, misclassification, and confounding, in a report; it is also used to evaluate all study designs (eg, cross-sectional, prospective and retrospective cohort, randomized controlled trial).

Quality Assurance

Two research assistants, both with graduate training in epidemiologic research, systematic review methodology, and biostatistics, perform the literature search and identify eligible reports. Screening and coding pilots are conducted to evaluate intercoder reliability and refine the protocols governing report eligibility and data extraction. The research assistants independently review, code, and appraise all literature, which is subsequently evaluated by the principal investigator and the project director. The principal investigator and project director resolve any issues that emerge throughout the study selection and data extraction processes. The data for all included reports are aggregated into an electronic database that is managed by the research assistants, project director, and principal investigator. The research team is guided by the study protocol that they developed at the start of the project. This SR/MA is registered at PROSPERO [CRD42016035687].

Data Analysis

The meta-analysis synthesizes report-level data that are collected on the following domains: study cohort, period, and geographic location; study design and methods; HCV incidence, prevalence, and reinfection; and participant characteristics, particularly factors understood to be associated with HCV infection (eg, age, sex, and duration of drug injection). We assess subgroups and the sensitivity of results—determined by report attributes, participant factors, and report quality—and, at each stage, heterogeneity, using Cochran Q and I^2. Summary estimates of the primary outcomes are derived using random-effects meta-analysis techniques. Meta-regression models assess the association between characteristics of the study or the sample (eg, location, time period, study quality, safe injection behavior, age, race/ethnicity) and HCV incidence and prevalence. Measures of relative effect are calculated, where possible. Data analysis is conducted in Stata (StataCorp LLC), and data visualization is performed in R (The R Foundation).

Results

The search strategy has been performed, and data collection is in progress. Data analysis will follow, and the final results of this SR/MA are expected by December 2017.

Discussion

This article describes the protocol for the SR/MA of the epidemiology of HCV among PWID. We will present global and regional estimates of incident and prevalent HCV infection, and we expect to produce results that identify correlates of incidence and prevalence. Our research contributes empirical evidence that informs scholarly, medical, and policy discussions concerning HCV. Moreover, because the risk behavior of PWIDs is a common route of infection for the transmission of other bloodborne viruses, this review also has implications for research in HIV and HBV.

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Authors' Contributions

HH designed the study. HH, AEJ, DJS, and JN developed and refined the study protocol. All authors read and approved the final manuscript. DJS is the guarantor.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol checklist: recommended items to address in a systematic review protocol.

[PDF File (Adobe PDF File), 55KB - resprot_v6i10e201_app1.pdf]

Multimedia Appendix 2

Search strategy for Cumulative Index to Nursing and Allied Health Literature (via EBSCOhost).

[PDF File (Adobe PDF File), 6KB - resprot_v6i10e201_app2.pdf]

Multimedia Appendix 3

Search strategy for Excerpta Medica database (via Ovid).

[PDF File (Adobe PDF File), 6KB - resprot_v6i10e201_app3.pdf]

Multimedia Appendix 4

Search strategy for ProQuest.

[PDF File (Adobe PDF File), 6KB - resprot_v6i10e201_app4.pdf]

Multimedia Appendix 5

Search strategy for PubMed.

[PDF File (Adobe PDF File), 6KB - resprot_v6i10e201_app5.pdf]

Multimedia Appendix 6

Summary statement of the grant and assessment of the study.

[PDF File (Adobe PDF File), 121KB - resprot_v6i10e201_app6.PDF]

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Abbreviations

HBV: hepatitis B virus
HCV: hepatitis C virus
HIV: human immunodeficiency virus
PWID: people who inject drugs
SR/MA: systematic review/meta-analysis

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Protocol

Financial Incentives Alone Versus Incentivized Partner Support for Promoting Smoking Cessation During Pregnancy and Postpartum: Protocol for a Non-Randomized Single-Blinded Study

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Abstract

Background: Smoking tobacco remains the most significant modifiable cause of adverse pregnancy outcomes and contributor to ongoing maternal and infant ill-health. Pregnancy for many is a time of heightened health focus, with the primary motivation being the well-being of the unborn child. Yet, many women continue to smoke throughout their pregnancy. Despite this heightened motivation and known health risks, interventions to date have not effectively curbed the rate of smoking during pregnancy and they remain as high as rates among the general population. One promising strategy has been to incentivize these women to quit. However, incentives-based studies have not shown or reported long-term efficacy. Here, we present the protocol of a trial exploring the effect of incentivized partner support on pre- and postpartum smoking cessation.

Objective: The aim of this study is to determine whether providing incentives to both the expectant mother and her support person in promoting short- and long-term smoking cessation during pregnancy is more effective than incentives to the expectant mother alone.

Methods: This protocol is designed as a non-randomized, single-blinded trial to determine the efficacy of incentivized partner support, compared to participant incentive only, in promoting smoking cessation during pregnancy and postpartum. All eligible pregnant women receiving antenatal care via the Tasmanian Health Service (Australia) will be invited to participate. Participants will be eligible for monthly quit-contingent shopping vouchers if they verify, via carbon monoxide breath sample, as being abstinent from smoking. Participating women will be eligible for vouchers until 6-months postpartum and will be followed up at 12-months postpartum.

Results: The recruitment phase of this study has concluded. Results are expected to be published by the end of 2018.

Conclusions: This study protocol extends the current literature on incentivized smoking cessation interventions for pregnant women by assessing the influence of incentivizing a support partner on short- and long-term abstinence. Key ethical considerations are discussed including potential for receipt (or not) of quit-contingent vouchers impacting negatively on the participant's relationship with their partner. The findings of the study may have important implications for the role support partners are assigned in smoking cessation programs targeting pregnant women.

Trial Registration: Australian New Zealand Clinical Trials Registry (ACTRN): 12615001158550; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=367981 (Archived by WebCite at http://www.webcitation.org/6tGKO28uh)

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KEYWORDS

smoking; pregnancy; financial incentives; contingency management; partner support

Introduction

Smoking and Perinatal Health

Smoking during pregnancy is recognized as the single most modifiable cause of poor pregnancy outcomes [1] and the risks to mother and baby have been reported extensively elsewhere [2]. Briefly, these risks include increased risk of miscarriage, preterm birth, low birth weight, major congenital abnormalities, and sudden infant death syndrome [2,3]. Less known long-term effects as a result of prenatal smoke exposure include increased risk of reduced neuromotor function, attention deficit hyperactivity disorder (ADHD), learning difficulties, and behavior dysregulation during childhood and adolescence [4-7]. Infant exposure to second-hand smoke has also been shown to further compound these negative health consequences [2]. Despite these known risks, many women continue to smoke during and after pregnancy, at rates comparable to the general smoking population [8,9]. Even when women manage to quit during pregnancy, most (up to 80%) relapse within 6 months of delivery [10]. Rates are considerably and consistently higher among certain already disadvantaged cohorts including young expectant mothers (in Australia, 34% of pregnant women 20 years or younger smoke) and women living in rural and remote areas (37% in Australia) [11]. More effective, targeted interventions are clearly needed for this high-risk group.

Interventions for Promoting Cessation Among Pregnant Smokers

One of the most effective strategies for promoting smoking cessation among pregnant women is incentives-based interventions [12,13]. Providing incentives for pregnant smokers to quit has been shown to not only increase abstinence rates several-fold compared to any other type of treatment, but also to increase mean birth weight [12,14]. Further, in a review of the most common interventions (including cognitive behavior therapies, stages of change, feedback, pharmacotherapies, and other therapies), incentives-based programs were found to be the most cost-effective, producing a net cost benefit of US $3482 after factoring in intervention costs [12,15,16]. Incentives-based programs for pregnant smokers appear to promote successful postpartum abstinence rates (approximately 25% abstinent at 3 to 6 months postpartum), but since few studies have included long-term postpartum follow-up, the long-term efficacy is not well understood [17]. While one study reported a 12-month postpartum follow-up with promising cessation rates (0% to 44% depending on model of care), this study included participants who had quit within 1 month of enrolment, and thus the effectiveness of incentives-based interventions at promoting long-term abstinence remains unclear [18].

Partner Support and Sustained Cessation

In a review of postpartum relapse prevention strategies, programs that involved the pregnant smoker's partner were deemed necessary to maximize long-term cessation success [19]. To date, only one randomized controlled trial (RCT) has been conducted to examine the effect of partner support [20]. Participants were randomized to 3 groups: usual care, counseling support (6 counseling telephone calls; 3 during pregnancy, 3 postpartum), and counseling support combined with partner-support facilitated by a tailor-made "it takes two" booklet and video (partner was usually baby's father who was also provided 6 separate counseling support telephone calls). No significant difference in participants' smoking behavior was found between the groups. Interestingly, the authors found that positive support (behaviors characterized by cooperation and reinforcement of quitting behavior such as "compliment you on not smoking") diminished linearly from baseline to 12 months postpartum and negative support (behaviors characterized by nagging and policing such as "comment on your lack of willpower") decreased through pregnancy before increasing again postpartum.

The importance of the quality of support provided in partner support interventions has been found to be critical in promoting cessation among non-pregnant smokers [21]. In a study exploring the effect of positive and negative support behaviors on quit rates among female smokers, Cohen and Lichtenstein showed that women who reported receiving a higher ratio of positive supportive behavior compared to negative (using a shortened version of the Partner Interaction Questionnaire) from their spouse were more likely to quit. This emphasis on quality of support may explain why other studies found no effect for partner support [20-22].

Combining incentives programs with partner support, particularly the co-habiting and/or romantic partner (eg, expectant father) that emphasizes positive support, may therefore be an approach that fosters more effective long-term cessation for pregnant smokers. To our knowledge, only one study to date has explored incentivizing social support to promote smoking cessation in pregnant women. Donatelle and colleagues [23] compared 2 groups: 1 receiving usual antenatal care and 1 which included both the women and their chosen female non-smoking supporter (providing unstandardized, non-formalized, "natural" peer support only) provided with quit-contingent shopping vouchers. Participants in the incentivized partner support group were more likely to be quit at the end-of-pregnancy (32% versus 9%) and at the 2-month postpartum (21% versus 6%) time points compared to usual care. Since this study was not fully factorial (eg, intervention groups consisting of social support only and incentives only, not included), the effect of partner support over and above incentives could not be determined. Furthermore, the support person in the Donatelle et al [23] study was not the pregnant women's spouse (eg, husband and/or father of child), but rather a female, non-smoking friend, who might arguably have had less vested interest in the health of the expectant child than the expectant father.

Objectives

The purpose of this study is to determine whether providing incentives to both support person and expectant mother, if she is able to quit smoking, is more effective than providing

incentives to expectant mother only, in promoting short- and long-term smoking cessation during pregnancy. In essence, the present study seeks to answer the question: "Can partners (eg, spouse) be incentivized to be more supportive and effective quit buddies to their pregnant smoking partners?"

Specifically, the study aims to determine whether (1) providing an incentive to both the support partner and expectant smoking mother to quit is more effective than providing an incentive to the pregnant smoker alone at promoting abstinence; (2) regardless of incentives, women who receive more positive cessation support from their partners, as measured by the Partner Interactive Questionnaire 20 (PIQ-20), are more likely to quit smoking; and (3) providing incentives for pregnant smokers to quit is more effective than "usual care" antenatal quit smoking services such as brief advice and referral to smoking cessation services (external telephone counseling and smoking cessation nurse) at promoting smoking cessation.

The primary outcome for the study is smoking status (ie, smoking or quit), as determined by self-report 7-day point prevalence, and carbon monoxide (CO) less than 7 particles per million (ppm) at the end-of-pregnancy time point. Secondary outcomes include effect of incentives on long-term (2 months and 12 months postpartum) abstinence and influence of the quality of partner support (positive compared to negative supportive behaviors) on smoking status.

Methods

Trial Design

This study will adopt a non-randomized, single-blinded, controlled 2-group (control and treatment) trial design.

Participant Recruitment

All eligible pregnant women who smoke and live in Tasmania (Australia) are invited to participate in the study. Statewide recruitment is facilitated by drawing on data from the Tasmanian Health Service's digital medical record (DMR) and encompasses multiple strategies to maximize reach. A research midwife, with access to the Tasmanian Health Service's DMR, conducts "cold calling" of all women who self-reported smoking in the last 7 days during their initial antenatal "booking in" appointment (usually around 10 weeks gestation). Using information stored on the DMR, the midwife pre-screens women for eligibility (eg, self-report smoking, 16 years or older) and telephones them to invite them to participate in the study. With their verbal consent, the details of interested women are recorded and forwarded to the research team.

Antenatal staff of the Tasmanian Health Service (including physicians and midwives) provide study information (in the form of a flyer) to eligible participants during antenatal appointments. With their consent, the contact details of interested women are forwarded to the research team. In addition, the study is advertised through flyers placed in general practitioner (GP) clinics, outreach centers and community hubs across Tasmania. Informal advertising via social media (eg, Facebook) and television and radio interview exposure may also be utilized. Consequently, potential participants could also self-refer to the study by contacting the researchers directly.

Eligibility Criteria

Women who express interest in participating in the study (either self-refer or consent to a health professional forwarding their contact details to research staff) are contacted by research staff and screened for eligibility using a previously validated protocol [24]. To be eligible for study entry, women must be (1) pregnant (20 weeks gestation or less); (2) at least 16 years of age; (3) self-report as being a current smoker ("even a single puff in the last 7 days"); (4) attending routine antenatal care provided by the Tasmania Health Service or participating GP center (Tasmanian, Australia); and (5) be able to attend a minimum of 3 appointments at 1 of the 3 data collection sites across Tasmania (Launceston General Hospital, Royal Hobart Hospital, or Mersey Community Hospital). Women younger than 18 years (but 16 years or older) require the consent of their parent, guardian, or senior antenatal health provider to participate in the study.

Potential participants are excluded from study entry if they self-report as non-smoking (ie, "have not smoked, even a single puff in last 7 days") or if they have a cognitive or intellectual impairment that will inhibit fulfillment of participation requirements (eg, completion of surveys and/or attend organized study appointments). Participants who are found to be "gaming" (eg, those who tell researchers they are pregnant and/or smoking untruthfully to enroll in study) are also excluded from further participation and their data discarded. All participants are asked to nominate and are encouraged to bring along to study visits a support person, preferably a person they co-habit with (eg, spouse, father of child, or family member).

Assignment of Interventions

Participants are assigned to the same group (either control or the treatment group) for 3 consecutive months (interchangeably for 18 months), such that participants recruited in the first 3 months are allocated to the control group and participants recruited in the following 3 months are allocated to the treatment group. This design was chosen to assist participant blinding to group allocation, given the heightened potential for the women recruited to know each other and/or discuss research participation. Since participants in this study are recruited following their first antenatal appointment, participants recruited around the same time will have similar due dates. As membership to parents' groups and hospital-run parentcraft classes is usually assigned by due date/gestation, and due to the relatively small recruitment pool (Tasmania has a population of 515,000 and only 3 tertiary hospitals), adopting a fully randomized, parallel group controlled design would likely jeopardize participant allocation concealment (ie, differing incentive amounts), thus introducing bias (eg, recruited women declining/delaying enrolment due to allocation, participants not being as motivated to quit smoking due to lesser incentive amount). As well as assigning participants to the same group in 3-month intervals, participants who report knowing another participants or are recruited by another participant are assigned to the same group.

Interventions

During their initial enrolment visit (visit 1), all participants and their support partners are offered a separate resource pack providing further information and quit references. The content of the packs, selected on the basis of existing resources developed and distributed by not-for-profit organizations and government-funded bodies (eg, Quitline, Cancer Council, and SIDS and Kids), includes informational brochures on the topics of smoking and pregnancy, quitting smoking during pregnancy, a guide for quitting smoking, and smoking and sudden infant death syndrome. A referral and resources summary list (eg, further websites and available mobile phone apps) is also provided that includes telephone numbers of local counseling services. The resource pack specifically designed for partners contains information about the effect of second-hand smoke on children, quit smoking products, and how to be an effective quit buddy. Following the single-blinded, consecutive-month schedule, women are allocated to either the control or treatment group during their enrolment session (Textbox 1).

Textbox 1. Control and Treatment group incentives.

- Group
  - Control
    - Only the participant is rewarded with a AUD $50 voucher if they verify as quit during monthly visits
  - Treatment
    - Both participant (1 x AUD $50) and their designated support person (1 x AUD $50) receive a shopping voucher if the participant verifies as quit during monthly visits
    - If partner is not present during study visits, participant collects both vouchers

All participants are encouraged to make a quit attempt in the 2 weeks following the enrolment visit in order to promote quit status (verified by less than 7 ppm CO breath sample) and enable incentive issue at the first monthly follow-up, although it is emphasized that each participant is able to decide their own quit timeframe and approach. No other formal smoking cessation counseling support is provided.

All participants are asked to attend 2 further study visits—visit 2 (end-of-pregnancy) and visit 3 (end-of-study)—and have the opportunity to attend monthly visits to verify their non-smoking status and receive incentive voucher/s.

Quit-Contingent Incentive Vouchers and Study Compensation

All participants attending a scheduled visit are provided with some form of voucher compensation. For participants who are still smoking, an AUD $10 voucher is offered. Participants who verify as quit are offered the shopping voucher amount consistent with their group allocation. If a participant is not abstinent at any visit during pregnancy, they are still eligible to receive the quit-contingent incentive at any subsequent visit during pregnancy if they provide a CO reading of less than 7 ppm.

Verification of Smoking Status

During each visit and telephone call, participants are asked if they have smoked, even a single puff, in the last 7 days. During study visits, participants complete a 14-day timeline follow-back questionnaire as an assessment of self-reported smoking. To verify self-report, all participants are required to provide 2 expired air CO samples using a piCO Simple Smokerlyzer [25]. Expired CO was chosen as the most appropriate biochemical verification method in this study as it is not sensitive to the use of nicotine-containing medication (such as nicotine replacement therapy which may be used by participants), is non-intrusive, immediate (facilitates immediate provision of quit-contingent incentive vouchers), and inexpensive. The CO readings are recorded and if the average of the 2 samples is less than 7 ppm, the participant's smoking status is recorded as quit and she receives a voucher incentive. A cut-off value of less than 7 ppm was selected based on recommendations from the National Institute of Health and Care Excellence [15], in addition to the precedent set by existing research in the field which accounts for likely second-hand smoke exposure (eg, from support partner) [18,26]. To check whether our results are sensitive to the CO cut-off value, we also repeat our primary analysis using a CO level of less 4 ppm as the cut-off for abstinence. Substantial discrepancies between the results obtained with the 2 cut-off values suggests that participants are "gaming" the system (that is, continuing to smoke but cutting down just enough to receive the abstinence reimbursement). Based on results of previous similar studies [27], we do not expect "gaming" among participants for incentives to be a significant issue.

Procedure

Study Visits and Follow-Up Calls

A schematic diagram summary of the time-schedule of visits, rewards, and data collection at each visit is shown in Multimedia Appendix 1.

Enrolment Visit

During the enrolment visit (visit 1) participants are asked to complete a battery of questionnaires and provide 2 CO breath samples. Regardless of group allocation, participants are asked to nominate a support person (they are asked to have this person in mind when completing the Partner Interaction Questionnaire), preferably the person they are living with (eg, partner or family member), whose contact details are recorded along with the participant's own details to assist with future correspondence. While no smoking cessation counseling is provided, participants

are offered a resource pack for themselves and their support partner.

End-of-Pregnancy Visit

Regardless of smoking status, all participants are required to attend an end-of-pregnancy study visit. This second visit occurs at approximately 8 months gestation and participants are asked to provide 2 CO samples and complete a series of questionnaires.

End-of-Study Visit

Regardless of smoking status, all participants are required to attend an end-of-study visit, which occurs at approximately 2 months postpartum. Participants are asked to provide 2 CO samples and complete a series of questionnaires including the End-of-Study Questionnaire.

Monthly Telephone Calls and Verification Visits

Monthly telephone calls are conducted with all participants to determine smoking status. During the phone calls, participants are asked "Have you had a cigarette (even a puff) in the past 7 days?" If a participant self-reports as abstinent, they are invited to attend a follow-up verification visit to verify their smoking status (and receive a voucher incentive), which is booked at their next convenience. If the participant self-reports smoking in the last 7 days during the monthly telephone call, they are advised that they are not eligible for the incentive that month and will be contacted again the following month. This monthly payment schedule limits the additional participation burden on participants, and where possible, is scheduled on days when they are attending routine hospital antenatal appointments. This monthly payment schedule was also utilized by the only other study published using incentivized partner support [23]. Participants who verify as abstinent at their end-of-study visit (visit 3) are eligible to receive monthly calls and incentives until 6 months postpartum. Participants who are still smoking at the end-of-study visit no longer receive monthly calls (and are ineligible for any further incentives) from that date. Multiple (up to 5) attempts are made to contact each participant for their scheduled monthly telephone calls and visits. Text messages (short message service, SMS) are also utilized to try to contact those difficult to reach. However, the study adopts an intention-to-treat approach such that if participants become un-contactable at any time throughout the study, it is presumed they are smoking [28].

12-Month Telephone Call and Visit

Each participant, regardless of smoking status, is contacted via telephone 12 months after the delivery of their baby. The 12-Month Follow-Up Questionnaire is administered via telephone and participants are asked their current smoking status. Participants who self-report abstinence (7-day point prevalence) during this call are invited to verify smoking abstinence via a CO breath sample in a follow-up visit and be offered an AUD$10 shopping voucher (regardless of verification status) to thank them for their participation. This marks the completion of their participation in the study.

Study Questionnaires

A battery of questionnaires are issued to participants during study visits.

Baseline Questionnaire

The Baseline Questionnaire was developed to obtain demographic information (eg, age, highest level of education, income), information about smoking characteristics (eg, smoking status, cigarettes per day, dependence [Fägerstrom Test for Cigarette Dependence [29]], smoking history, and partner's smoking characteristics), and pregnancy (eg, gestation, gravidity, smoking during previous pregnancies). This questionnaire is administered only once at study enrolment (visit 1).

Smoking Knowledge Quiz

The Smoking Knowledge Quiz was developed from existing publicly available and scientifically reliable smoking information and is similar to the questionnaire used in a previous study [30]. The quiz requires participants to answer questions regarding their knowledge of the safety and effectiveness of smoking cessation treatments and techniques during pregnancy, as well as the health risks associated with cigarette smoking for themselves and their baby. Participants' responses to this quiz are reviewed with the participant at the time of the enrolment visit to prompt discussion of health risks and available cessation aids. The quiz is administered once only at study enrolment (visit 1).

Smoking Status Questionnaire

The Smoking Status Questionnaire is a self-report, 14-day cigarette timeline follow-back which requires participants to report the number of cigarettes smoked each day for the previous 2-week period [31]. This questionnaire is completed at each study visit.

Reasons for Quitting Questionnaire

The Reasons for Quitting Questionnaire (RFQ) is a 24-item questionnaire measuring an individual's motivation for quitting [32]. Reponses to items such as "I want to quit smoking because I am concerned that I will suffer from a serious illness if I don't quit" are scored on a 5-point Likert scale from 0 (not at all true), to 4 (extremely true). This questionnaire is completed at each study visit.

Partner Interaction Questionnaire

The Partner Interaction Questionnaire (PIQ) is used to gather information about the level of partner support [33]. It includes 10 positive (PIQ-POS) (eg, "Express pleasure at your efforts to quit") and 10 negative (PIQ-NEG) (eg, "Comment on your lack of willpower") partner behaviors that could be expressed towards a quitting partner. This questionnaire is completed at each study visit.

End-Of-Study Questionnaire

The End-of-Study Questionnaire was developed to collect information after participants have had their baby and is conducted around 2 months postpartum during the scheduled end-of-study visit (visit 3). This questionnaire includes questions about smoking status, cigarettes per day, experience of study participation and receiving incentives, treatments/methods used to aid quit attempt, partner support, and partner smoking status, as well as any birth complications experienced.

12-Month Follow-Up Questionnaire

The 12-Month Follow-Up Questionnaire is administered via telephone during the 12-month follow-up telephone interview. This marks the completion of study participation. Participants are asked to describe their smoking status, experience of being in the study, details of partner support of quit attempts, and their overall general well-being and that of their baby. If participants are quit, they are invited to return to the study center to verify.

Fetal growth and birth outcomes are also collected from babies of consenting participants (a separate consent form is provided seeking access to this information) including head circumference, femur length, heart/vascular data, birth weight, Apgar score (overall health at birth), gestational age, and digital medical records of neonatal intensive care unit (NICU) or respiratory admissions (if applicable). These data will be used for exploratory analyses to determine any associations with intervention effects.

Sample Size and Checks

The study is powered on the primary hypothesis (H1) which requires a sample size of 108 (see below). This is consistent with a review of previous research in the area, which revealed sample sizes ranging between 40 and 220 with approximately equal group sizes [17]. To ensure particular features of the study protocol do not influence the data, checks will be conducted during the analysis phase to control for influence of different antenatal service sites being used for recruitment and testing, as well as any cyclical effects of the cyclical monthly recruitment design.

Planned Analyses

Analyses are planned to test each of the 4 hypotheses.

Hypothesis 1

The first hypothesis (H1) is that providing an incentive to both the support partner and expectant smoking mother to quit is more effective than providing an incentive to the pregnant smoker alone at promoting abstinence during pregnancy.

The quit rates of the treatment and control groups will be compared at the end-of-pregnancy time point (visit 2) using chi-square analysis. While no study to our knowledge has compared participant-only incentive with combined participant and support partner incentive, Donatelle et al [23] compared a usual care control group with an incentive plus partner incentive treatment group and found that at the end-of-pregnancy, 32% of treatment group participants had quit (n=105) compared with 9% in the control group (n=102), which indicates a large effect size (χ^2=18.4, N=207, *d*=0.62) [23]. Since the control group in the present study is also receiving incentives, it is anticipated that the effect size may be moderate, rather than large. As such, to determine if there is a significant difference in proportion of women who have quit between control group and treatment group, with the power of .80 to detect an effect size of 0.30, the study will require a total sample size of 108.

Hypothesis 2

The second hypothesis (H2) is providing an incentive to both the support partner and expectant smoking mother to quit is more effective than providing an incentive to the pregnant smoker alone at promoting abstinence in the postpartum period.

As per H1 above, treatment and control group abstinence rates will also be compared at the end-of-study (visit 3) and at 12-months postpartum follow-up time points to determine the effect of incentivized partner support on postpartum abstinence. A multi-comparison adjustment will be applied to control for family-wise error.

Hypothesis 3

The third hypothesis (H3) is regardless of incentives, women who receive more positive cessation support from their partners (as measured by PIQ-20) are more likely to quit smoking.

Participants, regardless of group allocation, will be regrouped to either PIQ-POS or PIQ-NEG, as determined by the ratio of positive compared to negative support they report receiving from their support partners. The abstinence rates of these regrouped PIQ-POS and PIQ-NEG participants will then be compared at 3 time points; end-of-pregnancy, end-of-study (2 months postpartum), and 12 months postpartum.

Hypothesis 4

The fourth hypothesis (H4) is providing incentives for pregnant smokers to quit is more effective than “usual care” antenatal smoking cessation support at promoting smoking cessation.

The quit rates of participating women will be compared to the average quit rate of a historical control of women receiving antenatal care by the Tasmanian Health Service from 2011 to 2015 [34].

Results

The recruitment phase of the study has concluded and postpartum data collection is ongoing. Data collection is anticipated to be complete by late 2017. Outcomes of the trial will be published within a year (12 months) of completing final 12-month follow-up data collection. The study results will be disseminated via conference presentations and papers published in academic peer-reviewed journals. The participants, healthcare professionals, and public will be informed of the study results through email correspondence and local media.

Discussion

The project has been reviewed and approved by the Tasmanian Health and Medical Research Ethics Committee (H0014568). Prior to enrolling in the study, all participants provide verbal and written consent. Furthermore, additional checks are conducted throughout the study to ensure participant safety in light of details receiving particular attention during the ethical review process. The first is the risk of a negative impact of the receipt (or not) of quit-contingent shopping vouchers on the study participant’s relationship with their partner, with the concern that this may be a potential trigger for family violence or other threat to the safety of the woman (and/or unborn child). During each study visit or telephone call, participants are asked if study participation is impacting negatively on their relationship with their partner. If real or perceived risk is present,

the study research officer ensures the safety of the participant by making urgent contact with and referral to the antenatal Social Work service (or after-hours emergency/crisis social work service) at the relevant public hospital to arrange safe accommodation and other services as indicated. The second is the risk of potential distress should a participant experience adverse pregnancy or other outcomes (eg, fetal or infant death) while involved in the study. The research midwife conducts monthly checks of participants' pregnancy and health status via the Tasmanian Health Service's digital medical records. In these rare occasions, no further contact is initiated with the participant and her involvement and data is withdrawn. However, should the participant request to continue to participate, she is welcome to do so.

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Conflicts of Interest

SGF has worked as a consultant for GlaxoSmithKline Consumer Healthcare and Chrono Therapeutics on matters relating to smoking cessation, has received travel funding from Pfizer, has received researcher-initiated project grant funding from Pfizer (through the GRAND initiative), and has served on an advisory board for Johnson & Johnson. These organizations were not involved in the current study in any way.

Multimedia Appendix 1

Summary of the time-schedule of visits, rewards, and data collection.

[PDF File (Adobe PDF File), 143KB - resprot_v6i10e209_app1.pdf]

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Abbreviations

AUD: Australian Dollars
CO: Carbon monoxide
DMR: digital medical record
GP: general practitioner
PIQ: Partner Interaction Questionnaire
PIQ-NEG: PIQ negative
PIQ-POS: PIQ positive
ppm: particles per million

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Protocol

Utilizing Consumer Health Informatics to Support Management of Hypertension by Clinical Pharmacists in Primary Care: Study Protocol

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Abstract

Background: Hypertension (HTN) is a major public health concern in the United States given its wide prevalence, high cost, and poor rates of control. Multiple strategies to counter this growing epidemic have been studied, and home blood pressure (BP) monitoring, mobile health (mHealth) interventions, and referrals to clinical pharmacists for BP management have all shown potential to be effective intervention strategies.

Objective: The purpose of this study is to establish feasibility and acceptability of BPTrack, a clinical pharmacist-led mHealth intervention that aims to improve BP control by supporting home BP monitoring and medication adherence among patients with uncontrolled HTN. BPTrack is an intervention that makes home-monitored BP data available to clinical pharmacists for use in HTN management. Secondarily, this study seeks to understand barriers to adoption of this intervention, as well as points of improvement among key stakeholders, so that larger scale dissemination of the intervention may be achieved and more rigorous research can be conducted.

Methods: This study is recruiting up to 25 individuals who have poorly controlled HTN from a Family Medicine clinic affiliated with a large Midwestern academic medical center. Patient participants complete a baseline visit, including installation and instructions on how to use BPTrack. Patient participants are then asked to follow the BP monitoring protocol for a period of 12 weeks, and subsequently complete a follow-up visit at the conclusion of the study period.

Results: The recruitment period for the pilot study began in November 2016, and data collection is expected to conclude in late-2017.

Conclusions: This pilot study seeks to document the feasibility and acceptability of a clinical pharmacist-led mHealth approach to managing HTN within a primary care setting. Through our 12-week pilot study, we expect to lend support for this approach, and lay the foundation for translating this approach into wider-scale implementation. This mHealth intervention seeks to leverage the multidisciplinary care team already in place within primary care, and to improve health outcomes for patients with uncontrolled HTN.

Trial Registration: Clinicaltrials.gov NCT02898584; https://clinicaltrials.gov/ct2/show/NCT02898584 (Archived by WebCite® at http://www.webcitation.org/6u3wTGbe6)

(JMIR Res Protoc 2017;6(10):e193) doi:10.2196/resprot.8059

KEYWORDS

hypertension; medication adherence; cell phones; telemedicine

Introduction

Background and Significance

Hypertension (HTN) is a serious public health concern in the United States, affecting approximately 78 million adults and burdening the health care system with an estimated US $42.9 billion in direct costs in 2010 [1,2]. HTN is a key risk factor for heart disease and stroke, which are the first and fourth leading causes of death in the United States, respectively [3]. Of patients with HTN, it is estimated that only approximately 50% achieve blood pressure (BP) control, and approximately 20% remain unaware of their condition [1]. Given the prevalence and high cost of HTN, coupled with poor rates of control, identifying strategies to assist patients in managing their HTN is imperative.

An important and effective strategy for HTN management is home BP monitoring [4-7], yet problems with data quality and latency can be abundant when patients maintain paper-based logs for self-monitoring [8,9], potentially compromising the effective and efficient use of paper-based logs in primary care. Additionally, clinical pharmacists can help manage chronic conditions such as HTN in primary care settings [10,11] and have themselves been shown to be an effective intervention for patient HTN management [12,13]. Despite evidence suggesting the efficacy of home BP monitoring and clinical pharmacists for HTN management, neither strategy is being widely used in primary care settings.

One potential solution that shows great promise is the use of mobile health (mHealth) approaches to bridge the gap between home monitoring and clinical pharmacist care. Approximately 95% of American adults have a cell phone, 77% have a smartphone, and the rate of smarphone adoption is increasing rapidly [14]. Moreover, the majority of individuals living with one or two chronic conditions report tracking at least one health indicator (70% and 80% respectively); a task that is greatly supported through the use of mobile technology [15].

mHealth interventions may therefore be a viable strategy to close the loop between patient self-monitoring and clinician management, thus potentially improving HTN management. The current utility of such interventions is often reduced however, as they are typically patient-facing and do not support bidirectional patient-provider communication. However, through a bidirectional intervention in which patient-provider interaction and automatic transmission of electronic data from home BP monitors to clinicians can occur in real-time, mHealth interventions may be a practical solution. Efficiencies in patient management could potentially lead to increases in the number of hypertensive patients that a clinical pharmacist could manage, as well as improvements in the quality of patient BP management. Moreover, mHealth interventions often contain other features that have been linked to chronic disease self-management, including data tracking, general/tailored education, and reminders, all of which may contribute to improved HTN control [16,17].

Study Objective

The purpose of this study is to establish feasibility and acceptability of BPTrack, which is a clinical pharmacist-led mHealth intervention that supports home BP monitoring and medication adherence among patients with uncontrolled HTN, and makes collected data available to the pharmacist for use in HTN management. Secondarily, this study seeks to understand barriers to adoption, as well as points of improvement among key stakeholders, so that larger scale dissemination of the intervention may be achieved, and more rigorous research can be conducted.

Methods

Overview

We are currently conducting a 12-week pre/postintervention pilot study of BPTrack, a clinical pharmacist-led mHealth intervention, which seeks to improve BP control among uncontrolled hypertensive patients recruited from a primary care setting, and who are receiving treatment for their HTN under the care of a clinical pharmacist embedded in the primary care clinic. The final protocol closely mirrored what was originally proposed to the funder (see Multimedia Appendix 1 and Multimedia Appendix 2 for original review scoring forms). The methods for this study have been approved by the University of Michigan IRBMED Institutional Review Board (HUM00105772).

BPTrack Intervention Description

The BPTrack intervention supports patient home BP monitoring and medication adherence tracking for sharing with a clinical pharmacist. BPTrack consists of two different mobile apps developed by the Tactio Health Group and modified from their TactioRPM Platform; one for the patient, and one for the clinical pharmacist. These modified mobile apps are intended for our research purposes only, have been rebranded with appropriate program logos, and are distributed by the University of Michigan via the Apple and Google Play app stores.

BPTrack is a patient-facing smartphone app for iOS and Android that supports home BP monitoring, medication adherence, and communication with a clinical pharmacist who is managing patients' HTN. BPTrack allows people to measure their BP using a compatible Bluetooth-enabled BP cuff (this study provides patient participants with a Welch Allyn Remote Monitoring Upper Arm Blood Pressure Device RPM-BP100), after which the BP reading is automatically synced with the BPTrack smartphone app, and transmitted to a secured cloud server. Individuals can also manually enter their BP data into the app, without syncing the BP cuff. Within the visual display, patient participants are provided a graph of their BP data over time (Figure 1), as well as mean, minimum, and maximum values for systolic BP (SBP), diastolic BP (DBP), and pulse. Color-coded data points on the graph highlight how a BP value compares to BP target goals; two hues of green represent normal BP or prehypertension, orange represents stage 1 HTN, and red represents stage 2 HTN (refer to Table 1 for actual assigned SBP and DBP ranges within BPTrack). To self-monitor medication adherence, BPTrack sends daily medication reminders that are coupled with educational messages focused on the importance of medication adherence for managing HTN (Figure 2). In addition, users can record their adherence data in free text via a *Notes* feature. Finally, BPTrack provides a

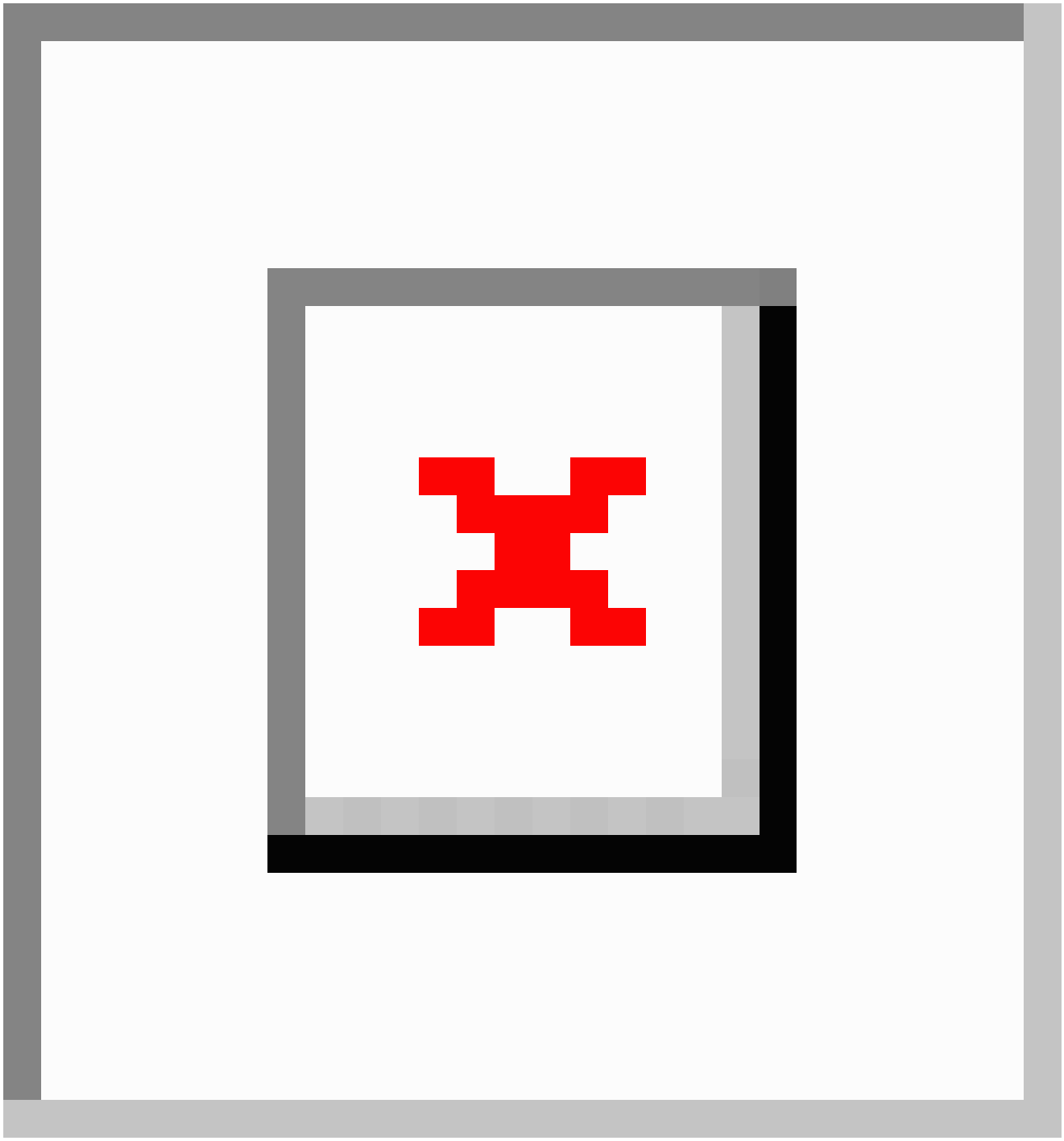
mechanism to send in-app messages directly to the clinical pharmacist.

BPTrack Pharm is a mobile app for the iPad, which is used by clinicians to monitor collected BP and medication adherence data from patients using the BPTrack app. BPTrack Pharm presents clinicians with a color-coded dashboard view to quickly highlight all enrolled patients' BP control (Figure 3), as well as a more detailed view for each individual patient, which allows the clinical pharmacist to view all collected BP and adherence data for each enrolled patient (Figure 4). BPTrack affords clinicians the ability to set custom BP goals for individuals, and to directly message a patient via the app.

Table 1. Assigned SBP and DBP ranges for blood pressure categorization in BPTrack.

Category	Color	Systolic Blood Pressure	Diastolic Blood Pressure
Optimal	Green	<120 mmHg	<80 mmHg
Prehypertension	Light green	≥120 mmHg to <140 mmHg	≥80 mmHg to <90 mmHg
Stage 1 Hypertension	Orange	≥140 mmHg to <160 mmHg	≥90 mmHg to <100 mmHg
Stage 2 Hypertension	Red	≥160 mmHg	≥100 mmHg

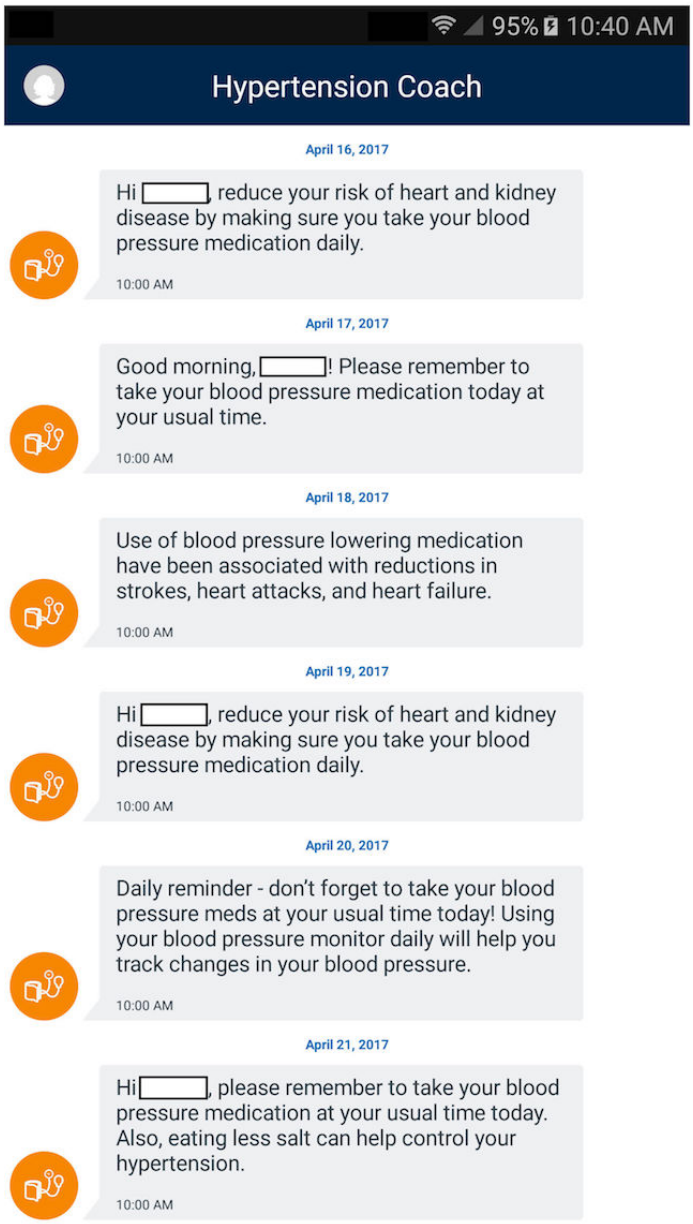
Figure 1. BPTrack blood pressure graph screen.



BPTrack Theoretical Underpinnings

Our approach to HTN management, which relies on daily BP and medication adherence self-monitoring, is rooted in a self-regulatory framework. In the theory of self-regulation, individuals participate in self-directed behaviors, thought to be managed through a dynamic feedback loop. In this loop, individuals process information about their past behavior and integrate the information into goals and motivation to change future behaviors (ie, self- monitoring) [18]. By engaging in daily BP and medication adherence self-monitoring, patient participants will have the opportunity to see progress made toward meeting BP goals, which (when combined with self-reflection on behaviors) should tap into the dynamic feedback loop to lead to possible behavior change.

Figure 2. BPTrack medication reminder screen.



Setting

This pilot study is being conducted with patients at a Family Medicine clinic affiliated with a large Midwestern academic medical center. The participating site generates over 29,000 patient visits annually (72% of which are adult visits) and serves a predominantly blue-collar, underserved African-American and Hispanic population. HTN is a prevalent chronic condition that is treated at the recruiting clinic.

Sample

We are enrolling up to 25 patient participants for this pilot study. To be eligible for participation, enrollees must be ≥18 years of age, have a smartphone compatible with the mobile intervention, have been previously diagnosed with HTN, have uncontrolled HTN (SBP >140 mmHg and/or DBP >90 mmHg on repeat measurements), be under the care of a primary care physician at the recruiting clinic, be taking at least one antihypertensive medication, and be English-speaking.

Figure 3. BPTrack Pharm main screen.

Potential enrollees are excluded if they are >65 years of age, are already under the care of a clinical pharmacist for HTN management or under the care of a cardiologist, are pregnant, have serious existing medical conditions that may make BP control difficult or necessitate frequent hospitalization (such as previous diagnosis of resistant HTN, steroid dependent asthma or emphysema, cirrhosis or hepatic failure, stage C or D chronic heart failure, stage IV or V chronic kidney disease, and terminal cancer or ongoing active chemotherapeutic or radiation therapy), or have other serious medical conditions (eg, stroke, dementia) that may affect their ability to self-monitor their BP.

Recruitment

Patient participants are recruited through recruitment flyer dissemination by clinic staff (physicians, medical assistants, clinical pharmacist, or other clinic staff) to potentially eligible participants, as well as targeted recruitment letters. To facilitate provider and staff referral, study flyers were provided to clinic staff and providers so that they can be handed directly to potentially eligible individuals as they are seen in clinic. Moreover, study staff are providing primary care physicians with lists of potentially eligible patients, identified through the electronic medical records system, who are scheduled to be seen in the clinic. The clinical pharmacist on this study is also directly recruiting patients who meet eligibility criteria. Recruitment

flyers list a study hotline that individuals must call in order to be screened for participation in the study.

In order to send targeted recruitment letters, study staff are conducting automated pulls of patient data from electronic health records to obtain mailing lists of patients at the recruiting site who meet clinical eligibility criteria. These targeted recruitment letters inform recipients that they are potentially eligible for a research study focused on HTN management and that they may receive a phone call to solicit their participation. In addition, recruitment letters provide contact information for study staff so that interested individuals can directly contact the team. Shortly after recruitment letters are distributed, study staff are calling potentially eligible participants to solicit participation.

Procedures

Any individual patient at the recruiting site who expresses interest by calling the study hotline is subsequently screened by phone. Once screened as eligible, patient participants are scheduled for an informed consent and baseline data collection appointment with study staff at the recruitment site, or another affiliated space. These visits take approximately 90 minutes to complete.

Figure 4. BPTrack Pharm individual screen.

After baseline data collection is complete, study staff help patient participants download the intervention app onto their smartphone, and train them on how to use the app. Participants are also given a Bluetooth-enabled BP monitor to take home, and are instructed on how to use it, as well as how to sync it to BPTrack. All BP monitors are checked before the patient

participant leaves the baseline data collection visit, and are tested against a manual BP reading taken by a trained study staff member. Although we are not calibrating the home BP monitors, we do look to see how well their readings compare with the manual BP readings. Once enrolled in the study, the clinical pharmacist sees patient participants as needed for ongoing HTN management.

Patient participants are also instructed on the BP monitoring protocol that we will adhere to in this study, and are instructed to take three consecutive BP readings twice daily, at varying times across days. Prior to BP monitoring, patient participants are instructed to: go to the bathroom before taking their BP, if needed; keep their arm at heart level by resting it on a table during monitoring; sit in a chair with a back, with feet flat on the floor for at least five minutes prior to monitoring; avoid tobacco, caffeine, or alcohol for 30 minutes prior to BP monitoring; avoid taking their BP immediately after exercise, when emotionally upset, or in pain; and to avoid talking while taking their BP.

In the event that a patient participant has an SBP >160 mmHg, SBP <100 mmHg, DBP >100 mmHg, or DBP <60 mmHg, they are instructed to wait five minutes and then recheck their BP using the previously described protocol. Patient participants are also instructed that if BP readings exceed these critical thresholds for three days in a row, they should contact the clinic. Finally, patient participants are instructed to call the clinic immediately if they are experiencing symptoms of dizziness, chest pain, severe headache, or visual changes.

Patient participants are instructed to follow the home BP monitoring protocol for 12 weeks, to ensure that the BP readings sync with the BPTrack app, and to self-monitor BP medication adherence. During this 12-week intervention period, the project's clinical pharmacist monitors home BP and medication adherence readings through the BPTrack Pharm clinician app, and manages patient participant HTN in concordance with their normal clinical practice. In the event that a patient participant exhibits continued elevated BP readings, the clinical pharmacist contacts them to determine whether the patient needs to come in to the clinic for follow-up, or whether to continue to monitor through the app. The clinical pharmacist is exercising their best clinical judgment in managing the research participants' BP.

At the conclusion of the 12-week intervention period, patient participants meet with study staff for their 12-week follow-up data collection visit, which takes approximately 60 minutes to complete. At this visit, the patient participants complete the Adherence to Refills and Medications Scale (ARMS) [19], they are asked to bring in all antihypertensive medications for a pill count, and interviews are audio recorded.

To compensate patient participants for their participation in the study and to reduce attrition, individuals receive US $25 upon completion of their 12-week follow-up data collection visit. Patient participants are also allowed to keep the BP monitor used in the study (valued at approximately US $100/monitor). In addition to incentives offered for participation, additional retention strategies implemented in past and current projects are being used, such as routinely obtaining contact information for the participant and up to three friends/relatives who can help locate them, as well as baseline and follow-up appointment reminders via phone and/or email. Individuals who leave the study early are compensated on a pro-rated basis, and are required to return the BP monitor.

After the study has finished, we will conduct interviews with the study's clinical pharmacist and other key stakeholders at the recruiting clinical site. Key stakeholders will be recruited through direct solicitation via email and phone calls; these stakeholders are expected to include clinic medical directors, primary care physicians, health systems administrators, and information technology personnel. These interviews will be audio recorded and transcribed for further analysis.

Measures

Through this study, we are collecting a variety of different measures to help determine the feasibility and acceptability of utilizing this approach in a primary care setting, including: *Patient Participant Characteristics*, *Blood Pressure*, and *Medication Adherence*.

Patient Participant Characteristics

At baseline, we administer an investigator-developed survey to assess patient participant demographics, health status, HTN history, medication use, and other characteristics.

Blood Pressure

At both baseline and 12-week follow-up, patient participant BP is assessed in the clinic by a manual BP reading taken by a trained study staff member or clinic staff. In addition, home BP readings will be downloaded from the BPTrack Secured Cloud at the conclusion of the study for further analysis.

Medication Adherence

At baseline and the 12-week follow-up, we assess medication adherence with two different measures: the ARMS and pill counts. The ARMS is a 14-item instrument that consists of two sub-scales that assess taking medications as prescribed, and refilling medications on schedule. The ARMS has been validated for use in a population with chronic disease and has been shown to have good performance characteristics among individuals with low literacy levels [20]. Upon enrolling in the pilot study, all patient participants are instructed to save all pill bottles for antihypertensive medications, even if empty, and bring them to the follow-up assessment. Patient participant HTN medications are identified from the patient's medical record. Information required for the pill count calculation is recorded from each prescription label including: drug name, strength, and dosage form; instructions for use; quantity dispensed; and dispensing date. Pill count adherence is determined by the following formula, [19]:

> % adherence = (quantity dispensed - quantity remaining)/([prescribed # tablets/day] x [# days between dispensing date and interview]) x 100

BPTrack and BPTrack Pharm Utilization

At the conclusion of the study, BPTrack and BPTrack Pharm utilization for patient and clinical pharmacist participants will be documented through log file analysis, with specific focus on the number of patient participant home BP readings, as well as

the frequency and duration of participant use of the BPTrack and BPTrack Pharm apps.

Health Care Utilization

Patient participant health care utilization will be conducted through a retrospective chart review of enrolled individuals in order to document the number and reason for primary care visits during the course of this study, including the frequency and nature of contacts with the clinical pharmacist (phone or in-person), with a primary care physician at the recruiting clinic, and the Emergency Department at the academic medical center.

Patient Participant Perceptions

At the conclusion of the 12-week study period, we will conduct an investigator-developed survey focused on patient participant perceptions of BPTrack including ease of use, usefulness, impact on health outcomes, and satisfaction. We will also conduct an open-ended interview using a standardized script to elicit additional qualitative feedback.

Key Stakeholder Utilization and Perceptions

At the conclusion of this pilot study, we will conduct an in-depth interview with the clinical pharmacist involved in this study to better understand perceptions of the system from a clinical perspective. Moreover, throughout the course of the pilot study, the pharmacist has been asked to maintain detailed logs of the time spent using the app, time spent monitoring and following-up with patient participants, and perceptions of the program. These logs will be collected and analyzed in order to document the personnel needs to maintain such a program. We will also conduct key stakeholder interviews with clinic medical directors, primary care physicians, health system administrators, and information technology personnel at the recruiting site and other affiliated clinical sites, to identify potential barriers to broader intervention dissemination, as well as strategies to overcome those challenges.

Statistical Analysis Plan

Descriptive statistics will be used to describe patient participant characteristics and perceptions, mHealth utilization, and clinical pharmacist utilization and perceptions. Categorical data will be displayed as frequencies and percentages, and Chi-square tests will be used for comparisons. SBP and DBP will be expressed as mean (standard deviation) and pre/postintervention BP means will be compared using 2-tailed paired samples t-tests.

The effect of clinical pharmacist contact with patient participants will be evaluated through changes in utilization of the mHealth app and changes in BP levels surrounding the time of contact. Models will be used to separately evaluate SBP and DBP levels over time, including pharmacist contact as a time-varying covariate using a mixed-effects regression approach. The mixed-model analysis accounts for the correlation of BP measures on the same individual across time. Similar analyses will be carried out on daily utilization of the mHealth app. Daily usage will be coded as a binary response and modeled using generalized estimating equations, including pharmacist contact with patient participants as a covariate to identify the odds of app usage before and after contact.

Results

Patient participant recruitment for the pilot study began in November 2016, and data collection is expected to conclude in late-2017.

Discussion

Principal Results

At the conclusion of this study, we expect to be able to demonstrate the feasibility and acceptability of using an mHealth approach for supporting clinical pharmacist-led HTN management in a primary care clinic. By placing clinically relevant home BP and medication adherence data from patients directly into the hands of a medical professional who has the potential to act upon it in a clinically relevant and timely manner, we may be better able to improve patient care for individuals who struggle to manage HTN. Moreover, by incorporating mobile devices that are already used by the target population, we are taking an inherently patient-centered approach to HTN management. This “bring-your-own-device” approach ensures that we are asking people to utilize technologies already incorporated into daily life, which is necessary for adequate translation from bench to bedside. We anticipate that through this pilot study, we may be able to document efficiencies that this type of program may create, and learn from our stakeholders how to overcome barriers to implementation and adoption, in advance of a larger scale roll-out.

Limitations

Perhaps the largest limitation of this pilot study is our limited sample size, which was chosen due to the pragmatics of recruitment and budgetary constraints. As highlighted by Leon et al, “the primary role of a pilot study is to example the feasibility of a research endeavor” [21]. Our intended sample size is large enough to satisfy the rule of thumb of 12 participants per group (set forth by Julious et al [22]) as appropriate for guiding sample size selection for pilot studies. Although we may not have adequate power to detect effects, this is a true feasibility trial in which we will be able to obtain preliminary data to support and plan for future implementations. Feasibility will be assessed on many different levels, including the feasibility of using BPTrack amongst our target population, within the primary care setting, and within the health system. In addition, the lack of a control or other comparison group is a limitation of our study design; however, given that this is a pilot study to preliminarily investigate the use of this approach in a clinical setting, our single group design is warranted. Future work should seek to incorporate a more robust research design.

Comparison to Prior Work

This type of clinical pharmacist-led mHealth approach to improving HTN management has been demonstrated to be effective within research settings. Although it was undertaken in a different population, a recent study by Margolis et al found that 57.2% of participants randomized to receive an intervention that involved pharmacist case management for HTN, plus home BP telemonitoring, were able to bring their BP down to

controlled levels at 6 and 12 months, versus 30.0% of those receiving usual care [13]. Moreover, at 6-months postintervention, 71.8% of intervention participants had controlled BPs versus 57.1% in usual care [13]. These findings provide strong evidence in support of this approach, yet their study was limited to a research setting, and was not integrated into routine clinical practice. Our pilot study seeks to lay the foundation for translating the Margolis et al findings into practice [13].

Conclusion

This pilot study was designed to document the feasibility and acceptability of a clinical pharmacist-led mHealth approach to managing HTN within a primary care setting. In our 12-week pilot study, we expect to lend support for this approach and lay the foundation for translating this approach into wider-scale implementation, in order to leverage the multidisciplinary care team already in place within primary care, and to improve health outcomes for patients with uncontrolled HTN.

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Authors' Contributions

LRB, HC, CRR conceived of the study. LRB, RK, NGR, MAP, HC, CRR designed the study. DNR, RK conducted data collection and study administration. LRB, RK, DNR prepared the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

MICR peer review report 1.

[PDF File (Adobe PDF File), 438KB - resprot_v6i10e193_app1.pdf]

Multimedia Appendix 2

MICR peer review report 2.

[PDF File (Adobe PDF File), 442KB - resprot_v6i10e193_app2.pdf]

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Abbreviations

ARMS: Adherence to Refills and Medications Scale
BP: blood pressure
DBP: diastolic blood pressure
HTN: hypertension
mHealth: mobile health
SBP: systolic blood pressure

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Protocol

Improving Neuromuscular Monitoring and Reducing Residual Neuromuscular Blockade With E-Learning: Protocol for the Multicenter Interrupted Time Series INVERT Study

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Abstract

Background: Muscle relaxants facilitate endotracheal intubation under general anesthesia and improve surgical conditions. Residual neuromuscular blockade occurs when the patient is still partially paralyzed when awakened after surgery. The condition is associated with subjective discomfort and an increased risk of respiratory complications. Use of an objective neuromuscular monitoring device may prevent residual block. Despite this, many anesthetists refrain from using the device. Efforts to increase the use of objective monitoring are time consuming and require the presence of expert personnel. A neuromuscular monitoring e-learning module might support consistent use of neuromuscular monitoring devices.

Objective: The aim of the study is to assess the effect of a neuromuscular monitoring e-learning module on anesthesia staff's use of objective neuromuscular monitoring and the incidence of residual neuromuscular blockade in surgical patients at 6 Danish teaching hospitals.

Methods: In this interrupted time series study, we are collecting data repeatedly, in consecutive 3-week periods, before and after the intervention, and we will analyze the effect using segmented regression analysis. Anesthesia departments in the Zealand Region of Denmark are included, and data from all patients receiving a muscle relaxant are collected from the anesthesia information management system MetaVision. We will assess the effect of the module on all levels of potential effect: staff's knowledge and skills, patient care practice, and patient outcomes. The primary outcome is use of neuromuscular monitoring in patients according to the type of muscle relaxant received. Secondary outcomes include last recorded train-of-four value, administration of reversal agents, and time to discharge from the postanesthesia care unit as well as a multiple-choice test to assess knowledge. The e-learning module was developed based on a needs assessment process, including focus group interviews, surveys, and expert opinions.

Results: The e-learning module was implemented in 6 anesthesia departments on 21 November 2016. Currently, we are collecting postintervention data. The final dataset will include data from more than 10,000 anesthesia procedures. We expect to publish the results in late 2017 or early 2018.

Conclusions: With a dataset consisting of thousands of general anesthesia procedures, the INVERT study will assess whether an e-learning module can increase anesthetists' use of neuromuscular monitoring.

Trial Registration: Clinicaltrials.gov NCT02925143; https://clinicaltrials.gov/ct2/show/NCT02925143 (Archived by WebCite® at http://www.webcitation.org/6s50iTV2x)

(JMIR Res Protoc 2017;6(10):e192) doi:10.2196/resprot.7527

KEYWORDS

e-learning; neuromuscular monitoring; objective neuromuscular monitoring; quantitative neuromuscular monitoring; residual neuromuscular blockade; protocol

Introduction

Muscle relaxants facilitate endotracheal intubation under general anesthesia and improve surgical conditions. Postoperative residual neuromuscular blockade, or residual blockade for short, occurs if the effects of the relaxant have not subsided or have not been sufficiently reversed before the patient is awakened [1]. Volunteer studies have shown partial paralysis to be associated with general muscle fatigue, double vision, and speech difficulty [2,3]. In clinical studies, residual blockade increased the risk of respiratory complications such as airway obstruction, hypoxemia, and tracheal reintubation as well as the risk of a prolonged length of stay in the postanesthesia care unit [4-7].

The depth of the neuromuscular blockade can be monitored intraoperatively with a neuromuscular monitoring device that measures the muscle response to peripheral nerve stimulation. Typically, the response of the adductor pollicis muscle, adducting the thumb, is measured using an acceleromyographic neuromuscular monitor following stimulation of the ulnar nerve at the level of the wrist [8]. In clinical studies, this type of objective neuromuscular monitoring reduced the incidence of residual blockade and symptoms of muscle weakness [9-11]. Hence, for more than a decade, experts in the field have recommended routine neuromuscular monitoring when administering muscle relaxants [12-15]. Nevertheless, surveys reveal that many anesthetists do not routinely apply neuromuscular monitoring, even if the equipment is available [16-18]. In particular, clinicians often refrain from applying neuromuscular monitoring when administering only the short-acting muscle relaxant succinylcholine because the paralytic effect subsides within 10 minutes in most, but not all, patients. However, it was recently confirmed that even patients receiving only succinylcholine are at risk of experiencing paralysis when awakened from anesthesia, especially if not monitored with a nerve stimulator [19,20].

Repeated local educational efforts in anesthesia departments may increase the use of neuromuscular monitoring and reduce the incidence of residual blockade [21,22]. As these efforts are time consuming and require the presence of expert personnel, it is relevant to consider if an e-learning module may provide an alternative method to increase the use of neuromuscular monitoring. E-learning can achieve results similar to traditional instructional methods, but few studies have assessed the impact of e-learning on patient outcomes, possibly because of the large sample size required [23].

The aim of the INVERT study is to assess the impact of an e-learning module on neuromuscular monitoring on the application frequency of objective neuromuscular monitoring and the incidence of residual neuromuscular blockade in patients monitored with a nerve stimulator.

We hypothesize that the e-learning module will increase the use of objective neuromuscular monitoring significantly in both patients receiving succinylcholine and patients receiving a nondepolarizing muscle relaxant.

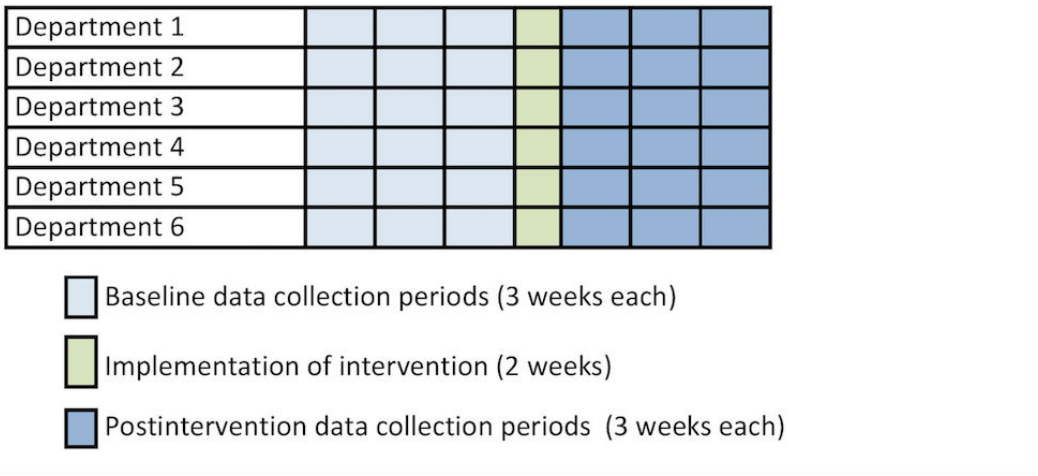
Methods

Design

The study is designed to assess the effect of an e-learning module on all three of the proposed levels of medical education translational research: knowledge and skills, patient care practice, and patient outcomes [24]. A “dilution” of the effect should be expected in the process of changing clinicians’ knowledge, in their behavior as well as actual patient outcomes [23]. Therefore, data from a large number of anesthesia procedures are likely required to obtain adequate strength. To make this feasible, we have chosen to conduct the study at all major hospitals in the Zealand Region of Denmark, where data on use of neuromuscular monitoring are automatically recorded in the anesthesia information management system MetaVision (iMDsoft®, Düsseldorf, Germany). Furthermore, we have chosen the interrupted time series design, in which data are collected repeatedly, at fixed intervals, before and after the intervention (Figure 1).

The effect of the intervention is analyzed statistically using segmented regression analysis, testing for changes in both the level and the trend of the outcome. The design is proposed to be the strongest quasi-experimental approach for assessing the longitudinal effect of interventions and also allows description of the timing of the effect of the intervention [25]. This design is well suited for our setting, where the number of participating departments is limited to the 6 departments of anesthesia at the teaching hospitals in the Zealand Region of Denmark, making experimental designs such as cluster randomized trials unfeasible [26]. Baseline data are being obtained from the descriptive study *“Use of neuromuscular blocking agents and neuromuscular monitoring in 7 Danish teaching hospitals—a cross-sectional study”* (NCT02914119), in which data are collected from the same hospitals in the year leading up to the intervention. The e-learning module was implemented over a period of 2 weeks, and we area again collecting data from all departments at fixed 3-week intervals.

Figure 1. Example of data collection for an interrupted time series study.



Eligibility

Departments

We are including the 6 anesthesia departments at the teaching hospitals in the Zealand Region of Denmark following agreement of the head of each department to participate.

Anesthesia Personnel

We are including the following anesthesia personnel: nurse anesthetists in training, certified registered nurse anesthetists, first- though fourth-year residents in anesthesiology, and certified anesthesiologists. We are excluding personnel without clinical functions, such as administrative personnel.

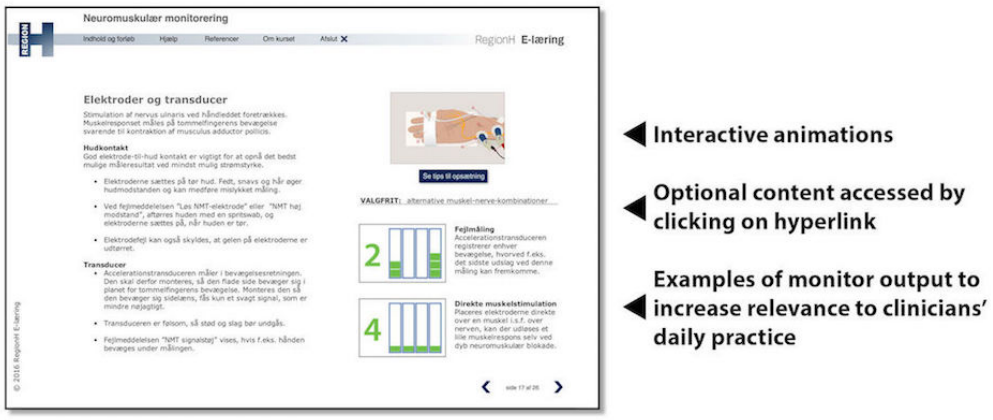
Patients

We are including and collecting data from all patients undergoing general anesthesia with neuromuscular blockade in each data collection period. Patients undergoing general anesthesia on more than one occasion will be included in the analyses as one case for every general anesthetic received.

Intervention: E-Learning Module

The investigator group has developed the e-learning module in collaboration with the Regional Unit for Development and Evaluation of Learning Technologies in the Capital Region of Denmark. Learning objectives for the module are based on a needs assessment, including focus group interviews with nurse anesthetists and anesthesiologists from 5 different Danish hospitals and clinical observations of neuromuscular monitoring use in practice (NCT02239965) as well as a previous Danish survey [18] and expert opinions. The main topics in the course are as follows: (1) background and clinical consequences of residual blockade, (2) neuromuscular monitoring and stimulation patterns, (3) practical tips on monitoring and troubleshooting equipment malfunction, and (4) reversal of neuromuscular blockade. The course participants are of different educational backgrounds and have anesthesia experience ranging from short periods to decades of employment. We have aimed to target this diversity in participant background by making the e-learning module adaptable to learners' needs, specifically by making part of the material optional (Figure 2) [27]. Furthermore, clickable animations are included to stimulate interaction and increase learning [28], while examples of monitor output make the module relevant to participants' daily practice. The course duration is approximately 30 minutes.

Figure 2. Screen shot from e-learning module.



Implementation of the Intervention

We recruited a local investigator at each study site. This person is responsible for motivating the anesthesia personnel to complete the e-learning module and introduce all new employees to it. On the first day of implementation, the local investigators introduced the e-learning module. The primary investigator also visited the departments in the intervention period and introduced the study, but without revealing the primary outcome to the participants. The participating departments ensured that the personnel could complete the module during their normal work hours, such as by having colleagues cover for them while they complete the module. Course progress was logged for each anesthetist, and email reminders were sent to ensure the highest possible completion rate. The local investigator and the head of department were also informed about the completion rate throughout the implementation period. To increase awareness about the study and the e-learning module, the local investigators distributed candies and pens with the INVERT study logo at intervals. New employees joining the departments after the intervention period were also included in the study. The module is available for ongoing access, meaning that learners can still access the module, such as for use as a clinical troubleshooting tool. All anesthetic practices and medication use are at the discretion of the individual anesthetist according to local guidelines.

Blinding

Given the nature of the intervention, it was not possible to blind the anesthesia personnel. However, they are not informed of the specific outcomes, only that the study "aims to assess the effect of the e-learning module on use of neuromuscular monitoring". The investigators in charge of data analysis will not have access to the data until after the final data collection period.

Outcomes

We will assess the effect of the e-learning module on knowledge, behavior, and patient outcomes. A meta-analysis of studies on the effect of Web-based learning indicates that an e-learning module will have greatest effect on knowledge, a smaller effect on skills, and a yet smaller effect on behavior and patient-related outcomes [23]. We have chosen the primary outcome based on what we believe to be of highest clinical relevance, balanced with the feasibility of collecting data on this outcome from thousands of patients.

Primary Outcome

- Application of neuromuscular monitoring in cases involving succinylcholine only
- Application of neuromuscular monitoring in cases involving a nondepolarizing muscle relaxant (with or without succinylcholine)

The primary outcome is divided because the two types of relaxants are used in different clinical situations: succinylcholine for "rapid sequence induction and intubation" and nondepolarizing relaxants for nonemergent tracheal intubation.

Secondary Outcomes

- Last recorded train-of-four (TOF) ratio (a stimulation pattern commonly used in neuromuscular monitoring, where a ratio < 0.9 is defined as residual blockade) before tracheal extubation in patients receiving a nondepolarizing relaxant
- Administration of the reversal agent sugammadex or neostigmine and repeated administration of the reversal agent
- Timing and dosage of reversal with sugammadex or neostigmine in relation to the neuromuscular monitoring values
- Time from administration of the reversal agent (sugammadex or neostigmine) to extubation
- Time from tracheal extubation or removal of the supraglottic airway device to discharge from the postanesthesia care unit in cases involving a nondepolarizing relaxant with or without neuromuscular monitoring
- Pre- and postcourse test scores as a measure of course participants' knowledge

Secondary analyses that may be performed if the data allow it include the incidence of respiratory complications, arterial oxygen desaturation, and the effect of the e-learning module at the individual level.

Data Collection

Data are recorded in the MetaVision anesthesia information management system either automatically or manually, by the anesthetist. TOF data are recorded automatically when the neuromuscular monitoring module is activated. The anesthesia information management system saves TOF data every minute, even if the neuromuscular monitoring module measures a TOF value every 12 seconds. To ensure that the reported TOF values at the time of tracheal extubation are not erroneously measured due to lack of fixation of the patient's hand, movements caused by the surgical personnel, or other factors, we will collect the last five TOF values before tracheal extubation and use the highest value, given that the values increase incrementally. We will develop an algorithm for choosing the last correctly measured TOF value and will perform manual validation on part of the dataset. Data manually entered into the anesthesia information management system include the type and dose of intravenous drugs and the time of tracheal extubation. The anesthetist enters these data by pressing a button in the software and can alter the time and the details, such as the dose of medicine administered, afterward if needed. Where possible, we will seek to validate these manually entered data, such as by comparing them to changes in ventilatory data from the anesthesia machine. In case of doubt about the correctness of data for a particular case, we will access the full dataset for that case in order to investigate further.

Sample Size Calculation and Statistical Analysis

A simulation-based sample size calculation revealed that the sample size necessary to detect an increase in neuromuscular monitoring from 40%-60% (with an 80% power) would require 3 consecutive data collection periods, each comprising approximately 100 patients per site, both before and after the implementation of the intervention. We expected to achieve

this sample size by letting each period be 3 weeks long. The baseline value of 40% was based on a 1-month data sample from quality assurance at the participating hospitals, while the increase to 60% reflects the minimal effect size that we believe would make it worthwhile to disseminate the course to other departments. It is possible that the effect of the module could "wear off" after the 9 weeks of postintervention data collection if either a loss of knowledge occurs or the motivation to use neuromuscular monitoring decreases after the study period. To assess this, we extended the postintervention data collection period beyond what the sample size calculation indicated. This extension is ethically justifiable because prolonging the data collection does not affect patient treatment and because the data are already automatically collected in the anesthesia information management system.

When analyzing the data, we will use segmented regression analysis [25]. All results will be reported with 95% confidence intervals when relevant. We will test continuous variables for normality by visual inspection before summarization with the mean (standard deviation). Non-normally distributed continuous variables and ordinal variables will be described as the median (95th percentile range) and categorical variables as the number (percentage), if not otherwise specified. Analyses will be performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). The investigators JLT and LTS will conduct the analyses. We will consider a two-tailed *P* value of less than 0.05 to be statistically significant.

Missing Data

In the analysis of the secondary outcomes, we will exclude cases with missing data on the outcome studied, that is, we will perform only per-protocol analyses. However, in reporting of the median TOF ratio at tracheal extubation, we will include both an analysis where a TOF count between 0 and 3 (and hence no TOF ratio reported) is included as a TOF ratio of 0 and a per-protocol analysis where only cases with a TOF ratio are included. Furthermore, we will report the proportion of patients transferred from the operating room while still tracheally intubated and, if possible, report the cause for this, such as severe residual neuromuscular blockade.

Ethical Considerations and Study Registration

The study solely uses data routinely registered in the anesthesia information management system. The Committees on Health Research Ethics for the Capital Region of Denmark have confirmed that the study does not need approval from the committee system and that there is no need for individual patient consent (protocol no. 16028220). The study is registered at clinicaltrials.gov (NCT02925143) and with The Danish Data Protection Agency (HGH-2015-063/04364).

Results

All 6 anesthesia departments agreed to participate in the study. The e-learning module was implemented simultaneously in all departments on 21 November 2016. Currently, postintervention data are being collected. We expect to publish the results in late 2017 or early 2018.

Discussion

We have designed a study that aims to assess the value of an e-learning module on neuromuscular monitoring at all levels of potential effect: knowledge and skills, patient care practice, and patient outcomes. We expect that the multicenter design and the large number of participants completing the e-learning module will increase the internal and external validity of results. The primary outcomes are automatically recorded in the anesthesia information management system, increasing the validity of the collected data.

While randomized controlled trials are the gold standard of design in clinical research, this design is sometimes unfeasible in medical education research. Participants, in our case anesthesia personnel, completing the e-learning module cannot be randomized individually to use or not use the knowledge that they gained from the module. Similarly, while it is practically possible to randomize patients at a particular hospital to receive treatment from either an anesthetist who had completed the module or one who had not, there would be a nesting effect that could affect the results, such as due to local traditions regarding neuromuscular monitoring. The effect of the intervention could also spill over from anesthetists in the intervention group to the control group, such as through teamwork or meetings. One way of overcoming this challenge would be to conduct a cluster randomized trial [26], but, as mentioned earlier, this was not possible because of the limited number of potential participating departments. It is important to note, however, that the INVERT study aims to answer the question "can use of neuromuscular monitoring be increased by implementing an e-learning module on the subject?", as opposed to assessing the effect of e-learning in general. Therefore, the interrupted time series design may very well be the optimum choice of design [25]. Furthermore, the baseline study describing use of neuromuscular monitoring in the participating departments in the year leading up to implementation of the e-learning module may, to some degree, account for not having a control group by describing an underlying trend in use of monitoring (ie, the departments function as their own historical controls).

There will be some limitations to the study. The anesthetist manually enters certain data in the anesthesia information management system, which should be taken into account when interpreting the results. Studies reporting on the incidence of residual neuromuscular blockade typically measure the TOF ratio upon arrival to the postanesthesia care unit. As this approach would require the presence of investigators in all departments at all times throughout the study period, it was not possible in our study. Instead, we chose to use the data that were readily available from the anesthesia information system, namely, the last recorded TOF ratio in the operating room. For this reason, we will not obtain data on this secondary outcome for patients without monitoring with a nerve stimulator. Finally, we did not design the study to assess the effect of the e-learning module at the individual participant level, but rather at the levels of each department, as a whole. However, if possible with the data obtained, the former will described in a secondary analysis.

Perspectives

One of the advantages of Web-based learning, such as an e-learning module, is that participant numbers can be increased with only small expenses [29]. If the e-learning module proves effective in increasing the use of neuromuscular monitoring, it may be implemented in all Danish anesthesia departments or in the training of anesthesiologists and nurse anesthetists both nationally and internationally.

In conclusion, with a dataset consisting of thousands of general anesthesia procedures, the INVERT study will thoroughly assess whether an e-learning module can increase anesthetists' use of neuromuscular monitoring.

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Conflicts of Interest

JLT received two research grants from the Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp. There were no other potential conflicts of interest.
MRG received research grants from the Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp and received speaker's fees from Merck.
The other authors had no conflict of interest to decare.

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Abbreviations

TOF: train-of-four

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Protocol

Adoption, Acceptability, and Effectiveness of a Mobile Health App for Personalized Prostate Cancer Survivorship Care: Protocol for a Realist Case Study of the Ned App

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Abstract

Background: By 2030, prostate cancer will be the most commonly diagnosed cancer in North America. To mitigate this impending challenge, comprehensive support mechanisms for disease- and treatment-specific changes in health and well-being must be proactively designed and thoughtfully implemented for streamlined survivorship care. mHealth apps have been lauded as a promising complement to current outpatient treatment and monitoring strategies, but have not yet been widely used to support prostate cancer survivorship needs. A realist evaluation is needed to examine the impact of such apps on the prostate cancer survivorship experience.

Objective: We seek to gain an understanding of how an mHealth app for prostate cancer survivorship care called Ned (No Evident Disease) is adopted and accepted by patients, caregivers, and clinicians. We also aim to determine the effect of Ned on health-related quality of life, satisfaction with cancer care, unmet needs, self-efficacy, and prostate cancer-related levels of anxiety.

Methods: The Ned case study is a 12-month mixed-methods embedded single-case study with a nested within-group pre-post comparison of health outcomes. We will give 400 patients, 200 caregivers, and 10 clinicians access to Ned. Participants will be asked to complete study assessments at baseline, 2 months, 6 months, and 12 months. We will conduct 30 semistructured qualitative interviews with patients (n=20) and their caregivers (n=10) poststudy to gain insight into their experience with the app.

Results: We recruited our first survivor in October 2017 and anticipate completing this study by May 2019.

Conclusions: This will, to our knowledge, be the first realist case study to evaluate an app for prostate cancer survivorship care. Prostate cancer survivors are set to increase in number and longevity, heightening the need for integrated survivorship solutions to provide them with optimal and durable outcomes. The knowledge gained from this study will comprehensively inform how and why Ned works, for whom, and in what circumstances. Understanding the impact of digital health interventions such as Ned on how survivors care for themselves is critical to realizing patient-centered care.

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KEYWORDS

prostate-specific antigen; prostate cancer survivorship; prostate cancer; patient-centered care; mobile health; mHealth; telemedicine; mobile health app; realist evaluation; case study

Introduction

Background

By 2030, prostate cancer will be the most commonly diagnosed cancer in North America [1,2]. The global population is also aging, with the number of those aged 60 years and over expected to rise from 1 in 10 currently to 1 in 6 in the next 10 years; the United Nations estimates that by 2050, this number will grow to be 1 in 3 [3]. Given the increased risk with age for this increasingly high-mortality cancer, an unprecedented population of prostate cancer survivors will require specialized support and services from a potentially underprepared health care system [4,5]. To mitigate these impending challenges, durable support mechanisms for disease- and treatment-specific changes in health and well-being must be proactively designed and thoughtfully implemented for streamlined survivorship care.

The definition of prostate cancer survivorship has changed with the understanding that the patient experience encompasses far more than just medical treatment [6]. Following diagnosis and primary treatment, patients are discharged into the community and face significant long-term health challenges as a result of their treatment; these include physical, rehabilitation-related, psychological, and emotional needs, coupled with the needs of their caregiver [7]. Seminal research on quality of life among prostate cancer survivors has revealed a decrease in quality of life across numerous domains, notably sexual and urinary function [8]. These physical aspects of prostate cancer survivorship are further exacerbated by anxiety in both patients and their caregivers as they follow their prostate-specific antigen (PSA) values to assess for recurrence [9]. These aspects should be systematically captured via patient-reported outcome measures (PROMs) to inform personalized, patient-centered, and value-based care [10]. Despite robust efforts, there has not yet been a successful initiative to link the collection of prostate cancer-specific PROMs with clinical markers such as PSA values in a way that facilitates and positively informs the clinical interaction; the combination of both measures may advance an evidenced-based understanding of both physiological and personal self-reported prostate cancer status.

Three critical problems have been identified in the overall clinical management of prostate cancer survivorship: (1) patients do not know how they are doing and how they compare with other matched patients; (2) clinicians are not optimally informed about patient issues in a systematic and evidenced-based manner; and (3) patients receive fragmented care [11]. There is also a lack of communication and information sharing between clinicians, patients, and caregivers, which adds further strain on survivor supportive care needs [12-14].

Digitally Mediated Prostate Cancer Survivorship Care

In recent years, digital health interventions have presented new opportunities and challenges for cancer care, with systematic reviews suggesting their overall usefulness and acceptance for cancer patients and their caregivers [15]. Research on how prostate cancer survivors understand the health information presented to them and communicate that information to their circle of care suggests that they are willing and able to use digital health interventions for illness management support [16]. Prostate and testicular cancer survivors in particular have a more positive attitude toward online contact with clinicians than do survivors of other cancer groups [17]. However, these survivors also have a greater need for decision-making support and preparation before communicating with health personnel [16]. Successes in remote and digital prostate cancer survivorship care delivery have been realized, with recent work on the effectiveness of urology telemedicine clinics suggesting that the remote delivery of general urologic care is cost effective and results in high patient satisfaction [18]. Efforts have also been made to incorporate electronic PROMs into the management of survivorship care for improved communication between patients and their care team [19]. This has been complemented by work in Web-based education programs for prostate cancer survivors transitioning from active treatment [20], as well as mobile phone-based interventions to increase adherence to oral antiprostate cancer medications [21]. Further, the collection of PROMs and their linkage with clinical prostate cancer registry data has been operationalized [22]. However, formal evaluations have not yet been conducted to examine the impact of these systems, leaving an unfinished translation from theoretical framework to practical implementation.

Ned: A Prostate Cancer Survivorship App

The recent endorsement of mHealth, broadly defined as a health intervention that has been operationalized into an app for patient use and is delivered or supported through the use of wireless devices (eg, mobile phones, tablets, media players, wearables), has been lauded as a promising complement to current outpatient treatment and monitoring strategies for chronic care [23]. In particular, the ubiquity of mobile phone use has facilitated the adoption of mHealth apps for immunization record keeping [24], heart health [25], and diabetes self-management [26]. In November 2012, a proof-of-concept mHealth app prototype for personalized prostate cancer survivorship care was conceptualized at the Hacking Health Codeathon in Toronto, Canada [27]. From 2014 to 2017, the app was translated from prototype to product, and a user-centered needs assessment and usability evaluation were conducted to inform app content and functionality (University Health Network Research Ethics Board [REB] ID#14-7510). Ned (No Evident Disease) is the first app to provide patients with access to individual-level PSA values streamed directly from the Ontario Laboratories Information System (OLIS) to their own smartphone. The mHealth app for patients and their caregivers, along with a clinician-facing app and complementary Web-based dashboard, were developed using Fast Healthcare Interoperability Resources, which facilitate interoperability with existing Canadian provincial and federal health care assets [28]. Ned aims to promote self-care by informing patients directly of their PSA results and providing them with a personalized view of their own symptoms. It supports real-time clinical decision making by providing clinicians with PROMs collected in-app, and includes a curated educational feed and support group links. Ned is not meant to take the place of an informative discussion between patient and provider; however, there is an acknowledgement that, in reality, patient-provider interactions may be brief, and patients may require additional communication channels, which may lead to

more meaningful interactions and improve shared decision making.

Innovative mHealth Clinical Trials

Previous work by our research group has identified a homogeneity in the range of study designs used to evaluate mHealth apps [29]. mHealth researchers have been reluctant to deviate from traditional study designs, namely the parallel-group randomized controlled trial. We believe there is value in diversifying the types of study designs used in the mHealth field—it is imperative that we broaden the range of research questions being asked to elicit useful, relevant, and timely research findings that keep pace with the technology under study [30-32]. We have therefore aimed to design an evaluation that asks not "does Ned work," but instead asks "how or why does Ned work or not work, for whom, to what extent, in what respects, in what circumstances, and over what duration?" [33]. We posit that this paradigm shift in evaluative approach will capture the nuanced stories of how Ned is received by its intended users and inform meaningful iterations of the app to optimize prostate cancer survivorship care.

Objectives

This protocol outlines a pragmatic, mixed-methods embedded single-case study with a nested within-group pre-post comparison of health outcomes, guided by Pawson and Tilley's realist evaluation principles [33], to elicit a context-focused and mechanism-driven understanding of outcomes derived from the use of Ned by patients, caregivers, and clinicians within a public hospital network in Toronto, Canada. The aims of this study are 2-fold: (1) to gain an understanding of how a prostate cancer survivorship app called Ned for viewing laboratory results and collecting patient-reported outcomes is adopted and accepted by patients, caregivers, and clinicians; and (2) to determine the effect of Ned on health-related quality of life, satisfaction with cancer care, unmet needs, self-efficacy, and prostate cancer-related levels of anxiety.

Methods

Theoretical Approach

We will use the realist evaluation framework to guide the interpretation of this case study [33,34]. Realist evaluations are designed to inform an understanding of how and why interventions work or do not work in particular contexts. They belong to a family of theory-based evaluation approaches that aim to establish the "program theory" of an intervention: the mechanisms that are likely to operate, the contexts in which they might operate, and the outcomes that will be observed if they operate as expected [35]. Realist approaches assume that nothing works everywhere for everyone, and that it is the context in which an intervention operates that will significantly affect outcomes. Researchers who engage with this methodology collect data on the contextual features that might affect how and for whom an intervention is expected to work, and then analyze the data to examine the interaction between context and mechanisms of action [36]. The adoption of this methodology has grown in the health services research community and is now recognized as a powerful approach to designing and analyzing complex evaluations [37]. Realist evaluations are particularly well suited for evaluating digital health interventions given the complex sociotechnical relationship between users and technology [38]. They are also more conceptually suited to capturing the dependency between a technology's success and its implementation plan [36]. We believe this approach will enable us to draw meaningful insights from our case study that are representative of how Ned performs across various use cases and stakeholder groups.

Trial Design

The Ned case study is a 12-month mixed-methods embedded single-case study with a nested within-group pre-post comparison of health outcomes. We will evaluate the adoption, acceptability, and effectiveness of Ned as perceived by the 400 patients, 200 caregivers, and 10 clinicians who are given access to the app. Our aims are both observational and experimental: we are interested in deriving a deep understanding of how Ned affects survivorship care, but also in establishing parameters of possible clinical change to inform the effect of the app on quality-of-life outcomes. We also seek to identify the process mechanisms required to introduce Ned into a public health network, specifically the resources required to support the platform. This knowledge will inform future innovation diffusion efforts for Ned as we look to scale the platform across Canada. We will employ a combination of semistructured interviews, questionnaires, and qualitative observations to illustrate a rich picture of how Ned is adopted, whether it is accepted, and the effect it has on how prostate cancer survivors and their care team experience survivorship care. We have obtained REB approval from the Trillium Health Partners (THP) hospital network for this research (THP REB ID#826). Table 1 outlines the multiple embedded units of analyses planned for this study.

Table 1. Summary of embedded units of analyses for the evaluation of the Ned app.

Embedded unit of analysis	Data sources
Patient, caregiver, and clinician adoption of Ned	Analytics log data on the number of patients, caregivers, and clinicians who are invited to open a Ned account, and the consequent number of Ned accounts created
Patient acceptance of Ned	Analytics log data on the frequency, duration, depth, and breadth of patient engagement with the app
	Interviews with 20 patients poststudy
	Web-based questionnaire assessing acceptability
	Qualitative observation of patients using Ned to access prostate-specific antigen results and submit patient-reported outcome measures
Caregiver acceptance of Ned	Analytics log data on the frequency, duration, depth, and breadth of caregiver engagement with the app
	Interviews with 10 caregivers poststudy
Clinician acceptance of Ned	Analytics log data on the frequency, duration, depth, and breadth of clinician engagement with the app
	Wed-based questionnaire assessing system use to be completed by 10 clinicians
Clinical effectiveness of Ned	Five validated patient-reported outcome measures (ie, quality of life, treatment satisfaction, unmet needs, self-efficacy, anxiety) administered at baseline, 2 months, 6 months, and 12 months

Eligibility Criteria

Patients must meet the following eligibility criteria to be enrolled into the study: (1) 18 years of age or older, (2) receiving care at the THP Mississauga Hospital or Credit Valley Hospital, (3) pathology report confirming prostate cancer diagnosis via transrectal, transperineal, or transurethral biopsy (standard 12-core template), (4) life expectancy more than 1 year, (5) no concomitant cancer diagnosis, (6) own a device that is compatible with the Ned app and is Web enabled through a data plan or Wi-Fi capabilities, or both (eg, laptop, desktop, tablet, smartphone), (7) able to read, write, and speak English.

Clinicians (ie, urologists, surgical oncologists, radiation oncologists) who are employed by the THP hospital group, practice at either the Mississauga Hospital or Credit Valley Hospital, and are involved in the care of patients with a diagnosis of prostate cancer are eligible to participate in this study; our research group has secured Privacy Impact Assessment and Threat Risk Assessment agreements with both hospitals. Caregivers must be paired with a patient who is enrolled in the study to be eligible for access to Ned. We broadly define caregivers here as a spouse, relative, friend, or formal caregiver of the patient who significantly contributes to their care.

Recruitment

Clinician Recruitment

The clinical champion for Ned is a urologist at THP and will initiate clinician recruitment through snowball sampling his colleagues (clinicians from urology, urologic oncology, radiation oncology, and medical oncology departments) from both THP hospitals. Clinicians who express interest in joining the study will provide the clinical champion with their primary contact number. The clinical champion will forward this number to the study coordinator (SC), who will initiate first contact with the clinician through a telephone call. The SC will provide the clinician with information about the study procedures and set a time to meet with the clinician to install Ned in their clinic. The SC will collect informed consent directly from the clinician at their clinic before setting up their Ned account. Once the SC sets up the account, the clinician will enter their medical license number to receive PSA values from OLIS and release them to patients. Clinicians can then invite and add patients from their roster into the study.

Patient Recruitment

Patients will be recruited into the study through an invitation from their clinician during a visit to the clinic. If patients express interest in using Ned as part of their survivorship care resources and meet the study eligibility criteria as assessed by their clinician, their email address will be collected by the clinician and forwarded to the SC. The SC will then initiate first contact with the patient through email to confirm study eligibility, provide a study sheet with a brief description of the study (eg, study purpose and procedures, relevant risks and benefits), and obtain digital consent through a Web-based consent form that can be digitally signed by the patient. Once the patient's digital consent is verified, they will be prompted to complete a series of demographic and baseline outcome questionnaires. The SC will receive a notification when the patient digitally consents to join the study and completes their baseline assessment, and will email the patient's clinician to open a Ned account on the patient's behalf. The clinician will log on to their own Ned account and invite their patient to use Ned. The patient will then have access to Ned and can invite and add their caregiver to use the app.

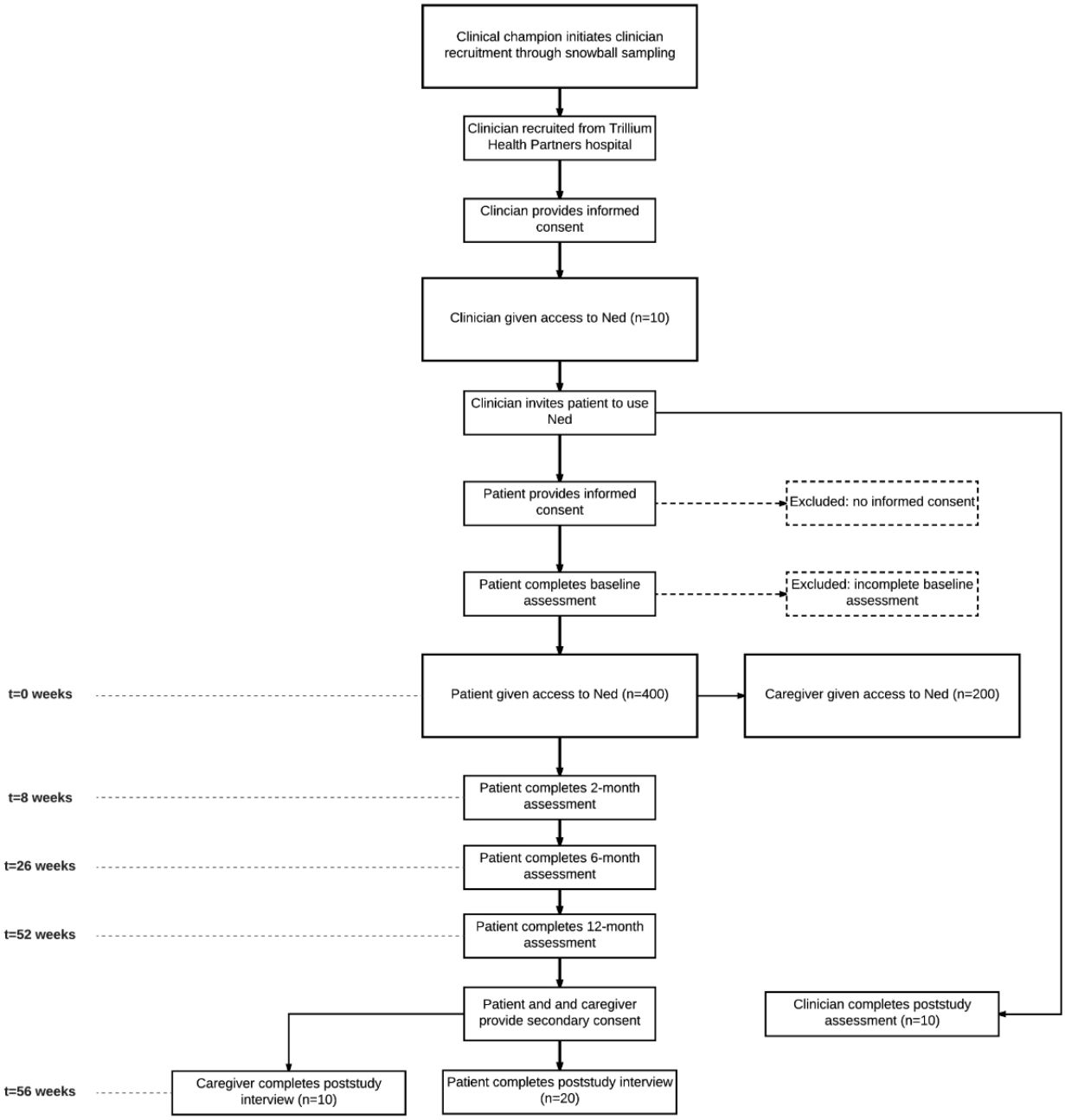
Caregiver Recruitment

Caregivers will be invited to use Ned by their partners through a feature in the patient-facing version of Ned that allows them to add a caregiver to view their health data and complete PROMs on their behalf. When the patient uses this feature, the caregiver will receive an email with a link to sign up for Ned. The patient

will verbally communicate a secret word to their caregiver, which the caregiver will then enter as part of the account creation process. The caregiver will then have access to Ned.

Figure 1 presents the study flow for patients, caregivers, and clinicians from recruitment through to study conclusion.

Figure 1. Ned study flowchart.



Consent

Clinicians will consent to participate in the Ned study by digitally signing a Web-hosted consent form provided to them by the SC in clinic. Patients will provide electronic consent by digitally signing a Web-hosted consent form provided to them by the SC through email. Caregivers will be asked to provide digital consent only if they express interest in attending a poststudy interview to share their experience of using Ned. Given that the "Add a caregiver" feature of Ned is controlled by the patient and is a native feature of the app itself, we believe that it is appropriate for patients to consent on behalf of any caregiver they add to use the app. Patients are clearly informed in their consent form that they have the ability to add a caregiver to use Ned; if they consent to using the app for the purposes of this research, they are consenting to be given access to all the features within Ned. Caregivers will be eligible to attend a poststudy interview only if their partner (the patient) has completed an interview themselves.

At study conclusion, we will ask patients and caregivers whether they would like to attend a poststudy interview to share their experience of using Ned. We will then collect a separate consent form from interested patients and caregivers at the interview. Rolling recruitment of patients who have completed the study

and their paired caregiver will be done until 20 patients and 10 caregivers have been interviewed.

Cost and Reimbursement

Patients will receive a Can $5 gift card for every study assessment completed and an additional Can $5 for completing all 4 study assessments, for a total of Can $25 as compensation for their participation in this study. If patients and caregivers choose to attend the 30-minute semistructured interview poststudy with the SC, they will receive a reimbursement of Can $25 for the cost of their parking. Clinicians will not be compensated for participating in this study.

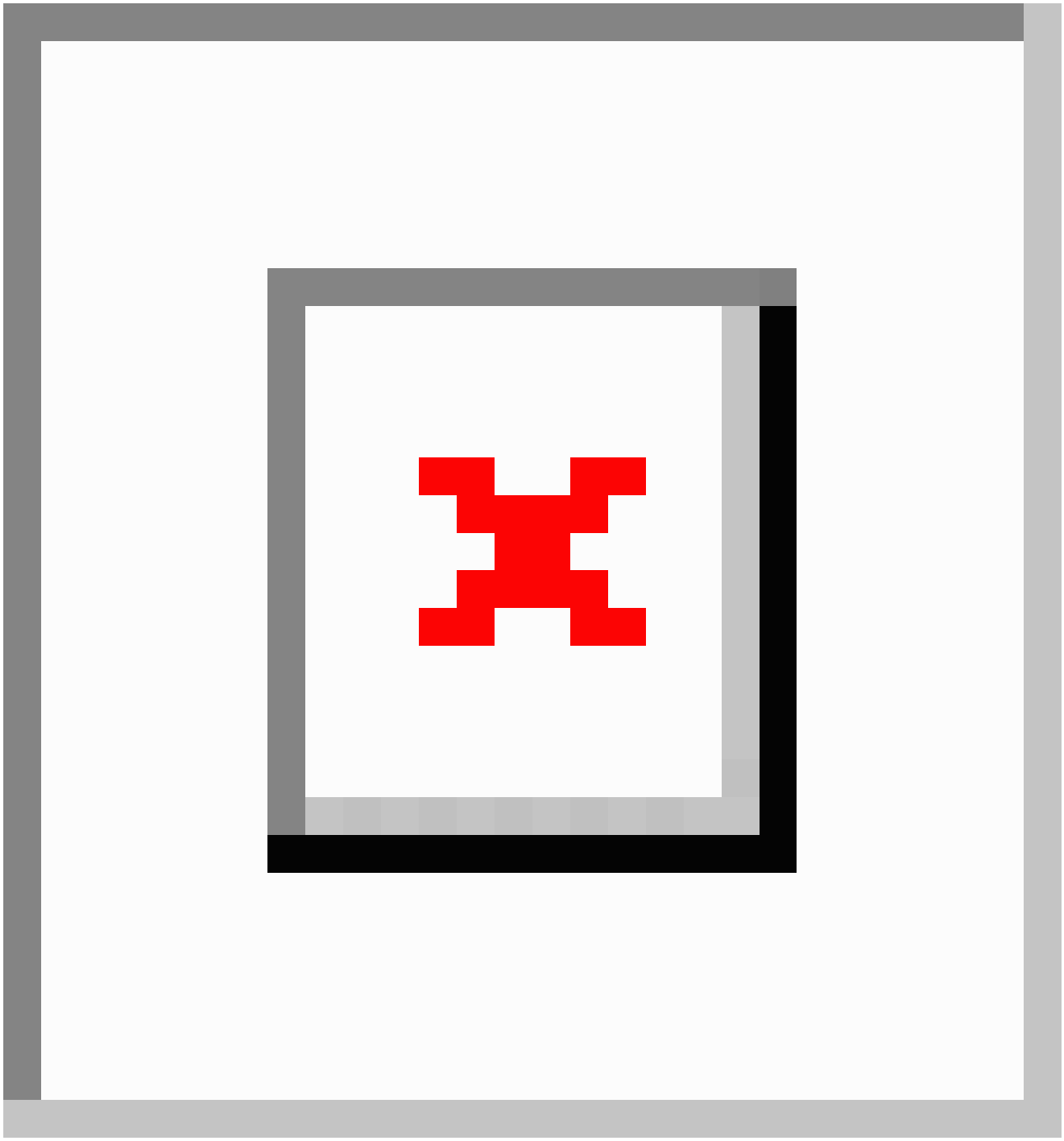
Intervention

The Ned app facilitates prostate cancer survivorship self-care and ownership of personal health data, and enables survivors to share their care plan with their caregiver and clinician to streamline care. Once patients complete the initial download of the Ned app and create an account, they are able to access all of Ned's features. Patients can check their PSA values from directly within the app once their clinician has approved and released them. All values are first sent from OLIS to the clinician on their version of the Ned app. The clinician must review and approve these values by physically clicking on a button that confirms their attestation to the validity and appropriateness of the value. Only after the clinician has approved and released the PSA value to their patient does it get sent to the patient, who can then view it on their version of the Ned app.

Patients will have scheduled monthly PROMs, specifically the Expanded Prostate Cancer Index Composite (EPIC-26) [39] and the Functional Assessment of Cancer Therapy-Prostate [40], to measure their prostate cancer-specific quality of life. Patients will be prompted to complete these PROMs in-app and submit them directly to be viewed by their clinician on the Ned clinician dashboard. Ned will provide immediate feedback to patients on their health and well-being status with the submission of every PROM.

The app also provides patients with access to Ned's Notes, a curated feed of educational content coupled with upcoming local social events related to prostate cancer survivorship care. Patients are able to add caregivers to their account; when granted access, caregivers can complete PROMs on behalf of the patient, view PSA results, and take freehand notes on observable health concerns. The centralized hosting of laboratory and PROMs data enables both patients and clinicians to have access to shared data, in the hopes of fostering greater informed decision making. The Ned clinician app and dashboard will provide clinicians with a list of alerts, both for out-of-range PSA and for PROM values. Clinicians can drill down into individual patient profiles and view their PSA values over time. They are also able to view all submitted PROM values and are alerted to outlier trends that require clinical intervention. Figure 2 presents (a) the graphical view of PSA results; (b) Ned's Notes; and (c) the EPIC-26 survey.

Figure 2. Screenshots of the Ned app. (a) Graphical view of prostate-specific antigen (PSA) results; (b) Ned's Notes; and (c) the Expanded Prostate Cancer Index Composite (EPIC-26) survey.



Data Collection

Adoption of Ned

Our decision to study the adoption of Ned by patients, caregivers, and clinicians was informed by previous pivotal evaluative work on the adoption, nonadoption, and abandonment of a personal electronic health record in the United Kingdom. Greenhalgh et al's [41] focus on adoption as a primary study outcome revealed a complex and dynamic narrative between patients and health care "experts:" there is a discrepancy between the expectations placed on patients to adopt health technology perceived as beneficial to them, and the reality of what patients actually perceive as beneficial for their own health and well-being [41]. We have therefore selected adoption as a core outcome for our own study and seek to identify the realist context-mechanism-outcome configurations to explain how Ned is adopted (or not) by its users. We define adoption as the active translation of intention into measurable action; this is operationalized as the number of patients, caregivers, and clinicians who are invited to open a Ned account and the consequent number of Ned accounts created.

Acceptability of Ned

To achieve effective health promotion using health technology, it is essential that patients perceive a given treatment to be an acceptable and welcome addition to their care [42]. The acceptance of technology has been widely studied, with efforts

made in recent years to contextualize this understanding within the health care domain [43]. We define acceptability here as the behavioral intention to use a technology, leading to actual use and consequent use behaviors. For this work, we have chosen to frame our measurement of acceptability through adapting and operationalizing the unified theory of acceptance and use of technology (UTAUT) model [42] into a quantitative questionnaire (Multimedia Appendix 1). The UTAUT is a theoretical model and instrument used to assess the likelihood of user acceptance for a new technology. It has been extensively used to evaluate the factors affecting the acceptance and use of new health technologies [44], including in an evaluation of patient acceptance of an automated text messaging system for improved prostate cancer screening adherence [45]. While the original model identifies 7 predictor constructs for behavioral intention (ie, performance expectancy, effort expectancy, social influence, facilitating conditions, hedonic motivation, price value, and habit), we felt it appropriate to modify the model to better align with the context in which Ned will be implemented. We have therefore removed 2 constructs from the overall model, hedonic motivation and price value, and have also added baseline belief in treatment credibility and outcome expectancy as a predictor variable for both behavioral intention and use behavior.

Our justifications for these decisions are as follows: hedonic motivation, defined as enjoyment while using technology, is not a relevant construct to evaluate Ned given that the app was designed to deliver PSA results, which are a source of anxiety for many prostate cancer survivors [9]. Previous research on patient portal acceptance using the UTAUT model has also recommended the removal of this construct, with the rationale that health technology primarily designed to deliver condition-specific information is intrinsically driven by the presence of a health *problem* —something that does not promote enjoyment [46]. Price value was also not an applicable construct for Ned, since patients will be receiving the app for free and will therefore be unable to comment on its value for money. Finally, we are asking patients to rate their belief in the treatment credibility and outcome expectancy of Ned to improve their survivorship care [47]. The degree to which patients initially believe that a given treatment will benefit their health and well-being has been shown to strongly affect treatment outcomes for chronic conditions [48]. We posit that a patient's initial belief in Ned will correlate with their ultimate acceptance of the app for survivorship care.

Effectiveness of Ned

While a substantial amount of research has been done to address the functional impairments caused by prostate cancer treatments, less emphasis has been placed on alleviating the psychological and emotional barriers faced by survivors throughout their survivorship experience. There is recognition that, while overall satisfaction with prostate cancer follow-up care is high, the presence of problematic treatment-related side effects is associated with higher psychological morbidity, poorer self-efficacy, greater unmet needs, and poorer overall health status [49]. Strategies for identifying those men with ongoing problems, alongside new interventions and models of care tailored to individual needs, are needed to improve quality of life. Novel solutions have been devised, notably the successful implementation of a real-time dashboard platform to integrate prostate cancer-specific PROMs into clinical settings that resulted in higher patient quality of life and satisfaction with care [10]. We are encouraged by this work and seek to explore whether our own technology, which combines the collection of PROMs with the provision of PSA values, can achieve similar outcomes. To establish the degree to which Ned can significantly improve how prostate cancer survivors experience their care, we chose to investigate the app's impact on 5 specific clinical outcomes: health-related quality of life, satisfaction with cancer care, unmet needs, self-efficacy, and prostate cancer-related level of anxiety. We have operationalized our outcomes using a collection of existing validated questionnaires that have been widely used in prostate cancer survivorship research to standardize our work and facilitate future meta-analyses [50]. We have also selected a data collection schedule matching that of the largest prostate cancer survivorship study ever conducted to enable the comparison of any generated data trends with existing population baseline data [8]. In addition to collecting outcomes data, we will also review patient charts to collect the following clinical variables: Gleason score, cancer stage, treatment group (ie, active surveillance, postsurgery, castration resistant, postradiation, postsalvage radiation, and hormone sensitive), and comorbidities. Table 2 lists the data collection schedule for all outcome measures.

Table 2. Data collection schedule for outcomes measures.

Measure	Data collection method	n	Baseline	2 months	6 months	12 months
Use data	Log data analytics software	610	Throughout study duration			
Demographic data	Web-based questionnaire	400	x			
Clinical data	Chart review	400	x			
Credibility/Expectancy questionnaire	Web-based questionnaire	400	x			
Expanded Prostate Cancer Composite	Web-based questionnaire	400	x	x	x	x
Prostate Cancer-Related Quality of Life Scales	Web-based questionnaire	400	x			
Service Satisfaction Scale for Cancer Care	Web-based questionnaire	400	x	x	x	x
Supportive Care Needs Survey	Web-based questionnaire	400	x	x	x	x
Self-Efficacy for Managing Chronic Disease Scale	Web-based questionnaire	400	x	x	x	x
Memorial Anxiety Scale for Prostate Cancer	Web-based questionnaire	400	x	x	x	x
Modified UTAUT[a] survey	Web-based questionnaire	400				x
Patient qualitative interviews	(1) Semistructured live interview (2) Qualitative observation of app use	20				x
Caregiver qualitative interviews	Semistructured live interview	10				x
Clinician System and Use Assessment Survey	Web-based questionnaire	10				x

[a]UTAUT: unified theory of acceptance and use of technology.

Health-Related Quality of Life

We will assess prostate cancer-specific quality of life and functional recovery after treatment using the EPIC-26 [39]. The EPIC-26 is a reliable and valid scale with 26 items assessing 5 health domains: urinary continence, urinary irritation, sexual function, bowel function, and hormonal expression. It is scored on a summary scale from 0 to 100, with higher scores corresponding to higher health states. We will also use the Prostate Cancer-Related Quality of Life Scales [51] to complement the EPIC-26, as the scales are designed with a stronger focus on patient perception and derived meaning from treatment outcomes. Each individual scale contains between 2 and 8 items and is rated on a 5-point Likert scale. We will specifically be using the following 6 scales: Health Worry, PSA Concern, Cancer Control, Informed Decision, Regret, and Outlook.

Satisfaction with Cancer Care

We will assess patients' satisfaction with their treatment outcomes using a cancer care-specific adaptation of the Service Satisfaction Scale [52,53]. This scale is often used in combination with the EPIC-26 to capture the relationship between quality of life and satisfaction with outcomes [8]. It consists of 16 items and measures several aspects of satisfaction, including satisfaction with outcomes, provider manner and skill, health information, and access. Responses are scored and converted to a scale from 0 to 100, with higher scores indicating higher levels of patient satisfaction.

Unmet Needs

We will use the 34-item Supportive Care Needs Survey Short Form (SCNS-SF34) [54] to assess a patient's current level of need across 5 domains: psychological, health system and information, physical and daily activity, patient care, and support and sexuality. This validated instrument has been previously used in prostate cancer survivorship studies, where it led to the determination that the most prevalent unmet needs are related to sexual issues, concerns about significant others, and anxieties around the possibility of recurrence [9]. We will be using a modified version of the SCNS-SF34 with a simplified response format, which was validated for use with prostate cancer survivors [55].

Self-Efficacy

The Self-Efficacy for Managing Chronic Disease Scale [54] was developed to measure self-efficacy in people with chronic conditions. It has been previously used in a cancer patient population, and has also been adapted to assess cancer-specific self-management behaviors. We will therefore be using the adapted Cancer Survivors Self-Efficacy Scale for this research [49]. Patients will rate their confidence to perform 6 self-management behaviors on a scale of 1 to 10. A mean score will then be calculated, with a higher value indicating greater self-efficacy. Previous investigations into prostate cancer survivor self-efficacy have been positive; patients reported being generally confident with their ability to keep their symptoms or health problems from interfering with their lives. In relation to cancer specifically, patients were also generally confident they could access information and support, deal with problems the cancer may have caused, and contact their clinicians with

any problems. We are interested in exploring whether our patient population will share a similar self-efficacy status.

Prostate Cancer-Related Level of Anxiety

We will assess the psychological difficulties faced by prostate cancer survivors using the Memorial Anxiety Scale for Prostate Cancer (MAX-CP) [56], which has been validated to measure anxiety in men with prostate cancer receiving ambulatory care. This 18-item scale consists of 3 subscales measuring anxiety related to prostate cancer, fear of recurrence, and PSA-related anxiety. In the original validation study, it was anticipated that patients with rising PSA levels would display more PSA-related anxiety; however, this hypothesis received only limited support and correlated modestly with changes in MAX-CP scores. We would like to further explore this correlation in our own patient population to better understand the sensitivity of PSA-related changes to anxiety status.

Patient Experience of Ned

In addition to exploring the acceptability of Ned by patients, we will also ask them about their experience using the app to capture emerging themes of how it translates into a real-world setting. We will conduct semistructured interviews with 20 patients at study conclusion, alongside a qualitative observation session where we will ask patients to perform a series of tasks in Ned while observed by an evaluator. The contents of this interview will be modeled after the Greenhalgh interview framework [41] (Multimedia Appendix 2). This will help us to determine the design-translation gap and improve the app's workflow. The research team will recruit interviewees through snowball sampling all patients who complete their 12-month study assessment and consent to being interviewed. This will mean that patients who are enrolled earlier will have a greater chance of being interviewed poststudy about their experience with Ned. Our justification for this decision is proactive in nature: we want to understand how patients experience Ned as early as possible so that we can address any reported concerns or difficulties with the app and improve it for the remaining participants in the study. This will ultimately ensure that the least number of patients possible will be exposed to an unfavorable version of Ned.

Caregiver Experience of Ned

The experience of prostate cancer survivorship is often a shared one, with the caregivers of survivors taking on the responsibility of advocating for greater survivorship care [57]. Caregivers should be fully integrated into the circle of care and have access to the same information as patients do if they are expected to effectively advocate on their behalf. We believe that for Ned to have a meaningful impact on the survivorship experience, the app must enable caregivers to easily access their partner's health data to create a full record of care. Ned must also be a seamless and facilitating addition to the tasks of care. As caregivers advocate for their partners' health needs, a fluid transfer of data between patient, caregiver, and clinician that can be referenced and acted upon during point-of-care interactions may help to improve overall survivorship care. With Ned as a resource, caregivers may be able to prevent the loss of laboratory results and gain the opportunity for evidence-based discussions of symptoms where clinical interactions are not subject to recall bias and nerves. We will explore how caregivers perceive using Ned to support their partners through conducting a semistructured interview with 10 caregivers, the contents of which will be modeled after the Greenhalgh interview framework [41] and the modified EPIC-Partner framework [8,57] (Multimedia Appendix 3).

Clinician Experience of Ned

Future scalability and sustainability efforts for Ned will depend on how clinicians perceive the app and their willingness to champion its use in hospitals and homes. We will use the Canada Health Infoway System and Use Assessment Survey to assess clinician adoption, use, and satisfaction with Ned alongside information and system quality [58]. We have modified the original survey to elicit Ned - specific insights and will be delivering the survey to 10 clinicians as a Web-based questionnaire to maximize convenience and ease of survey completion.

Sample Size

The appropriate sample size for single-case research depends on the specific research question being investigated and cannot be calculated in the same way as group designs such as the randomized controlled trial. In his seminal writing on case study designs, Yin recommends abandoning traditional sampling logic in favor of reflecting on the number of replications that are desired to maximize both certainty of research findings and external validity [59]. However, we recognize that our study design diverges from traditional case study methodology in nesting a within-group pre-post comparison of health outcomes aimed at identifying possible parameters of clinical change from baseline to study conclusion. We have therefore diverged from Yin's recommendations and performed a sample size calculation powered to detect a minimal clinically important difference (MCID) of 4 with a standard deviation of 22.25 on the EPIC-26. We selected the most conservative MCID and the median standard deviation from the range of validated values (MCID range 4-12, SD range 12.6-31.9), which have been widely used in prostate cancer survivorship research [60]. With 90% power, an effect size of Cohen d=0.16, and a 2-sided significance level of 5%, a minimum of 317 participants are required to detect this MCID. We anticipate a dropout rate of 20%, bringing our total sample size to 400 prostate cancer survivors for recruitment. We performed this calculation using the G*Power 3.1 software [61]. We will actively recruit the 400 patients required to power our within-group pre-post comparison of health outcomes, but we do not have a predetermined sample size for caregivers and clinicians. We anticipate that 10 clinicians will accept the invitation to join the Ned study and 50% of patients will share Ned with their caregivers. This will result in a total study sample size of 610 participants, composed of 400 patients, 200 caregivers, and 10 clinicians.

Data Analysis

Qualitative Interview Data

The audio recordings for all 30 interviews will be transcribed verbatim. Two members of our research team, (ie, a researcher and research analyst) will first separately code data from 3

patient and 3 caregiver interviews, and record insights and reflections from the data. A conventional qualitative content analysis approach will be used to code qualitative data [62]. Specifically, both researcher and analyst will read through the first interview transcript from beginning to end, similar to reading a novel. Then, they will reread and sort the transcript to identify similar phases, patterns, themes, sequences, and additional important features [63]. These words will become preliminary codes and organized into a coding scheme for use on the remaining 2 interviews. The researcher and analyst together will compare codes and either combine or add new codes. These generalizations will be examined in light of existing knowledge, and representative descriptive texts will be generated. These texts will inform a study codebook, which will then be used to code the remaining 17 patient and 7 caregiver interviews. This codebook will also inform the content analysis process, where descriptive texts will be divided into appropriate thematic categories [64]. We will use the case study analytic techniques of pattern matching and explanation building to build a valid realist program theory [59]. All interview transcripts will be analyzed and coded using NVivo version 11 (QSR International).

Quantitative Survey Data

Descriptive statistics will first be conducted on all variables to identify methodological data trends and parameters. We will analyze differences in baseline demographic and clinical variables using Pearson chi-square and nonparametric Wilcoxon rank sum tests. Given that we will be asking the same patients to complete repeated outcome measures across 4 time periods, we will account for autocorrelation effects through the use of linear generalized estimating equations, which are a multivariate analog of linear regression for longitudinal data and recommended for use in longitudinal repeated-measures data analyses [65,66]. Our data analysis strategy to answer the following questions is as follows:

(1) What is the effect of Ned on health-related outcomes over time? To assess the effect of Ned on quality of life, satisfaction with cancer care, unmet needs, self-efficacy, and prostate cancer-related level of anxiety domains, we will use generalized estimating equation models containing indicators for each study time point to assess whether the average study assessment scores at 2 months, 6 months, and 12 months were significantly different from baseline values.

(2) Is there a relationship between patient engagement with Ned and changes in health-related outcomes over time? We will explore whether patients who engage with the content and functionality of the app experience improvements in their health and well-being by building linear regression models for use and outcomes data.

(3) Is there a relationship between health-related outcomes? To understand whether changes in health-related outcomes share a similar direction and magnitude, we will perform Pearson correlation analyses to test for a correlational relationship between outcome variables.

(4) Do demographic and clinical variables affect changes in health-related outcomes? We will first conduct independent *t* tests and 1-way independent analyses of variance to determine whether there were differences in health-related outcomes for all categorical demographic and clinical variables, and Pearson correlation analyses for all continuous variables. We will then perform multiple linear regression analyses with health-related outcomes as dependent variables and all significant predictor variables from our preliminary analyses as independent variables.

We will triangulate both quantitative and qualitative data to develop the realist context-mechanism-outcome pattern configurations required to generate a program theory that explains how Ned is experienced by patients, caregivers, and clinicians.

Results

We recruited our first survivor in October 2017 and expect to reach our sample size requirements by March 2018. The anticipated completion date for this work is May 2019, and we aim to disseminate study findings through peer-reviewed publications and presentations starting September 2019.

Discussion

While there is mounting evidence to support the provision of digital prostate cancer survivorship care [18-22], there has not yet, to our knowledge, been an integrated effort to combine care strategies into a single platform for access by patients and their circle of care. Clinical researchers have not yet developed or comprehensively investigated digital interventions capable of eliciting the personal and medical context required to provide appropriate survivorship care. Further, with few exceptions [21,67-69], most existing studies for evaluating digital prostate cancer survivorship resources have been primarily formative in scope and have focused on nascent Web-based technologies [20,70-73]. This leaves a gap in the literature for evaluative research to build on this foundation of knowledge and advance a realist understanding of how to adopt and implement digital prostate cancer survivorship solutions across diverse contexts.

We have endeavored to design an evaluation that can respectfully explore the nuanced relationship between prostate cancer survivors and a technology designed to improve their survivorship care. To our knowledge, this is the first realist case study evaluation of an mHealth platform for prostate cancer survivorship care. The case study design employed for this work is supported by a mixed-methods approach to data collection [59], a strong theoretical grounding in realist principles [33], a pragmatic data collection schedule that aligns with existing implementation timelines [74], and a shared focus between observational and experimental investigation [75]. We have made efforts to select study instruments that are thoughtful in their wording and specific to prostate cancer survivorship, so that patients will understand the relevance of what is being asked of them. Our inclusion of caregiver interviews as both a distinct exploration into the health and well-being of partners and also a complement to the patient survivorship experience is more comprehensive than focusing on survivors alone.

It is acknowledged that most men with a diagnosis of prostate cancer will die *with* it, not *of* it [76-78]; therefore, prostate cancer is a chronic condition that requires effective management. We posit that Ned has the potential to support this management through the systematic monitoring of outcomes and may contribute to a measurable and meaningful shift in health and well-being. The lives of prostate cancer survivors are marked by unresolved needs that are not often addressed through their interactions with their circle of care [79]. We are hopeful that by providing survivors, caregivers, and clinicians with a foundation of shared health information, Ned will initiate informed conversations around the provision and acceptance of empathetic care.

Prostate cancer survivorship care will be at the forefront of health care resource allocation by 2030. Prostate cancer survivors are set to increase in number and longevity, heightening the need for integrated survivorship solutions to provide them with optimal and durable outcomes. We believe that Ned marks the proactive start of a shift in prostate cancer care innovation. We aim for this research to explore the app's potential to empower the survivorship experience and inform a new era of prostate cancer survivorship care.

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Conflicts of Interest

AF and University Health Network jointly own intellectual property rights to the Ned app. Under the respective agreements with their organizations, AF and JAC are entitled to personally benefit from any commercial use of the intellectual property.

Multimedia Appendix 1

Ned patient acceptance and use of information technology survey.

[PDF File (Adobe PDF File), 306KB - resprot_v6i10e197_app1.pdf]

Multimedia Appendix 2

Ned patient interview questions.

[PDF File (Adobe PDF File), 291KB - resprot_v6i10e197_app2.pdf]

Multimedia Appendix 3

Ned caregiver interview questions.

[PDF File (Adobe PDF File), 276KB - resprot_v6i10e197_app3.pdf]

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Abbreviations

EPIC-26: Expanded Prostate Cancer Index Composite
MAX-CP: Memorial Anxiety Scale for Prostate Cancer
MCID: minimal clinically important difference
OLIS: Ontario Laboratories Information System
PROM: patient-reported outcome measure
PSA: prostate-specific antigen
REB: research ethics board
SC: study coordinator
SCNS-SF34: 34-item Supportive Care Needs Survey Short Form
THP: Trillium Health Partners
UTAUT: unified theory of acceptance and use of technology

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Protocol

Multisite Semiautomated Clinical Data Repository for Duplication 15q Syndrome: Study Protocol and Early Uses

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Abstract

Background: Chromosome 15q11.2-q13.1 duplication syndrome (Dup15q syndrome) is a rare disorder caused by duplications of chromosome 15q11.2-q13.1, resulting in a wide range of developmental disabilities in affected individuals. The Dup15q Alliance is an organization that provides family support and promotes research to improve the quality of life of patients living with Dup15q syndrome. Because of the low prevalence of this condition, the establishment of a single research repository would have been difficult and more time consuming without collaboration across multiple institutions.

Objective: The goal of this project is to establish a national deidentified database with clinical and survey information on individuals diagnosed with Dup15q syndrome.

Methods: The development of a multiclinic site repository for clinical and survey data on individuals with Dup15q syndrome was initiated and supported by the Dup15q Alliance. Using collaborative workflows, communication protocols, and stakeholder engagement tools, a comprehensive database of patient-centered information was built.

Results: We successfully established a self-report populating, centralized repository for Dup15q syndrome research. This repository also resulted in the development of standardized instruments that can be used for other studies relating to developmental disorders. By standardizing the data collection instruments, it allows us integrate our data with other national databases, such as the National Database for Autism Research. A substantial portion of the data collected from the questionnaires was facilitated through direct engagement of participants and their families. This allowed for a more complete set of information to be collected with a minimal turnaround time.

Conclusions: We developed a repository that can efficiently be mined for shared clinical phenotypes observed at multiple clinic sites and used as a springboard for future clinical and basic research studies.

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KEYWORDS

clinical data repository; Dup15q syndrome; patient-centered; clinical phenotypes; cohort discovery

Introduction

Background and Significance

Duplications of the proximal arm of chromosome 15q11.2-q13.1 result in the genetic condition Duplication 15q syndrome (Dup15q syndrome). Duplications can be either interstitial (3 copies) or isodicentric (4 copies). Most cases are *de novo* and maternally derived, although some interstitial paternally derived cases have been described [1]. Common phenotypes in most individuals affected by Dup15q syndrome include hypotonia, motor and language impairment, intellectual disability, autism spectrum disorder, developmental disability, and seizures [2].

The Dup15q Alliance is a nonprofit parent support organization that supports patients and families affected by Dup15q syndrome, organizes yearly scientific and family meetings, and promotes awareness about Dup15q syndrome. The Dup15q Alliance consists of a 12-member Board of Directors, a Professional Advisory Board staffed by clinical and research professionals, several organizational committees, individuals and families living with Dup15q syndrome, and community volunteers [3]. Historically, Dup15q syndrome research has been limited by the relative rarity of this condition and the geographic distance of patients to clinic locations. In an effort to overcome these limitations, the Dup15q Alliance established a group of clinic sites whose goal is to focus specifically on the needs of individuals with this syndrome. As a result of this initiative, a collaboration of 5 Dup15q syndrome clinics has led to the development of a central data repository to support current and future research.

Objective

The primary objective of this project is to establish a national deidentified database with clinical and survey information on individuals diagnosed with Dup15q syndrome. This paper documents how stakeholder engagement tools, collaboration methodologies, and communication protocols were used to establish a first-of-its-kind national Dup15q syndrome data repository that will support future research efforts and encourage expansion of collaborative research on Dup15q syndrome among academic and medical institutions.

Methods

Design

This multisite research collaborative of institutions and individuals with an interest in Dup15q syndrome was initiated with the goal of identifying and developing new treatments and improving the standard of living for individuals with the syndrome and their families. To initiate the project, the Dup15q Alliance organized a series of communication sessions via conference calls and meetings. Attendees included Dup15q syndrome research and clinical professionals from the Dup15q Alliance's Professional Advisory Board, members of the Dup15q Alliance's Board of Directors, biomedical informatics professionals, research study coordinators, and other clinical investigation professionals. These communication sessions emphasized the project's adherence to a team science approach and partnership. Five partnering clinical sites were identified and several key protocols were established, including plans for establishing the necessary compliance and governance for a multisite study of this magnitude, a standardized set of clinical and behavioral metrics to be collected by each site (Table 1), communication protocols to be used for future collaboration among the study participants and administrating partners, technical specifications for the data warehousing tools to collect and store study data, and a stakeholder engagement plan for attracting, engaging, and retaining additional participants and families.

Setting

The 5 primary Dup15q syndrome clinics serve as the foundational setting for the project. These sites are the Dup15q Center of Excellence at Massachusetts General Hospital, the Geisinger Dup15q Developmental Clinic, the Dup15q Clinic at Minnesota Epilepsy Group, the University of Tennessee Le Bonheur Duplication 15q Clinic (closed July 2017), and the University of California Los Angeles Dup15q Clinic. Many of these sites include affiliated universities, research laboratories, and other vital resources that contribute to the project.

Effective implementation of technology tools is essential to support the research. The Research Electronic Data Capture (REDCap) [4] application is used to build our standardized clinical record database and securely store the supporting data for the study. Each clinic securely logs in to the Le Bonheur Children's Hospital's instance of REDCap for data collection. The repository is set up to collect longitudinal data. The frequency of the visits is determined by the clinicians at each clinic. At this time, following the first visit, no additional survey information is collected from the families, but the possibility exists for the initiation of multisite subprojects involving survey data. For example, gastrointestinal and nutrition surveys were initiated at the Memphis site. The data from subsequent visits are collected and entered by the clinicians or coordinators. Other Web-based tools and software aimed at supporting team collaboration and data sharing are used to implement the study's communication protocols, help eliminate geographical barriers, and promote innovation.

Table 1. List of tasks involved in the development of data collection instruments and protocols.

Task	Approach
Monthly collaboration sessions to establish data collection instruments and processes	A series of face-to-face meetings and conference calls that included leaders and representatives from various areas of interests from the Dup15q Alliance: researchers, clinicians, biomedical informaticists, and Dup15q syndrome study participants and their families. The resulting products of these meetings were a standardized set of clinical and behavior metrics to be collected across multiple clinical sites and the initial framework for standardized data collection protocols to ensure consistency and reliability in the collected data.
Identification of validated data collection instruments and protocols and acquisition of proper licensing and permission for use	To benefit as much as possible from professionally validated data collection tools, the group decided to identify and incorporate into this study, where appropriate, previously established and validated clinical data collection instruments. Working with the Dup15q Alliance, study partners initiated contact with vendors of data collection instruments and protocols protected by copyright laws to acquire proper licensing and permission to use these tools for this project.
Curating data for compliance with the National Database for Autism Research	Since Dup15q syndrome is one of the most common identifiable molecular causes of autism, a long-term goal of the study is to include the data collected during this multisite study in the data available via request from the National Database for Autism Research (NDAR). We researched NDAR's data standards to ensure the collection instruments established for this project stored the appropriate variables to generate a global unique identifier for each individual in accordance with NDAR's data standards.
Building a standardized clinical research database for Dup15q syndrome	The data collection instruments developed in the 3 previous steps of this process were translated into forms and surveys in a standardized clinical research database by the biomedical informatics professionals serving as the data managers for the study. Extensive functionality testing of these electronic forms, surveys, and the logic embedded within them was conducted by the data managers and clinical research collaborators.
Incorporating the data collection instruments into the clinical workflow	Even though data collection is an essential aspect of conducting meaningful research, we did not want data collection to interfere with clinical processes or negatively impact patient treatment. Thus, the biomedical informaticists worked closely with research coordinators and clinicians to optimize the data collection instruments for seamless integration into the clinical workflow. This involved the biomedical informaticists shadowing the clinicians during patient interaction and iterative development of the data collection instruments to improve the electronic forms for use in the clinical settings and enhanced usability of the surveys for study participants and their families.

Participants and Stakeholders

Most of the study's participants and stakeholders are based within the clinical sites, including treating physicians, research scientists, research study coordinators, biomedical informatics professionals, and study participants and their relatives. Members of the Dup15q Alliance are also actively involved in this study, serving as administrative leaders and ambassadors for awareness and providing financial support.

Protection of Human and Animal Subjects

The individuals in this database have signed an informed consent for each clinic site which gives permission for their deidentified clinical and survey data to be collected in the database repository. Each clinic site is responsible for obtaining institutional review board (IRB) approval for this study at their respective institution.

Compliance and Governance

The relationships among all stakeholders and data type and data exchange among stakeholders was clarified in initial face-to-face meetings and conference calls between the central leadership of the Dup15q Alliance, the principal investigators of this project, and the biomedical informatics team at the Children's Foundation Research Institute (CFRI) at Le Bonheur Children's Hospital (LBCH), a large referral hospital in Memphis, TN.

A project plan was drafted documenting the identity and mission of the Dup15q Alliance, project goals, and the role of the LBCH biomedical informatics team as the data management core. In this document, the business relationship between the Dup15q Alliance and the data management core and the relationship between the Dup15q Alliance and the contributing clinics were defined. The project phases and informatics workflow were also elucidated. Once all parties agreed upon the governance and structure, LBCH's legal team reviewed the plan. Additional discussions and clarification occurred among the partnering groups, including discussion with legal representation of the 2 major partners, the Dup15q Alliance and LBCH. A business associate agreement was drafted and executed between the Dup15q Alliance and LBCH for the data management and related services that the biomedical informatics core would provide to the Dup15q Alliance, in compliance with the Health Insurance Portability and Accountability Act (HIPAA)–Health Information Technology for Economic and Clinical Health Act (HITECH) Omnibus Final Rule. The legal relationships between the Dup15q Alliance and its partner institutions at various clinic site locations as it pertains to data sharing are managed by the Dup15q Alliance. The deidentified clinical and survey data collected from all sites belong to the Dup15q Alliance as per the business agreement.

Stakeholder Engagement

All participants and families receiving Dup15q syndrome clinical care at the participating sites are approached for voluntary participation in the deidentified data repository.

Prior to any data transfer to the repository database or participation in any additional studies, informed consent is obtained at each clinic site as per their institutional guidelines

and federally accredited IRB or equivalent group within the institution. The decision to opt out from participating in the data repository results in continued excellent standard of care for the patient at the specialty clinic without data being entered into the deidentified dataset. If participants and/or families agree to participate, data obtained during clinical evaluation are entered in the database to facilitate standardized procedures across clinic sites. REDCap is used to generate a clinical report for the patient's medical record prior to a deidentified version being uploaded to the research repository database to support research cohort discovery. The REDCap database is password protected and available only to appropriate IRB-approved study personnel on the HIPAA-secure institutional networks as required by applicable state and federal statutes and laws.

Communication and Collaboration Protocols

Communication and collaboration for the project began with face-to-face meetings with representatives from participating stakeholders. During these meetings, the framework for communication protocols and standards was established to ensure routine follow-up and inclusion of collaborators. Subsequent monthly communication via conference calls and emails ensured collaboration among the study participants.

The biomedical informatics professionals serve as data managers for the study and communicate information related to the study's integrated database to all other study participants. These biomedical informaticists work with other key stakeholders to establish a communication workflow that allows all study collaborators to be informed of new developments and important information regarding study data. On a monthly basis, biomedical informaticists communicate with research coordinators at each of the participating sites, generate and provide monthly status updates and integrated data summaries to the principal investigator, and are actively involved in face-to-face meetings facilitated by the study's leading clinical site. When a new site is added to the repository, executed IRB and business associate agreements are obtained from the hosting institution, after which data managers initiate contact with the leadership of the new collaborating site, provide standardized data collection instructions, and conduct iterative communication until the new site's data collection instruments and procedures are consistent with those of existing clinical partner sites.

To communicate with study participants while also keeping other key stakeholders engaged, we incorporated a novel direct feedback mechanism to include stakeholders in the data collection processes. Once an individual is scheduled to come to a clinic site in the network, they are placed in a holding area of the database where basic information is collected and consent for the repository is obtained. Shortly after study participants and their families consent to participating in the study, they receive the first in a series of electronic questionnaires. Families are continuously engaged throughout the project via these self-paced, electronic surveys sent through REDCap via email to collect data about the study participant's behavior and health details. This is a semiautomated process where 56% is entered manually by the clinicians/coordinators and 44% is completed directly by the families. Table 2 defines the common questionnaires and instruments that all clinics participating in the repository currently collect.

Data from these instruments are submitted directly to the database through a user-friendly Web interface. We have found this method of stakeholder engagement highly successful as a data collection technique based on the rate of completion of these questionnaires. The high level of responsiveness demonstrates the investment families and affected individuals are willing to commit to research aimed at improving treatment and quality of life for those living with Dup15q syndrome.

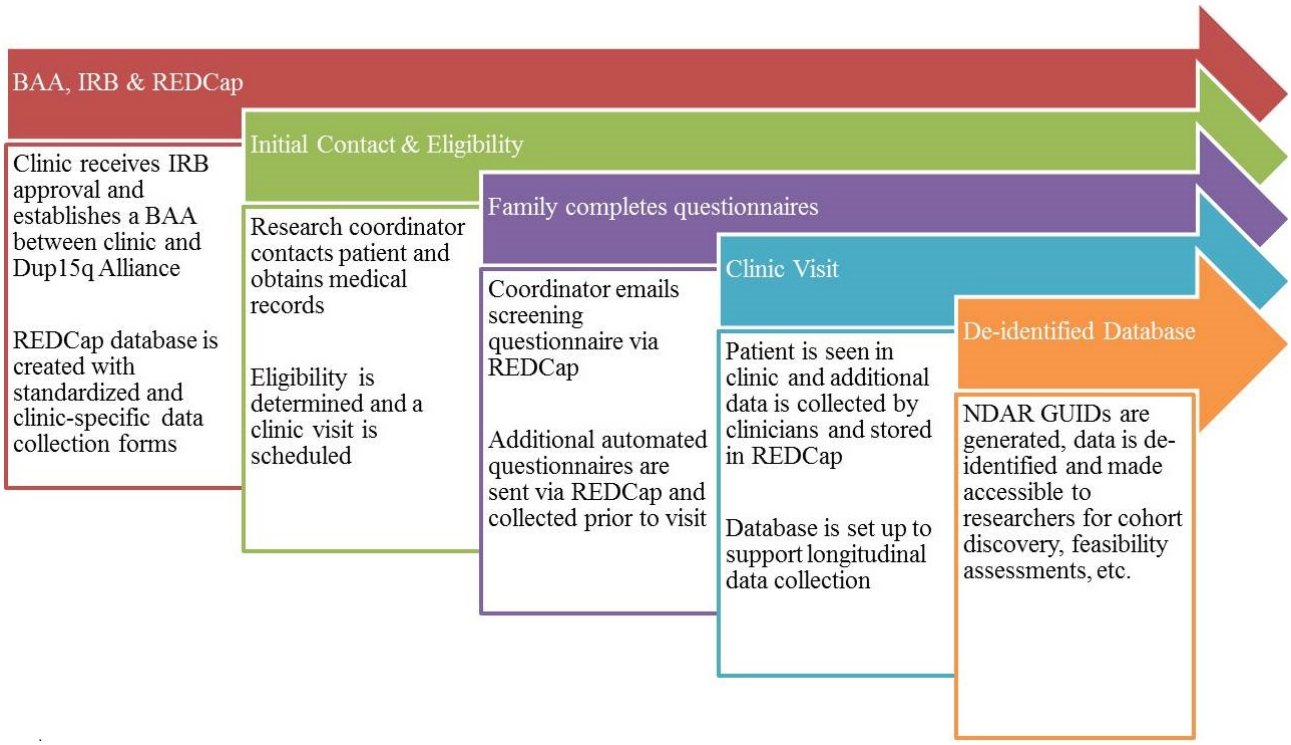
Registry-Building Process, Data Collection, and Sharing

It was necessary to build a central patient registry to allow researchers to seamlessly integrate registry information with clinical data management systems in order to facilitate collaboration, cohort research, management of derivative studies, follow-up scheduling, and data quality management. The primary component of the registry is use of metadata management to collect data and synchronize it between clinics. This metadata is derived from common data elements defined by national standards (for example, the National Database for Autism Research [NDAR]) to ensure interoperability and sharing and provide functions to standardize, add, modify, and configure registry and associated clinic-specific related metadata. The cohort research registry database is a collection of deidentified patient information from the repository data formatted into the traditional data mart architecture with integrated analytical tools to search for the patient populations that meet certain criteria. This research repository database is integrated with the central registry database to form follow-up research studies based on this unique cohort. Our central registry maintains data integrity and data quality over its entire life cycle, which includes storing, processing, and retrieving data. The registry provides researchers with tools for creating additional data collection instruments, security control, follow-up scheduling, auditing for missed follow-ups, and quality management on the data collected to identify discrepancies or missing information for the data collection.

Table 2. List of standardized questionnaires and instruments.

Standard collection tools	Description	Who completes?
Duplication 15q screening questionnaire	This questionnaire collects information about the child's name and the child's eating habits, sleeping habits, seizures, and medications being taken. Its purpose is to act as a guide to determine which specialties the child needs to see when coming to the clinic.	Parent
Demographics	Race, sex, and ethnicity of the child, birth mother, and birth father based on the Clinical Data Acquisition Standards Harmonization standard.	Parent
Consent and Duplicaton 15q subtype	This instrument is used to document if the patient's family consented to be a part of the database. It also is used to document the duplication subtype of the patient for categorization.	Clinician/ coordinator
Seizures	This questionnaire collects information on participants who have and/or are experiencing seizures. It documents types of seizures, medications the patient has taken and side effects, and the age of the participant when the seizures presented.	Parent
General physical and neurological exam	This instrument documents any body system abnormalities that may be observed at the time of the examination. This includes measures such as cerebellar/coordination, muscle strength, plantar response, reflexes, and muscle tone and bulk.	Clinician/ coordinator
Children's Sleep Habits Questionnaire (CSHQ) [5]	The CSHQ is a parent/guardian-reported screening questionnaire used to document child's typical sleep habits, sleep behavior, and any difficulties they may have regarding sleeping and waking.	Parent
Family history	This questionnaire is used to document the conditions prevalent in the child's family history. Additionally, it also collects the history of related information from pregnancy through birth.	Parent
Autism Diagnostic Observation Schedule (ADOS) [6]	The ADOS is a semistructured assessment of communication, social interaction, and play (or imaginative use of materials) for individuals suspected of having autism or other pervasive developmental disorders.	Clinician/ coordinator
Mullen Scales of Early Learning [7]	The Mullen Scales of Early Learning serve the purpose of assessing cognitive and motor ability. Five scales—gross motor, visual reception, fine motor, expressive language, and receptive language—are used for targeting strengths and weaknesses in children. The Mullen test is generally used for evaluating intellectual development and readiness for school.	Clinician/ coordinator
Questionnaire of pediatric gastrointestinal symptoms	This questionnaire documents information about the child's reflux issues and bowel movements (gastrointestinal problems are often coincident with autism).	Parent
Vineland Adaptive Behavior Scales II [8]	The Vineland II is an instrument used for diagnosing and classifying intellectual and developmental disabilities and other disorders such as autism, Asperger syndrome, and developmental delays.	Clinician/ coordinator
Seizures in Dup15q	This seizure questionnaire is a more comprehensive survey about seizures participants may be experiencing.	Parent
Child Behavioral Checklist (CBCL) [9]	The CBCL is a parent-reported questionnaire that documents where the child was rated on various behavioral and emotional problems.	Clinician/ coordinator
Social Communication Questionnaire (SCQ) [10]	The SCQ helps evaluate communication skills and social functioning in children who may have autism or autism spectrum disorders.	Clinician/ coordinator
Social Responsiveness Scale (SRS-2) Scores [11]	The SRS-2 is used to identify social impairment associated with autism spectrum disorders and quantifies its severity.	Clinician/ coordinator
Behavioral Assessment System for Children (BASC-2) Scores [12]	The BASC-2 tool is used to evaluate changes in behavior or emotional status.	Clinician/ coordinator

Figure 1. Schematic of workflow process.

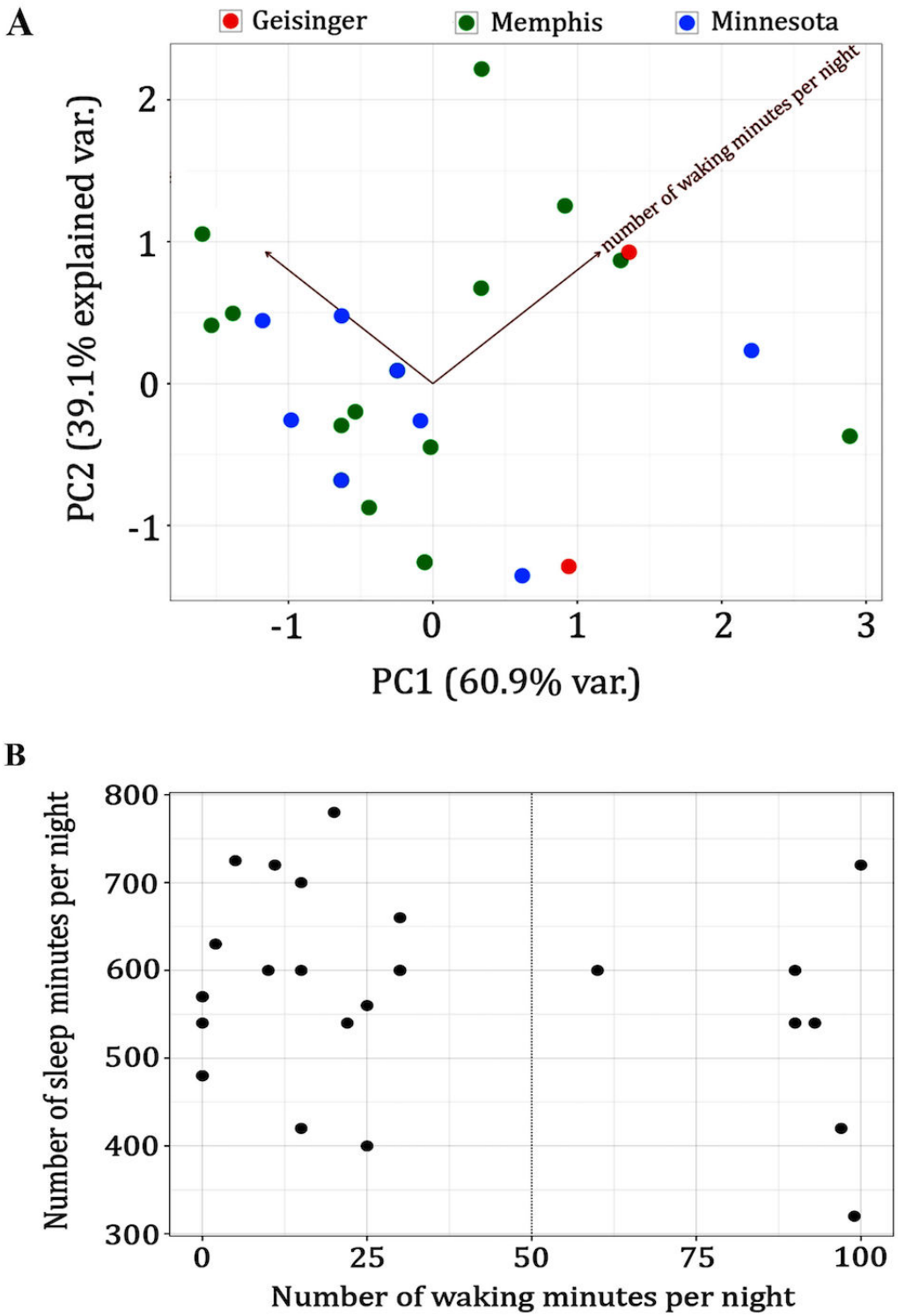


Only deidentified aggregate data is available to researchers from the central registry via the research cohort repository database. Clinical data can be disseminated from the repository database as a limited data set in order to gain insights into the condition, with the end goal being ongoing improvement of patient care. Research data use agreements and local institution IRB approval must be signed by a researcher before a limited data set can be shared. The Dup15q Alliance and LBCH data management core are working together to develop policies and procedures addressing a process flow to handle requests for access to the data from nonparticipant stakeholders. It is our goal that meaningful results will be presented at local, regional, national, and international meetings as well as published in peer-reviewed journals and professional newsletters and, eventually, included in textbooks. Figure 1 illustrates the overall workflow of this process. The consortium provides semiannual summaries of research activities, including comprehensive presentation and publication lists, to participants through the Dup15q Alliance website and mass emails. Because this is an ongoing clinical endeavor and a repository database, it is unclear when the clinical repository data collection phase will end.

Results

The Dup15q repository was built in 2014 by the CFRI biomedical informatics team at the University of Tennessee Health Science Center Le Bonheur Duplication 15q clinic in Memphis, Tennessee, under the direction of Dr Lawrence Reiter. It currently houses data from 96 participants with Dup15q syndrome. Of the participants with demographic data captured, 9.7% were African American, 85.5% were white, <2% were Asian, 45.2% were male, and 79.1% were between 2 and 16 years old (mean age 7.56 [SD 6.02] years [range 1 to 26 years]). Much of the collected data (deidentified) capture features of the condition such as intellectual, motor, and behavioral difficulties; speech and language problems; seizures; and sleep disturbances and gastrointestinal problems. It allows us to begin a dialog about the patterns emerging from these data sets. For example, we found evidence for 2 types of sleep disturbances in people with Dup15q syndrome. In both, individuals awaken in the middle of the night. However, most of these individuals fall back to sleep in under 25 minutes, whereas a small number remain awake for more than an hour (Figure 2). Furthermore, principal component analysis [13] reveals that the driving factor behind this variance is not where the individual's data were collected, meaning that this is a sleep issue across individuals at multiple clinic sites. The repository will soon be used to study the effectiveness of various medications such as those for epilepsy in people with Dup15q syndrome.

Figure 2. (A) A plot of 2 principal components (minutes per night vs number of waking minutes per night) applied to patient sleep date (N=23) from 3 sites. Note that there is a clear separation between groups of data but that both groups contain individuals from all 3 sites. (B) Plot of the number of sleep minutes versus the number of waking minutes (N=23). Note that 7/23 individuals were awake >50 minutes once aroused, while the majority of subjects stayed awake less than 25 minutes.



Discussion

Initial Developments and Findings

This repository created a collection of standardized instruments that are used across all clinic sites for collecting data. Because these instruments were derived from common data elements defined by national standards, such as the NDAR, these tools are directly transferrable to other studies involving developmental disorders or autism spectrum disorders.

One aspect that sets this multisite study apart from other similar research projects is the reliance on study participants and their families for direct data entry and curation of study data. We found that families were very compliant and completed 82.4% of the questionnaires assigned to them. Typically, very few families needed follow-up reminders before completing the electronic surveys that were sent to participants and their families. The turnaround time for questionnaires being sent to survey completion is minimal. This may be a reflection of how vested these individuals are in participating in studies that can help reach the goals of this research alliance.

Challenges

One of the most challenging aspects of the project was establishing a common dataset to be collected across all participating clinical sites. It was important to limit the information being collected to a reasonable number of data elements that can be entered consistently by various data curators while also collecting enough data to allow for meaningful future analysis to support a multitude of yet-to-be-determined research hypotheses.

The number of clinical partners participating in the study had both positive and negative effects. Increasing the number of clinical sites involved in the study allowed for a more diversified population of Dup15q syndrome study participants and a higher volume of patient data collected throughout the life of the study. However, increased number of clinical partners also meant having a larger number of institutions with varying areas of interests, all of whom had to agree on the data points to be collected and the governance model that prescribed how those data are to be managed and used. Understandably, each site has their own vested interests, organizational policies, and experienced clinical research leaders with differing opinions on how to accomplish this goal.

Through monthly collaboration meetings with researchers, physicians, and family representatives, the group established a well-defined scope for this project that met many of the common research objectives of all participating clinical partners. To address research objectives beyond the scope of this project, the group established a compromise that allowed each clinical site to collect, in addition to the common dataset, additional data to support each site's institutional research objectives and strengths in areas such as epilepsy, developmental disorders, genetics, and autism.

We found it challenging for data to be consistently entered by the clinicians. While we optimized the data collection instruments for seamless integration into the clinic's workflow, in some cases, these instruments could not be completed online. This then required clinicians to expend time to go back and enter data manually. This proved to be more challenging than originally expected. Also, in some cases, moving from paper to electronic forms was not an option for some of the instruments used in the repository. This challenge was addressed by integrating reminders for the clinicians into our communication plan to encourage timely data entry. We also followed up with individual clinicians, if needed.

Conclusion

The successful initialization of this centralized clinical data repository provides a resource for clinicians, researchers, research subjects, and others affected by or interested in Dup15q syndrome to develop a better understanding of this rare condition through combined data from many clinic sites. Our future work includes the development of a cohort discovery platform that will allow researchers to engage with the Dup 15q Alliance, increase the number of collaborations across clinical and academic institutions, and improve the overall treatment and quality of care for those living with Dup15q syndrome.

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Conflicts of Interest

None declared.

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Abbreviations

ADOS: Autism Diagnostic Observation Schedule
BASC-2: Behavioral Assessment System for Children
CBCL: Child Behavioral Checklist
CFRI: Children's Foundation Research Institute
CSHQ: Child Sleep Habits Questionnaire
Dup15q syndrome: Duplication 15q syndrome
HITECH: Health Information Technology for Economic and Clinical Health
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
LBCH: Le Bonheur Children's Hospital
NDAR: National Database for Autism Research
REDCap: Research Electronic Data Capture
SCQ: Social Communication Questionnaire
SRS-2: Social Responsiveness Scale

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Protocol

A Mobile Phone App to Support Young People in Making Shared Decisions in Therapy (Power Up): Study Protocol

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Abstract

Background: Evidence suggests that young people want to be active participants in their care and involved in decisions about their treatment. However, there is a lack of digital shared decision-making tools available to support young people in child and adolescent mental health services (CAMHS).

Objective: The primary aim of this paper is to present the protocol of a feasibility trial for Power Up, a mobile phone app to empower young people in CAMHS to make their voices heard and participate in decisions around their care.

Methods: In the development phase, 30 young people, parents, and clinicians will take part in interviews and focus groups to elicit opinions on an early version of the app. In the feasibility testing phase, 60 young people from across 7 to 10 London CAMHS sites will take part in a trial looking at the feasibility and acceptability of measuring the impact of Power Up on shared decision making.

Results: Data collection for the development phase ended in December 2016. Data collection for the feasibility testing phase will end in December 2017.

Conclusions: Findings will inform the planning of a cluster controlled trial and contribute to the development and implementation of a shared decision-making app to be integrated into CAMHS.

Trial Registration: ISRCTN77194423; http://www.isrctn.com/ISRCTN77194423 (Archived by WebCite at http://www.webcitation.org/6td6MINP0). ClinicalTrials.gov NCT02987608; https://clinicaltrials.gov/ct2/show/NCT02987608 (Archived by WebCite at http://www.webcitation.org/6td6PNBZM)

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KEYWORDS

shared decision making; child and adolescent mental health services; mHealth app; feasibility trial

Introduction

Policy makers have emphasized the need for shared decision making to become standard practice and for service users to experience "No decision about me without me" across health care settings [1]. These goals are active within child and adolescent mental health services (CAMHS) in the United Kingdom. For instance, the Chief Medical Officer's 2012 annual report [2] stated that shared decision making is central to the government's commitment to improving the health outcomes of children and young people with long-term conditions. A key ambition puts "children, young people and their families...at the heart of decision making" [2].

The Health Foundation [3] describes shared decision making as both a philosophy and a process requiring a partnership between patients and professionals. Decisions are made collaboratively about assessments, interventions, and support strategies. Shared decision making is a key element of a broader person-centered care perspective. Person-centered care principles include offering patients personalized care, support, and treatment while enabling and empowering them to build their own capabilities [4]. In line with this, shared decision making places value on a patient's expertise of their daily lives and difficulties and aims to empower them to communicate their personal values in any decision [5].

There is increasing evidence that ensuring collaborative practice and shared decision making in interventions with those with long-term physical or mental health conditions may contribute to improved self-management and patient activation along with better treatment outcomes [6-9]. Findings from child health settings show that young people have the capacity to be involved in the decisions around their care [10]. However, using shared decision making in the context of CAMHS has unique challenges. This includes the difficulties of initiating complex conversations with highly vulnerable and stressed children [11]. Furthermore, the decisions that arise within a CAMHS context often require ongoing deliberation rather than leading to a clear decision point. They are also likely to involve the multiple perspectives of, for example, families, social workers, and schools. The quality of the therapeutic relationship and availability of resources to support the process were other key factors identified by a recent systematic review [12]. These had an impact on the provision of person-centered care and shared decision making in CAMHS.

In spite of the challenges, findings suggest that once shared decision-making approaches are adopted in CAMHS, clinicians do not report additional risks or adverse events [13]. Conversely, young people's involvement in decision making may make key decisions more explicit and planned and therefore potentially less risky. Furthermore, child and parent experiences of shared decision making have been shown to be associated with higher levels of symptom improvement [14].

Young people want to be involved in making decisions about their health care and report feeling more in control of their care when they are included in decisions [15]. Parents also feel that their children should be involved in the decision-making process as it may increase their self-esteem and improve their overall welfare [15]. Clinicians appear to experience implementing shared decision making with young people in 3 possible ways: they may feel apprehensive due to perceived risks, they may feel "clunky" if they lack confidence in how to introduce the approach, or they may feel confident once they have found a natural way to incorporate shared decision making into the way they work [13].

Presently, shared decision making is used inconsistently within CAMHS both nationally and internationally. An Australian study asked young people with diagnoses of depressive disorders about their experiences of treatment decision making [16]. Their levels of involvement varied greatly, as did their satisfaction with their levels of involvement. In the National Health Service (NHS), a need to improve patient engagement in decisions around their care has been identified [17]. For instance, young people express an unmet need for access to developmentally appropriate, personally relevant, and accurate information to empower them to make informed decisions about their mental health care [18,19].

Interventions to support shared decision making in mental health services are emerging internationally. Simmons et al [16] developed an online, evidence-based decision aid to support young people facing treatment choices for moderate to severe depression. The aid includes an outline of treatment options, the evidence for each one, and the likelihood of experiencing symptom improvement and side effects plus a space for patients to record what is most important to them.

Interventions are also emerging within CAMHS in the United Kingdom. For example, a range of tools and approaches to support shared decision making has been developed in 4 UK CAMHS [4]. These tools include decision aids such as choice cards and option spreadsheets plus tools to support the identification and expression of feelings, problems, and goals such as a "getting to know you" booklet. The objective of these tools was to change the relationship between young people and their clinicians by encouraging active involvement from young people. Supporting young people to ask questions independently and raise the issues they want to discuss can also facilitate shared decision making [20]. These tools increased collaboration between young people and clinicians, and shared decision making was best facilitated when clinicians were open to changing behaviors and processes and young people were enthusiastic about moving toward a more collaborative relationship with their clinician [4].

Interventions in child mental health settings which include shared decision making have been shown to improve quality of life and satisfaction [21,22]. Online decision aids for young people with depression were found to be acceptable and useful for clinicians and young people [16].

Young people have advised that technology that is engaging, easy to access, informative, empowering, and provides support between sessions would be a particularly useful addition to therapy [23]. The use of technology in mental health care is recommended by the National Institute for Health and Care Excellence 2011 best practice guidance [24], and evidence supports the effectiveness of using mobile phone apps in therapy

[25]. Indeed, young people report already using technology as an informal complement to treatment [23].

Encouraging findings have also emerged from an evaluation of tools supporting young people's mental health through preparing for discussions, mood tracking, and self-management [26]. Young people, parents, and clinicians report feeling positive about integrating the use of certain apps into interventions for young people in mental health settings [27]. However, the content of many youth mental health apps is not based on psychological theories or evidence-based practice [28]. It has been argued that more research is required to better understand how best to integrate digital mental health tools into services [23].

To the best of our knowledge, there are presently no apps designed for and tested in UK CAMHS that support young people to become more actively involved in their care and the decisions surrounding their care. Our research project aims to develop and rigorously test an evidence-based mobile phone app, Power Up, for young people to use alongside CAMHS appointments. This app will provide tools aiming to support young people's voices in therapy, facilitate a more patient-centered approach, and increase shared decision making. Power Up will enable young people to record their questions, plans, decisions, and diary entries and support young people to decide and remember to whom they could communicate these things. By providing a digital space for young people to prepare what they want to bring to a session, Power Up can support them to actively engage in and direct their therapy.

Study 1 will aim to elicit opinions of young people, parents, and clinicians on an early version of the app, which will inform further developments. A feasibility trial will then be conducted in study 2, which will aim to collect the necessary parameters to plan a cluster controlled effectiveness trial of Power Up.

Methods

App Development

New and existing tools that support young person activation, empowerment, and shared decision making will be developed. From existing projects, which the present authors have been involved in, a number of evidence-based paper and online tools to support young people making shared decisions in CAMHS have been developed. These tools aim to provide young people with relevant, accessible information, tailored advice, support with self-management activities, and decision aids [13,29]. Aspects of these tools will be combined with newly developed tools to create the new app, Power Up. The app development process will adhere to best practice guidance for patient decision aids [30], quality criteria for health mobile apps [31,32], and design and evaluation guidelines for mental health technologies [33].

A shared decision-making model for clinical practice was developed by Elwyn et al [34] that identified 3 key steps: choice talk, option talk, and decision talk. During choice and option talk, collaborative decision making is introduced and justified to the patient, and options are then presented. Within decision talk, patients must be encouraged to form and express preferences. The capacity for young people to be involved in such decision talk was identified as a key barrier to shared decision making and person-centered care in CAMHS [12]. Indeed, Elwyn et al [34] identified that some patients are likely to need time and resources to consider what their preferences are and that this deliberation may need to be done outside of the clinical encounter. Power Up therefore aims to provide young people with this space to record their experiences and consider their preferences, consequently increasing their capacity to be involved in decision talk.

Patient and Public Involvement

Key stakeholders will be heavily involved in the development of Power Up through patient and public involvement (PPI) sessions. A user-centered agile development process will enable feedback from stakeholders to iteratively inform the design of the app. Through these sessions, young people with experience in accessing services, parents, and CAMHS clinicians will be consulted to ensure that the app's development is stakeholder-led. These groups will be consulted regarding initial ideas proposed for the app's content, importance and appropriateness of each tool, suitability of the wireframes (images of the functional elements of each screen), design elements, and protocol as it is developed.

PPI will be actively involved in the governance and delivery of the research. A PPI group will be facilitated by the PPI lead (KM) and 2 young advisors with expertise in shared decision making who have been recruited, trained, and supported by the PPI lead in line with best practice guidelines [35]. The group will be actively involved in project governance; cofacilitation of coproduction sessions with local service user groups; design and review of information sheets, informed consent forms, recruitment material, and interview schedules for young people, carers, and therapists; and dissemination of findings. The group will lead coproduction sessions with local service user groups who will act as advisory partners to the project, feeding into management, content development, beta-testing, and feedback for further development. While the project is primarily aimed at supporting shared decision making in young people, it is also crucial to engage with parents and carers. The PPI group will lead coproduction sessions and interviews with parents and carers to ensure their expertise informs project management, content development, and feedback for further development. Coproduction sessions will focus on feedback from young people about the design and refinement of Power Up and making it more intuitive, wording sections for clarity, recruiting for the study, using the app within sessions, and encouraging Power Up to be a personal space for young people.

Power Up Content and Design

A recent scoping review of approaches to support shared decision making in young people showed that many were not aimed solely at young people; instead, many were aimed at parents [36]. Moreover, those that were aimed at young people tended to miss key areas of shared decision making and tended to be used within or just before appointments rather than being a tool that could help manage difficulties outside of sessions and help young people express their opinions. In addition to this, none were interactive apps; they were instead confined to

websites, mostly detailing information. Power Up addresses these gaps by allowing decisions to be tracked, revisited, and reviewed over the course of treatment. Power Up is an app for young people in CAMHS to use independently. The Power Up app will provide young people with tools to use within and between CAMHS sessions. The objective of these tools is to empower young people to be more actively engaged in their care and decisions about their care by providing a space for them to record and prepare what they want to bring to and share in a therapy session.

Users of the Power Up app will not be able to digitally share information that they enter. The value of young people being able to communicate directly with their clinician through the app was considered. It was concluded that, in the context of a feasibility trial, the information governance and data security issues around data sharing through the app could not be sufficiently mitigated at this time. Presently, therefore, Power Up provides a private space for young people to use alongside their CAMHS sessions.

There are 4 key tools in which young people can use text, audio, video, and photos to create entries. In My Questions (see Figure 1 for screenshot), young people can record questions they would like to ask people in their support network (eg, their CAMHS clinician) and record their responses. In My Diary (Figure 2), young people can record session journals and daily journals, describing their thoughts, feelings, and experiences. In My Plans (Figure 3), young people can record step-by-step plans for achieving goals or tackling difficulties. My Decisions (Figure 4) is a space for young people to enter a decision they want to work through (eg, returning to school). The young person then adds pros (eg, keeping up with school work) and cons (eg, fear of being bullied) for the decision, assigning a weight to the importance of each one.

Additionally, users will record a list of all the people in their support network, including their CAMHS clinician, in My People when they first download the app. As Power Up users add entries to the app, they will be reminded to consider if they want to talk to any of the individuals in My People about their entry.

Finally, the Help and Support tool will signpost young people to other relevant resources giving information and advice. Young people will be able to add their own links and phone numbers to the list.

Our research project will be executed across 2 phases: development and feasibility testing.

Figure 1. My Questions.

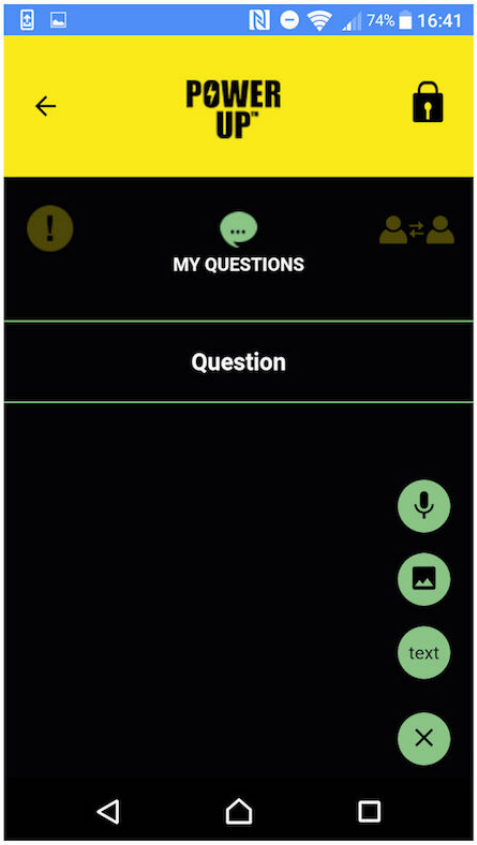


Figure 2. My Diary.

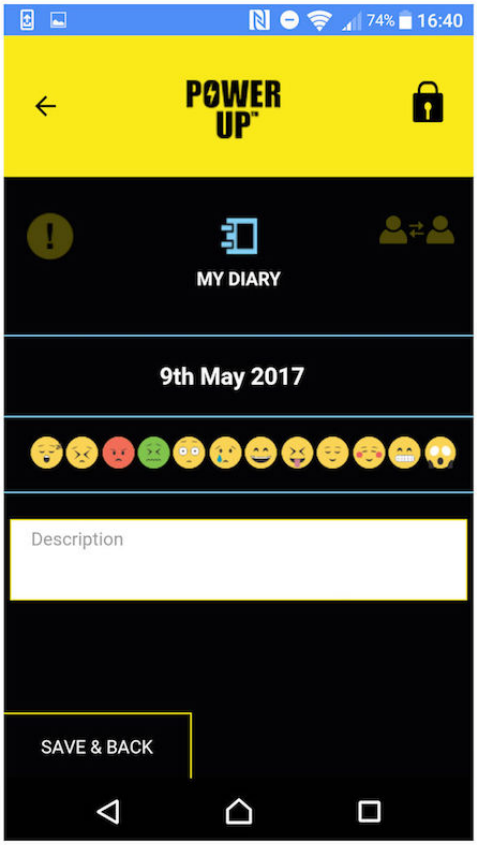


Figure 3. My Plans.

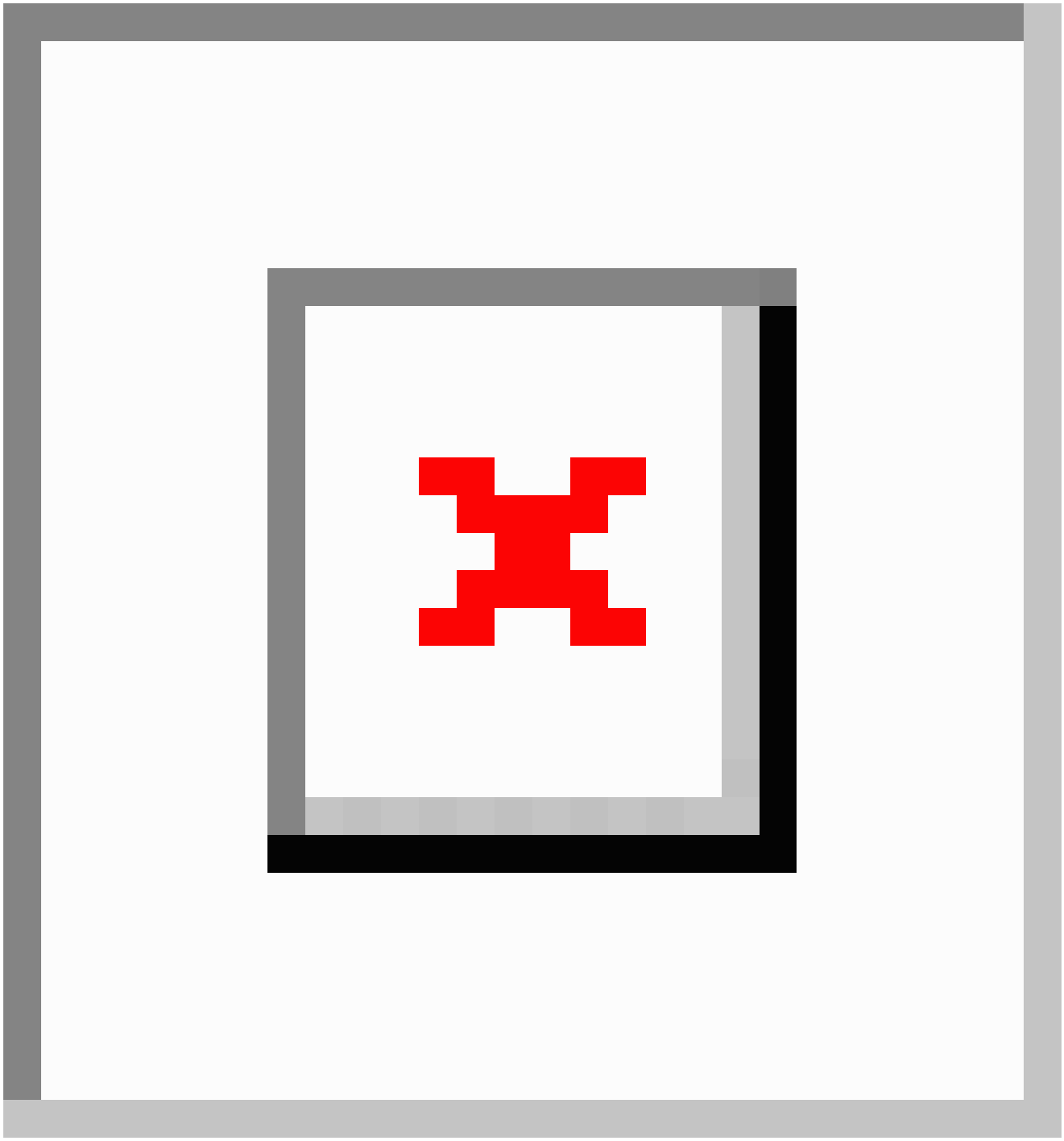
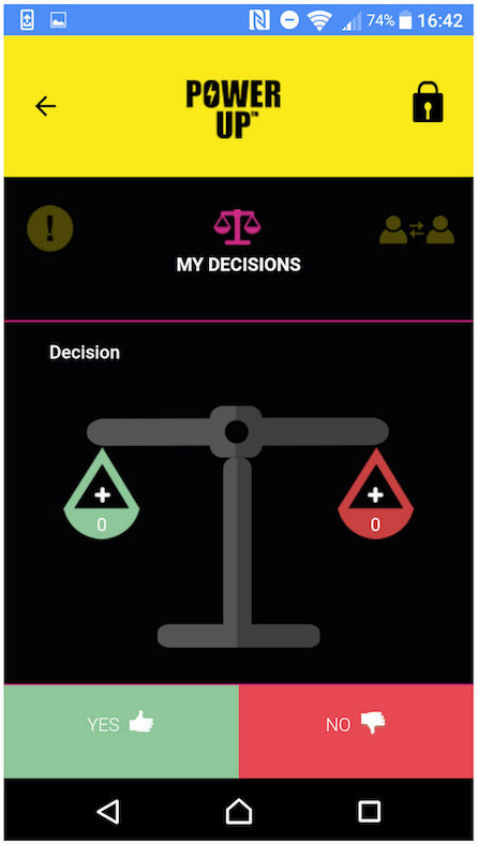


Figure 4. My Decisions.



Study One: Development Phase

Participants and Design

Using a qualitative design, semistructured interviews and focus groups will be conducted to elicit the opinions of group members concerning the structure and content of a prototype of Power Up. Up to 30 participants will be recruited to study 1: 10 young people, 10 parents and carers, and 10 clinicians. Young people recruited to this study will be aged 11 to 19 years, currently attending sessions in CAMHS, and presenting with emotional difficulties such as anxiety or depression. A clinician will have confirmed that the young person does not have any vulnerability that would make taking part in the study inappropriate to their context. Parents and carers recruited to this study will be over 18 years old and a parent or carer of a child currently attending sessions in CAMHS. All participants will be able to understand English sufficiently to provide informed consent.

Procedure and Materials

Participants will be recruited at 3 London CAMHS sites. Contact will be made with various sites well in advance of the study's start date to ascertain potential interest in the whole project.

Clinicians

At the commencement of study 1, the key contact person at each site will set up an initial meeting between clinicians and researchers. During this initial meeting, clinicians will be invited to participate in a focus group or interview. They will be given an information sheet that provides details of the purpose of the study and what their involvement would require. Approximately 10 clinicians will be recruited across the 3 services, and a date will be set between researchers and clinicians by phone or email. They will sign an informed consent form before they take part in the interview or focus group.

Young People and Parents

In the initial meeting, clinicians will also receive training on the young person recruitment procedure for stages 1 and 2. Clinicians will select young people currently attending CAMHS by reviewing their patient lists to identify young people who fit the inclusion criteria. The training will highlight that selection bias should be avoided during this process as the views of young people with a range of levels of engagement with therapy are necessary to understand how the app may or may not be used. The number of people screened on the patient lists, number who met the inclusion criteria, and number approached will be recorded.

Through a postal letter, telephone, or face-to-face conversation, young people and their parents or carers will be given information about the study. Young people and their parents or carers will indicate to a member of CAMHS staff or the research team, through a telephone or face-to-face conversation, that they are interested in taking part in the project.

Before the interview or focus group, all participants will read an age-appropriate information sheet outlining the purpose and details of the study. If the young person is aged 15 years or younger, their parent or carer will also be given an information sheet to read. Their parent or carer will sign a parental consent form agreeing for them to take part in the study before the

interview or focus group. The young person will sign an assent form indicating they would like to take part. Young people who are aged 16 years or older and their parents or carers will sign their own informed consent forms before they take part. Interviews are expected to last up to an hour.

In the focus groups and interviews, researchers will share the first version of Power Up with participants on a mobile phone. Researchers will talk the participants through the features of the app, and then participants will be given some time to try out this app on a mobile phone provided by the research team. Questions will be asked according to a semistructured topic guide (see Multimedia Appendix 1). Participants will be asked to talk the interviewer through their thoughts as they are looking at the app. Afterwards, questions about the app's content, usability, usefulness, and design will be asked. At the end of the focus group or interview, participants will be debriefed. They will be given contact details for the researchers should they wish to ask any questions or withdraw their data. Ideally, young people and carers will take part in separate interviews and focus groups; if this is not possible, the researcher will aim to elicit responses from all participants to ensure the voices of young people and carers are heard. Interviews and focus groups will be transcribed verbatim and analyzed using the framework approach to identify themes pertaining to the usefulness, functionality, and design of Power Up to be fed back to the design team and inform subsequent iterations of the app [37]. The analysis will compare and contrast responses from different groups to identify similarities and differences between young people, carers, and clinicians.

Study Two: Feasibility Testing Phase

Participants and Design

In the feasibility testing phase, young people's experiences of CAMHS while using Power Up will be compared to young people's experiences of CAMHS without using the app. Study 2 is designed as a feasibility trial using a waitlist control design. A total of 60 young people, who are aged 11 to 19 years old, have recently been referred to CAMHS, and are presenting with emotional difficulties will be recruited to the trial. A clinician will have confirmed that the young person does not have any vulnerability that would make taking part in the study inappropriate to their context. They will also understand English well enough to provide informed consent or assent if they are younger than 16 years old. First, 30 young people will be recruited to the control phase of the trial where they will receive management as usual. Subsequently, 30 different young people will be recruited to the intervention phase of the trial where they will be given Power Up to use alongside management as usual.

Procedure

Participants will be recruited in 7 to 10 London CAMHS sites. Clinicians will identify young people who are in their initial sessions in CAMHS. Young people and their parent or carer will be given information about the trial, and they will indicate to a member of CAMHS staff or the research team, through a telephone or face-to-face conversation, that they are interested in taking part in the project. For the control phase and the intervention phase, each service will be required to recruit 5 to 10 young people (for a total of 30 young people across services for each phase). This initial contact by services and subsequent recruitment by researchers will replicate the processes described in study 1.

If the young person is recruited during the control phase, they will meet with a researcher, along with their parent or carer, at a convenient time and place in the early stages of their therapy (up to the third treatment session). The researcher will take informed consent using the same procedures as described in study 1. The young person will then complete a battery of measures that take an estimated 15 minutes to complete. The young person's parent or carer and clinicians will also complete a short questionnaire each.

Three months later all participants will be recontacted by the researchers and a time will be arranged for them to complete the same battery of measures a second time. Their clinician will also be asked to report the young person's presenting problems, type of interventions used, number of sessions attended, number of missed appointments, and length of appointments.

Data collection for the intervention phase will replicate the control phase procedures. For those recruited to the intervention phase, the researcher will also help the young person to download Power Up onto their phone and will talk them through its functions after completing the first time measures. The young person will then be able to use Power Up as much as they want throughout their therapy at CAMHS, within and between sessions. In the intervention phase, a total of 10 to 12 young people and 10 to 12 clinicians across services will also take part in a posttrial interview where they will be asked about their experiences of and opinions on using Power Up in CAMHS.

At the end of their involvement in the trial, participants will be debriefed by a researcher. All participants will be offered 5 pounds (US $6.63) travel reimbursement at the end of their involvement in the study. They will be given contact details for the researchers, should they wish to ask any questions or withdraw their data.

Measures

Demographic Characteristics

Participants will be asked to report their age, gender, ethnicity, any disabilities, and first language.

Patient Activation Measure–Mental Health

The Patient Activation Measure–Mental Health (PAM-MH) is a patient-reported tool for measuring engagement in mental health care. The 13 items are used to measure patients according to 4 activation levels: skills, knowledge, confidence, and behaviors critical for coping with and managing mental health. Statements such as "When all is said and done, I am the person who is responsible for taking care of my mental health" will be rated using a 5-point response scale ranging from disagree strongly to agree strongly. PAM-MH was adapted from the physical health Patient Activation Measure; an examination of psychometric properties found it appears to be a reliable and valid measure [38]. It has been used in a number of studies with people accessing mental health services (see, for example, Matthias et al [39]). In the proposed feasibility trial, we will

collect necessary parameters for planning a full prospective parallel cluster controlled trial to test the effectiveness of Power Up. We consider a minimal clinically important difference to be 55.10 on the PAM-MH in the management as usual arm (indicating they lack confidence to take action to manage their mental health difficulties) versus 67.10 in the Power Up arm (indicating they are able to take action to manage their mental health difficulties) [9].

CollaboRATE

CollaboRATE is a 3-item patient-reported shared decision-making measure. The measure assesses the extent to which an explanation of the health issue is given and patient preferences are elicited and integrated. A 10-point response scale from no effort was made to every effort was made is used to measure how much effort was made to "help you understand your health issue," "listen to the things that matter most to you about your health issues," and "include what matters most to you in choosing what to do next." Concurrent validity with other shared decision-making measures and good interrater reliability have been demonstrated in a range of doctor-patient encounters [31]. However, its psychometric properties have yet to be tested in child mental health services. The authors of this study are involved in another study looking at the psychometric properties of CollaboRATE with children and young people.

Shared Decision Making Questionnaire

The Shared Decision Making Questionnaire (SDM Q-9) is a 9-item patient-reported shared decision-making questionnaire. Responders rate their agreement with 9 statements related to the decision-making process in healthcare consultations. One minor revision was made to the original version of the SDM Q-9; each item was changed from "my doctor" to "the clinician" to make the items applicable to any professional working with young people in CAMHS. Statements such as "The clinician made it clear that a decision needs to be made," "The clinician helped me understand all the information," and "The clinician and I selected a treatment option together" are rated on a 6-point response scale ranging from completely disagree to completely agree. The SDM Q-9 shows a high internal consistency (Cronbach alpha >.9), face validity, and high acceptance [40]. However, its psychometric properties have yet to be tested in child mental health services.

Experience of Service Questionnaire

The Experience of Service Questionnaire (ESQ) is a self-completion questionnaire that assesses children and young people's views of services with respect to accessibility, humanity of care, organization of care, and environment. Responders rate their agreement with 13 statements, such as either "certainly true," "partly true," "not true," or "don't know." The ESQ was developed and piloted with CAMHS attendees and has good precision in differentiating satisfaction with care on an individual level in this population [41]. For this study, 4 items of the ESQ will be used as a proxy measure of shared decision making: "I feel that the people who saw me listened to me," "It was easy to talk to the people who saw me," "My views and worries were taken seriously," and "I have been given enough explanation about the help available there." These items have previously been used as a proxy measure of shared decision making [14].

Youth Efficacy/Empowerment Scale–Mental Health

The Youth Efficacy/Empowerment Scale–Mental Health (YES-MH) assesses youth perceptions of efficacy with respect to managing their own mental health condition (self), managing their own services and supports (service), and using their experience and knowledge to help peers and improve service systems (system). The 7 items of the self subscale and 8 items of the service subscale will be used in this research. Responders rate their agreement with statements such as "I feel I can take steps toward the future I want" and "When a service or support is not working for me, I take steps to get it changed" on a 5-point response scale from almost or almost always to never or almost never. Initial analysis of the psychometric properties of this scale when used with 14- to 21-year-olds showed evidence of a clear factor structure and good internal reliability for the self subscale (Cronbach alpha=.88) and the service subscale (Cronbach alpha=.83) [42].

Strengths and Difficulties Questionnaire

The Strengths and Difficulties Questionnaire (SDQ) is a self-report behavioral screening questionnaire for children and adolescents measuring symptoms and functioning; 25 items capture 5 subscales, which measure emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior. Responders rate their agreement with statements such as "I get very angry and often lose my temper" as either "not true," "somewhat true," or "certainly true." The impact supplement includes 8 items which inquire about chronicity of the difficulties, distress, social impairment, and burden to others. Responses to questions such as "Do the difficulties interfere with your everyday life?" are given using a 4-point response scale ranging from not at all to a great deal. Internal consistency has been judged as satisfactory; the mean Cronbach alpha was calculated as .73 [43]. The SDQ has been used with young people as a clinical assessment tool and in developmental, genetic, social, clinical, and educational research studies.

Client Receipt of Services Inventory–Children's Version

The Client Receipt of Services Inventory–Children's Version (CSRI) provides information on service utilization as reported by the main carer of the child in the family [44]. Information on background, household circumstances, employment and income, school support, and health service use is recorded regarding the retrospective period of 6 months. For each service type, the number and average duration of contacts is recorded. The CSRI has been previously used in child mental health contexts [45].

Dyadic OPTION Scale

This is a 12-item instrument to measure the extent to which patients have been involved in shared decision making from the viewpoint of the clinician. This instrument was adapted from the observer OPTION which underwent extensive psychometric testing. The 2 scales show convergent validity [46], and a systematic review has concluded that the dyadic OPTION scale is the most promising tool for measuring

components of shared decision making [47]. Twelve statements, such as "A health problem was identified, where it was made clear that a decision was needed," "Different options (including the possibility of doing nothing) were discussed," and "It was made sure that information had been understood," are measured on a 4-point response scale ranging from strongly agree to strongly disagree.

Acceptability Measures

Participants will also be asked to complete a questionnaire about the acceptability of all the above measures.

Ethics and Informed Consent

Ethical approval has been obtained from Queen Square National Research Ethics Service and the Health Research Authority along with relevant local research governance and site-specific approvals. The trial has been registered with the ISRCTN registry [ISRCTN77194423] and ClinicalTrials.gov [NCT02987608].

Participant information sheets and informed consent forms will be given to all young people (assent forms for young people aged under 16 years), parents or carers, and clinicians. These forms were developed in conjunction with the Core Research Group and the Advisory Group, in particular the PPI coordinator and 2 representatives. The forms will inform participants that participation is entirely voluntary and that it will not impact their care if they decide not to take part. The risks and benefits to the participating people will be addressed and it will be made clear that the data obtained from the study will be confidential and their privacy ensured. Consent forms will also make the participant aware of their right to withdraw at any point during the research.

Planned Analysis

Study One: Development Phase

Focus groups and interviews will be recorded and transcribed verbatim. They will then be analyzed using thematic analysis. Themes will give an understanding of what young people, parents and carers, and clinicians think of the content and format of Power Up. Further developments to the app will be made in response to these themes.

Study Two: Feasibility Testing Phase

Descriptive statistics will be used to characterize the participants in terms of sociodemographic profile. The primary outcome measure of the feasibility trial, the standard deviations and intraclass correlation coefficients of the shared decision-making measures, will identify the parameters to enable planning for the subsequent trial. These will be used to calculate the sample size for the future planned cluster controlled trial. In addition, the acceptability of studying Power Up in a cluster controlled trial will be examined using recruitment and retention rates, number of sessions attended, and number of individuals who refuse treatment. The feasibility of studying Power Up will be indicated by the number of patients failing to comply with the full clinical/research protocol and qualitative information obtained from the posttrial interviews with clinicians and young people.

The secondary outcome measures, an initial indication of the impact that Power Up may have on a young person's clinical outcomes, are the change in patient activation, empowerment, and SDQ scores pre- and postintervention. Qualitative information regarding the impact of Power Up will also be obtained from the posttrial interviews with clinicians and young people.

The results of this study will clarify the feasibility and acceptability of studying Power Up in a prospective cluster controlled trial. In addition, the results will highlight the possible utility and challenges of implementing Power Up with young people in CAMHS.

Results

Funding has been secured from the National Institute for Health Research (NIHR)–Central Commissioning Facility to cover the full length of the project. Interviews were completed for study 1 in December 2016. The project is currently in the control phase of the feasibility trial, and 10 CAMHS sites have been recruited to take part in the study. The intervention phase of the feasibility trial commenced in June 2017. It is anticipated that data collection will be completed by December 2017.

Discussion

The trial and its findings will inform the development and implementation of a shared decision-making app for CAMHS. It will be the first of its kind for young people managing emotional problems in the NHS. This will contribute to the growing use of technology to support children and young people with mental health difficulties.

In addition, the findings will inform the planning of a prospective cluster controlled trial. This larger study will give further evidence of the app's efficacy in promoting shared decision making in CAMHS while reducing missed appointments and increasing positive outcomes. This will also indicate the potential financial savings the app could have for services. It is hoped that this research and the future trial can work toward putting children, young people, and their families at the heart of decision making about their care.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Topic guides.

[PDF File (Adobe PDF File), 52KB - resprot_v6i10e206_app1.pdf]

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Abbreviations

CAMHS: children and adolescent mental health services
CSRI: Client Receipt of Services Inventory–Children's Version
ESQ: Experience of Service Questionnaire
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
NIHR: National Institute for Health Research
PAM-MH: Patient Activation Measure–Mental Health
PPI: patient and public involvement
SDM Q-9: Shared Decision Making Questionnaire
SDQ: Strengths and Difficulties Questionnaire
YES-MH: Youth Efficacy/Empowerment Scale–Mental Health

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Protocol

Home Blood Pressure Management Intervention in Low- to Middle-Income Countries: Protocol for a Mixed Methods Study

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Abstract

Background: Control of hypertension in low- and middle-income countries (LMICs) is poor, often less than 10%. A strong body of evidence demonstrates that home blood pressure management lowers blood pressure, and recent guidelines from the National Institute for Clinical Health and Excellence recommends home blood pressure monitoring. However, the preponderance of data on the benefits of home blood pressure management comes from studies in high-income countries.

Objective: The objective of the study is to examine whether an intervention of home blood pressure management is feasible in LMICs. Home blood pressure management is defined as self-monitoring of blood pressure and self-titration of antihypertensive medications. We will identify barriers and facilitators of home blood pressure management and explore unique contextual factors in LMICs that influence implementation of home blood pressure management.

Methods: Participants will be recruited from 6 sites from 2015 to 2018. Patients and health care workers will be included. We will use mixed methods including focus groups, interviews, and standardized checklists. When possible, we will adapt materials from prior successful studies so that they are culturally and contextually appropriate.

Results: This ongoing study is funded by the World Heart Federation. The information that is obtained will be used to develop a randomized clinical trial of home blood pressure management in LMICs.

Conclusions: The data generated from this qualitative study will provide much needed information from patients and health care workers about barriers and facilitators of home blood pressure management and unique contextual factors that might influence implementation of home blood pressure management in LMICs.

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KEYWORDS

blood pressure; home management; self-management; LMIC

Introduction

Background

Control of hypertension in low- and middle-income countries (LMICs) is poor [1]. It has been documented that home blood pressure (BP) management significantly lowers BP when compared to usual care in high-income countries [2-6]. One study of home BP management in a high-income country (N=527) showed, at 6 months after intervention, a decrease in systolic blood pressure (SBP) of 12.9 mm Hg (95% CI 10.4 to 15.5) in the self-management group versus 9.2 mm Hg (95% CI 6.7 to 11.8) in the control group. The decrease in SBP was even higher at 12 months after intervention: 17.6 mm Hg (95% CI 14.9 to 20.3) and 12.2 mm Hg (95% CI 9.4 to 14.9), respectively [3]. This strategy for BP management has been incorporated into the National Institute for Health and Care Excellence guidelines in the United Kingdom [7]. As such, our research question is relevant to public health efforts and clinical practice.

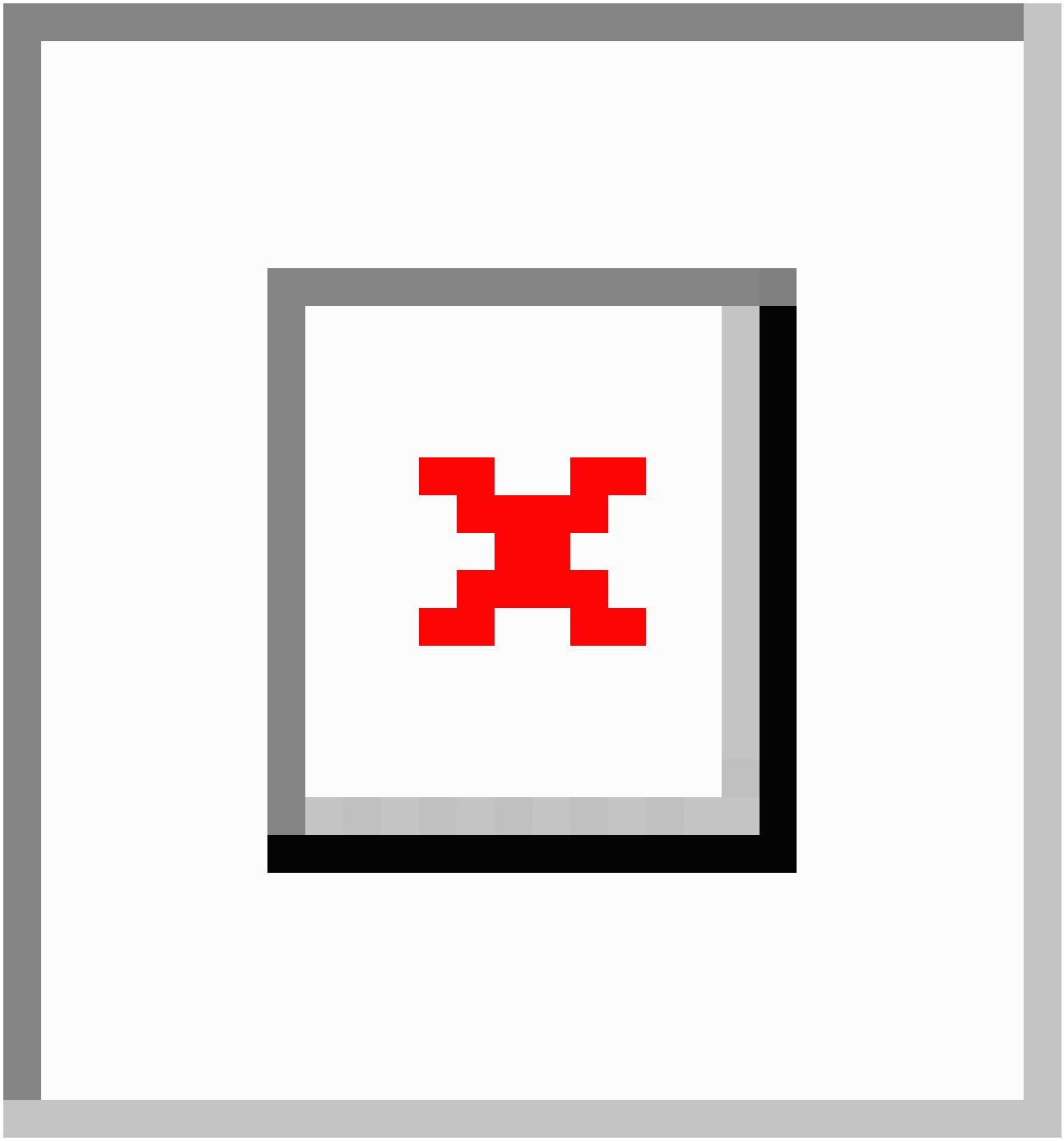
Recent data suggest that the utility of home BP monitors may be limited in resource-restricted settings in the United States [8]. However, there are little data from LMICs [9]. One recent clinical trial in Mexico and Honduras documented that individuals using a BP monitor combined with automated interactive voice response messages had SBP levels 4.2 mm Hg (95% CI –9.1 to 0.7; *P*=.09) lower on average than control group. Furthermore, a subgroup of individuals with low literacy showed a higher decrease, 8.8 mm Hg (95% CI –14.2 to –3.4; *P*=.002). However, this study had important limitations such as short duration of follow-up, small sample (N=181), and limited interface with the health care system [9].

The potential impact of this work is high because of the high global burden of hypertension in LMICs and the double burden of disease in health care systems of these countries; therefore, identification of innovative and effective strategies to control BP is critical. To the best of our knowledge, our study aims to be one of the first to provide evidence of the feasibility and acceptability of home BP management in these settings. Figure 1 shows our conceptual framework for the relationships between home BP management context and BP. We hypothesize that self-management will optimize management of BP in a low-income setting by reducing delays in medication titration and improving adherence to antihypertensive medication.

The overall objective of this project is to examine whether an intervention of home BP management, without telemonitoring, is feasible in LMICs. Given that this project will be conducted in LMICs, we will not use home BP telemonitoring technologies. For home monitoring of BP, we will use the M6 Comfort Blood Pressure Monitor (Omron Healthcare) device. To our knowledge, the M6 Comfort was not developed with consideration for challenges with power supply and, to address this, we provided a fresh set of batteries each time a new participant used the BP monitor. Of note, the BP monitors and batteries used at the Malawi site were purchased in South Africa, because quality of local batteries is a challenge and the Omron brand is not readily available locally.

There are important implications of this work regardless of the findings. The data generated will provide much needed information from patients about barriers and facilitators of home BP management. We will learn about challenges patients may have with using a home BP monitor in an LMIC setting, role of caregivers in home monitoring, and general interest in a clinical trial that we hope to conduct regarding home management of BP. Additionally, we will obtain information on health care provider perspectives on intervention feasibility and acceptability and possible importance of medication dose titration as a component of self-management of BP. The findings from this qualitative study will guide the development and refinement of a clinical trial of home BP management in LMICs.

Figure 1. Conceptual framework describing the relationship between home blood pressure management context and blood pressure.



Aims and Hypotheses

Aim #1: To assess the barriers, facilitators, and context for home BP management in LMICs.

Hypothesis A: There will be unique contextual patient-level factors such as hypertension awareness, duration of diagnosis, comorbidities, availability of a caregiver, patient-provider relationship, and access to health care that will inform the design of a clinical trial of home BP management in LMICs.

Hypothesis B: There will be unique contextual provider-level factors such as location and size of practice, patient-provider relationship, and comfort with home medication titration protocol that will inform the design of a clinical trial of home BP management in LMICs.

Aim #2: To conduct a process evaluation to explore intervention feasibility and acceptability.

Aim #3: To beta-test home BP monitors and titration protocols and materials.

Methods

Human Subjects

To ensure the protection of human subjects, we obtained ethical clearance at all participating sites. Institutional Review Board applications were submitted prior to beginning all work.

Informed Consent

Written informed consent will be obtained from study participants prior to any study activities involving data collection.

Study Population

Aim 1

To address aim 1, we will obtain information from patients, family caregivers, and health care providers. The goal is to understand the barriers and facilitators of self-monitoring BP and medication self-titration in LMICs. We will recruit 24 to 36 patients, family caregivers, and stakeholders at each of the 6 sites: Gilgit, Pakistan; Blantyre, Malawi; Bangalore, India; Dhaka, Bangladesh; Lima, Peru; and Douala, Cameroon. Countries were selected based on the availability of research partners with interest and capacity to conduct this work. Sampling will be purposive and heterogeneous to capture individuals with family caregivers and those without and those with longer standing hypertension (≥3 years) and those with a newer diagnosis (<3 years). However, we will exclude participants with resistant hypertension. Study participants will be selected through outpatient medical clinics in each city. Patients from the practices that meet the inclusion criteria will be invited to participate in the study. Key informants (ie, health care providers) from the health care teams and health care systems will be invited through local contacts.

Aim 2

For aim 2, we will recruit 8 to 10 health care providers at each of the 6 study sites. The goal is to understand the feasibility and acceptability of self-monitoring BP and medication self-titration from the perspective of health care providers in LMICs. We will recruit a purposive sample of participants with a goal of obtaining equal numbers of men and women. We will also consider age group, type of provider (eg, physician, nurse, community health worker), specialty, and location of practice (ensure that this is complementary with where intervention trial activities may occur at a later date). The sample size of the focus groups with health care providers will be evaluated by study investigators for thematic saturation and redundancy. If new issues emerge, we will enroll additional providers, but if there is thematic saturation and redundancy no additional interviews will be conducted.

Aim 3

For aim 3, we will choose 5 patients (some of them will have a family caregiver) at the trial site who meet study inclusion criteria. We will seek the assistance of clinic staff in identifying patients and their caregivers. The sample size for this aim will be evaluated by study investigators for thematic saturation and redundancy. If new issues emerge for the patients as they do the beta-testing, we will enroll additional patients to better understand these issues. However, if there is redundancy in the information we receive, no additional patients will be included. Patients will be asked to use the BP monitors and diaries and provide feedback. We will also recruit providers who would likely participate in our future intervention study about self-management of BP. This will include 10 physicians, nurses, and community health workers. They will be asked to review the study's medication titration protocol and provide feedback.

Procedures

Aim 1

Perspectives of patients, family caregivers, and health care workers will be obtained using 2 qualitative research techniques: focus group discussions (patients and family caregiver) and in depth semistructured interviews (health workers). At least 2 focus groups of patients with their family caregivers will be formed in each city with 6 to 9 participants in each group. The sample size of the focus groups will be evaluated by study investigators for thematic saturation and redundancy. If new issues emerge we will enroll additional participants, but if there is thematic saturation and redundancy no additional interviews will be conducted. The focus group discussion guide was developed collaboratively using literature review and expert and local team input. Key informant interviews will use a semistructured interview guide developed by the same process. Key informants from the health care systems will include primary care physicians and cardiologists, nurses, and community health workers.

Data collection and data analysis guides and protocols will be standardized across sites to ensure cross-national comparisons of qualitative data, and they will be adapted so that they are culturally and contextually appropriate. We will also use standardized checklists and interviews to obtain information from study participants, and data collection will be conducted by individuals trained in qualitative research methods. The broad themes that will be examined in our qualitative study are summarized in Figure 1, and the interview guides are shown in Multimedia Appendices 1 and . The themes include barriers and facilitators to home BP management in LMICs. We are interested in factors that may occur at the individual level and at the provider level. The individual-level factors are shown in Figure 1 and include age, gender, education, awareness of hypertension, duration of hypertension diagnosis, comorbidities, family structure, caregiver, and access to health care. Provider-level factors are also shown in Figure 1 and include age of the provider, practice type, location of practice, clinical inertia, and size of practice.

The outcomes of interest for the qualitative data examined in aim 1 are barriers, facilitators, and context for home BP management.

Aim 2

A semistructured interview will be conducted with health care providers at each site. The interview will cover the following topics: overall experience and attitude about high BP, whether patients are currently asked to measure and monitor their own BP, what are possible barriers to treatment and adherence to BP management strategies, role of the health care provider in helping patients with high BP management, whether they would be interested in participating in an intervention about self-management of BP, and general thoughts about strategies to improve the lives of patients and the treatment of high BP. We will also obtain feedback from providers about the approach that would be used by the patient for self-titration of medication.

We are interested in knowing about the following topics: the appropriateness of the frequency of medication titration, clarity and readability of instructions, comfort level of the health care team with the actions recommended, and what can be done to improve successful use of the self-titration protocol by patients.

The outcomes of interest for the qualitative data examined for aim 2 are the perspectives of the health care providers on intervention feasibility and acceptability.

Aim 3

The procedures to beta-test the home BP management approach involve 4 steps.

First, patients and caregivers will be trained by study personnel and instructed to use the BP monitor and to record readings in a diary. The patient will perform a BP measurement in front of study staff. The study staff will use predetermined criteria to assess adequacy of training. The patient will be retrained immediately if required. If despite 2 attempts during training the patient is unable to correctly measure his or her BP, a caregiver will be asked to measure the BP. If the caregiver also fails after 2 attempts, the patient and caregiver will be excluded from the study.

Second, study personnel will provide patients with a BP monitor and diary to use at home. Consistent with the protocol for the recently completed highly successful TASMIN trial, patients will be asked to measure their BP 2 times a day over 1 week: once in the morning and once in the evening. They will be required to take 2 readings 5 minutes apart at each time point and record the values in the study diary.

Third, at the end of the week, patients will be asked to return to the clinic for an interview about their experience and how it could be made better and to complete an interviewer-administered usability scale. The interviewer will ask patients for feedback on the following topics: overall experience and attitude towards the monitor, whether they were able to successfully monitor their own BP, what are possible barriers to monitoring their own BP, role of the caregiver in helping to monitor their BP management, what could be done to improve their experience with monitoring their BP at home, and whether they would be interested in using a monitor if selected to do so for the future trial. We will also ask about process variables including whether the patient read and understood the BP diary, the number of BP readings that are stored in the monitor; and the number of BP readings that are recorded in the diaries. The usability scale captures information on multiple aspects of using the BP monitor (eg, ability to understand BP readings, comfort of cuff).

Last, while patients are at the clinic, we will also show them a hypothetical medication up-titration protocol based on their current hypertension medication regimen. This hypothetical protocol will have been designed and approved by a study physician in consultation with the treating physician. Patients will be asked for feedback on barriers and facilitators that may affect fidelity to the hypothetical protocol. We are specifically interested in the clarity and readability of instructions and comfort level of patient and family caregiver with the actions recommended.

The outcomes of interest for the qualitative data examined for aim 3 are patient success with using the home BP monitor, barriers to monitoring BP at home, role of caregiver in home monitoring, interest in a clinical trial about home management of BP, patient understanding of the daily BP diary, number of BP readings taken at home, usability of home BP monitor, clarity of instructions for using the home BP monitor, and fidelity to a hypothetical medication titration protocol.

Data Management and Analysis

We have guidelines for the number of participants that will be recruited at each site for the study. However, the final sample size for interviews and focus group discussions will be determined based on the principle of saturation. Once the interviews and group discussions begin, the researchers will determine based on the information obtained whether involving another participant or group will add important new data. If no important new data will be added, no additional interviews, focus groups, or beta-testing will be conducted.

All interviews and group discussions will be digitally recorded upon receiving the consent of participants. Recorded interviews and focus group discussions will be reviewed by the local researcher in order to extract the relevant data for analysis. Using the coding on the spot method, each researcher will record the data in the original language in a common template. Data matrices will be then translated into English. The coding on the spot method consists of dividing the interviews (or focus group discussions) into 1-minute segments. The recording is played back for exactly 1 minute at a time, then it is paused and the researcher summarizes what has been said in that minute in the assigned box. If the researcher finds a quote that condenses the main views expressed by the participants, this quote will be transcribed verbatim in the quote box in the language in which it was originally recorded. It is possible that the researcher will not find any useful quotes. If there is an observation that the researcher considers useful for data analysis it will be noted. After completing each recording, the researcher will verify the information entered in the matrix to ensure it is clear and nonredundant. It is also possible that a new topic emerges from the data extraction process, and it is possible for this new topic to be added. Relevant data is that which provides information around the core 7 research topics: (1) BP management and measurement, (2) medication adherence and medication titration: barriers and facilitators, (3) patient-physician relationship, (4) characteristics of the local health care system, (5) perceptions about home BP monitoring, (6) understanding of BP measurements, and (7) social support.

Interim data analysis will occur alongside the data collection. After each data collection round (interview or focus group discussion), the data will be reviewed by the research team to further refine the data collection processes. Data will be analyzed across different languages. Coding and categorization will be carried out by at least 2 team members trained in qualitative methods. Reports of the analysis will be produced for each site for review of local team members. The analysis will use both inductive codes and a priori categories. Final collation of the analyses using the English translations will be centralized for the final analysis. All data from beta-testing of

the home BP monitors and titration protocols will be used in an iterative process to adapt and improve BP monitoring and titration materials and protocols.

This study will be conducted over a 30-month period (see Table 1). In addition to obtaining Institutional Review Board approval, study activities will include translation of study material, training of data collectors, implementation of mixed methods, data analysis, and manuscript writing.

Table 1. Timeline of activities.

	Months									
Timeline (2015-2016)	1	3	6	9	12	15	18	21	24	27
Obtain Institutional Review Board approval	x	x	x							
Translate study materials	x	x	x							
Train data collectors		x	x	x						
Conduct focus groups			x	x	x	x	x	x	x	
Analyze data					x	x	x	x	x	
Write manuscript						x	x	x	x	x

Results

This protocol refers to an ongoing study funded by the World Heart Federation. The standardized protocol is being implemented in 6 different LMICs. The information that is obtained will be used to develop a randomized clinical trial of home BP management in LMICs. We expect that there will be unique contextual factors that need to be accounted for before the highly successful interventions from high-income countries can be used.

Discussion

The rationale for this study is based on (1) documentation that control of hypertension in LMICs is poor, often less than 10%, (2) a strong body of evidence that home BP management lowers blood pressure, (3) recent guidelines from the National Institute for Clinical Health and Excellence that recommend home BP monitoring, and (4) the observation that the preponderance of data on the benefits of home BP management comes from studies in high-income countries.

The data generated from this qualitative study will provide much needed information from patients and health care workers about barriers and facilitators of home BP management and unique contextual factors that might influence implementation of home BP management in LMICs. A clinical trial of home BP management is needed to quantify the potential benefits in this setting.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Semistructured interview guide for patients and family caregivers.

[PDF File (Adobe PDF File), 36KB - resprot_v6i10e188_app1.pdf]

Multimedia Appendix 2

Semistructured interview guide for health care providers.

[PDF File (Adobe PDF File), 40KB - resprot_v6i10e188_app2.pdf]

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Abbreviations

BP: blood pressure
LMIC: low- and middle-income country
SBP: systolic blood pressure

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Protocol

External Validation Study of First Trimester Obstetric Prediction Models (Expect Study I): Research Protocol and Population Characteristics

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Abstract

Background: A number of first-trimester prediction models addressing important obstetric outcomes have been published. However, most models have not been externally validated. External validation is essential before implementing a prediction model in clinical practice.

Objective: The objective of this paper is to describe the design of a study to externally validate existing first trimester obstetric prediction models, based upon maternal characteristics and standard measurements (eg, blood pressure), for the risk of pre-eclampsia (PE), gestational diabetes mellitus (GDM), spontaneous preterm birth (PTB), small-for-gestational-age (SGA) infants, and large-for-gestational-age (LGA) infants among Dutch pregnant women (Expect Study I). The results of a pilot study on the feasibility and acceptability of the recruitment process and the comprehensibility of the Pregnancy Questionnaire 1 are also reported.

Methods: A multicenter prospective cohort study was performed in The Netherlands between July 1, 2013 and December 31, 2015. First trimester obstetric prediction models were systematically selected from the literature. Predictor variables were measured by the Web-based Pregnancy Questionnaire 1 and pregnancy outcomes were established using the Postpartum Questionnaire 1 and medical records. Information about maternal health-related quality of life, costs, and satisfaction with Dutch obstetric care was collected from a subsample of women. A pilot study was carried out before the official start of inclusion. External validity of the models will be evaluated by assessing discrimination and calibration.

Results: Based on the pilot study, minor improvements were made to the recruitment process and online Pregnancy Questionnaire 1. The validation cohort consists of 2614 women. Data analysis of the external validation study is in progress.

Conclusions: This study will offer insight into the generalizability of existing, non-invasive first trimester prediction models for various obstetric outcomes in a Dutch obstetric population. An impact study for the evaluation of the best obstetric prediction models in the Dutch setting with respect to their effect on clinical outcomes, costs, and quality of life—Expect Study II—is being planned.

Trial Registration: Netherlands Trial Registry (NTR): NTR4143; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4143 (Archived by WebCite at http://www.webcitation.org/6t8ijtpd9)

(JMIR Res Protoc 2017;6(10):e203) doi:10.2196/resprot.7837

KEYWORDS

external validation; first trimester; prediction models; pregnancy; risk assessment

Introduction

Perinatal mortality is an important quality indicator of perinatal care. The main causes of perinatal mortality are asphyxia, preterm birth (PTB), and born small-for-gestational-age (SGA) [1,2]. Pre-eclampsia (PE) is commonly related to SGA and induced preterm birth [3]. Another concern is the rising incidence of gestational diabetes mellitus (GDM), leading to large-for-gestational-age (LGA) infants [4]. Children born LGA are at increased risk of asphyxia and birth injuries [5]. Early identification of pregnancies at risk of these complications is important considering the substantial short- and long-term consequences for the health of mother and child. Women at high risk could benefit from further testing, increased surveillance, and preventive interventions.

A number of first trimester prediction models have been published addressing important obstetric outcomes including PE, GDM, spontaneous PTB, and infants born SGA or LGA [6]. These risk models are based on maternal characteristics, routine antenatal tests (eg, blood pressure), and sometimes include more complex predictors like specialized tests (eg, uterine artery Doppler and cervix length measurements) or biomarkers. Although some complex factors have been reported to improve discrimination, a drawback is that most of these tests provide additional costs, are not readily available in general antenatal settings, and are possibly inconvenient for pregnant women [7].

While the reported performance of most non-invasive prediction models is promising [7], few models have been externally validated in independent cohorts [8-16]. Evaluating the model's performance in another population than the one used for model development is crucial before applying a model in daily practice to guide patient care [17,18].

This paper describes the design of a study aimed to externally validate existing first trimester obstetric prediction models, based upon maternal characteristics and standard measurements (eg, blood pressure), for the risk of PE, GDM, spontaneous PTB, and SGA and LGA infants among Dutch pregnant women (Expect Study I). Results of a pilot study on the feasibility and acceptability of the recruitment process and the comprehensibility of the Pregnancy Questionnaire 1 are also reported. Adequately performing models will be considered for use in clinical practice. We are planning an impact study—Expect Study II—to evaluate the application of adequately performing models (in association with tailored care paths) as compared with care-as-usual in Dutch obstetric care.

The specific objectives of the Expect Study I are (1) to identify published first trimester obstetric prediction models, based solely upon maternal characteristics and standard measurements (eg, blood pressure), for the outcomes PE, GDM, spontaneous PTB, SGA infants, and LGA infants; (2) to evaluate prospectively the predictive performance of these first trimester obstetric prediction models in a Dutch cohort of pregnant women; (3) to update, if necessary, the best performing models to the validation cohort; and (4) to measure maternal health-related quality of life, costs, and satisfaction aspects of current Dutch obstetric care for use as care-as-usual comparison to the intended Expect Study II.

Methods

Selection of Prediction Models

Systematic searches were performed in PubMed to identify all published first trimester obstetric prediction models using "prediction model" and its synonyms as search terms combined with relevant outcome terms and MeSH terms. The search terms were restricted to title and abstract fields (tiab). The detailed search strategies are available in Multimedia Appendix 1. Articles written in languages other than English, German, French, or Dutch were excluded. Citation lists of relevant articles were checked to select additional articles. The search was first performed in April 2013, before finalizing the study questionnaires, and will be updated before the start of each validation analysis per outcome. The first author screened all citations, and together with the last author, assessed the eligibility of the full text articles. In cases of disagreement, a third reviewer was used.

Prediction models were eligible for consideration if the following criteria were met: (1) the article presented the development of a prediction model or an update of a previously developed model, (2) the model contained multiple predictors, (3) predictors were routinely collected in Dutch obstetric care (maternal characteristics or blood pressure), (4) predictors were available and/or measured before 16 weeks and 0 days of gestation, (5) the model was based on weighted risk predictors, and (6) outcome of the model was PE, GDM, spontaneous PTB, SGA infants, or LGA infants. Authors of the original studies were contacted if the model intercept, regression coefficients, or definitions of predictors were not available.

Study Design and Population

A multicentre prospective cohort study was performed among women living in the south-eastern part of The Netherlands (province of Limburg). Six hospitals and 36 midwifery practices recruited pregnant women less than 16 weeks pregnant and aged 18 years or older between July 1, 2013 and January 1, 2015. Follow-up took place until December 31, 2015. Pregnancies ending in a miscarriage, termination before 24 weeks of gestation, and women lost-to-follow-up were excluded.

The Medical Ethics Committee (MEC) of the Maastricht University Medical Centre evaluated the study protocol and declared that the study did not fall within the scope of the Dutch Medical Research Involving Human Subjects Act (WMO) (MEC 13-4-053). An independent physician was available for consultation by (eligible) participants.

Recruitment

Eligible pregnant women visiting their midwife (approximately 85%) or obstetrician (approximately 15%) in the first trimester of pregnancy received verbal and written information about Expect Study I [19]. They were also asked whether they were willing to receive further information by email or telephone. If so, contact details were entered into an online system by their caregiver and used to send an automated information email about the study. Pregnant women were asked to complete a Web-based questionnaire before 16 weeks of gestation (Pregnancy Questionnaire 1) and 6 weeks after the due date (Postpartum Questionnaire 1). During the visit, blood pressure and heart rate were routinely measured and the results were given in writing to the women on the information leaflet in order to self-report in Pregnancy Questionnaire 1 [20,21].

Study questionnaires could be accessed through the Expect Study website [22] by use of a personal login code contained in the written information and information email. Women agreeing to participate gave online informed consent and answered the eligibility criteria before the start of Pregnancy Questionnaire 1. Paper-and-pencil questionnaires were available upon request. Three reminders were sent by email during 3-day intervals if Pregnancy Questionnaire 1 was not accessed or incomplete. Women who completed Pregnancy Questionnaire 1 were invited 6 weeks after the due date to complete Postpartum Questionnaire 1. Three email reminders were sent during 6-day intervals, and in case of non-response, a paper-and-pencil version of Postpartum Questionnaire 1 was sent (provided that the postal address was available). In Pregnancy Questionnaire 1, women were invited to fill out, on an optional basis, 3 additional questionnaires about costs, quality of life, and satisfaction of current obstetric care around 24 and 34 weeks of gestation (Pregnancy Questionnaires 2 and 3), and 6 weeks after the due date together with Postpartum Questionnaire 1 (Postpartum Questionnaire 2). Again, automatic reminders were sent out in case of non-response. Pregnancy status was asked at the beginning of Pregnancy Questionnaires 2 and 3. Women who reported a miscarriage or termination were referred to the end of the questionnaire and not invited for further questionnaires. Women not responding to Pregnancy Questionnaire 2 received no further invitations for the additional questionnaires, only for Postpartum Questionnaire 1. Women not responding to Pregnancy Questionnaire 3 were invited; however, for Postpartum Questionnaire 2. Medical records and discharge letters were requested from care providers.

A pilot study was carried out in the region of Maastricht before the official start of inclusion (March 25, 2013 to May 10, 2013) to assess the feasibility and acceptability of the recruitment process and the comprehensibility of Pregnancy Questionnaire 1. Evaluation questions about the recruitment process and form, content, and clarity of the questions were added to Pregnancy Questionnaire 1. If permission was given, participants were also approached by telephone.

Data Collection

Inclusion, follow-up, and data collection of participants were managed by use of a logistic application specifically developed for Expect Study I. Questionnaires were developed by the research team and where possible, validated questionnaires were included.

Pregnancy Questionnaire 1 contained questions about the following topics: socio-demographic characteristics, anthropometric data, medical conditions, obstetric history, lifestyle, medication, vitamin and mineral supplements, fruit intake, dietary intake of vitamin D and calcium (selection questions from the Dutch National Food Frequency Questionnaire tool [23]), sun exposure, family history of medical conditions and obstetric outcomes, mental health (Edinburgh Depression Scale [24,25]), health status (EQ-5D-3L and cognitive dimension [26,27]), current pregnancy, and blood pressure and heart rate measurements.

The following aspects were collected in Postpartum Questionnaire 1: pregnancy outcome, pregnancy complications, labor and delivery, and neonatal outcomes. We also added several questions about the biological father.

The additional questionnaires—Pregnancy Questionnaires 2 and 3 and Postpartum Questionnaire 2—assessed maternal health status (EQ-5D-3L and cognitive dimension [26,27]), state anxiety (State-Trait Anxiety Inventory [28]), patient satisfaction, and costs of current obstetric care. Satisfaction was assessed antepartum (Pregnancy Questionnaires 2 and 3) by means of the Patient Satisfaction Questionnaire Short Form (PSQ-18) [29] and postpartum (Postpartum Questionnaire 2 or delivered at Pregnancy Questionnaire 2 or 3) by the Pregnancy and Childbirth Questionnaire (PCQ) [30]. To evaluate the costs of current obstetric care, all midwifery, hospital, and other care institution costs associated with care for pregnant women and their newborns from the beginning of pregnancy up to around 6 weeks after the due date were requested. In Pregnancy Questionnaire 3 and Postpartum Questionnaire 2, the date of the last completed additional questionnaire was indicated so that participants could see what period was to be covered.

Data from the medical records and letters of discharge were extracted and entered into a predesigned datasheet using Microsoft Access. All records were verified by a second researcher.

An overview of the items collected in the study questionnaires and data extracted from medical records and discharge letters is provided in Multimedia Appendix 2.

Outcome Measures

Primary study outcomes were maternal and perinatal adverse outcomes predicted by the selected prediction models. The maternal outcomes were PE and GDM. PE was defined as pregnancy induced hypertension (PIH) accompanied by proteinuria (at least 300 mg protein in a 24 hour urine collection) [31]. PIH was defined as systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least 90 mmHg (Korotkoff V) after 20 weeks gestation, measured twice in a previously normotensive woman [31,32]. GDM was defined as a diagnosis of hyperglycemia during pregnancy, in a woman without pre-existing diabetes mellitus. The Dutch national guideline, in line with the World Health Organization guideline on Diagnosis and Classification of Diabetes Mellitus, defined hyperglycemia as the presence of either a fasting plasma glucose of 7.0 mmol/l or greater or 2-hour plasma glucose of 7.8 mmol/l or greater following a 75 g oral glucose tolerance test [33,34]. Perinatal outcomes included spontaneous PTB, SGA infants, and LGA infants. Spontaneous PTB is a delivery before 37 weeks of gestation started by primary contractions or spontaneous rupture of membranes. SGA and LGA were defined as an infant with a birth weight below the 10th percentile or above the 90th percentile, respectively, corrected for gestational age, ethnicity, gender, and parity [35].

The following secondary outcomes associated with the primary outcomes and important determinants of child morbidity and mortality were also measured: perinatal death (stillbirth or death within 7 days after birth, after 22 weeks of gestation), asphyxia (Apgar score of less than 7 after 5 minutes), admission to a neonatal intensive care unit (within 28 days after birth), SGA infants below the 2.3 percentile, PTB before 32 weeks of gestation, severe PE (delivery before the 34th completed week), instrumental delivery, cesarean section, and referral from midwife to obstetrician during delivery.

Sample Size

No generally accepted rules are available for the calculation of required sample sizes for external validation studies of prediction models. We followed the rule of thumb by Vergouwe et al (2005), which states that at least 100 events and 100 non-events are necessary in order to be able to detect relevant differences between model performance in the derivation set and the validation set [36]. Assuming that each primary outcome would affect 4% or more of the pregnancies, we needed to collect data from about 2500 women. We aimed to recruit 2750 women, allowing for 10% loss to-follow-up.

Statistical Analysis

Data analysis of the external validation study is in progress. Missing values will be handled by imputation, as analysis of only complete cases can lead to biased results [37]. Predictive performance of each prediction model will be evaluated by assessing discrimination and calibration [38,39]. Discrimination is the ability to distinguish between individuals who will develop the outcome from those who will not and will be assessed by calculating the c-index (area under the receiver operating characteristic curve [AUROC]). Calibration is the degree of agreement between predicted and observed probabilities. We will evaluate whether models may benefit from recalibration. Based on their final calibration and discriminative power, models will be ranked with respect to their predictive performance. The statistical analysis will be described in detail in the validation articles.

Results

Pilot Study

A total of 6 midwifery practices and 1 university hospital invited 95 pregnant women to participate. In total, 25 (26%, 25/95) women gave informed consent, of whom 21 (84%, 21/25) completed Pregnancy Questionnaire 1 fully and 4 (16%, 4/25) only partially because of technical problems. Of the participants, 70 (74%, 70/95) invited women who did not wish to fill out Pregnancy Questionnaire 1 could have return a non-participation form, but only 1 form was returned indicating that the woman "did not want to invest time in research." The participants were positive about the recruitment process and only minor revisions were needed in the content of Pregnancy Questionnaire 1. In reaction to the low response rate, we made improvements to the recruitment process by asking contact details of informed pregnant women to send reminders about the study by email or telephone. Furthermore, a leaflet was designed to make the written information more concise and attractive, and we distributed information through social media and posters for promotion. Lastly, half of the pilot study participants declared that an incentive would increase their motivation to participate, and that they preferred higher probability of receiving a low-cost reward in comparison to a lower chance of getting an expensive incentive. On the basis of this information, low-to-medium cost incentives were invoked in the recruitment procedure (lottery of 27 gift cards and 2 photo shoots).

Validation Cohort

The flowchart for enrolment and data collection of the validation cohort is shown in Figure 1. A total of 2794 women accessed the study website and gave online informed consent. Pregnancy Questionnaire 1 and Postpartum Questionnaire 1 were filled out by 2762 (98.85%, 2762/2794) and 2178 (78.86%, 2178/2762) women, respectively. Medical records were retrieved for 2598 (94.06%, 2598/2762) women. A completed Postpartum Questionnaire 1 or medical record was available for 2614 (94.64%, 2614/2762) women (validation cohort). General baseline characteristics and the primary outcomes of the validation cohort are shown in Table 1.

Table 1. Baseline characteristics and primary outcomes validation cohort of Expect Study I (N=2614).

Baseline characteristics (less than 16 weeks of gestation)	Observed validation cohort, n (%)
Age in years, mean (SD)	30.2 (3.9)
Ethnicity	
Caucasian	2533 (96.90%)
African-Caribbean	3 (0.11%)
Asian	20 (0.77%)
Hispanic	11 (0.42%)
Mixed	47 (1.80%)
Tertiary education	1420 (54.32%)
BMI[a] , mean (SD)	24.2 (4.3)
<18.5	87 (3.33%)
18.5-24.9	1665 (63.70%)
25-29.9	585 (22.38%)
30-39.9	263 (10.06%)
≥40	9 (0.34%)
Medical history	
Chronic hypertension	28 (1.07%)
Diabetes mellitus	11 (0.42%)
Renal disease	5 (0.19%)
Smoking during pregnancy	
Ever	318 (12.17%)
Current	157 (6.01%)
Alcohol consumption during pregnancy	
Ever	479 (18.32%)
Current	9 (0.34%)
Nulliparous	1326 (50.73%)
Conception	
Spontaneous	2440 (93.34%)
Ovulation induction	93 (3.56%)
IVF[b]/ICSI[c]	81 (3.10%)
Obstetric history	
Prior pre-eclampsia	72 (2.75%)
Prior gestational diabetes mellitus	15 (0.57%)
Prior preterm birth <37 weeks of gestation	141 (5.39%)
Prior birth weight <10th percentile	108 (4.13%)
Prior birth weight >90th percentile	170 (6.50%)
Primary outcomes	
Pre-eclampsia	76 (2.91%)
Gestational diabetes mellitus	74 (2.83%)
Spontaneous PTB <37 weeks of gestation	127 (4.86%)
Birth weight <10th percentile	206 (7.88%)
Birth weight >90th percentile	224 (8.57%)

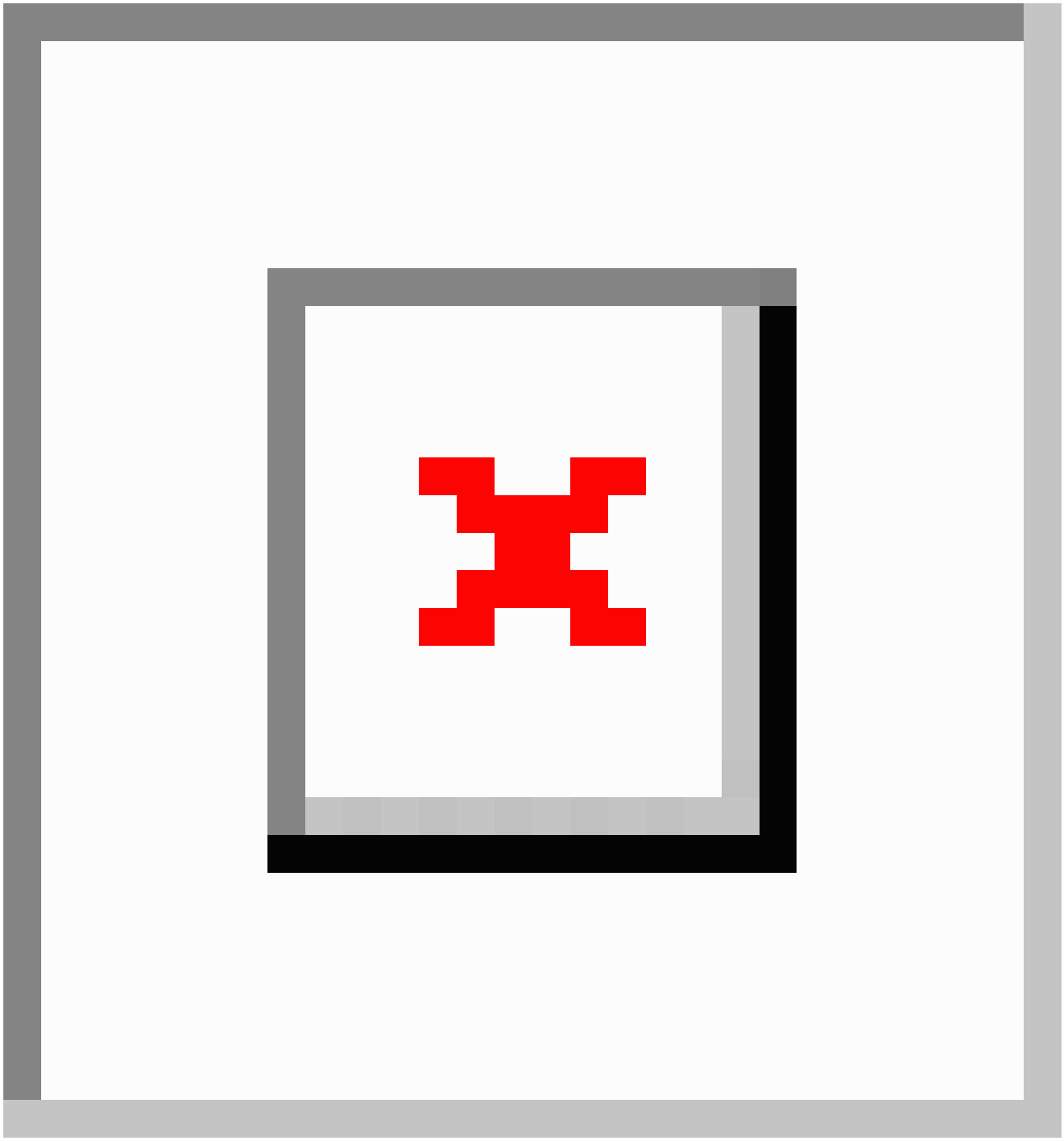
[a]BMI: body mass index measured in kg/m^2.

[b]IVF: in vitro fertilization.

[c]ICSI: intracytoplasmic sperm injection.

Of the women included in the validation cohort, 1548 (59.22%, 1548/2614) gave permission to be invited for the additional questionnaires. Pregnancy Questionnaire 2 was filled out by 891 (57.56%, 891/1548) women. Of the women who started the first additional Pregnancy Questionnaire 2 and were still pregnant, 795 (89.5%, 795/888) women filled out Pregnancy Questionnaire 3. Postpartum Questionnaire 2 was filled out by 744 (83.5%, 744/891) women.

Figure 1. Inclusion and data collection of Expect Study I. The components in the dotted box represent the additional questionnaires. A total of 1548 participants gave permission to receive additional questionnaires (a).



Discussion

Here, we describe the protocol of a study that aims to assess the predictive performance of multiple first trimester obstetric prediction models within an independent Dutch population. In this way, prediction models with similar outcomes can be compared and best performing models can be selected [40].

In the evaluation of a prediction model, external validation is an essential step. Generally, the predictive performance of the

model decreases in the validation dataset due to model over-fitting in the development cohort [18,41]. Existing independent external validation studies of non-invasive, first trimester obstetric prediction models for GDM showed stable discriminative performances, with the highest AUROCs for the models by Nanda et al (AUROC 0.79) and Van Leeuwen et al (AUROC 0.76-0.77) [13-16]. For the outcomes early and late PE, only a few models based upon maternal characteristics and blood pressure have been externally validated and AUROCs declined to around 0.70 [8-12]. A limitation is that the numbers of events in these validation studies were (extremely) low, especially for early PE. No independent external validation studies of non-invasive prediction models for overall PE, spontaneous PTB, SGA infants, and LGA infants have been published.

The main strength of our study is the prospective cohort design, which enables optimal measurement of predictors and outcomes [42]. Recruitment by multiple centers improves the likelihood of obtaining a representative sample of the obstetric population, which is especially important in the obstetric care system in The Netherlands in which most pregnant women start antenatal care with a midwife. Web-based questionnaires were used as a data collection tool, which is efficient in a population with high access to the Internet, as it improves data quality and less missing data due to the incorporation of validation checks. Moreover, it is also more user-friendly in comparison to paper-pencil forms as non-relevant follow-up questions could be hidden, speeding up completion [43].

If one or more prediction models turns out to be externally valid, eventually after model updating, it is not self-evident that the model will be useful in clinical practice. The prediction models can only lead to improved outcomes for mother and child if they can guide healthcare professionals and individuals in their decision making regarding further management that are tailored to individual risk profiles, including additional testing, preventive interventions, lifestyle changes, monitoring, or treatment [42].

Statistical performance measures are important aspects of a prediction model, but they do not indicate its clinical usefulness. Even if the statistical performance is less good, the model may predict better compared to usual practice, and vice versa [44-46]. We plan to evaluate the clinical utility of the validated models by decision analysis. Decision analysis provides insight whether the model is better than usual care by combining test characteristics with evidence on consequences of the outcome, effects and burden of the further management, and costs [18]. In case a model is worth considering for implementation in clinical practice, it is necessary to determine the most optimal threshold value for risk classification. Finally, we will assess the effects of applying prediction models with tailored care paths on decision-making and health outcomes in Dutch obstetric care, as compared with care-as-usual (Expect Study II).

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Authors' Contributions

The study was developed by LS, HS, and MS in collaboration with RDV, CD, IK, AM, MN, and JN. All collaborators are considered as co-authors as they have significantly contributed to the design of the study. LM elaborated and carried out Expect Study I under the supervision of LS and HS. The manuscript was drafted by LM in collaboration with LS and HS. All authors critically reviewed and approved the final manuscript.

Conflicts of Interest

None declared

Multimedia Appendix 1

Search strategies first-trimester obstetric prediction models.

[PDF File (Adobe PDF File), 5KB - resprot_v6i10e203_app1.pdf]

Multimedia Appendix 2

Data collection study questionnaires and medical records.

[PDF File (Adobe PDF File), 610KB - resprot_v6i10e203_app2.pdf]

Multimedia Appendix 3

Reviewer comments (3 reviewers) and rebuttal grant application ZonMw. The Netherlands Organization for Health Research and Development, Pregnancy and Childbirth program (ZonMw grant 209020007). [ENGLISH].

[PDF File (Adobe PDF File), 1MB - resprot_v6i10e203_app3.pdf]

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Abbreviations

AUROC: area under the receiver operating characteristic
GDM: gestational diabetes mellitus
LGA: large-for-gestational-age
MEC: medical ethical committee
PE: pre-eclampsia
PIH: pregnancy induced hypertension
PTB: preterm birth
SGA: small-for-gestational-age

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Protocol

Uterine Fundectomy in Patients With Benign Etiology Undergoing Hysterectomy: New Surgical Technique

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Abstract

Background: Hysterectomy is the most common surgical procedure in gynecology, not only in cases of malignancies but also in many benign cases. Many uterine preservation techniques have been introduced as alternatives to hysterectomy.

Objective: We aimed to propose a new uterine surgical procedure. In this paper, we compare the utility of this new technique to the limitations of current procedures.

Methods: Uterine fundectomy may be considered as a subtotal hysterectomy. In this new technique, the uterine fundus including all pathologic tissue is cut as a reverse trapezoid by monopolar cautery. The upper side of the trapezoid, which includes the whole uterine fundus, is removed, but the fallopian tubes and cornual segment are preserved. A small uterine cavity remains, as well as the endometrial tissue lining it.

Results: Patient recruitment for this study began in April 2017 and is expected to end approximately 12 months later. Assessment of the primary outcomes is expected to take place in April 2018.

Conclusions: Uterine preservation is particularly critical in developing new surgical approaches that can lead to a positive impact on patient satisfaction. This protocol outlines the first attempt to prospectively test surgical fundectomy in candidates for hysterectomy for benign indications.

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KEYWORDS

hysterectomy; uterine; fundectomy

Introduction

Hysterectomy is the most common surgical procedure in gynecology, not only in cases of malignancies but also in many benign cases, such as uterine fibroids, endometrial hyperplasia, adenomyosis, dysfunctional uterine bleeding, and cervical intraepithelial neoplasia [1]. For benign cases, there are many possible hysterectomy procedures. The surgical technique is selected based on the reason for surgery, the general condition of the patient, and the surgeon's experience and skills. A variety of surgical techniques exists, including minimally invasive procedures (laparoscopic) and traditional open surgical procedures (laparotomy). Minimally invasive surgical procedures include laparoscopic hysterectomy and robotic-assisted laparoscopic hysterectomy [2]. Open surgical procedures include radical hysterectomy, where surgeons

remove the uterus and surrounding tissues and cervix; a total hysterectomy, where the entire uterus and cervix are removed; and subtotal or partial hysterectomy, where the uterus is surgically removed but the cervix is left in place.

In the past decade, many uterine preservation techniques have been introduced as alternatives to hysterectomy. These techniques use modern technology and show reliable and comparable results [3]. In a randomized controlled trial, women in the subtotal hysterectomy group had a significantly better quality of life and improved body image compared to the total hysterectomy group [4]. It seems that hysterectomy performed with ovary preservation can still affect the function of the ovaries. It has been reported in women who have undergone hysterectomy compared with the control group (no surgical procedure) that postmenopausal symptoms occur earlier, probably due to the reduction of ovarian blood flow.

Here we aim to propose a new uterine surgical procedure and to compare the utility of this technique to the limitations of present procedures.

Methods

Overview

Uterine fundectomy is used only in patients who have indications for benign uterine conditions, where only the pathologic part of the uterine body is removed. The neck of the uterus (cervix) and a part of the uterine and endometrial tissue are preserved, so that menstrual periods remain. An important feature of uterine fundectomy is the preservation of the uterus in women after surgical treatment. Thus, uterine blood vessels, adnexa (appendages), and ovaries remain with no surgical manipulation and ovarian function is not affected. The most important thing about this technique is the choice of patient. This procedure is performed only in benign cases of patients with uterine surgical indication, and in those who wish to preserve the uterus. However, this procedure does not preserve fertility because the remaining uterine cavity is very small. Replacing a hysterectomy with the uterine fundectomy in appropriate cases can preserve menstrual bleeding and ovarian function, as well as maintaining a positive impact on patient satisfaction.

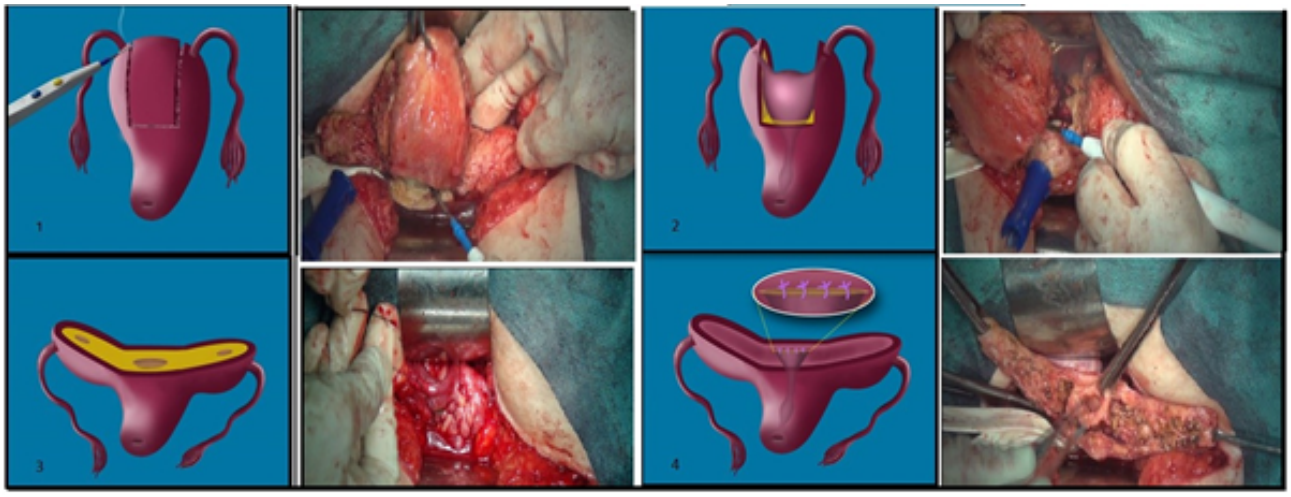
Recruitment

Patients will be initially recruited from a pool of women who choose to have a hysterectomy for benign indications. Researchers will then notify them about the study protocol and ask about their interest in participating. Inclusion criteria consists of premenopausal women aged 36-50 years, candidates for hysterectomy for benign indications, and those patients who signed the informed consent and agree to participate. Women with a history of cancer, hereditary cancer, and those patients who are candidates for surgery because of a malignant pathology will be excluded.

Surgical Procedure

In uterine fundectomy, to prevent intra-operative bleeding, a tourniquet is placed on the lower segment of the uterus below the ovaries. Thus, uterine and ovarian arteries are temporarily closed. Then, the uterine body is cut as a reverse trapezoid by monopolar cautery (Figure 1). The upper side of the trapezoid, which includes the whole uterine fundus, is removed, but the fallopian tubes and cornual segment are preserved. The lower and smaller border of the trapezoid is 1 cm above the internal os of the uterus. Thus, a small uterine cavity remains, as well as the endometrial tissue lining it. The roof of the new uterine cavity, is closed separately by a 2-0 vicryl suture. The lateral uterine segments are sutured to the upper surface and closure is performed. Dead space closure is performed with 0 vicryl suture. After ensuring complete restoration, the tourniquet is opened and complete homeostasis established.

Figure 1. Illustration and photos of the new uterine surgical procedure.



Outcomes

Primary outcome measures will be the number of participants having subjective symptoms after fundectomy. Sexual symptoms will be assessed with a questionnaire. Secondary outcome measures will be the evaluation of pelvic organ prolapse after surgery and patients' quality of life.

Ethical Approval

Women will be asked to sign the informed consent after reviewing the study protocol and consent form. The research will be approved by Sarem Hospital Ethical Committee.

Results

Patient recruitment began in April 2017 and is expected to end approximately 12 months later. Thus, assessment of primary outcomes of interest is expected in April 2018.

Discussion

Principal Findings

Uterine preservation is particularly critical in development of new surgical approaches that can lead to a positive impact on patient satisfaction. In the current subtotal hysterectomy, uterine arteries are cut off and thus the blood supply and ovarian adnexal flow are diminished, ultimately affecting ovarian function. This almost certainly affects the patients' quality of life. But in uterine fundectomy, because there is no manipulation of the uterine arteries, typically no ovarian dysfunction occurs. In addition, in uterine fundectomy no harm occurs to the pelvic floor, minimizing subsequent issues. The duration of surgery and the amount of bleeding in uterine fundectomy are less than in the other techniques. Further, uterine preservation may also have a psychologically positive effect on a woman's quality of life. However, it should be noted that uterine fundectomy does not preserve fertility, because the remaining uterine cavity is very small and the amount of endometrial lining is minimal.

Conclusion

This protocol outlines the first attempt to prospectively test surgical fundectomy in patients who are candidates for hysterectomy for benign indications. Study results are expected to show improved quality of life in patients, offering more positive options for women in the future.

Acknowledgments

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Conflicts of Interest

None declared.

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Protocol

Real-World Treatment Sequences and Outcomes Among Patients With Non-Small Cell Lung Cancer (RESOUNDS) in the United States: Study Protocol

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Abstract

Background: Survival outcomes are related to treatment choices in a line of therapy and to treatment sequences across all lines of therapy.

Objective: The Real-World Treatment Sequences and Outcomes among Patients with NSCLC (RESOUNDS) study is designed to (1) evaluate treatment sequences used for patients who receive at least two lines of therapy for non-small cell lung cancer (NSCLC) in the United States and (2) evaluate patient outcomes in terms of progression-free and overall survival related to treatment sequencing. Additional objectives include the evaluation of symptoms, comorbidities, and health care resource utilization and costs.

Methods: Patients will be censored at loss to follow-up due to leaving the health plan or reaching the end of the study period.

Results: This study is ongoing.

Conclusions: The RESOUNDS cohort study is a novel approach to building a comprehensive dataset that mimics a prospective observational study using linked patient-level data from four real-world data sources. This study will provide timely information on the sequencing of treatments for patients with NSCLC.

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KEYWORDS

cancer; non-small cell lung cancer; chemotherapy; regimen; line of therapy; treatment sequence; progression-free survival; overall survival; real-world data

Introduction

Lung cancer is the second most common cancer in the United States and the leading cause of cancer-related death, with an estimated 158,040 Americans dying in 2016 from the disease [1]. The two types of lung cancer are small cell and non-small cell lung cancer (NSCLC)—NSCLC accounts for roughly 83% of cases [2]. The US Food and Drug Administration recently approved several novel biologic agents (eg, ramucirumab, nivolumab, and pembrolizumab) [3-6]; as a result, the treatment of NSCLC is rapidly evolving. However, the appropriate timing and most effective sequence of these new agents in the care of patients remains unknown. Previously, care was delivered in distinct lines of therapy, as it was unknown if the patient would be able to continue treatment over time. However, with the advent of newer agents demonstrating improved overall survival outcomes in the postprogression setting, providers now can consider treatment strategies over time. As with many other cancers, lung cancer is increasingly being treated as a chronic condition. As novel agents continue to demonstrate improved

survival outcomes in NSCLC, additional data are needed across lines of therapy to identify the optimal sequencing of these agents for the optimization of patient care.

The study of treatment sequences in a randomized controlled trial (RCT) would be extremely challenging, due to not knowing which patients will progress to a second line and to the treatment heterogeneity used in current practice settings across lines of therapy. A sequence can be studied only in patients who receive more than one line of therapy. Recent data suggest that less than half of NSCLC patients will receive a second line of therapy [7]. As a result, a randomized trial would have to double the enrolling patient size beyond the number necessary to ensure statistical power to obtain a sufficient sample of evaluable patients receiving a sequence of agents. Further, for data to be relevant to clinical decision makers, the treatment choices should reflect those available. An RCT of multiple treatment arms would similarly require that sample sizes be increased to ensure that all relevant treatments be applied consistently across the population. Alternatively, prospective observational trials may be conducted that do not rely on randomization but instead permit usual treatment practices to occur as data are being collected. This is appealing to providers and patients who wish to maintain the ability to make treatment choices based on preferences for care. However, a prospective observational trial would still require a very large study population to be enrolled and followed over time, further increasing the time and cost of such a study. The research team has designed the current study as an alternative to these costly and long-term prospective trial designs. The **Re**al-World Treatment **S**equences and **Ou**tcomes among Patients with **NS**CLC **(**RESOUNDS) study was designed to mimic a prospective observational study by using longitudinal data from large pre-existing databases. The enrollment date (termed "index date" for this study) is defined as the start of second-line therapy, and real-world data sources (eg, medical records, claims data) are being culled to create a longitudinal de-identified patient-specific study record retrospectively and contemporaneously from the time of initial diagnosis through the end of the follow-up period.

The primary objective of this study is to describe treatment sequences used for patients who receive at least two lines of therapy for NSCLC in the United States, while secondary objectives include outcomes of survival, disease progression and response, health care resource utilization and costs, and factors associated with treatment decision making. This study integrates multiple pieces of data (ie, medical records, claims, oncology clinical care pathway data, and death index data) in order to gain depth of data related to clinical and economic outcomes as well as to provide a wider breadth of information than is feasible in an RCT or traditional prospective observational trial. This novel approach to mimicking a prospective trial with pre-existing data sources is expected to speed the timing of generating robust outcome data, minimize participant burden, and increase the generalizability of findings to the broader NSCLC population in the United States.

HealthCore, a wholly owned subsidiary of Anthem, Inc., explores health care claims data from Anthem members and investigates health plan clinical cancer care data collected from oncologists participating in a quality improvement initiative designed to provide members diagnosed with cancer access to quality, evidence-based, cost-effective medical care (referred to as "HIRE Oncology"). The quality improvement program provides treating physicians enhanced reimbursement when the treatment regimen is aligned with National Comprehensive Cancer Network and/or American Society of Clinical Oncology guidelines. This program provides physician incentives to use treatment regimens for each line of therapy that are included in the guideline. Additionally, medical records will be reviewed for data not available in other sources (eg, imaging reports, results of biomarker testing). The use of these data has been validated for use in observational research studies [8]. Eli Lilly and Company and HealthCore are conducting this study using these and other linked data resources to better understand the sequencing of care for patients diagnosed with NSCLC.

Methods

Study Aims

The overarching goal of the RESOUNDS study is to better understand treatment sequences among patients who received at least two lines of therapy for NSCLC. To achieve this goal, the following specific aims will be pursued for the overall population as well as for specific treatment sequences: (1) describe baseline demographic and clinical characteristics, (2) evaluate clinical outcomes (eg, Eastern Cooperative Oncology Group [ECOG] or Karnofsky performance status, tumor response, disease progression, symptoms, and survival), (3) evaluate health care resource utilization (eg, hospitalizations, emergency room visits, hospice and long-term care, medication use, radiation therapy, imaging) and costs, and (4) evaluate the factors associated with selection of and changes in treatment, including treatment changes and discontinuation of therapy. An exploratory objective will evaluate differences in overall survival among specific subgroups of interest, such as treatment regimen by line of therapy, histology (squamous vs nonsquamous), and treatment sequences.

Design and Data Sources

This retrospective, observational cohort study uses the integration of HealthCore Integrated Research Environment (HIRE) Oncology data, which are built through multiple sources of data from the Cancer Care Quality Program, HealthCore Integrated Research Database (HIRD) administrative claims data, and National Mortality Registries, supplemented by medical records data. All procedures for this study have been approved by the New England Independent Review Board, which granted a waiver for the research pursuant to 45 CFR (Code of Federal Regulations) §164.512(i) on June 30, 2016.

HealthCore Integrated Research Environment

The HIRE contains a large administrative health care database that can be linked to data sources, including inpatient and outpatient medical records, national vital statistics records, member and provider surveys, and point-of-care clinical data to provide a fully integrated, comprehensive dataset. This study will utilize multiple data sources from within HIRE: (1) claims data from HIRD, (2) Cancer Care Quality Program data, (3) National Mortality Registry data, and (4) data from medical

records. Figure 1 illustrates the study design, and Figure 2 demonstrates the data sources proposed for this study.

HealthCore Integrated Research Database

HIRD is a single payer insurance database that contains administrative health care claims integrated across data sources and types (ie, professional claims, facility claims, outpatient pharmacy claims, outpatient laboratory results, and enrollment information) as well as across years (from 2006 through the most recent month). Data are geographically dispersed and are obtained from 14 Anthem, Inc. affiliated health plans in the Northeastern, Mid-Atlantic, Southeastern, Midwest, Central, and Western regions of the United States, representing members in each of the 50 states. HIRD includes data from January 2006 for all the plans represented in the database. As of December 2015, these data contained information from 38.8 million patient lives with medical and pharmacy eligibility, and 25.8 million patient lives eligible for medical chart review, of which 6.0 million are currently active in the health plan.

Figure 1. Data sources used for this study.

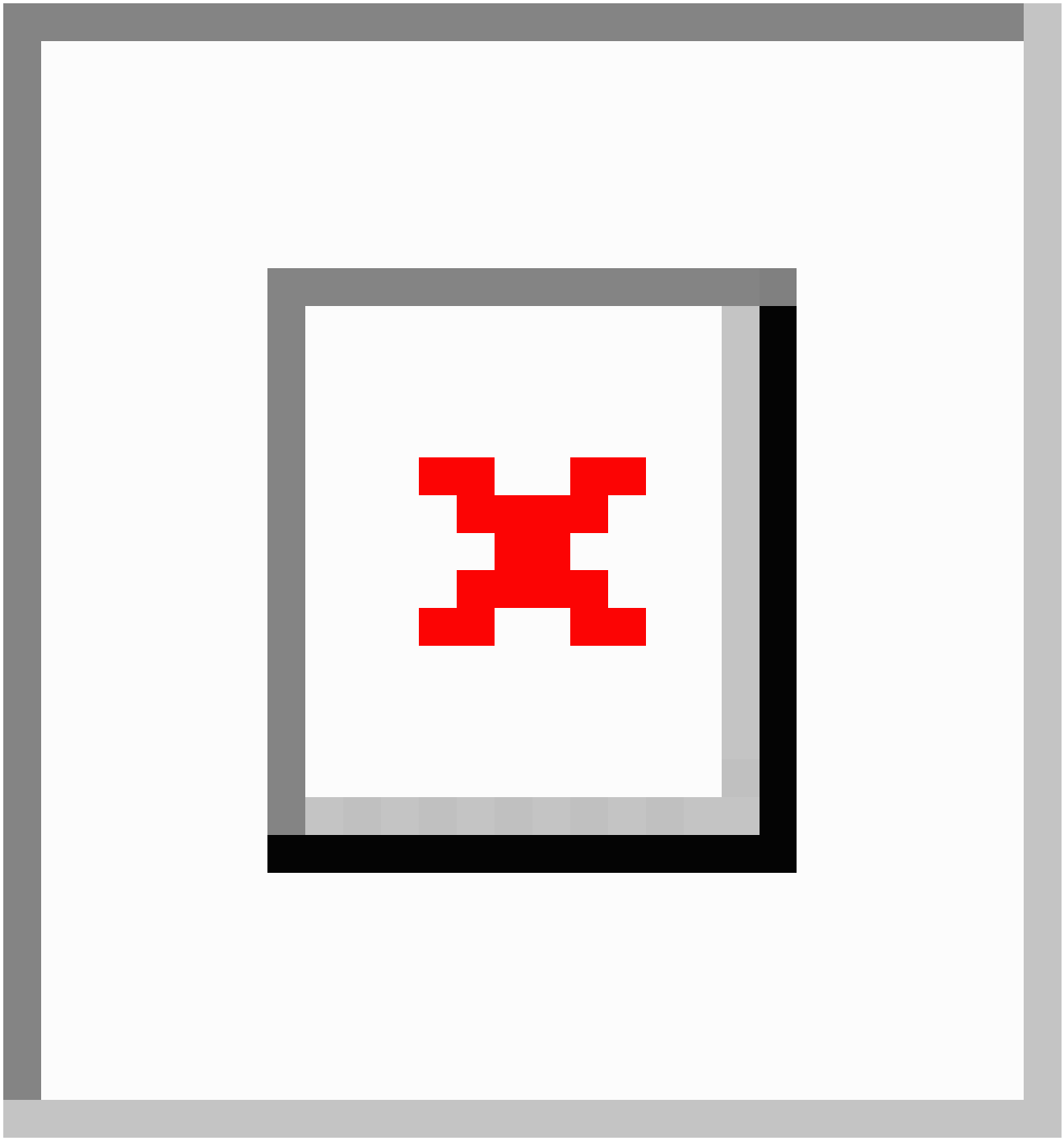
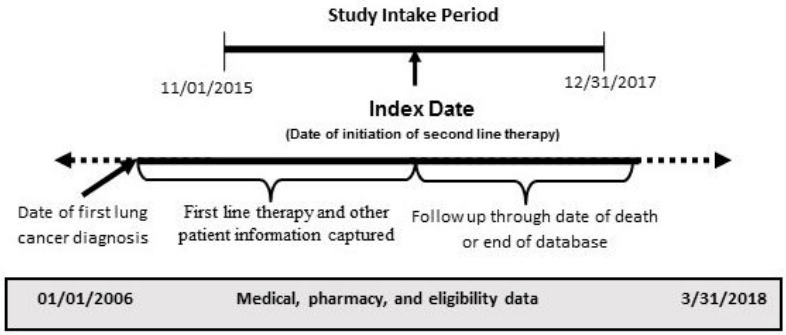


Figure 2. Study time frame.



Note: The index date may be at any time within the intake period.

Cancer Care Quality Program

This program offers evidence-based cancer treatment information enabling physicians to compare planned cancer treatment regimens against evidence-based clinical criteria [8]. The program has identified certain cancer treatment pathways, selected based on current clinical evidence, published literature, and national guideline recommendations, which have shown to be efficacious, less toxic, and cost effective. The physicians participating in the program receive additional reimbursement per patient for prescribed treatment regimens that align with the identified pathway, encouraging evidence-based quality care for the patients and cost benefits for the physicians. Data are obtained when physicians request approval for this pathway-based enhanced reimbursement as well as prior authorization for the various cancer treatments. As of September of 2015, the program has been implemented in all of the Anthem health plans. Cancer treatment pathways collect clinical, demographic, and treatment data for the three highest volume cancers, namely breast, lung, and colorectal. These data are available for a subset of individuals in HIRD via direct patient linkage.

The following clinical information is collected for the Cancer Quality Care Program and is integrated with the medical and pharmacy claims data contained within HIRD: cancer type, cancer stage, tumor biomarkers (eg, epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK] status), line of treatment (ie, adjuvant/post-operative, first line, second line, third line or more, maintenance), and physician specialty. Since the program was rolled out sequentially in the various Anthem health plans over 15 months, the number of patients has incrementally increased over time. All Anthem health plans are participating as of the start date of this study.

HIRD is hosted on servers contained within HealthCore's Data Coordination Center, which is located in a locked suite within HealthCore's facility. Access to this database is through password-protected, 128-bit Secure Socket Layer (SSL) encrypted connections.

National Mortality Registry

Data from HIRD are linked to mortality registries via patient identifiers to determine date of death using the Death Master File (DMF) provided by the Social Security Administration (SSA). These data include greater than 80 million individual recorded deaths reported to the SSA (approximately 95% of all deaths that occur in the United States). Cause of death cannot be determined using the DMF. Data from the SSA will also be supplemented with data from HIRD that contain discharge data indicating death for those patients who died in the hospital setting.

Medical Record Data

Patients will be identified from HIRD claims data, and their medical records will be targeted for abstraction by contacting the patients' providers. A chart abstraction form will provide the chart abstractor with information on what data are to be abstracted from the charts and forwarded to the study team. Charts are successfully abstracted for approximately 65% of patients on average. Thus, not all patients will have available chart data.

To help ensure the consistency of data collection, the chart reviewers (eg, nurses, pharmacists, and physicians) have received detailed training on the study's design. Training for abstraction also includes a detailed review of the standardized data collection forms approved by the New England Institutional Review Board. Clinical information that is abstracted or redacted from the medical and hospital charts is entered into a secure electronic database with a masked identifier so that it can be matched with corresponding electronic claims data without the use of individually identifiable information.

Eligibility Criteria

The eligible patient population must meet the following criteria:

- Patients with squamous or nonsquamous metastatic NSCLC who have initiated second-line therapy with pemetrexed, ramucirumab, docetaxel, pembrolizumab, nivolumab, gemcitabine, paclitaxel, necitumumab, vinorelbine, cisplatin, carboplatin, bevacizumab, afatinib, nab-paclitaxel, atezolizumab, and/or erlotinib.
- Patients must have ≥1 medical claim with a diagnosis for lung cancer (*International Statistical Classification of Diseases*, 9th or 10th Revision, Clinical Modification [ICD-9-CM] codes 162.2x-162.9x or ICD-10-CM codes C34.xx) prior to initiation of second-line therapy.
- Second-line therapy must be initiated between November 1, 2015, and December 31, 2017.

- For claims data, there must exist at least 90 days of health plan enrollment prior to the date of initial first-line chemotherapy to ensure a complete patient record is available.
- Patients age ≥18 at the initial diagnosis of lung cancer.

Patients with small-cell lung cancer and patients <18 years old as of the earliest observed lung cancer diagnosis date are excluded.

After determining eligibility, patient medical records will be reviewed to ensure that the patient has NSCLC due to the nonspecific nature of ICD-CM-9 and ICD-CM-10 codes alone and that the treatment in the medical record verifies what is identified in the claims data to ensure the patient has received at least two lines of therapy. This ensures an advanced/metastatic cohort for this study. Patients will be identified from the HIRD and HIRE Oncology datasets, with verification from the medical record.

Study Timeframe

Patients will be identified based on initiation of second-line therapy between November 1, 2015, and December 31, 2017 (referred to as the "intake period"). The "index date" for each patient (similar to the enrollment date in a prospective observational trial) is defined as the start date of the second line of therapy (line of therapy is defined by the treating oncologist in the HIRE Oncology dataset). Patient history will be examined as far back as the first observed diagnosis for lung cancer (identified via claims or medical records, where applicable). Patients will be followed forward in time for as long as possible (eg, until death or disenrollment from their health plan or end of the study period). The final claims data base will be created in June 2018, at which point data will be available through at least March 2018. The RESOUNDS study design is shown in Figure 1.

Variables and Timing

Due to the observational nature of this study, data will be collected from a variety of sources as the events occurred, rather than at prespecified time points. All instances of data consistent with the variables of interest will be included with their respective dates from the patient record. No restrictions or limitations are made on the number or frequency of variables collected. The data to be captured include patient demographic and clinical characteristics (eg, age, sex, height, stage of disease, tumor histology, date of diagnosis, health plan type, geographic region, race/ethnicity, smoking status), body weights and laboratory measures, chemotherapy, biologic and targeted agents received (including doses and dates received), regimens and lines of therapy, supportive care and other pharmaceuticals received, radiation therapy and dates received, surgery and procedures and dates, physician notes for reasons of treatment initiation, discontinuation or change, performance status, symptoms, tumor response as physician assessed, tumor response per Response Evaluation Criteria in Solid Tumors (RECIST) criteria [9]; largest tumor dimension at each imaging study; date of death; ALK, EGFR, or programmed death-ligand 1 (PD-L1) testing and dates of tests; disease and treatment symptoms; health care resource use (eg, emergency room visits, hospitalizations, physician visits); diagnostic testing; and health care costs (Figure 1). Each of the variables in this study is collected from the previously described data sources used within the study to ensure accuracy. For example, claims data (eg, HIRD dataset) do not contain clinical data such as disease stage or histology. Therefore, these data are linked to the HIRE dataset (which contains both stage and histology as mandatory collection fields) and are further verified in the patient medical record. Similarly, chemotherapy medications are identified in claims data using generic product identifier and Healthcare Common Procedure Coding System values. First-line therapies are further verified in the medical record, and subsequent therapies are verified in the HIRE data. For other variables, such as resource utilization (eg, hospitalization, emergency room visits) and costs, the HIRD data (eg, claims) are the primary source, as this dataset records all health care related activity submitted to the insurer from any provider for care received by the patient at any health care setting.

Statistical Analysis Plan

Calculations were performed to determine the statistical power to detect overall survival differences over varying sample sizes. Two scenarios were modeled: (1) the median survival is 6 months in group A and 9 months in group B, and (2) median survival times are 6 months in group A and 12 months in group B. Other assumptions include 12 months of accrual and 12 months of follow-up. Table 1 presents the sample sizes from 10-300 with their resulting power assuming equal number of patients in each treatment group, significance level at .05 in a two-sided test, and assuming no loss to follow-up. It is expected that approximately 400 patients will be included in this study, and the size of the subgroups (eg, treatment regimens and sequences) for comparison will be a result of the treatment patterns and practices of their treating oncologists. Assignment of treatment is not being made in this observational study. The survival analyses are exploratory in nature in this study, and the magnitude of results, rather than statistical significance, will be used to inform potential future studies examining survival in more detail with larger and sufficient sample sizes.

Descriptive analysis will be performed to describe treatment sequences among NSCLC patients with at least two lines of therapy. Univariate statistics will include means, standard deviations, medians, and interquartile range for continuous variables, and relative frequencies and percentages for categorical variables. Kaplan-Meyer survival analysis will be used to estimate the time to event metrics for the entire study population and by each second-line regimen cohort. Additional subgroups include histology (squamous vs nonsquamous), line of therapy, and treatment sequences (eg, sequencing of immunotherapy, chemotherapy, biologic/targeted therapy drug classes). While the use of multiple data bases is expected to minimize the rate of missing data, there is the risk of missing data. For these variables, the number and percent missing will be reported, but no imputation will be made for those variables that cannot be confirmed in the medical record.

The decision to move from one treatment regimen to the next will be analyzed using classification and regression tree analysis. The goal will be to use this recursive partitioning technique to

find the factors most highly associated with treatment changes. This will be done for treatment changes overall (without differentiating treatment lines) and by each treatment line (eg, the first treatment change will be the start of second line; the second treatment change will be the start of third-line therapy). Furthermore, within each treatment change the outcome will be the specific change in therapy from line n to line n+1, where n=1, 2, 3. Analysis of specific treatment sequences from one line to the next will be limited to sequences with sufficient sample size for analysis.

Statistical testing will be performed for the outcome of overall survival for select comparison groups. The survival analyses are exploratory in nature and statistical testing will be performed only if there are at least 50 patients in each group. Survival analyses will adjust for covariates. Due to the limited number of patients expected in some of the subgroups, only 5-10 covariates will be included in the models to avoid overfitting the data. The following demographic covariates will be included in all statistical models: patient age, sex, health plan type, geographic region, and Deyo Comorbidity Index score [10]. Additional potential covariates to be included in each model will be selected according to their bivariate statistical significance (P<.05) with the outcome. These potential covariates include disease stage at initial diagnosis, smoking status, race/ethnicity, body mass index, and date of first diagnosis. No adjustment will be made for multiple testing.

Interim analyses for the descriptive/noncomparative endpoints are planned at semi-annual intervals through 2018. These descriptive data may be useful to inform the development of new trials or may be informative as to the changing nature of NSCLC care during the study period.

Table 1. Calculated statistical power for varying sample sizes for two different survival scenarios, assuming no loss to follow-up.

Median survival time[a]	Total N	Power
9	10	.089
9	20	.128
9	30	.169
9	40	.210
9	50	.250
9	60	.291
9	80	.369
9	100	.443
9	120	.512
9	140	.576
9	160	.633
9	180	.684
9	200	.729
9	220	.769
9	240	.804
9	260	.834
9	280	.860
9	300	.883
9	320	.902
9	350	.925
9	370	.938
9	400	.953
12	10	.158
12	20	.269
12	30	.376
12	40	.475
12	50	.564
12	60	.642
12	80	.765
12	100	.851
12	120	.908
12	140	.944
12	160	.967
12	180	.981
12	200	.989
12	220	.994
12	240	.996
12	260	.998
12	280	.999
12	300	>.999
12	320	>.999
12	350	>.999

Median survival time[a]	Total N	Power
12	370	>.999
12	400	>.999

[a]Compared to a group of patients with median survival of 6 months using log-rank test for equality of survival curves. Power was calculated assuming equal number of patients in each treatment group, significance level at .05 in a two-sided test, and no loss to follow-up.

Discussion

Principal Considerations

Observational research can provide highly generalizable data and can be used to conduct comparative effectiveness research as a complement to RCTs [11]. When designed appropriately, data from retrospective sources can be used to address scientific questions in a timely and cost-effective manner. The RESOUNDS study has been designed to address complex questions in the care of patients with NSCLC during a time where treatment strategies are changing and evolving. Rather than predefine the sequences of interest, this study will examine how physicians are treating patients and the outcomes associated with these sequences. As with observational study designs, these data will result in hypothesis-generating rather than definitive results from a priori hypotheses. However, these data may be used to guide the development of future RCTs, to better understand the optimal sequences, and to inform evidence-based medicine. At this time, little is known about the sequence of care for NSCLC, and this study will provide a robust dataset from which to address these and future research questions.

Limitations

Limitations of these data may include undercollected or missing data. For example, ECOG performance status, while a standard data item in cancer RCTs, is not routinely collected in patient care settings and may not be available for all patients. Similarly, tumor growth and progression is not commonly defined per RECIST criteria outside of a clinical trial setting and may not be applied to all imaging reports. Therefore, some of the research questions of interest may have underpopulated data. Similarly, while PD-L1 status may be an important research question, it is not currently being evaluated in the majority of NSCLC patients. This may result in a relatively small population that cannot be statistically compared or may result in the inability to evaluate patient outcomes by PD-L1 status. Therefore, as the data are not known until the time of analysis, no adjustments will be made to any study objective and no imputations will be made for missingness. As the comparative analyses are largely exploratory in nature, these will be conducted only if there is a sufficient sample with complete data.

Conclusion

The RESOUNDS cohort study is a novel approach to building a comprehensive dataset that mimics a prospective observational study using real-world data sources. This study will provide timely information on the sequencing of treatments for patients with NSCLC.

Conflicts of Interest

LMH, GCC, KW, ZL, AS, and ABO are employees of Eli Lilly and Company. DMK and LY are employees of HealthCore, Inc, which received funding from Eli Lilly and Company to conduct this study.

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Abbreviations

ALK: anaplastic lymphoma kinase
DMF: Death Master File
ECOG: Eastern Cooperative Oncology Group
EGFR: epidermal growth factor receptor
HIRD: HealthCore Integrated Research Database
HIRE: HealthCore Integrated Research Environment
ICD-9-CM, ICD-10-CM: International Statistical Classification of Diseases, 9th or 10th Revision, Clinical Modification
NSCLC: non-small cell lung cancer
PD-L1: programmed death-ligand 1
RCT: randomized controlled trial
RECIST: Response Evaluation Criteria in Solid Tumors
RESOUNDS: Real-World Treatment Sequences and Outcomes among Patients with NSCLC study
SSA: Social Security Administration

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Protocol

Côte d'Ivoire Dual Burden of Disease (CoDuBu): Study Protocol to Investigate the Co-occurrence of Chronic Infections and Noncommunicable Diseases in Rural Settings of Epidemiological Transition

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Abstract

Background: Individual-level concomitance of infectious diseases and noncommunicable diseases (NCDs) is poorly studied, despite the reality of this dual disease burden for many low- and middle-income countries (LMICs).

Objective: This study protocol describes the implementation of a cohort and biobank aiming for a better understanding of interrelation of helminth and Plasmodium infections with NCD phenotypes like metabolic syndrome, hypertension, and diabetes.

Methods: A baseline cross-sectional population-based survey was conducted over one year, in the Taabo health and demographic surveillance system (HDSS) in south-central Côte d'Ivoire. We randomly identified 1020 consenting participants aged ≥18 years in three communities (Taabo-Cité, Amani-Ménou, and Tokohiri) reflecting varying stages of epidemiological transition. Participants underwent health examinations consisting of NCD phenotyping (anthropometry, blood pressure, renal function, glycemia, and lipids) and infectious disease testing (infections with soil-transmitted helminths, schistosomes, and Plasmodium). Individuals identified to have elevated blood pressure, glucose, lipids, or with infections were referred to the central/national health center for diagnostic confirmation and treatment. Aliquots of urine, stool, and venous blood were stored in a biobank for future exposome/phenome research. In-person interviews on sociodemographic attributes, risk factors for infectious diseases and NCDs, medication, vaccinations, and health care were also conducted. Appropriate statistical techniques will be applied in exploring the concomitance of infectious diseases and NCDs and their determinants. Participants' consent for follow-up contact was obtained.

Results: Key results from this baseline study, which will be published in peer-reviewed literature, will provide information on the prevalence and co-occurrence of infectious diseases, NCDs, and their risk factors. The Taabo HDSS consists of rural and somewhat more urbanized areas, allowing for comparative studies at different levels of epidemiological transition. An HDSS

setting is ideal as a basis for longitudinal studies since their sustainable field work teams hold close contact with the local population.

Conclusions: The collaboration between research institutions, public health organizations, health care providers, and staff from the Taabo HDSS in this study assures that the synthesized evidence will feed into health policy towards integrated infectious disease-NCD management. The preparation of health systems for the dual burden of disease is pressing in low- and middle-income countries. The established biobank will strengthen the local research capacity and offer opportunities for biomarker studies to deepen the understanding of the cross-talk between infectious diseases and NCDs.

Trial Registration: International Standard Randomized Controlled Trials Number (ISRCTN): 87099939; http://www.isrctn.com/ISRCTN87099939 (Archived by WebCite at http://www.webcitation.org/6uLEs1EsX)

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KEYWORDS

cohort study; biobanking; biomarkers; Taabo HDSS; dual disease burden; humans; hypertension; diabetes mellitus; malaria; helminths

Introduction

There is an alarming increase in the prevalence of noncommunicable diseases (NCDs) in low- and middle-income countries (LMICs). Although this is generally considered the result of an increase in life expectancy and westernization of lifestyle, these common and widely accepted NCD risk factors do not provide a complete picture [1]. In fact, within high-income countries, the risk of cardiovascular disease among migrants from LMICs remains elevated [2,3]. A relevant component of NCD may be attributed to infection/inflammation and neglected tropical diseases (NTDs), which, despite the epidemiological transition, remain high in LMICs, particularly in their neglected populations [4]. For Côte d'Ivoire, the 2010 Global Burden of Disease study showed both infectious diseases (IDs) and NCDs to be key drivers of morbidity and mortality [5]. On one hand, ID morbidity and mortality rates remain high, especially in the most vulnerable communities. On the other hand, there is a high prevalence of NCD risk factors, as evidenced already by the 2005 population-based World Health Organization Steps study in Abidjan and surroundings [6]. In the Taabo health and demographic surveillance system (HDSS) for routine monitoring of vital statistics in south-central Côte d'Ivoire, NCDs were the main cause in 20% of the deaths, which were mostly of cardiovascular origin, while IDs remained the primary cause of death [7].

Inflammation and Cardiometabolic Phenotypes

Cardiovascular disease and diabetes mellitus contribute significantly to the disease burden in LMICs. They are also of particular interest with potential links to infections, as they are associated with altered immune and inflammatory responses [8]. Cardiovascular disease, diabetes, and their preclinical phenotypes (eg, atherosclerosis and metabolic syndrome) as well as their causal risk factors (eg, obesity, smoking, and air pollution) are associated with inflammation. Systemic low-grade inflammation promotes insulin resistance and atherosclerotic plaque formation. Barker formulated the hypothesis of the childhood origin of chronic age-related conditions [9], and in fact, inflammation is already associated with carotid intima media thickness and insulin resistance in children and adolescents [10]. For populations in LMICs, the link of cardiovascular disease and diabetes with inflammation implies that individuals surviving lethal IDs by mounting a strong inflammatory response may become more susceptible to age-related inflammatory phenotypes later in life [3,11-13]. In addition, repeated and chronic infections may lead to subtle cell and organ damage and permanent derailment of the immune system, which could enhance susceptibility to NCD risk factors later in life. In fact, a significant proportion of the disability-adjusted life years attributed to cardiovascular disease in LMICs is related to inflammation precursors, such as rheumatic fever and other NTDs [4]. The role of infections as risk factors for diabetes remains poorly understood [14] even though it is thought that diabetes puts patients at higher risk for infections that are prevalent in LMICs [8,15]. Thus, there is an overall lack of adequate data to determine the true extent of cardiovascular disease and diabetes that result from or are prevented by infections in LMICs.

Helminth Infections and Cardiometabolic Phenotypes

Helminth infections contribute substantially to the NTD-associated global burden of disease, and several are highly prevalent in many parts of the world [16]. Soil-transmitted helminths and schistosomes are among the most prevalent infections in human populations in LMICs [17]. The contribution of helminths to NCD is the focus of intense research [18-21]. Individuals with heavy and chronic helminthic infections can suffer from malnutrition, stunted growth, anemia, and cognitive impairments, which may have a direct impact on NCD risk or an indirect impact through lifestyle measures [22]. Several animal models show a beneficial influence of helminth infections on metabolic homeostasis [19,23]. Cross-sectional epidemiological studies showed an inverse relationship between diabetes and lymphatic filariasis [24,25]. Infection with soil-transmitted helminths was associated with lower insulin resistance and lipid levels [26]. While studies on schistosomiases and strongyloidiasis reported negative association with glucose tolerance [27,28], other studies reported a beneficial effect, and even lower prevalence of diabetes in association with *Schistosoma japonicum* [29]. A study of Australian Aboriginal adults revealed a strong inverse relationship between infection with *Strongyloides stercoralis* and type 2 diabetes [30]. Epidemiological evidence on helminths and hypertension is very limited. A study among schoolchildren in Uganda found helminth infections to be positively associated with blood

pressure [31]. Generally, helminth infections are clinically asymptomatic, but their direct and indirect effects on the host's immune system might be of particular relevance to the host's susceptibility to NCDs. The NCD risk may further depend on the host-pathogen relationship based on their co-evolved genetic variation. Endemic helminth infections likely exerted a strong selective pressure contributing to specific genetic host factors conferring an altered risk for immune-mediated diseases [32].

Malaria and Cardiometabolic Phenotypes

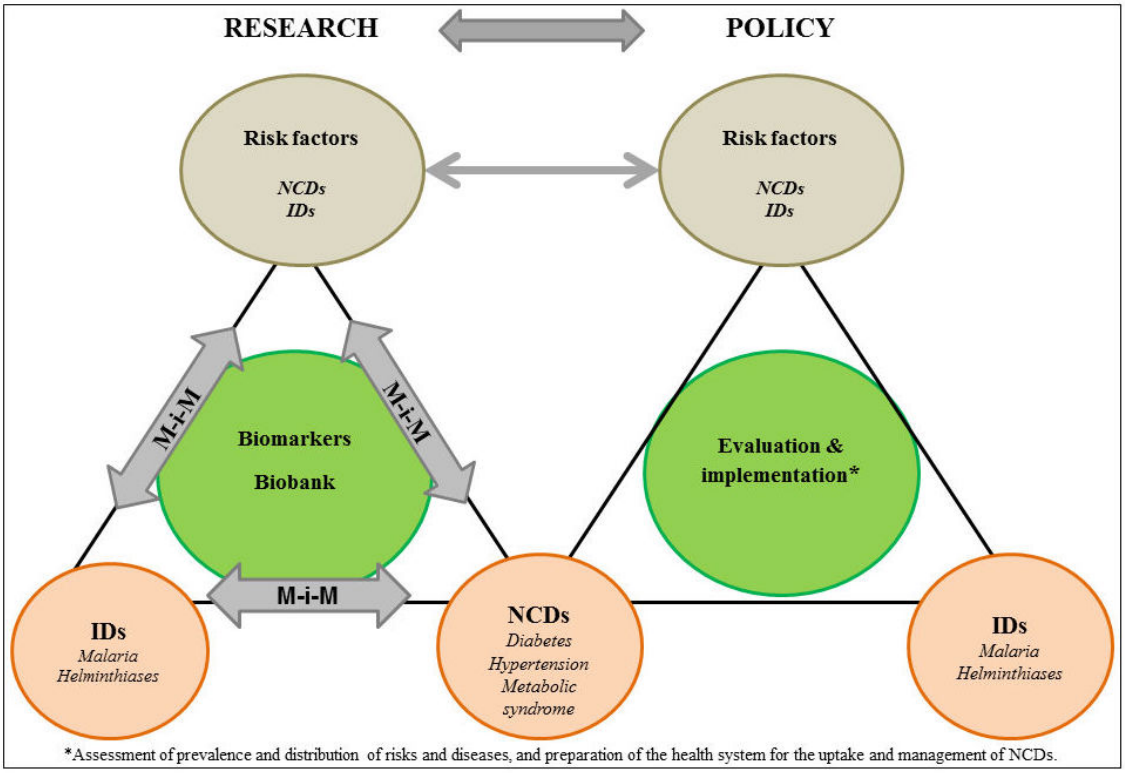
Malaria still ranks highest on the Global Burden of Disease list for many African countries, including Côte d'Ivoire [5]. In the first 3 years of running the Taabo HDSS, malaria contributed to 20% of all registered deaths, ranking as the number one cause of death [7,33]. Although fever, a common symptom of malaria, can go along with stress-induced hyperglycemia [34,35], there is a lack of epidemiological evidence on the association of malaria with parameters of the metabolic syndrome or diabetes. According to clinical studies, malaria, even in the uncomplicated form, led to altered lipid profiles, which in some cases were prolonged, despite malaria treatment [36]. The malaria-related changes in lipid profiles have not been studied for their potential role in atherosclerosis and hypertension. A higher prevalence of *Plasmodium falciparum* infection was found among persons with diabetes [37]. In addition, fasting glucose, glycosylated hemoglobin (HbA1c), and insulin resistance were higher among non-diabetic persons with malaria [38]. Maternal malaria has also been demonstrated to have an impact on blood pressure and glucose in the offspring, thereby increasing the risk of developing hypertension and diabetes later in life [9]. Recent evidence from the African Genome Variation Project demonstrated that genetic loci under positive selection in individuals of African compared to European descent were related to malaria susceptibility on one hand (*CR1*) and osmoregulation and hypertension (*ATP1A1* and *AQP2*) on the other hand [39]. Interestingly, preliminary evidence suggests that variation in *CR1* may be related to coronary artery disease and hypertension [40]. Individuals of African descent have higher levels of circulating angiotensin-II due to its protective effects on malaria, thus genetic positive selection of the variants in the renin-angiotensin-aldosterone system may have been driven by malaria [41]. African-Americans have a higher prevalence of hypertension than Caucasians living in the same settings [42]. Hence, it has been hypothesized that persons with ethnic origins from malaria-endemic regions may be more susceptible to hypertension (due to co-evolution and positive selection of protective genetic variants).

Relevance Health and Demographic Surveillance System With Integrated Biobanks

A complex array of different infection, environment, host lifestyle, and genome interactions are expected to drive immunological and inflammatory diseases, necessitating individual-level complex data to disentangle these disease networks. Hence, there is a pressing need to better understand the links between IDs and NCDs, to enable the development of integrated approaches for intervention against this dual disease burden. In LMICs where vital statistics and setting-specific health information are scarce, HDSS is recognized as a powerful platform for assessing and longitudinally monitoring key demographic parameters and disease burden [43,44]. Moreover, HDSS provides a unique means for population-based epidemiological and health systems research, and evidence collected in the context of HDSS effectively feeds into policy [44,45].

The integration of biomarkers into research protocols are of relevance to assign causality to observed associations, improve mechanistic understanding of diseases, and identify novel targets for disease screening, diagnosis, treatment, and surveillance. The availability of broad "-omics" analyses of biospecimens allows for systemic approaches (including systems medicine and exposome research) that will strengthen the investigation of disease mechanisms and considerably improve the understanding of disease mechanisms [46,47]. Applying the "meet-in-the-middle paradigm", linking biomarkers to both exposures and health outcomes—or in the case of this project to both IDs and NCDs—will allow the investigation of biomarkers likely to play a role in the causal pathway from exposure to disease (Figure 1). Therefore, this methodological approach of meet-in-the-middle is of potential relevance for identifying preventive and therapeutic targets [48,49]. Venous blood (suitable for cytokine profile, DNA extraction, and subsequent methylation profile typing) [50], urine (suitable for metabolomics profile detection) [51], and stool samples (suitable for gut microbiome typing) [52,53] constitute common biospecimens applied towards biomarker assays in disease mechanistic linkage. Novel protocols for biospecimen sampling, processing, and storage are essential for the establishment of high-quality biobanks in remote areas of LMICs in the context of dual disease burden research.

Figure 1. Framework of the CoDuBu study (IDs: infectious diseases; NCDs: noncommunicable diseases; M-i-M: meet-in-the-middle paradigm).



Objectives of the CoDuBu Study

The overarching goal of this project is to deepen our understanding of the dual burden of IDs (helminthiases and malaria) and NCDs (hypertension and diabetes) among adults in the Taabo HDSS in south-central Côte d'Ivoire, to set the stage for future mechanistic research, and to translate key findings into policy action. We will pursue the following specific objectives:

1. To conduct a population-based cross-sectional survey in adults from rural and semi-urban parts of the Taabo subdistrict to assess (a) the prevalence, intensity, and distribution of helminth (*Ascaris lumbricoides*, *S. stercoralis*, hookworm, *Trichuris trichiura*, *Schistosoma haematobium*, and *Schistosoma mansoni*) and *Plasmodium* infections, (b) the prevalence and distribution of metabolic syndrome, hypertension, and diabetes, and (c) the co-occurrence of these IDs and NCDs and the distribution of these comorbidities and their respective risk factors at the level of individuals.
2. To establish a biobank consisting of blood, urine, and stool as an investment for future longitudinal biomarker research on the mechanistic link between helminth and *Plasmodium* infections, and hypertension and diabetes.
3. To prepare the local health system for the uptake and management of NCDs through assessment of deficiencies and provision of necessary training, instruments, and facilities to the local health staff and health centers.

Methods

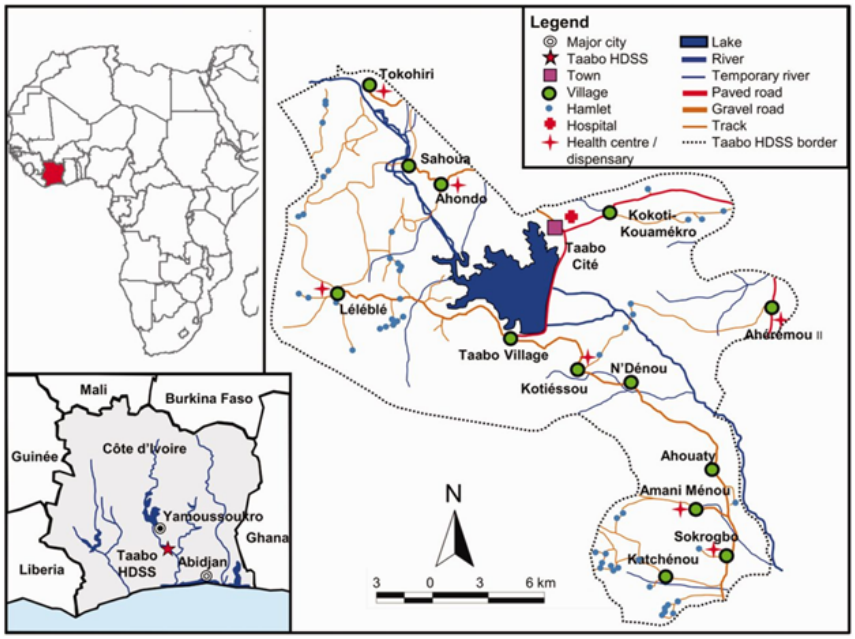
Location

The study was conducted in the Taabo HDSS, which is located about 150 km north-west of Abidjan, in the Agneby-Tiassa region of south-central Côte d'Ivoire. The Taabo HDSS covers a surface area of about 980 $km^2$and includes an urban setting (Taabo-Cité), 13 villages, and more than 100 small hamlets [33]. The Taabo HDSS was set up in 2008 and has been operational since 2009. It collects longitudinal demographic data at the individual and household level, usually done in three rounds per year [33,54]. The 2012 demographic information of the Taabo HDSS has been published elsewhere [33]. In brief, crude birth and mortality rates were 33.9 and 8.2 per 1000 population. In- and out-migration rates were 136.9 and 160.1 per 1000 population respectively, with a population growth rate of 2.5 per 1000 population. Male to female ratio was 104:100, and total fertility rate was 4.8 children per woman. Life expectancy was 61 years for males and 65 years for females. Main disease patterns include malaria and NTDs [33]. Deaths are usually reported by key informants, and verbal autopsies are conducted using standard protocols to determine causes of death [7,33]. Main causes of death include malaria, HIV/AIDS, and tuberculosis [7]. Specific in-depth questionnaire and epidemiological surveys have previously been carried out on subsamples of the population to deepen the understanding of malaria, NTDs, and iron-deficiency anemia [54-58]. The HDSS population (approximately 42,000 individuals from 6700 households) is predominantly Ivorian, with Akan as the main ethnic group. There are eight health facilities in the Taabo HDSS area: a 12-bed hospital in Taabo-Cité and seven health centers

and dispensaries across the 13 villages [33]. Figure 2 shows a map of the Taabo HDSS.

We selected three areas from the Taabo HDSS for the purposes of this study. Selection was based on degree of urbanization, potential to provide at least one adult per household towards reaching an effective sample size, prevalence of malaria and helminthiases from preliminary surveys, availability of health center for examination, proximity to the main hospital in Taabo-Cité for ease of referral, and higher potential for follow-up. We therefore selected Taabo-Cité, Amani-Ménou (40 km from Taabo-Cité in the south) and Tokohiri (36 km from Taabo-Cité in the north) reflecting semi-urban, rural, and very rural settings in the Taabo HDSS.

Figure 2. Map of the Taabo HDSS, located in south-central Côte d'Ivoire. The sites of the CoDuBu baseline study were Taabo-Cite, Tokohiri (36 km north of Taabo-Cite) and Amani-Menou (40 km south of Taabo-Cite). (Figure is reused with permission from Oxford Academic Journals [33]).



Preparation

For site preparation, the study team visited the district and village chiefs and informed them about the study. In addition, the hospital and health centers in the selected sites were visited for assessment of diagnostic and treatment capabilities for hypertension and diabetes and for malaria and helminthiases. Informing the local population about the study included information events planned by the HDSS staff, in collaboration with the CoDuBu study team. The HDSS field staff had 2-day training on performing interviews and instruction of participants on biospecimen collection. The medical team also underwent 2-day training on health examinations and laboratory screening. The study procedures were piloted on 10 local residents, who would not be participating in the main study.

Design

This was a population-based cross-sectional study among adult participants aged ≥18 years, randomly sampled within the selected Taabo HDSS areas. The examinations and interviews were conducted between April and August 2017. A biobank was established for future biomarker research based on biospecimens collected from the participants. The survey occurred in two phases.

Phase I (health examination; April and May 2017) took place over 2 days for each participant. The first day included obtaining informed consent, provision of materials and instructions for biospecimen collection (clean plastic container and OMNIgene.GUT tube (DNA Genotek Inc) for stool and BD Vacutainer urine collection system (Beckton, Dickinson & Co) for urine, at participants' residences. The next morning, while participants underwent health examinations (at the health center) in a fasting state, fresh morning stool and urine samples collected at home were transferred cooled (~4°C) to the Taabo-Cité central laboratory for immediate pre-analytic processing. In the field, health examinations included point-of-care glucose, hemoglobin, HbA1c, lipids tests, anthropometry (height, weight, neck, arm, waist, and hip circumference), blood pressure, pulse, temperature, as well as preparation of dried blood spots (DBS) on filter papers. At the end of the examination, blood sample (stored at 4°C within 10 minutes of venepuncture) and DBS were sent to the laboratory for further processing. Multimedia Appendix 1 shows the detailed flow of the health examination in the field.

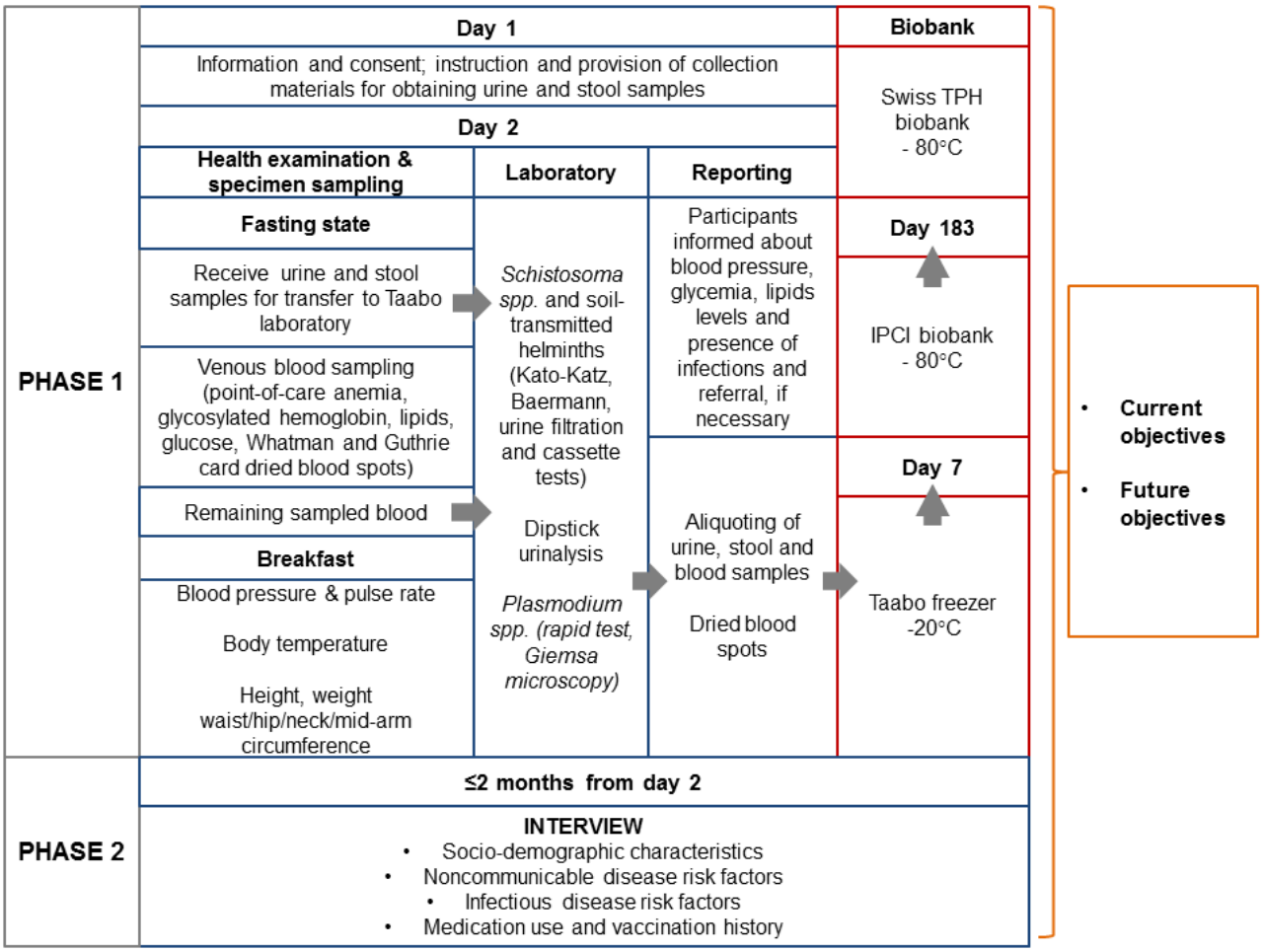
In the laboratory, blood samples were applied towards malaria diagnoses (rapid test and microscopy) and further aliquoted and stored (together with the DBS) in a -80°C biobank. Stool from the plastic container was analyzed for helminth eggs (or larvae), and urine was subjected to *S. mansoni* test and dipstick urinalysis (for blood, proteins, blood, glucose, urobilinogen, bilirubin, leucocytes, ketones, nitrites, pH, and specific gravity). Urine samples that tested positive for blood underwent a filtration method for *S. haematobium*. The remaining urine and OMNIgene.GUT-stabilized stool were aliquoted and transferred to the -80°C biobank. Case reporting and management of diagnosed IDs and NCDs were incorporated within the health

examination period (Figure 3). Multimedia Appendix 2 shows the detailed flow of the laboratory work.

In Phase II (interview; June-August 2017), participants were interviewed on a third day, following health examinations. Interviews assessed among other factors, sociodemographic characteristics, health status, ID and NCD risk factors, medication and vaccination history, health care use, as well as knowledge and attitudes regarding NCDs.

Two study teams of about 10 persons each were responsible for the conduct of the study. The teams included 1 research staff (supervision of adherence to study protocol), 1 medical doctor (supervision of physical examination), 3 study nurses (conduct physical examination and point-of-care tests), 1 laboratory supervisor (supervision of work-up and analyses of biospecimens), 1-2 laboratory technicians (work-up and analyses of biospecimens), 2 HDSS field staff speaking the local language(s) and resident in the study area (informed consent, instruction for home biospecimen collection and health interviews), and 1 driver.

Figure 3. Overall flow of the CoDuBu study (Swiss TPH: Swiss Tropical and Public Health Institute; IPCI: Institut Pasteur de Côte d'Ivoire).



Sample Size Estimation and Sampling of Participants

For the descriptive cross-sectional study, using *Plasmodium* infection and diabetes as our disease co-occurrence of reference, we would expect a malaria prevalence of 30% [59] and diabetes prevalence of 6% [60] in adults. The expected prevalence of co-occurrence assuming independence was 2%. The health district of Tiassalé, where Taabo HDSS is located, has an estimated population of 200,000 [33]. Therefore, for a population of 200,000, with an error margin of 1%, a 95% confidence level, and an expected malaria and diabetes co-occurrence prevalence of 2%, we would need 751 participants. Assuming a nonresponse rate of 30%, the sample size becomes 976. A sample size of 1000 would therefore be enough for the descriptive baseline study.

A main hypothesis to be addressed in an envisaged, not-yet funded follow-up survey, would be that the average change in HbA1c would be higher in persons malaria-positive at baseline. For the power calculation, we assume a malaria positivity rate of 30% and a true difference in average change of HbA1c between malaria-positive and negative persons of at least 30% of the standard deviation (SD) sigma of individual changes. If these individual changes were normally distributed, this would mean that the median of change in malaria-positive persons coincides with the 62ndpercentile in malaria-negative persons. Under this assumption, 560 persons being re-assessed for HbA1c at follow-up would provide a power of 90% to detect a statistically significant difference in the mean change of HbA1c between the two groups at the usual 5% level. However, a larger sample size is warranted in order to be able to compensate for

potential reductions in statistical efficiency resulting from lower than expected malaria positivity prevalence or from variations in the prevalence of malaria-positivity or in the SD sigma across the three study sites. With 30% loss to follow-up, we would still have 700 persons to be re-assessed at follow-up, which would provide a moderate safety margin and allow for the adjustment of weak confounder variables. Therefore, the 1020 participants we sampled from the three selected areas of Taabo HDSS will enable adequate representation of the population and ensure enough statistical power to test our hypotheses.

A random sampling technique was used to select about 2000 participants satisfying the inclusion criteria in the three selected sites. The inclusion criteria included (1) registration in the Taabo HDSS, (2) residence in Taabo-Cité, Amani-Ménou, or Tokohiri, (3) one adult per household, and (4) age ≥18 years. Stratified sampling technique was applied to select 513, 254, and 253 participants from Taabo-Cité, Amani-Ménou, and Tokohiri respectively (ratio of 2:1:1). This corresponds to the overall distribution of adults (Taabo-Cité=3905, Amani-Ménou=2094, Tokohiri=1626) and households (Taabo-Cité=1508, Amani-Ménou=567, Tokohiri=616) in the three areas. Selected participants from each stratum were then invited for participation in a random fashion until the target sample size in each site was reached.

Recruitment of Participants and Written Informed Consent

After an information event for the village population, informed consent from potential participants was obtained at their homes, in-person by HDSS field workers who are in close contact with the local population. In order to obtain written informed consent, the field workers explained the purpose, procedures, benefits, and potential harm of the study. The concept of establishing a biobank for future studies was also explained, and participants were made aware that their information would be treated in a coded manner to allow the establishment of a longitudinal study if they decided to participate. The voluntary nature of the study was explained to the participants. Participation in all or parts of the study, as well as nonparticipation was free of negative consequences. Sufficient time for asking questions on the aims and procedures of the study was provided to the participants. If a subject decided to participate, they signed the informed consent sheet. Illiterate participants put a cross in the presence of a literate witness. Consent for re-contact in the future was specifically obtained from all participants towards the establishment of a longitudinal cohort.

Assessment of Health-Related Phenotypes

Textbox 1 summarizes the health-related phenotypes expected from the study. These phenotypes will be derived from physical examinations; laboratory analyses of venous blood, urine, and stool; and in-person interviews with a questionnaire.

Physical Examination

Body temperature was measured with an Omron auricular thermometer (Omron Healthcare). Systolic and diastolic blood pressure were measured three times, at least 3 minutes apart, after sitting quietly for about 10 minutes, using an Omron Oscillograph (Omron Healthcare). The mean of the last two measurements will be taken for analyses. Hypertension will be defined as a mean systolic blood pressure ≥140 mm Hg or mean diastolic blood pressure ≥90 mm Hg.

Height and weight were measured using a SECA bodymeter (0.1 cm accuracy) and weighing scale (0.1 kg accuracy), respectively. Precision of the bodymeter was checked regularly by measuring the height of the placement of the bodymeter using a tape rule, and the weighing scale was verified using a known 10 kg weight. Neck circumference was measured using a SECA ergonomic tape below the laryngeal prominence in front and the mid-cervical spine behind. Mid-arm circumference was measured at the midpoint between the shoulder and the elbow. Waist circumference was measured at the end of passive expiration over the narrowest part of the trunk between the lowest rib and the iliac crest, or if this is not clearly evident, at the level of the umbilicus. Hip circumference was measured using the same tape, at the maximal circumference between the iliac crest and the crotch. Waist circumference, waist-hip ratio, and body mass index will be described in absolute values and categorized according to various guidelines [61].

Laboratory Screening

Venous Blood

A total of 7 mL of venous blood was collected in a fasting state for laboratory screening and storage in biobank. Five mL of venous blood (collected using an ethylenediaminetetraacetic acid [EDTA] tube) was used for the assessment of glucose, HbA1c, lipids, as well as for assessment of *Plasmodium*, and anemia. HemoCue Glucose 201 RT device was used to measure fasting glucose (HemoCue AB) and was calibrated regularly. Afinion AS100 Analyzer (Alere GmbH) was used as the point-of-care test for HbA1c (where the method has been validated for HbA1c testing in settings with high prevalence of hemoglobinopathies) and lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides). Afinion test kits were stored at 4°C, with regular calibration of the analyzers. For assessment of *Plasmodium* infection, thick and thin blood films were prepared on microscope slides. For the diagnosis of *Plasmodium*, the slides were air-dried, stained with Giemsa, and examined under a microscope by experienced laboratory technicians for *Plasmodium* species identification and parasitemia. The number of parasites was counted against 200 leukocytes or 500 leukocytes if number of parasites was 10, assuming a standard count of 8000 leukocytes per µl of blood [62]. Additionally, a drop of blood was subjected to a rapid diagnostic test for malaria using ICT ML01 malaria Pf kit (ICT Diagnostics). Anemia was indirectly assessed by the hemoglobin level, using HemoCue Hb 301 device (HemoCue AB), adhering to World Health Organization recommendations [63]. The remaining EDTA-buffered blood was processed into the biobank.

Two mL of venous blood (collected using a dry tube) was used to prepare DBS on custom printed diagnostic cellulose filter paper (Whatman) for DNA methylation profile and neonatal Guthrie cards for cytokine profiles.

Textbox 1. Key health-related phenotypes in the CoDuBu study investigating the co-occurrence of common infectious diseases and noncommunicable diseases in Côte d'Ivoire.

A. Key phenotypes from the physical health examination:

1. Distribution of body temperature (auricular temperature)
2. Distribution of height, weight, waist and hip circumference, prevalence of obesity
3. Distribution of blood pressure and heart rate and prevalence of hypertension

B. Key phenotypes from the laboratory screening:

1. Prevalence of *Plasmodium* infection
2. Prevalence of urogenital schistosomiasis (*Schistosoma haematobium*)
3. Prevalence of intestinal schistosomiasis (*S. mansoni*)
4. Prevalence of species-specific soil-transmitted helminths (*Ascaris lumbricoides*, hookworm and *Trichuris trichiura*)
5. Prevalence of *Strongyloides stercoralis*
6. Prevalence of anemia
7. Prevalence of prediabetes/diabetes
8. Prevalence of dyslipidemia

C. Key phenotypes from interview (>200 variables covering risk factors and effect modifiers):

1. Prevalence of doctor's diagnoses/treatments, including HIV, tuberculosis
2. Prevalence of health symptoms related to cardiovascular diseases, diabetes, respiratory diseases, and infectious diseases
3. Distribution of access to quality care
4. Distribution of knowledge related to noncommunicable diseases and risk factors
5. Prevalence/exposure to noncommunicable disease risk factors: tobacco smoking, physical activity, nutrition, alcohol consumption, environmental exposures (air pollution from fossil fuels, occupational exposures, noise annoyance), gender/reproductive factors, stress, resilience, depression, and other psychosocial factors

D. Other variables derived from the Taabo health and demographic surveillance system database:

1. Sociodemographic factors (age, sex, nationality, ethnicity, marital status, pregnancy history, educational level, occupation, socioeconomic status assessed by a household-based asset index)
2. Household characterization (size, water supply, sanitation and cooking facilities, building characteristics, and residential history)

E. Biobank:

1. Dried blood spots/aliquots from venous blood: genetic variation, DNA methylation, cytokine profile
2. Stool: gut microbiome
3. Urine: metabolome

Urine Sample

A midstream morning urine sample was collected using BD Vacutainer system (Beckton, Dickinson & Co) and transferred to the laboratory for processing. Nine mL of urine was taken from the vacutainer using a separate vacuette, which was later processed into the biobank. A small amount (10-20 µl) of urine was used for the detection of *S. mansoni*, using the point-of-care circulating cathodic antigen cassette (ICT Diagnostics), following the manufacturer's instructions [64], resulting in the following classification: negative or three levels of positives (1+, 2+, or 3+). Dipstick urinalysis to detect proteins, blood, glucose, urobilinogen, bilirubin, leucocytes, ketones, nitrites, pH, and specific gravity was applied using the Roche Combur-10 test (Roche Diagnostics). Urine samples testing positive for blood were subjected to filtration test for the diagnosis of *S. haematobium*. Positive results were expressed as the number of *S. haematobium* eggs per 10 mL of urine, according to World Health Organization guidelines [65].

Stool Samples

Fresh morning stool samples were collected into plastic containers with a volume of 125 mL and tightly fitting lids. Samples were transferred to the laboratory in a cool box and worked up the same day. For the diagnosis of *S. mansoni* and soil-transmitted helminths, duplicate 41.7 mg Kato-Katz thick smears were prepared from each stool sample [22] and examined under a microscope. Infection intensities were expressed in eggs per gram of stool. For the diagnosis of *S. stercoralis*, the Baermann technique was employed, where an apricot-sized stool sample was placed on a gauze-lined mesh in a glass funnel equipped with a rubber tube and a clamp, covered with deionized

water, and illuminated from below with a bulb. After 2-3 hours, the lowest 50 mL of the liquid was drained, centrifuged, and the sediment examined under a microscope for *S. stercoralis* larvae [22]. A separate stool sample was also collected in a self-administered manner by the participants (following the manufacturer's instructions) using the OMNIgene.GUT tube, which contains microbial stabilizer.

Pre-Analytic Processing of Biospecimens and Biobanking

DBS prepared on filter papers were sealed in air-tight bags containing dessicants and stored at -20°C in the Taabo laboratory. The DBS will be applied towards DNA and cytokine profiles. The DNA that will be extracted from the DBS (Whatman FTA cards) will facilitate research into genetic variations and DNA methylation [50]. EDTA blood was stored as 1.5 mL aliquots in cryotubes at -20°C in Taabo laboratory. Midstream morning urine specimens collected into sterile 9 mL vacuettes were stored as uncentrifuged and centrifuged 1.5 mL urine aliquots. Centrifugation was done at 1600 g and 4°C for 15 min [66], and the supernatant immediately aliquoted in cryotubes stored at -20°C in Taabo laboratory. Urine aliquots will be applied to metabolomics profiles and will be normalized to creatinine during the analytic process. Stool samples from the OMNIgene.GUT tube were stored in 0.5 mL aliquots in cryotubes at -20°C freezer in Taabo laboratory. These stool aliquots will be applied towards the metagenomic investigations of the gut microbiota.

DBS, blood, urine, and stool samples stored at -20°C in the Taabo laboratory (with the freezer being connected to a back-up generator) were transferred (on dry ice, on a weekly basis) to the Institut Pasteur de Côte d'Ivoire (IPCI) biobank for permanent storage at -80°C (Figure 3). On completion of the survey and therefore of biospecimen collection, the biobank will be mirrored as two identical banks hosted at IPCI (Abidjan, Côte d'Ivoire) and the Swiss Tropical and Public Health Institute (Swiss TPH; Basel, Switzerland). The mirroring of biobanks increases the safety of the biospecimens. Biomarkers derived from these "-omics" analyses can serve as exposure biomarkers, health-related phenotypes, or markers of susceptibility of exposures and diseases.

In-Person Interviews

The in-person interviews were done using a tablet-based questionnaire in Open Data Kit format [67], lasting between 45 and 60 minutes. Questions covered demographic factors (eg, age, sex), water supply and sanitation facilities (availability and use), know-how, attitude, and behavior towards tobacco smoking, physical activity, obesity, alcohol consumption, and nutrition. They also included environmental risks (eg, exposure to mosquito coils, pesticides, indoor biomass fuels), gender, hormonal and reproductive factors, psychosocial stressors and resilience to them, disease symptoms (respiratory, cardiovascular, and diabetes), family history of disease, medical diagnoses and treatments, vaccination history, and access to health care.

Data Management

Data from in-person interviews were collected using Open Data Kit, whereas health examination and laboratory data were collected as paper-based records, which are later uploaded into the Open Data Kit format. Data quality was assured through (1) formulation of standard operating procedures for all aspects of the study, (2) extensive and careful training of the study team according to the standard operating procedures, (3) onsite supervision of field activities ensuring adherence to protocol, and (4) continuous monitoring and internal evaluation of data entry during the field and laboratory work. Data collected on paper will be double-entered in two stages and later cross-checked to ensure accuracy and prevent data manipulation during or after the study. The software used will keep track of all changes made to the data. All data will be merged into a single database at the end of data entry using STATA version 14.0 (STATA Corporation).

Data Analyses

The detailed CoDuBu data, enabled in part by HDSS routine data collected just before the start of this survey (Textbox 1), and the broad consent obtained from participants will allow us to test numerous hypotheses. The broad range of the CoDuBu research framework translates into a broad set of statistical methods. Analytical study plans or project proposals will be developed and submitted to statistical review at participating organizations. Collected data will include continuous and categorical variables. Results from the cross-sectional study will be described accordingly, reporting categorical variables as percentages with 95% confidence intervals, and continuous variables as medians with interquartile ranges. To explore associations between predictors and health outcomes, linear or logistic regression models will be used, as appropriate. Urban and rural differences in associations will be tested, as well as fixed and random effects study area models. Sampling weights will be applied to analyses to ensure a correct representation of the population. Missing data will be reported as separate categories and included in multivariable models. If full case analyses are performed, adjustment for data missingness will be done using appropriate methods for missing data imputation.

Ethical Approval and Data Protection

Ethical approvals for the study were obtained from the Ethics Committee Northwest and Central Switzerland (reference no. 2016-00143; obtained May 2, 2016) and the Côte d'Ivoire National Research Ethics Committee (reference no. IORG00075; obtained March 24, 2017). Data entry will be done using password-protected tablet computers. Only participant identifiers, but not names of participants will be included in electronic health databases. Paper-based records from the laboratory and filled-in forms such as biospecimen-collection forms also contain only the participant identifier and are kept in a locked cupboard in a room with access restricted to the project personnel. The CoDuBu data will be handled only by authorized staff at the CoDuBu partner organizations.

After completion of the data entry/cleaning, identical databases for the CoDuBu project will be stored at Centre Suisse de Recherches Scientifiques en Côte d'Ivoire (CSRS) in Abidjan,

Côte d'Ivoire, and Swiss TPH in Basel, Switzerland. Access to data in the context of a project application will need approval from the bipartite project leaders. Collaborating researchers will receive datasets for analyses that are coded only with the participant identifier, stripping any other identifying information (eg, name, birth date) from the dataset. Data transfer agreements will be signed with external scientific collaborators.

Biospecimen aliquots were barcode-labeled and doubly coded (a separate biospecimen identifier that is different from the participant identifier), improving confidentiality of participants. At the IPCI and Swiss TPH biobanking facilities, freezer temperatures are supervised and recorded continuously by two independent temperature control systems that assure biospecimen safety. Access to freezers and biospecimens are restricted to key study personnel. Access to biospecimens for biomarker analyses in the context of a project will need approval from the project leaders. The principal investigators will prioritize the future relevant research questions and coordinate submission of future research projects to the ethics committees in Côte d'Ivoire and Switzerland. Biospecimen transfer agreements will also be signed with external scientific collaborators.

Generation of the identifiers was done systematically. The participant identifier consists of six characters where the first two are the site number (10, 11, and 12 for the three sites) and the last four characters are the participant's serial number within the study site (starting from 0001). For instance, the first participant from site 10 was assigned a participant identifier of 100001. The biospecimen identifier comprises nine characters: a different site identifier (21, 31, 41) as well as different within-site serial numbers (starting from 0247), and biospecimen-specific suffices (uncentrifuged and centrifuged urine and stool). Thus, the first stool aliquot from the first participant in site 21 was assigned 210247STL1. A file linking the participant identifier to the biospecimen identifier and finally to the existing unique Taabo HDSS identifier was created and kept only by the co-principal investigators of the CoDuBu project.

All data generation, management, storage and analyses, as well as the storage and management of biological samples, strictly follow the Swiss and Côte d'Ivoire legal requirements for data protection.

Health Systems Preparation and Diagnostic Follow-Up

At the end of the data collection for this baseline survey, participants were informed on IDs, NCDs, and their risk factors in order to promote healthy lifestyle. Information and education campaigns—through radio, posters, and flyers—were established for education of the population. Participating health centers were equipped with facilities for hypertension and diabetes screening, and the main hospital at Taabo-Cité was made a referral central center for initial NCD diagnosis and treatment in the area. Medical staff on the project were trained and certified for performing electrocardiography. Participants who were diagnosed with any screened infection were treated free of charge. Participants diagnosed with any NCD were followed up for confirmation. Transportation fees for confirmation and first month of treatment were covered by the study. Further management are being co-ordinated by study partners in Côte d'Ivoire, ensuring patient enrollment in a subsidized treatment plan.

Results

In September 2017, we had completed participant recruitment and questionnaire administration. In parallel to the questionnaire administration, data cleaning and processing of the health examination results were employed and should be completed by the end of October 2017. We expect the preliminary results by December 2017. Study findings will be published in peer-reviewed literature and presented at national and international conferences.

Discussion

Principal Considerations

Results from this comprehensive baseline survey will provide an overall insight into the relationship between IDs and NCDs in a primarily rural setting of Côte d'Ivoire that is undergoing rapid epidemiological transition. The understanding of potential mutual influences between IDs and NCDs is relevant because their co-occurrence at an individual level will require the adaptation of health service provision towards integrated care. If IDs and NCDs influence each other (and their risk factors) in light of the increasing prevalence of NCDs, country-specific risk estimates will be needed to increase the precision of local disease burden towards a deeper understanding of global burden of disease. In addition, if IDs increase NCD susceptibility and induce a shift towards a younger age of onset, this would also require adaptation in the target population for NCD screening in LMICs and country-specific contexts. Research into the dual disease burden, particularly in the context of biobanks and biomarkers, will improve the mechanistic understanding of the ID-NCD relationship and refine health impact assessment of ID and NCD prevention and control programs. The preparation of the health system will improve awareness of NCD risk factors, educate local health staff on disease management, and create a referral center in an area that, thus far, had limited expertise, necessitating lengthy travel to receive adequate care.

The integration of this project into the Taabo HDSS made the execution of the baseline study quite cost-effective. Apart from providing a recruitment base as well as sociodemographic information of the population, the HDSS made it easier to recruit individuals given their familiarity with research and confidence in the system. In addition, the system provides a low risk for loss to follow-up since their sustainable field work teams hold close contact with the local population. In case of loss to follow-up, we would have the reasons and address them accordingly.

A pilot survey served to identify bottlenecks, which were addressed prior to launching this comprehensive baseline survey. We generally did not have much difficulty in undertaking the baseline study. Although the study area is mostly rural with a relatively lower literacy level and considerable poverty, the awareness for health research is high. This is explained by health research and interventions dating back to the late 1990s [68]

and the establishment and running of the Taabo HDSS since 2009, including specific health surveys, large-scale NTD control interventions, and strengthening the health system [7,33,54]. Since most of the previous studies in the area have been on children [56-59,69], the village chiefs were pleased that our study would focus on adults and would be the first one to investigate cardiovascular and metabolic diseases.

The project partners have the necessary collective expertise in ensuring a successful execution of the project [49,68-73]. The current project was implemented in close collaboration between CSRS, Swiss TPH, IPCI, Institut National de Santé Publique, Ligue Ivoirienne contre l'Hypertension Artérielle et les Maladies Cardiovasculaires, and Université Félix Houphouët-Boigny. CSRS is one of the leading centers in Africa in integrated research on health, environment, and nutrition. The Taabo HDSS is a major resource center of CSRS, and several multiyear research projects have been jointly implemented in the Taabo HDSS and have generated high-quality data regarding the etiology of anemia, the epidemiology of malaria, and integrated control of zoonoses and NTDs [54-59,69], which have contributed to national policies regarding these diseases. Swiss TPH has a track record in IDs and NCDs research, which forms the basis for the scientific objectives of this project. Swiss TPH is running the only Swiss-wide chronic disease cohort and biobank (Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults), participates at the forefront of exposome research [49,71,74], and its coordinators have vast experience in biobanking (Swiss Biobanking Platform). The Université Félix Houphouët-Boigny is the largest public university in Côte d'Ivoire with several laboratories covering ecology, parasitology, and zoology. Institut National de Santé Publique coordinates management of diabetes on a national level, while Ligue Ivoirienne contre l'Hypertension Artérielle et les Maladies Cardiovasculaires coordinates the efforts at public health control of cardiovascular disease at the national level.

There is an existing team of 30 experienced staff operating the Taabo HDSS, including field workers, data managers, and administrative staff [33]. Local physicians and nurses will also contribute to the manpower needed for the overall execution of this project. Expertise in biobanking available from Swiss TPH, CSRS, and IPCI (responsible for the Côte d'Ivoire national biobank) will ensure effective sample preservation, handling, and processing during the project and beyond.

Limitations

Despite the novelty of our research focus, we expect some limitations. First, our sample size is relatively limited compared to other NCD cohorts. Although this limitation is mainly related to funding, our estimation shows that we would have enough statistical power to detect relevant trends and associations. We also do not expect a lot of loss to follow-up as all participants willingly accepted to be re-contacted in due course. The success of the baseline survey will lead to application for competitively acquired funds towards expansion in planned follow-up surveys, both population-wise and health endpoint-wise, giving a clearer picture of initially observed trends and associations. We could not perform HIV and tuberculosis testing due to logistic/cultural reasons. Both conditions are dependent on immunologic pathways, and their related markers could modify or mediate ID-NCD relationships. However, questions about these conditions are covered in the questionnaire and we would therefore rely on self-reported history or use of medications for these infections in the baseline cross-sectional investigations. Efforts will be made to include these tests in the follow-up survey.

Conclusion

The CoDuBu study will fill the void of lacking data in areas of potential links between IDs and NCDs and shed new light on respective risk factors. Our findings will lead to the development of integrated approaches, which hold promise for cost-effective prevention and management of dual disease burden. Future research from established research infrastructure will contribute to local capacity building, deeper understanding of the cross-talk between IDs and NCDs and treatment, and precise country-specific burden of disease and risk factor estimates to guide policy.

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Authors' Contributions

VLK, DK, EKN, JU, BB, and NPH designed the study, wrote the original study protocol, and obtained funding for the baseline study. All other authors contributed to the development of the study protocol. NPH and BB are the principal investigators. ICE, CE, FKB, and SK are the main coordinators of the study. ICE and NPH wrote the first draft of the manuscript. All authors read and provided comments on the drafts and approved the final version of the paper prior to submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Detailed flowchart of field activities for the CoDuBu study.

[PDF File (Adobe PDF File), 77KB - resprot_v6i10e210_app1.pdf]

Multimedia Appendix 2

Flow of laboratory tests and biobanking in the CoDuBu study.

[PDF File (Adobe PDF File), 97KB - resprot_v6i10e210_app2.pdf]

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Abbreviations

CoDuBu: Côte d'Ivoire Dual Burden of Disease study
CSRS: Centre Suisse de Recherches Scientifiques en Côte d'Ivoire
DBS: dried blood spot
HbA1c: glycosylated hemoglobin

HDSS: health and demographic surveillance system
HIV: human immunodeficiency virus
ID: infectious disease
IPCI: Institut Pasteur de Côte d'Ivoire
LMICs: low- and middle-income countries
NCD: noncommunicable disease
NTD: neglected tropical disease
Swiss TPH: Swiss Tropical and Public Health Institute

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Original Paper

Tapering Practices of Strongman Athletes: Test-Retest Reliability Study

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Abstract

Background: Little is currently known about the tapering practices of strongman athletes. We have developed an Internet-based comprehensive self-report questionnaire examining the training and tapering practices of strongman athletes.

Objective: The objective of this study was to document the test-retest reliability of questions associated with the Internet-based comprehensive self-report questionnaire on the tapering practices of strongman athletes. The information will provide insight on the reliability and usefulness of the online questionnaire for use with strongman athletes.

Methods: Invitations to complete an Internet questionnaire were sent via Facebook Messenger to identified strongman athletes. The survey consisted of four main areas of inquiry, including demographics and background information, training practices, tapering, and tapering practices. Of the 454 athletes that completed the survey over the 8-week period, 130 athletes responded on Facebook Messenger indicating that they intended to complete, or had completed, the survey. These participants were asked if they could complete the online questionnaire a second time for a test-retest reliability analysis. Sixty-four athletes (mean age 33.3 years, standard deviation [SD] 7.7; mean height 178.2 cm, SD 11.0; mean body mass 103.7 kg, SD 24.8) accepted this invitation and completed the survey for the second time after a minimum 7-day period from the date of their first completion. Agreement between athlete responses was measured using intraclass correlation coefficients (ICCs) and kappa statistics. Confidence intervals (at 95%) were reported for all measures and significance was set at $P<.05$.

Results: Test-retest reliability for demographic and training practices items were significant ($P<.001$) and showed excellent (ICC range=.84 to .98) and fair to almost perfect agreement (κ range=.37-.85). Moderate to excellent agreements (ICC range=.56-.84; $P<.01$) were observed for all tapering practice measures except for the number of days athletes started their usual taper before a strongman competition (ICC=.30). When the number of days were categorized with additional analyses, moderate reliability was observed (κ=.43; $P<.001$). Fair to substantial agreement was observed for the majority of tapering practices measures (κrange=.38-.73; $P<.001$) except for how training frequency (κ=.26) and the percentage and type of resistance training performed, which changed in the taper (κ=.20). Good to excellent agreement (ICC=.62-.93; $P<.05$) was observed for items relating to strongman events and traditional exercises performed during the taper. Only the time at which the Farmer's Walk was last performed before competition showed poor reliability (ICC=.27).

Conclusions: We have developed a low cost, self-reported, online retrospective questionnaire, which provided stable and reliable answers for most of the demographic, training, and tapering practice questions. The results of this study support the inferences drawn from the Tapering Practices of Strongman Athletes Study.

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KEYWORDS

Internet; survey; periodization; implement training; resistance training

Introduction

The sport of strongman is relatively new and is similar to the sports of weightlifting and powerlifting, where training is primarily focused on the improvement of maximal strength and power to improve competition performance [1-3]. Unlike the sports of weightlifting and powerlifting, substantial between-competition differences can be observed in the types of events, required distances for carrying events, and incorporation of one repetition maximum (1RM) events versus repetitions with a given load. Such between-competition differences would appear similar to those that are experienced by CrossFit athletes [4], which may therefore influence the way strongman athletes taper for strongman competitions. The taper is the final period of an athlete's training before a major competition and is of paramount importance to performance and the outcome of the event [5-8]. Winwood et al [1] found that 80% of strongman athletes incorporated some form of periodization into their training, which suggests that the majority of strongman competitors design their training to emphasize particular adaptations with the goal of increasing physical performance. As strongman and weightlifting athletes may be at greater risk for injury during competition compared to training [9], a successful taper that allows strongman athletes to recover from their recent training stressors may also reduce their risk of in-competition injury. Little scientific research currently exists regarding how to taper for strength sports, and no research exists on how strongman athletes taper for strongman competitions.

In recent years Internet-based comprehensive self-report questionnaires have been administered among strongman athletes [1,10] and strength and conditioning coaches [11]. Such surveys have elicited high response rates and provided valuable information on how strongman competitors train, the injury epidemiology associated with strongman training, and how coaches utilize strongman implements in the training of their athletes. However, a limitation to these studies was that no data were reported to verify the reliability of the survey items. Reliability refers to the consistency of answers obtained by the same respondent when a measurement is repeated on different occasions [12,13]. Test-retest reliability is measured by having the same respondents complete a survey at two different points in time to see how stable their responses are [14]. Researchers have recommended the intraclass correlation coefficient (ICC) for assessing reliability of continuous data [15-17], along with the kappa statistic, which provides a measure of agreement for categorical data corrected for chance [15,18,19].

Previous studies that have tested the reliability of Internet survey methods have demonstrated that Web-based methods are reliable [14,20-22] and can be more suitable alternatives to traditional methods [21,22]. Such studies strengthen the scientific rigor of collecting information via the Internet. Internet-based surveys have the potential to reach populations of interest across the globe, are cost efficient, and have the advantage of minimizing data collection and entry errors [21]. The popular use of social media sites (eg, Facebook) and access to the Internet via smartphones and tablets have further increased survey accessibility for respondents, which could enhance response rates.

Information on the reliability of the Internet assessment method for use with strength athletes, including the strongman population, is currently lacking. *The Tapering Practices of Strongman Athletes* survey created for this study was based on nine interview questions used with powerlifters [23,24]. Our tapering practice questionnaire has included the addition of several questions, as well as changes to the wording of original questions used in previous studies [23,24]. Based on these changes, it has become desirable to conduct a reliability study of the updated questionnaire. The present study assessed the test-retest reliability of the questionnaire on a large and diverse sample group of strongman athletes. It was hypothesized that the questionnaire would be a reliable measure for assessing the training and tapering practices of strongman athletes.

Methods

Participant Recruitment and Inclusion Criteria

Strongmen athletes were recruited through professional networks and multimedia methods similar to previously described procedures [1,10]. The networking site Facebook was the primary method used to recruit the strongman athletes, and identified strongman athletes were sent a letter via Facebook Messenger. The letter contained an invitation to participate in the research and the link to the online survey. Presidents of strongman clubs in New Zealand, Australia, Europe, the United States, and the United Kingdom were contacted to email the survey to their club members. The survey was available in two language options (English and Russian). An information sheet outlining the objectives and purpose of the study was situated on the first page of the online survey. Participants were asked to indicate their consent by participating in the survey. The software that was used allowed participants to exit the survey at any time and complete it at a later date, allowing participants to provide their data at the time most suitable to them. Surveygizmo [25] was used to launch the electronic survey on the Internet. The methods and procedures used in this study were approved by the Toi Ohomai Institute of Technology Research Committee (R17/05).

Participant inclusion criteria included strongman athletes who were between 18 and 65 years of age and had competed in at least one strongman competition. The criterion for a completed survey was that the participants completed the first three sections of the questionnaire on demographics, training practices, and tapering.

Research Instrument

Strongman athletes completed a self-reported 4-page retrospective *Tapering Practices of Strongman Athletes Survey* created for this study, which was based on interview questions used with powerlifters [23,24]. The original *Strongman Tapering Practices Survey* was pilot tested with university professors and strongman athletes to ensure its ease of use with this population. As a result of pilot testing, the survey was slightly modified, including clarifications and improvements to the wording of a small number of questions, before it was administered online.

The *Strongman Tapering Practices Survey* consisted of four main areas of inquiry, including demographics and background information, training practices, tapering, and tapering practices. Demographic and background information included questions on gender, age, height, body mass, resistance training experience, strongman training experience, and competitive level. The training practices section included questions pertaining to frequency, duration, and types of training. Types of training were categorized as cardiovascular training (aerobic and anaerobic), strongman implement training, and traditional training. Strongman implement training was defined as exercises using any nontraditional training implements (eg, stones, tires). Traditional exercises were standard exercises performed in the gym by regular weight trainers and strength athletes (eg, squat, bench press). Participants were requested to detail their common/typical values for each question. For the tapering section, athletes were asked to indicate if they utilized a taper or not and their reasons why. The tapering practices section included questions on taper length and type, strategies used, and how training altered during the taper (ie, volume, intensity, duration, type of training performed, and when last performed before competition). Tapering was defined as, "a reduction in training volume over a period of time prior to a strongman event or strongman events." Classifications of tapering (ie, step taper, linear taper, and exponential taper with a slow or fast decay) were defined according to the taper types previously described and applied [26]. Closed questions were used for Sections 1 and 2, with open and closed questions used for Section 3.

Response Rate and Reliability Data

During the 8-week period in which the survey was open, 690 participants accessed the online survey, which included those that observed the survey, partially completed the survey, and the 454 that completed the survey. The key questions from the questionnaire selected for test-retest reliability are presented in Multimedia Appendix 1.

One hundred and thirty participants responded on Facebook Messenger indicating that they were going to complete the survey, or had already completed the survey. These participants were sent an email via Facebook Messenger and asked if they could complete the online questionnaire again for a test-retest reliability analysis. Of these 130 participants, 64 strongman athletes (49.2% response rate) accepted this invitation and completed the survey for the second time after a minimum 7-day period from the date of their first completion. To distinguish this dataset from other survey responses, participants indicated their demographic data (ie, age, height, body mass, and country of birth) so their retest survey responses could be identified and matched to their initial survey response. A test-retest analysis was done on this dataset to determine the reliability of the online strongman tapering practices questionnaire. No participants responded to the Russian language option, so the reliability study was only conducted on the English language survey.

Data Analyses

Descriptive statistics were used to describe the cohort characteristics. Test-retest reliability for dichotomous and categorical data was computed using the kappa statistic with asymptotic standard error [27]. The kappa statistic was chosen because it is more robust than percent agreement alone, as it takes agreement by chance into consideration. Reliability was then rated using the scale developed by Landis and Koch for the purposes of comparing the reliability of the questions [27]. Reliability of the kappa statistic was rated as poor (below .00), slight (.00-.20), fair (.21-.40), moderate (.41-.60), substantial (.61-.80), or almost perfect (.81-1.00). Any missing values were indicated as *excluded* in the analyses. Reliability of continuous measures was evaluated by ICCs using a two-way random effects model, absolute agreement, and average measures ICC [28]. ICCs were classified as follows: poor (<.40), moderate (.41-.60), good (.61-.80), or excellent (>.81) [29,30]. Confidence intervals (at 95%) were calculated for all reliability measures. Data were collected using SurveyGizmo [25] and analyses were conducted using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Significance levels were set at $P<.05$.

Results

Cohort Characteristics

Sixty-four participants completed the online survey twice over the 8-week period. Participants were between 20 and 54 years of age, with a distribution of 46 males (46/64, 72%) and 18 females (18/64, 28%). Thirty-six participants (36/64, 56%) had competed in national amateur strongman championships, 17 (17/36, 27%) had competed at the local or regional level, and 11 (11/64, 17%) athletes had competed professionally (Table 1).

Test-Retest Reliability Results

The test-retest reliability of continuous data for demographics and training practices of all strongman athletes (N=64) is reported in Table 2. Significant correlations ($P<.001$) were observed for all measures and reliability was excellent for all questions (ICCs=.84 to .98).

Table 1. Cohort characteristics

Characteristics	All participants, N=64 (SD[a])	Sex	
		Male, n=46 (SD)	Female, n=18 (SD)
Age, years	33.3 (7.7)	33.0 (7.9)	33.9 (7.1)
Height, cm	178.2 (11.0)	182.5 (9.0)	167.3 (7.9)
Body mass, kg	103.7 (24.8)	112.5 (21.7)	80.1 (16.7)
Resistance training experience, years	12.3 (7.9)	14.2 (7.8)	7.6 (6.3)
Strongman training experience, years	4.8 (3.6)	5.5 (3.4)	3.1 (3.4)
Strongman competition experience, years	4.0 (3.1)	4.4 (3.0)	2.9 (3.1)

[a]SD: standard deviation

Table 2. Test-retest reliability of continuous data for demographics and training practices of all strongman athletes. Intraclass correlation coefficient $P<.001$ for all values.

Test-retest reliability	n	Number of response options	ICC	95% CI	Qualitative inference
How many years of general resistance training experience do you have?	62[a]	41	.94	.90 to .96	Excellent
How many years of strongman implement training experience do you have?	62[a]	36	.97	.96 to .98	Excellent
How many years have you been competing in the sport of strongman?	64	32	.98	.96 to .99	Excellent
On average, how many days per week do you train?	63[b]	7	.86	.77 to .92	Excellent
On average, how many cardiovascular conditioning training sessions (includes both aerobic and anaerobic conditioning) do you perform per week?	64	16	.88	.81 to .93	Excellent
On average, how many resistance training sessions (includes both strongman and traditional training sessions) do you perform per week?	64	16	.84	.74 to .90	Excellent
On average, how long are your training sessions (to the nearest 15 minutes)?	64	13	.87	.79 to .92	Excellent

[a]n=64; valid=62; excluded=2

[b]n=64; valid=63; excluded=1

Table 3. Test-retest reliability of continuous data for strongman athletes who said they taper for strongman competitions (n=53).

Test-retest reliability	n	Number of response options	ICC (P-value)	95% CI	Qualitative inference
How many days would you consider your usual "taper" to be before a strongman competition?	43[a]	40	.30[f]	-.31 to .62	Fair
How many weeks out from a strongman competition do you train with the highest volume? (ie, sum of sets x repetitions x load)	43[a]	22	.72 (<.001)	.49 to .85	Good
How many weeks out from a strongman competition do you normally train with the highest intensity? (ie, highest load/degree of effort)	44[b]	11	.56 (.004)	.19 to .76	Moderate
What would be your estimated drop in your average training volume (as a percentage) during your taper?	37[c]	11	.77 (<.001)	.56 to .88	Good
How many days before a strongman competition do you cease to train?	43[a]	17	.81 (<.001)	.65 to .90	Excellent
How many days out before an important strongman event do you usually perform your final training session (at any weight)?	41[d]	15	.84 (<.001)	.70 to .92	Excellent
How many days before an important strongman event do you usually perform your final heavy training session (>85% 1RM)?	42[e]	15	.64 (.001)	.33 to .81	Good

[a]n=53; valid=43; excluded=10

[b]n=53; valid=44; excluded=9

[c]n=53; valid=37; excluded=16

[d]n=53; valid=41; excluded=12

[e]n=53; valid=42; excluded=11

[f]Poor reliability (adjusted categorical data is presented in Table 4);

The test-retest reliability of continuous data for strongman athletes who said they taper (n=53) for strongman competitions is reported in Table 3. Significant correlations were observed for all measures except for the number of days athletes considered their usual taper to be before a strongman competition (ICC=.30). Due to the importance of this question for the wider study, an additional analysis was conducted in which days were categorized into ranges (ie, <7, 7-10, 11-14, >14 days). The results of this analysis are included in Table 4.

Reliability was excellent for the number of days before a strongman competition that athletes ceased to train (ICC=.81) and the number of days out from an important strongman event when the final training session (at any weight) occurred (ICC=.84). Reliability was good for the number of days out from an important strongman event when the final heavy training session (>85% 1RM) occurred (ICC=.64). Good reliability was also observed for athletes' estimated drop in average training volume (as a percentage) during the taper (ICC=.77) and for the weeks out from a competition in which they trained with the highest volume (ie, sum of sets x repetitions x load; ICC=.72). Reliability was moderate for the number of weeks out from a strongman competition that athletes normally trained with the highest intensity (ie, highest load/degree of effort; ICC=.56).

The test-retest reliability of categorical data for demographics, training practices, and tapering practices of strongman athletes is reported in Table 4. Kappa was significant for the majority of measures except for how training frequency (κ=.26) and the percentage and type of resistance training performed changed in the taper (κ=.20). Reliability was almost perfect for the highest level of competition athletes had competed at (κ=.85). Substantial reliability was observed for athletes indicating that they were self-coached or if they had a coach (κ=.66), if they tapered for strongman competitions (κ=.67), and if they always tapered for strongman competitions (κ=.73). Reliability was moderate for what the athletes' usual resistance training looked like per week (κ=.45) and for how their training intensity (κ=.56) and training duration (κ=.48) changed throughout the taper. Moderate reliability was also observed in the additional analysis for the number of days athletes considered their normal taper to be (κ=.43). Reliability was fair for the type of tapering athletes used (κ=.38) and what the athletes' cardiovascular training looked like per week (κ=.37).

Table 4. Test-retest reliability of categorical data for demographics, training practices, and tapering practices of strongman athletes.

Test-retest reliability	n	Number of response options	Kappa (asymptotic standard error)	P-value	95% CI	Qualitative Inference
Demographics and Training Practices						
What is the highest level of strongman competition you have competed at?	64	4	.85 (.06)	<.001	.73 to 96	Almost perfect
Are you self-coached or do you have a coach?	64	3	.66 (.07)	<.001	.53 to .80	Substantial
On average, what does your usual resistance training look like per week?	63[a]	8	.45 (.08)	<.001	.30 to .60	Moderate
On average, what does your cardiovascular training look like per week?	63[a]	9	.37 (.07)	<.001	.23 to .51	Fair
Tapering and Tapering Practices						
Do you or have you ever used tapering when preparing for a strongman competition?	64	2	.67 (.12)	<.001	.43 to .92	Substantial
How many days would you consider your usual "taper" to be before a strongman competition?	44[b]	4	.43[c](.10)	<.001	.23 to .64	Moderate
Which type of tapering do you use?	44[b]	4	.38 (.11)	<.001	.16 to .60	Fair
Do you always use a taper before strongman competitions?	44[b]	2	.73 (.18)	<.001	.37 to 1.0	Substantial
How does your training intensity change during your taper?	44[b]	3	.56 (.12)	<.001	.33 to .79	Moderate
How does your training frequency change during your taper?	44[b]	3	.26 (.14)	.07	-.01 to .52	Fair
How does your training duration (ie, time per training session) change during your taper?	44[b]	3	.48 (.13)	.001	.22 to .73	Moderate
Does the percentage and type of resistance training you do (eg, percent traditional type training and percent strongman implement training) change in your taper?	44[b]	2	.20 (.15)	.19	-.09 to .49	Slight

[a]n=64; valid=63; excluded=1

[b]n=64; valid=44; excluded=20

[c]Kappa derived from the categorization of taper days (ie, <7, 7-10, 11-14, >14 days)

The test-retest reliability of continuous data relating to strongman events and traditional exercises is reported in Table 5. Significant correlations were observed for all measures except for the days before competition the Farmer's Walk was performed, which showed poor reliability (ICC=.27).

Reliability was excellent for the loads used in the Yoke Walk (ICC=.91), Farmer's Walk (ICC=.81), stone lifts/work (ICC=.81), and bench press (ICC=.93), and for the days before competition that the deadlift was performed (ICC=.87). Good reliability was observed for the loads used in the log lift/press (ICC=.74), deadlift (ICC=.73), squat (ICC=.69), and overhead presses (ICC=.71), and for the days before competition that the log lift/press (ICC=.62), Yoke Walk (ICC=.74), stone lifts/work (ICC=.75), squat (ICC=.73), overhead presses (ICC=.71), and bench press (ICC=.75) were performed.

Table 5. Test-retest reliability of continuous data relating to strongman events and traditional exercises. ICC analysis conducted when responses were n>11.

Test-retest reliability	n	ICC (P-value)	95% CI	Qualitative inference
Could you please choose FIVE of your core strongman exercises and the corresponding days out from competition you would last perform the exercise and what loads you would use?				
Log lift/press				
Days when last performed before competition	37	.62 (.003)	.25 to .81	Good
What loads were used	35	.74 (<.001)	.49 to .87	Good
Yoke Walk				
Days when last performed before competition	32	.74 (<.001)	.47 to .87	Good
What loads were used	32	.91 (<.001)	.81 to .95	Excellent
Farmer's Walk				
Days when last performed before competition	28	.27 (<.001)	-.52 to .66	Poor
What loads were used	27	.80 (<.001)	.57 to .91	Excellent
Stone lifts/work				
Days when last performed before competition	16	.75 (.01)	.28 to .91	Good
What loads were used	24	.81 (<.001)	.57 to .92	Excellent
Could you please choose FIVE of your core traditional exercises and the corresponding days out from competition you would last perform the exercise and what loads you would use?				
Deadlift				
Days when last performed before competition	32	.87 (<.001)	.74 to .94	Excellent
What loads were used	31	.73 (<.001)	.43 to .87	Good
Squat				
Days when last performed before competition	28	.73 (.001)	.42 to .87	Good
What loads were used	27	.69 (.003)	.31 to .86	Good
Overhead presses				
Days when last performed before competition	15	.71 (.01)	.19 to .90	Good
What loads were used	14	.71 (.02)	.64 to .91	Good
Bench press				
Days when last performed before competition	11	.75 (.03)	-.11 to .93	Good
What loads were used	11	.93 (<.001)	.72 to .98	Excellent

Discussion

This study examined the test-retest reliability of *The Tapering Practices of Strongman Athletes Survey* designed to determine how strongman athletes taper for strongman competitions. The results supported our initial hypothesis and indicated that the self-reported questionnaire, delivered using Internet commercial software, provided stable and reliable answers for the majority of measures. The sample of 64 athletes who participated in this study represents 14.1% of the 454 strongman athletes who participated in the wider *Tapering Practices of Strongman Athletes Survey* study (publication under review). Our sample size of 64 athletes is similar to (or higher than) other recent test-retest reliability studies recalling physical activity behaviors among specific populations [14,31,32].

Significantly high test-retest reliability results were observed for data relating to strongman demographics and training practices (ICCs=.84-.98). Researchers have found that items that assess habits have higher reliability scores than items assessing attitudes and awareness [33]. It is quite likely that because strongman training practices are repetitive behaviors, they may be more clearly remembered by strongman athletes.

Of the categorical data, only two items (training frequency and the percentage and type of resistance training performed changed in the taper) did not show significant agreement. The remaining items showed significance and demonstrated acceptable agreement. It is important to note that values for kappa rarely exceed .75 due to the adjustment for chance agreement [34]. Therefore, the categorical results relating to strongman training

practices and tapering practices tended to exhibit favorable kappa values overall.

Only two items (days before competition the Farmer's Walk is performed, and the number of days strongman athletes considered their usual taper to be) did not show significant reliability. The remaining items showed significance and exhibited moderate to excellent reliability values overall (ICCs=.56-.98). Another study utilizing an online survey reported that the Farmer's Walk is the most commonly used exercise among strongman athletes (n=167) [1]. As such, it may be more difficult for athletes to recall exactly when the exercise was last used during the taper. Furthermore, every strongman competition is somewhat unique, which may affect the taper employed (ie, length of taper and training volume), thus making the recall of some taper activity more difficult. The four items in the current study (training frequency, percentage and type of resistance training performed, number days before competition the Farmer's Walk is performed, and the length of taper) that did not show significant reliability related to specific questions on the taper. Researchers have suggested that recalling behaviors over limited time periods requires a more complex cognitive process than recalling behaviors over longer periods [35].

Due to the importance of quantifying the strongman athletes' mean taper length and the poor reliability associated with the taper length described as a continuous variable in the current study, we conducted an additional analysis in which the data (in days) were categorized (ie, <7, 7-10, 11-14, >14 days). Significant moderate reliability (κ=.43; P<.001) was then observed for the number of days athletes considered their normal taper to be. These additional categorical analyses will be used in the wider study, as this is an effective approach for presenting important data rather than omitting the data due to poor reliability.

There were a number of limitations to the current study. The survey was open for 8 weeks and the participants exhibited some variation in the time between test and retest (mean 27.5 days, SD 14.1). Such an approach was warranted in this study, as many athletes were actively involved in competition and were competing overseas or in different states. If the exact time between test and retest was more stringent, a substantial loss of participants would likely have been observed. Leppink and Pérez-Fuster [36] have suggested that the length of the test-retest interval should be long enough that memory or practice effects can fade, and at the same time not too short for historical changes to occur on part of the respondent. The moderate and fair scores associated with what the strongman athletes' usual resistance and usual cardiovascular training looked like per week (κ=.45 and κ=.37, respectively) may have been influenced by training regime changes over time. Another limitation of this study was insufficient power to allow us to explore differences between different subgroups of the sample. It would have been interesting to determine if differences in reliability measures existed between sex and competitive level.

In conclusion, *The Tapering Practices of Strongman Athletes* questionnaire is a low-cost instrument that is straight-forward to administer and provides stable and reliable answers. The questionnaire could easily be modified to fit the needs of other competitive weight lifting sports (ie, weightlifting, powerlifting, CrossFit, and Highland Games) and presents an effective online tool for assessing tapering practices leading up to competition. Further research could investigate how strongman athletes prepare themselves for strongman events on competition days and investigate strategies used for optimal arousal.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Questionnaire items tested for reliability.

[PDF File (Adobe PDF File), 49KB - resprot_v6i10e211_app1.pdf]

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Abbreviations

1RM: one repetition maximum
ICC: intraclass correlation coefficient
SD: standard deviation

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Original Paper

Knowledge Management Framework for Emerging Infectious Diseases Preparedness and Response: Design and Development of Public Health Document Ontology

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Abstract

Background: There are increasing concerns about our preparedness and timely coordinated response across the globe to cope with emerging infectious diseases (EIDs). This poses practical challenges that require exploiting novel knowledge management approaches effectively.

Objective: This work aims to develop an ontology-driven knowledge management framework that addresses the existing challenges in sharing and reusing public health knowledge.

Methods: We propose a systems engineering-inspired ontology-driven knowledge management approach. It decomposes public health knowledge into concepts and relations and organizes the elements of knowledge based on the teleological functions. Both knowledge and semantic rules are stored in an ontology and retrieved to answer queries regarding EID preparedness and response.

Results: A hybrid concept extraction was implemented in this work. The quality of the ontology was evaluated using the formal evaluation method Ontology Quality Evaluation Framework.

Conclusions: Our approach is a potentially effective methodology for managing public health knowledge. Accuracy and comprehensiveness of the ontology can be improved as more knowledge is stored. In the future, a survey will be conducted to collect queries from public health practitioners. The reasoning capacity of the ontology will be evaluated using the queries and hypothetical outbreaks. We suggest the importance of developing a knowledge sharing standard like the Gene Ontology for the public health domain.

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KEYWORDS

EIDs; public health; systems engineering; knowledge representation; teleological function; knowledge management; ontology; semantic reasoning

Introduction

The 2014 Ebola epidemic in West Africa reminded the public health community again of the weaknesses in preparing for and responding to emerging infectious diseases (EIDs). The epidemic directly affected the health and economies of multiple countries in West Africa for 2 years and resulted in 11,299 deaths among 28,599 suspected infections [1]. The initial international response was regarded as slow and uncoordinated by many experts [2], an indication of the poor application of the lessons learned from prior global pandemics.

Effective coordination and communication of information among different stakeholders are necessary components of a strong response to an EID outbreak [3]. Public health coordination and communication requires not only sharing resources and specialties but also sharing, managing, and using knowledge effectively. This is a recognized challenge in practice [4-8]. Knowledge sharing and management is not a single government task. It needs the collaboration of multiple groups across several sectors. Such effort, however, is usually hindered by geographical, temporal, and political constraints. Lack of a strong public health infrastructure in many countries and the persistent problems in our global health governance structure could exacerbate the crisis and complicate the collaboration [4]. The spatial-temporal dynamics of outbreaks further complicate the real-time preparedness and response processes [9-11]. Moreover, how to use the knowledge from prior pandemics to make a prompt decision under current conditions perplexes the public health community.

Different approaches have been employed to address this challenge. Recent progress includes influenza information management [12], public health meta-knowledge analysis [13], and public health surveillance [14]. Semantic reasoning has been used to address the spatial-temporal difficulties of epidemic management [9]. However, advances in the knowledge management of public health have been limited. In this work, we demonstrate how to apply systems engineering concepts to develop a knowledge management framework facilitated by ontology and semantic reasoning.

The public health system is a complex adaptive system [6]. We can tackle its complexity using a systems engineering–based approach [15]. Systems engineering, first proposed by Bell Telephone Laboratories in the 1940s [16], describes an interdisciplinary engineering methodology that focuses on how to design and manage complex systems. It emphasizes the joint effect of system components, their dynamical interactions, and the environment. Systems engineering promotes the development of risk management in various industries, including aerospace, defense, chemical, and nuclear. Venkatasubramanian [17] discusses the necessity of the systems engineering idea for risk management in a complex system. Leveson [18] develops a systems engineering–based modeling framework to assess risks of engineered systems. There are other similar efforts in different domains [19-21]. EID preparedness and response resemble risk management in many engineering disciplines. Recently, systems engineering concepts have gained considerable attention in the public health community. The National Academy of Engineering and the Institute of Medicine have advocated the widespread application of systems engineering tools [22]. Systems engineering methods such as Markov models are used to enhance public health preparedness [23].

As a result, we propose a novel systems engineering–inspired, ontology-driven knowledge management approach. In this work, we demonstrate how to develop the ontology and semantic rules to manage knowledge and support decision making. This ontology could also serve as a part of other applications, such as a public health training or practice tool. Its flexibility enables the integration with other ontologies.

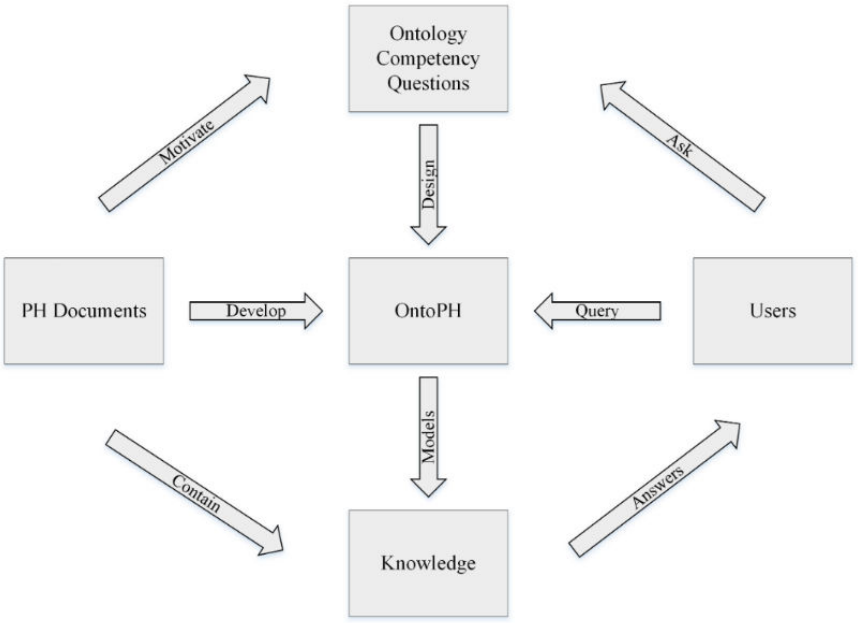
Methods

Overall Architecture

Public health knowledge management aims to systematically manage tasks and support decision making, which view implicit and explicit knowledge as key strategic resources [24]. Knowledge management needs storage, retrieval, and utilization of public health knowledge. We propose the ontology-driven knowledge management approach as shown in Figure 1, which decomposes public health documents to elements of knowledge and stores them in an ontology, namely, the Public Health Document Ontology (OntoPH). OntoPH was developed using ontology competency questions as guidance. Grüninger and Fox [25] state that an ontology should answer competency questions proposed based on the motivation of the ontology. Competency questions define the terminology and specify the definitions and constraints of the terminology. Knowledge is modeled using the terminology and retrieved via semantic rules. An inference engine accesses knowledge models and assembles and manipulates elements of knowledge in the ontology to draw conclusions about EID preparedness and response.

Public health knowledge is mainly preserved in public health documents, which include guidelines, procedures, and academic publications. They are the most important media to share, store, and manage knowledge because they are vetted, high-quality, generated by an authoritative content source, verifiable by a trusted source, and up to date and regularly updated [5]. In order to support decision making, OntoPH's corpus should meet at least 2 requirements: breadth and depth. Breadth means the corpus should cover many, if not all, fields that are involved in public health decision making. Depth means the corpus should contain not only global-level guidelines but also local-level procedures.

Figure 1. Systems engineering inspired ontology-driven knowledge management approach.



Function-Based Knowledge Representation

The first task is to represent knowledge preserved in public health documents. Effective knowledge storage and retrieval requires a knowledge representation, which addresses both hierarchical complexity and semantic heterogeneity. The hierarchical complexity of public health knowledge is rooted in the multiple layers of public health activities. Public health practitioners need different chunks of knowledge in various contexts to prepare for and respond to EIDs. Health workers in the clinic, for example, demand knowledge about disease diagnosis, whereas the department of health wants to know how to manage and coordinate. Knowledge always serves some purposes. The health workers' knowledge leads to accurate diagnoses. The department of health's knowledge achieves effective emergency response. Multiple layers of public health activities are linked via their purposes. For example, to better respond to emergencies, departments of health require the health workers to diagnose diseases more effectively.

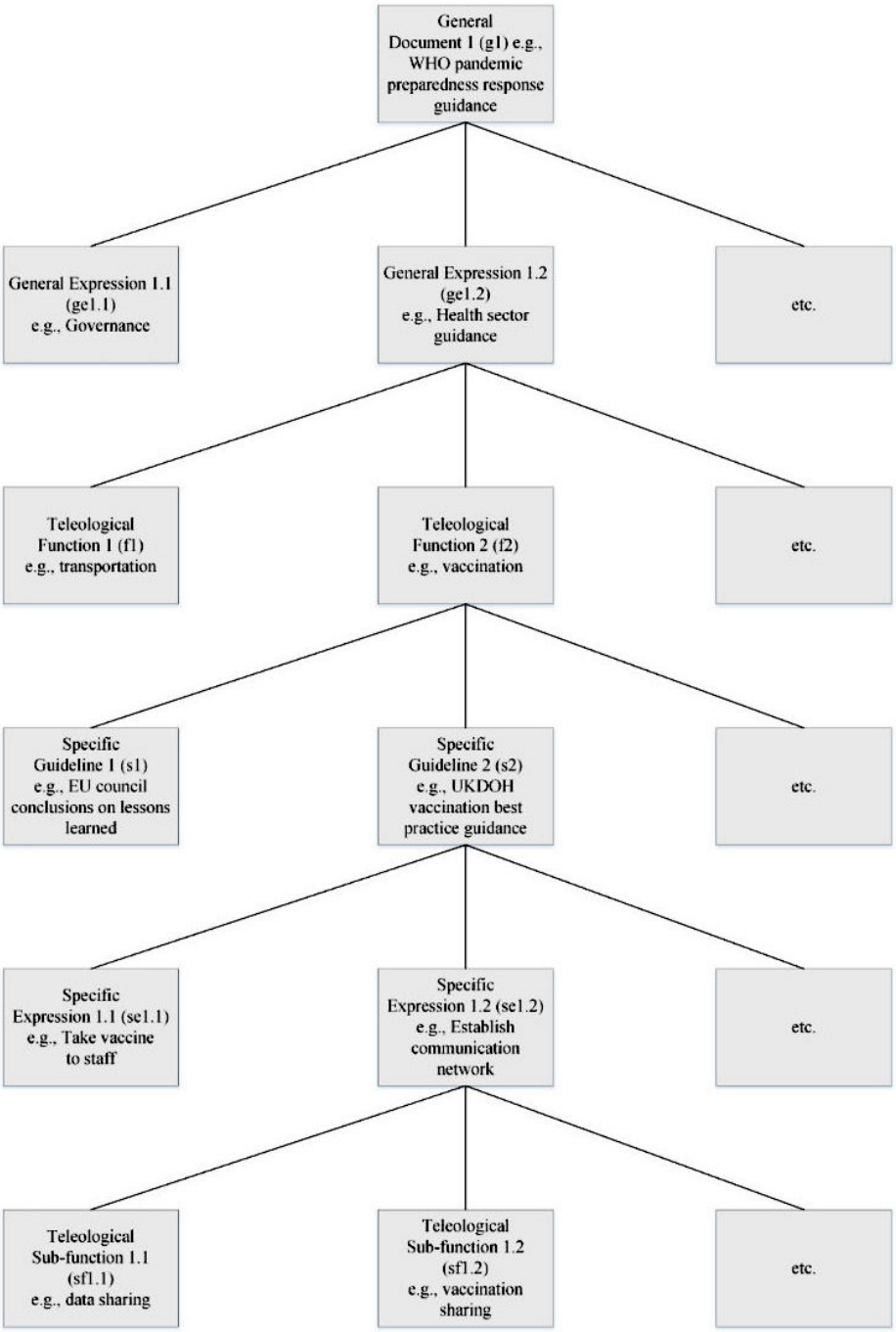
Semantic heterogeneity, on the other hand, is the result of the cross-reference of public health knowledge, which is a mixture of various fields such as medical science, epidemiology, biology, and engineering [8]. For instance, the knowledge of physician training lies in the intersection of medical science (ie, what skills to train) and management science (ie, how to train). Nonetheless, the 2 aspects share the same purpose (ie, training physicians for better EID preparedness). A recent study by Venkatasubramanian and Zhang [26] finds that complex system activities usually have 4 common purposes: communication, decision making, processing, and sensing. Training, as part of education, is an important type of implementation activities.

One can resolve both hierarchical complexity and semantic heterogeneity by identifying the purpose of knowledge, for a piece of knowledge could serve different purposes under different conditions. Venkatasubramanian and Zhang [26] identify the importance of means-end relation in complex system risk management and propose a systems engineering framework to explicate the relation. Adopting this idea, our approach models elements of knowledge based on their means-end relations. We use teleological functions to represent the purposes of knowledge elements. Unlike mathematical functions that map a set of inputs onto a set of permissible outputs, teleological functions emphasize the means to realize a goal by indicating the common purpose between 2 connected entities. The 4 common purposes induce 4 types of teleological functions. A function-based knowledge representation has been used in many fields including engineering [27-30] and data science [31].

To develop such a function-based knowledge representation, we first classify public health documents into 2 categories, general documents that contain general public health principles and specific documents that store evidence-based procedures. There exists a gap between the 2 types of documents: general documents are usually too general to implement, whereas specific documents are mostly event-specific thereby limiting their usefulness for new events. We organize knowledge of general documents as a teleological function of that of specific documents: $knowledge_{\text{general doc}} = f(knowledge_{\text{specific doc1}}, knowledge_{\text{specific doc2}},...)$, where f is a teleological function. Specific activities expand a general guideline with specific recommendations. For example, since the 2009 influenza A H1N1 pandemic, many specific documents have discussed vaccination preparedness and distribution [32,33]. The World Health Organization (WHO) also has issued general guidelines for vaccination preparation during the pandemic [34]. The function vaccination describes activities related to vaccination preparedness and distribution. Therefore, the equation can be rewritten as $knowledge_{[34]} = vaccination\ (knowledge_{[32]}, knowledge_{[33]})$, meaning that WHO guidelines about vaccination can be expanded with specific activities and, hence, bridge the gap. The function-based knowledge representation is depicted

as a tree structure shown in Figure 2. The root of the tree is a public health document, and the leaves are the event-based procedures. A general document (eg, g1) contains general knowledge expressions (eg, ge1.1 and ge1.2). A general knowledge expression specifies a teleological function. For instance, the WHO guideline [34] points out roles of the health and nonhealth sectors in vaccination sharing and distribution activities. We can label this knowledge expression with a function vaccination (eg, f2). Specific guidelines (eg, s2) elaborate the teleological functions and define many specific knowledge expressions (eg, se1.2). Specific knowledge expressions can further indicate subfunctions (eg, sf1.2), which include detailed procedures and instructions. Unlike specific procedures, teleological functions are event independent. The same functions can apply to different events with similar fundamental lessons. The tree structure demonstrates how general documents and specific documents are linked via teleological functions. The function-based knowledge representation handles the hierarchical complexity through the tree structure of documents and manages the semantic heterogeneity by grouping distinct activities under the same function. Teleological functions define the scope and intention of the specific documents. They let a specific document elaborate a general document by adding actionable items.

Figure 2. The tree structure of function-based knowledge.

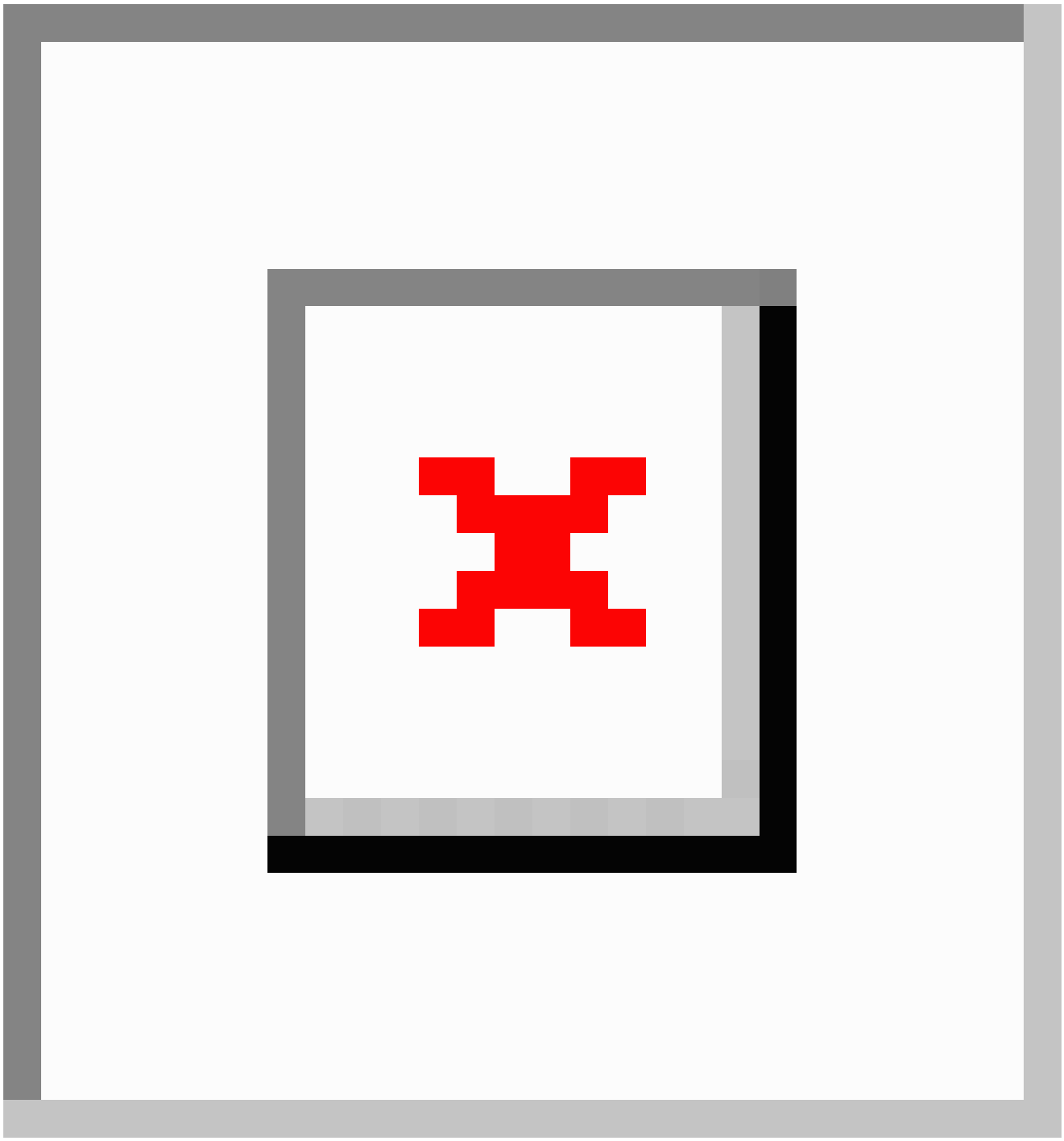


Ontology Development

Background

An ontology is a formal description of entities and their properties, relationships, and constraints [25]. It is widely used for the information system and knowledge management. An ontology consists of classes, individuals, and properties. Classes are a collection of concepts in the domain of discourse. Individuals are instances of each class. Properties are relations between classes, values restrictions, or instance descriptions in the domain of discourse. An ontology models knowledge by axiomatizing concepts as well as the relationships between them [35]. Knowledge is defined and organized in a layer style (see Multimedia Appendix 1). Terms with similar meanings are classified as synonyms. A list of synonyms is defined as a concept. Concepts form a hierarchy and are connected by relations. Concepts and relations constitute general axioms that represent the knowledge of discourse. Figure 3 shows the ontology development process, which consists of 3 steps: (1) concept extraction: extracting knowledge from the corpus; (2) ontology assembly: decomposing knowledge into terms, relations, constraints, and descriptions, integrating these components to form an ontology; and (3) reasoning: creating semantic rules to enable knowledge retrieval.

Figure 3. Ontology development process.



Concept Extraction

There are 2 concept extraction methods available: manual annotation and natural language processing (NLP) annotation. Manual annotation requires domain experts to review and annotate every term in the corpus per predefined criteria. Manual annotation provides high accuracy but requires tremendous human effort. On the other hand, NLP annotation automatically recognizes and classifies terms into predefined categories [36]. NLP annotation is much more efficient than manual annotation but at the cost of accuracy. Usually, an NLP-based information retrieval performs clustering or classification to identify key concepts. The performance is usually measured by precision or recall [37].

Ontology Assembly

OntoPH includes 199 classes, 78 properties, and 1234 axioms (see Multimedia Appendices 2-8). We developed the general structure of OntoPH based on the Legal Knowledge Interchange Format (LKIF) core ontology. The LKIF core ontology was developed by the European Project for Standardized Transparent Representations to extend a legal accessibility consortium to cater to a continuing need for a standard vocabulary of basic legal terms [38]. We expanded this legal term vocabulary to include public health vocabulary.

OntoPH is structured in a modularized nature. Modularization improves the reusability, scalability, and maintenance of an ontology [39,40]. OntoPH has 7 modules: space-time, agent, action, role, process, document, and event. Inheriting all modules, OntoPH core ontology has 9 main classes (Textbox 1). The space class defines spatial concepts such as region and nation. The time class describes temporal concepts such as time point or period. The resource class specifies resources used for public health preparation and response. The action class defines potential actions for an EID event. Actions are categorized regarding the 4 basic teleological functions: communication, control, implementation, and monitoring [26]. Subclasses of the action class represent specific functions under the 4 basic functions. The process class describes both continuous and discrete event flows. The agent class lists all the intelligent and nonintelligent agents involved in a process or an action. The description class describes the state and role of any agent, action, or process. The medium class summarizes different types of public health documents, such as legal or nonbinding documents. Last, the expression class represents the knowledge expressions of the documents.

Textbox 1. Ontology main classes and subclasses.

Action

- Communication
- Control
- Implementation
- Monitoring

Agent

- Animal
- Human
- Organization
- Other agent
- Pathogen

Description

- Attribute
- Role

Expression

- Argument
- Assertion
- Assumption
- Declaration
- Evaluative proposition
- Evidence
- Fact
- Feedback
- Intention
- Knowledge
- Observation
- Qualification

Medium

- Document
- Sample

Process

- Continuous process
- Discrete process

Resource

- Equipment material
- Financial
- Human resource
- Intellectual tool

Space

- Area

- Space point

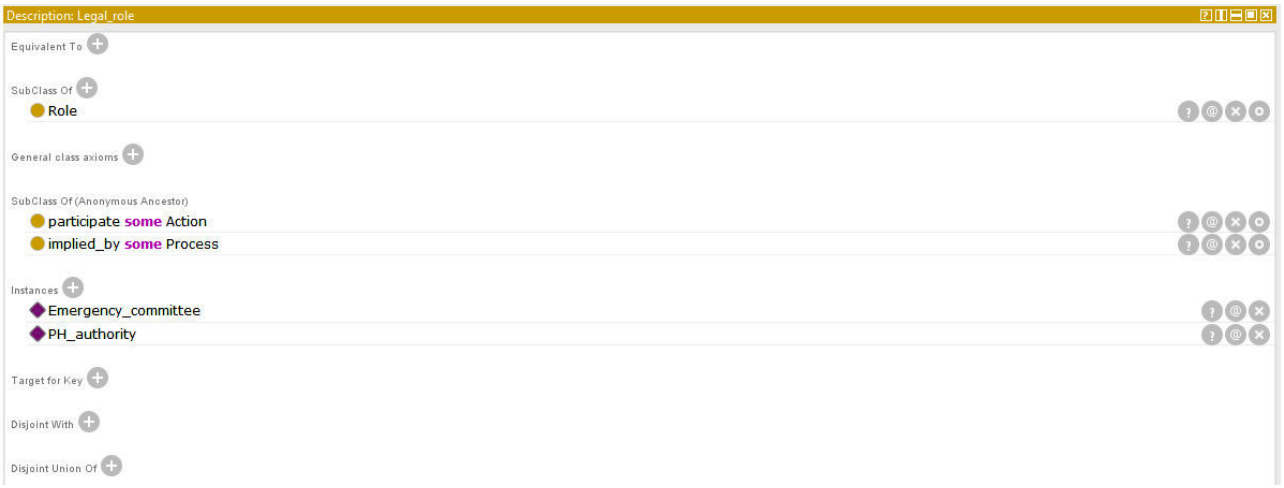
Time

- Period
- Time point

OntoPH properties (see Multimedia Appendices 6 and 7) define the relationships between classes and subclasses. For instance, participate (Figure 4) has a domain of role and a range of action, indicating that a role participates in some actions. This property has an inverse of participate_by. OntoPH contains individuals extracted from public health documents. For example, legal_role, a subclass of role, has individuals of emergency committee and public health authority (Figure 5).

Figure 4. Protégé screenshot for property participate.

Figure 5. Protégé screenshot for individuals of Legal_role.



Semantic Rules and Reasoning

OntoPH is developed using web ontology language (OWL) under the Protégé environment [41]. Logic-based semantic rules allow OWL to "exploit the considerable existing body of logical reasoning to fulfill important logical requirements" [42]. They imply answers to the competency questions. OntoPH answers 3 types of questions: (1) the relation between actions and roles, (2) the relation between roles and the condition of interest, and (3) the relation between actions and the condition of interest. OntoPH uses time, space, resource, and process classes to describe the conditions of an EID outbreak. Hence, we can construct the following informal competency questions:

1. What action must a role perform?
2. What are the roles specified by an action?
3. What are the actions required under a condition of interest?
4. What are the roles specified under a condition of interest?

Informal competency questions should be translated to a formal format so that an ontology can retrieve the elements of knowledge to answer them [25]. We denote $T_{ontology}$ as a set of axioms in the ontology, G_{ground} as a set of ground instances, and Q as a first-order sentence using only predicates in the language of $T_{ontology}$. We can formulate the formal translations for the 4 informal competency questions.

1. Let *Q(action)* denote a sentence that describes some actions. Given a ground formula G_{role} defining instances of a role, determine the possible actions, as shown in Figure 6.
2. Let *Q(role)* denote a sentence that describes some roles. Given a ground formula G_{action} defining instances of an action, determine the possible roles, as shown in Figure 7.
3. Let *Q(action)* denote a sentence that describes some actions. Given a ground formula $G_{condition}$ defining instances of a condition, determine the possible actions, as shown in Figure 8.
4. Let *Q(role)* denote a sentence that describes some roles. Given a ground formula $G_{condition}$ defining instances of a condition, determine the possible roles, as shown in Figure 9.

Semantic rules link axioms *T* with instances *G* and entail a first-order sentence *Q*, which is the answer to the competency question.

Semantic rules are created using semantic web rule language (SWRL), a rule language for the semantic web. SWRL rules apply unary predicates for describing classes and data types, binary predicates for properties, and some special built-in n-ary predicates [43]. An example SWRL rule is shown in Textbox 2.

Textbox 2. A simple example of semantic web rule language rule.

(Person(?x), hasParent(?x,?y), hasParent(?x,?z), hasSpouse(?y,?z) → childOfMarriedParents(?x)

This rule describes the assertion that someone is a child of married parents. Letters with a question mark (eg, *?x*) denote variables. Person(*?x*) indicates that a variable *x* is a person. The binary relation hasParent(*?x*, *?y*) indicates that person *x* has a parent *y*. The formal formula is shown in Figure 10, which reads: there exists persons *x*, *y*, and *z*. If *x* has parent *y*, and *x* has parent *z*, and *y* and *z* are spouses, then *x* is a child of married parents. SWRL rules translate natural language assertions into computable forms (Figure 10).

We create SWRL rules in 3 steps. First, public health experts review documents and identify knowledge expressions. For example, the WHO Technical Advice for Case Management of Influenza A (H1N1) in Air Transport (WHO Advice Air Transport) [44] is a WHO-issued guideline for air transportation case management. It specifies the procedures that the pilot in command should follow when a suspicious case is identified. We identify a knowledge expression pilot_in_command_action under the expression class. Second, public health experts create logic expressions for knowledge expressions. This intermediate step translates a procedure into a formal representation. For example, the pilot_in_command_action can be written as logic expressions, as shown in Figure 11.

Logic expressions and natural language are interchangeable. The first expression in Figure 11 shows that WHO Advice Air Transport contains specifications about pilot actions. The pilot in command should report any suspicious activities on the flight. The second expression in Figure 11 shows that WHO Advice Air Transport requires communication between agencies. The public health authority should communicate with other agencies. Third, public health experts work with ontology engineers to develop the SWRL rules based on the logic expressions from step 2. Textbox 3 shows the SWRL rule created for the same example. The rule first states the knowledge expression and its parent document. Then, it specifies the roles (Pilot and PH_authority) and the expected actions.

Textbox 3. Semantic web rule language rule for the pilot_in_command_action example.

Guideline(Case_management_H1N1_Airtransport_guidance), Knowledge(Pilot_in_command_actions) → contains(Case_management_H1N1_AirTransport_guidance, Pilot_in_command_actions)

Nonhealth_sector(Pilot), Reporting(?reporting), contains(Case_management_H1N1_AirTransport_guidance, Pilot_in_command_actions) → participate(Pilot, ?reporting)

Legal_role(PH_authority), Interactive_network(Communication_between_agencies), contains(Case_management_H1N1_AirTransport_guidance, Pilot_in_command_actions) → participate(PH_authority, Communication_between_agencies)

Logical inference connects documents with knowledge expressions. An inference process is depicted in Figure 12. WHO Advice Air Transport carries many knowledge expressions. One of them informs the chief pilot's actions for an EID emergency during a flight mission. This piece of knowledge then implies that pilots and public health authorities should report suspicious cases and communicate with each other in time.

Reasoning results are presented per individual. Figure 13 shows the reasoning results of Mayor's Office of Emergency Management under the department class. Given an individual, we obtain a list of sentences, such as "Mayor's Office of Emergency Management performs delivery strategy." These sentences in fact are the elements of knowledge.

Figure 6. The formal expression of competency question 1.

$$T_{condition} \cup T_{action} \cup G_{role} \vDash Q(action)$$

Figure 7. The formal expression of competency question 2.

$$T_{condition} \cup T_{role} \cup G_{action} \models Q(role)$$

Figure 8. The formal expression of competency question 3.

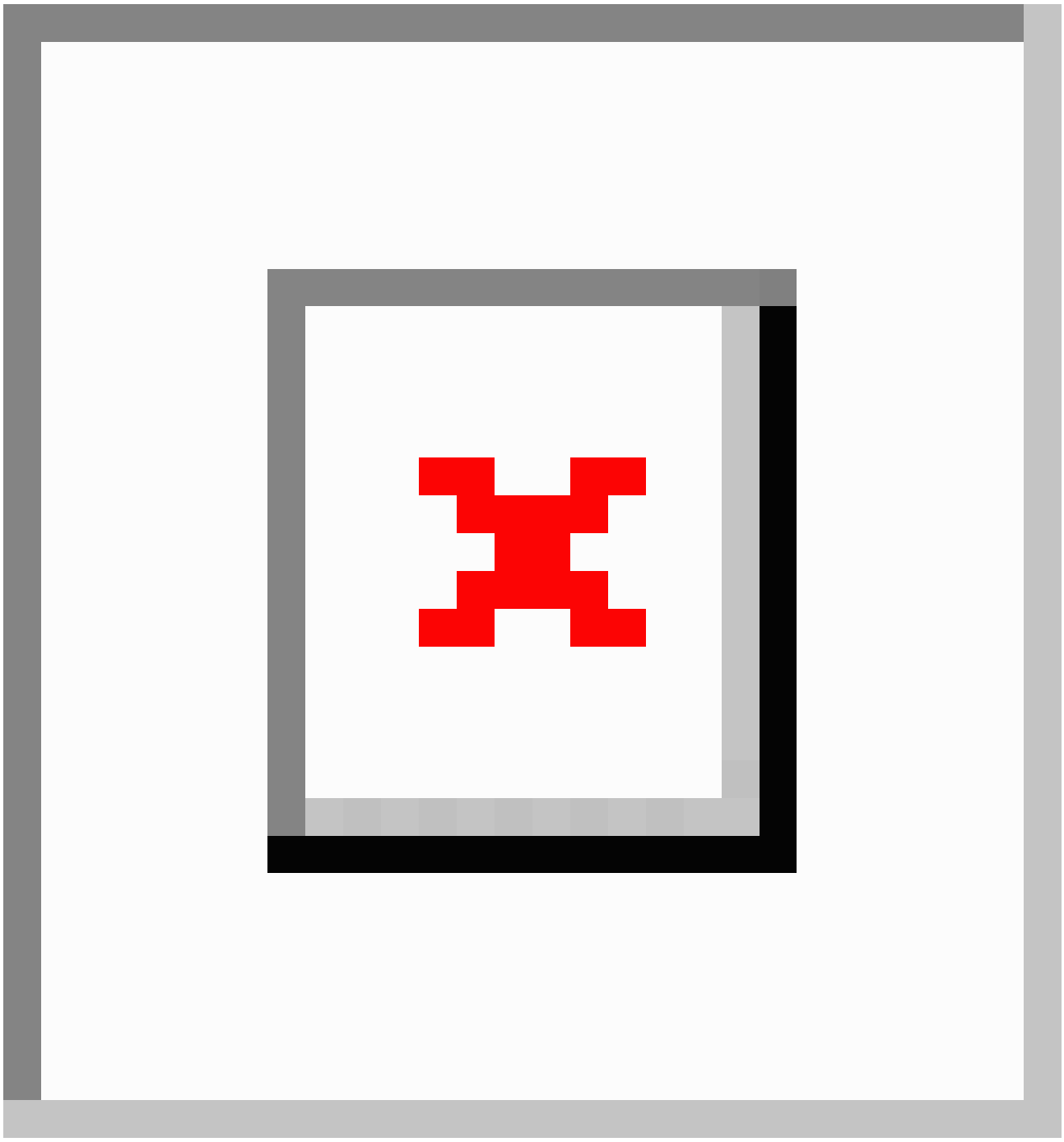


Figure 9. The formal expression of competency question 4.

$$T_{action} \cup T_{role} \cup G_{condition} \models Q(role)$$

Figure 10. The formal expression of someone is a child of married parents.

$$(\exists x, y, z: Person)[hasParent(x, y) \wedge hasParent(x, z) \wedge hasSpouse(y, z)] \models childOfMarriedParent(x)$$

Figure 11. The formal expression of pilot in command action.

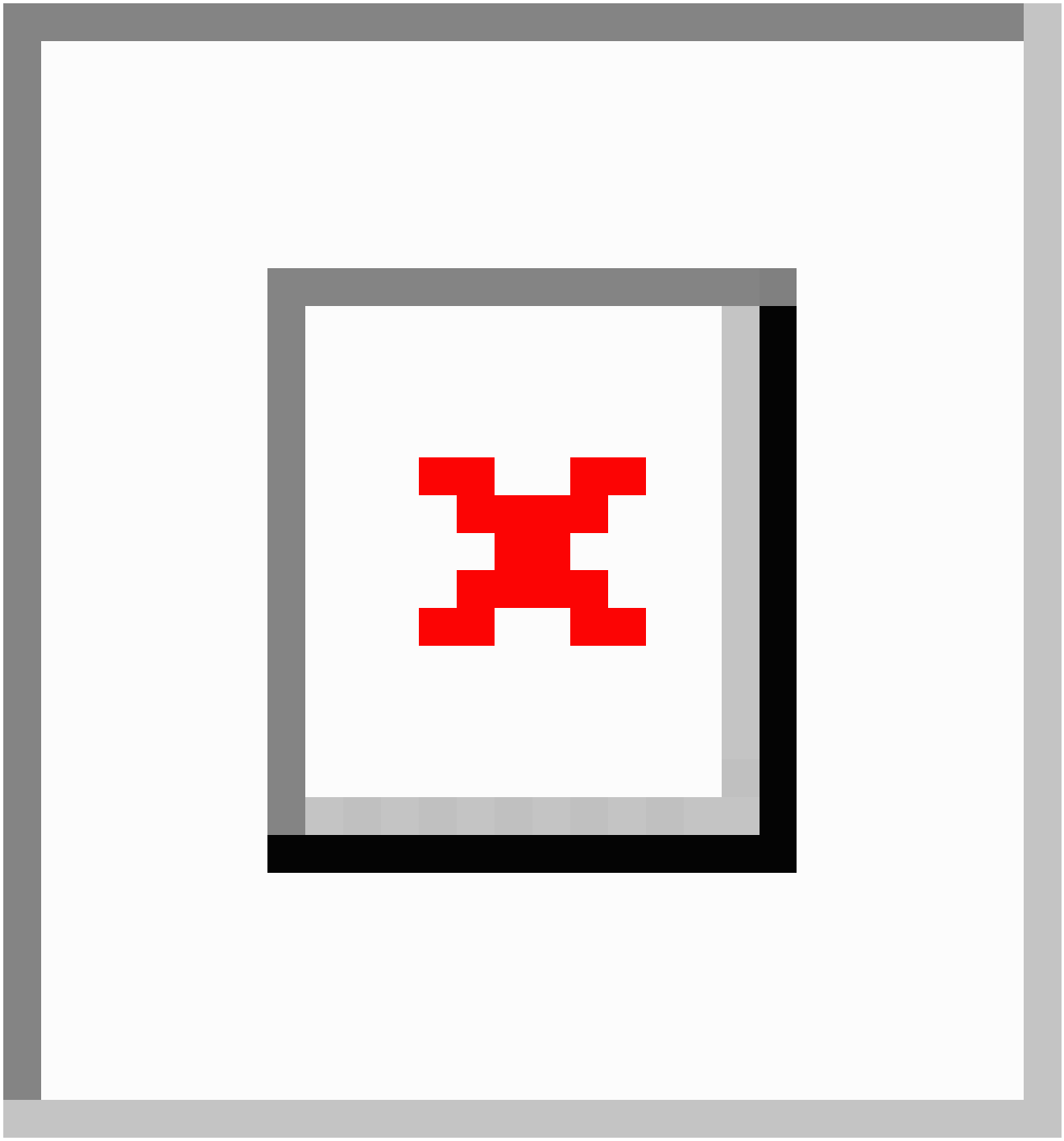


Figure 12. An inference process.

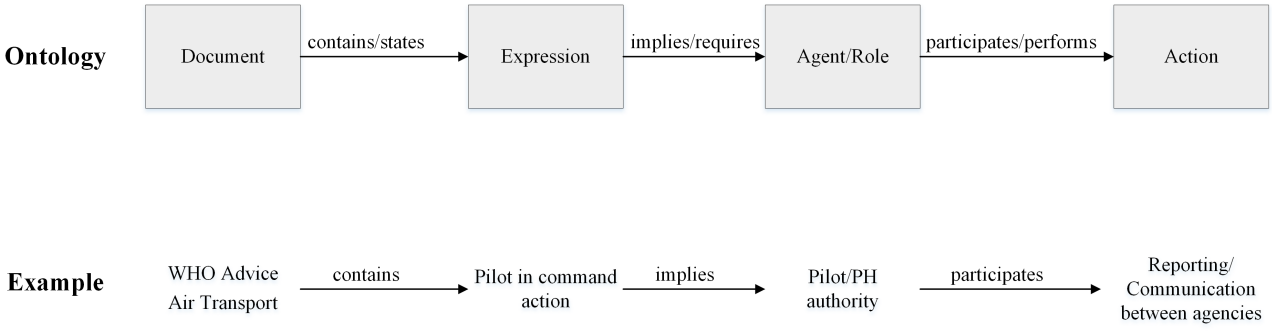
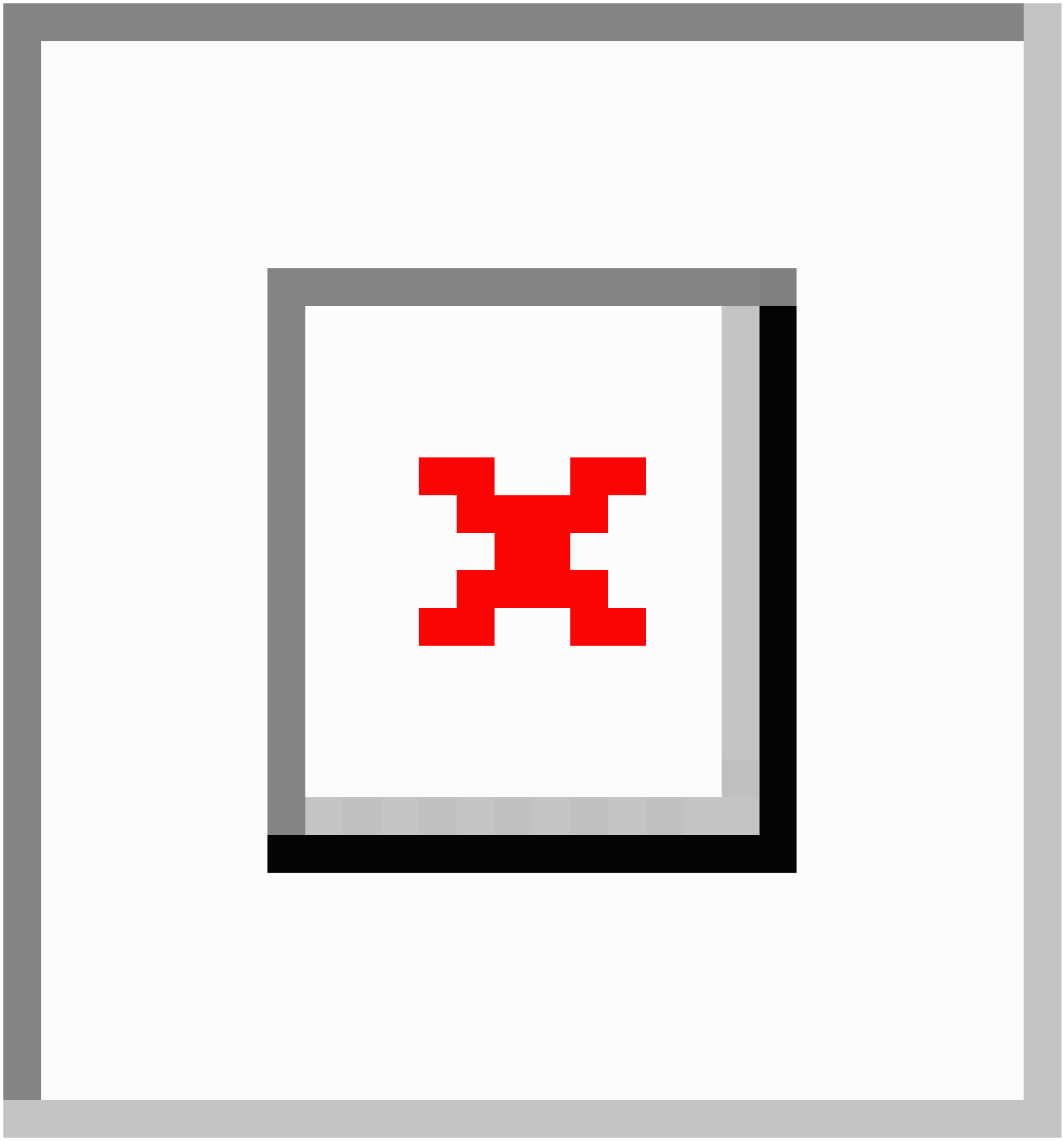


Figure 13. Reasoning results for Office_of_Emergency_Management.



Results

Concept Extraction Results

The corpus, with 135,946 words in total, consists of the US Code [45], federal level regulations [32,33,46,47], international health regulations [34,44,48,49], and pandemic evaluations of outbreak responses [50,51]. They cover all types of public health documents aforementioned. The US Code is the generic legal document, which ensures that the ontology aligns with laws. The federal regulations and the international health regulations are guidelines regarding surveillance, transportation, and preparedness. The evaluations are chosen per disease. H1N1 and West Nile Virus are 2 specific diseases chosen for illustration. These 2 cases were selected because they are well-studied recent emerging diseases with an impact on health resources both locally and globally. In addition, their impacts on health and geographical coverage are both significant. We wanted to evaluate case examples where the primary infection risk is associated with different infection transmission routes in order to evaluate the potential for having a unified framework for EIDs.

We implemented a hybrid concept extraction approach. NLP methods are used to preprocess the corpus. By removing stop words and tagging the parts of speech, one can extract meaningful and most frequent terms and relations using text mining tools like KHCoder [52]. The classification work is done manually with 2 domain experts reviewing every term and relation and deciding their descriptions and constraints. OntoPH

is built upon these terms and relations. Domain experts and ontology engineers work collaboratively to select and annotate documents. Such a team-based method has been used extensively in many scientific studies and applications, such as hazard and operability analysis in chemical engineering [53]. Such a team should be as small as possible while maintaining sufficient expertise. In a series of meetings, team members work together to select documents. Conflicts must be resolved before the list of documents is finalized. Each domain expert annotates a part of the corpus and reviews others' annotations. This practice, therefore, keeps the corpus and annotation as objective as possible.

Ontology Evaluation

The quality of ontology is critical. It affects not only the quality of reasoning results but also the effectiveness of the application. Ontology can be evaluated on many aspects, namely, vocabulary, syntax, structure, semantics, representation, and context [24]. Extensive research has been conducted to formally evaluate the quality of ontologies [24,54-57]. Among these methods, we follow the Ontology Quality Evaluation Framework (OQuaRE) approach [55], which adapts the International Organization for Standardization standards for Software Quality Requirements and Evaluation. OQuaRE assesses 6 characteristics and 39 subcharacteristics of an ontology using quality metrics. Quality metrics are composed of primitive and derived measurements. Primitive measurements are metrics that can be measured directly on the ontology, such as number of classes, number of relations, etc. Derived measurements are combinations of some primitive ones [55]. With a scale of 1 to 5 (1=not acceptable and 5=exceeds the requirement), it rates every aspect of an ontology. The final score is the arithmetic average of individual scores of all characteristics. The details of this method can be found in Duque-Ramos et al [55]. We include 30 out of the 39 subcharacteristics in our evaluation. The other 9 subcharacteristics, which require expert subjective assessment, are excluded. The evaluation results of the OntoPH core ontology are presented in Table 1. The evaluation indicates that the OntoPH core ontology is satisfactory, with an average score of 4. Problems have been found on redundancy and controlled vocabulary, mainly due to the relatively small corpus size.

Table 1. Ontology evaluation results.

Characteristics	Subcharacteristics	OQuaRE score
Structural		
	Formalization	5
	Formal relations support	4
	Redundancy	2
	Consistency	5
	Tangledness	4
	Cycles	5
	Cohesion	4
	Domain coverage	4
Functional adequacy		
	Controlled vocabulary	2
	Schema and value reconciliation	4.67
	Consistent search and query	4
	Knowledge acquisition representation	3.67
	Clustering	2
	Similarity	4
	Indexing and linking	4.5
	Results representation	5
	Text analysis	5
	Guidance	5
	Decision trees	4.5
	Knowledge reuse	4.28
	Inference	4.67
Compatibility		
	Replaceability	3.5
Transferability		
	Adaptability	3.5
Operability		
	Learnability	4.17
Maintainability		
	Modularity	3
	Reusability	4
	Analyzability	3.8
	Changeability	4
	Modification stability	4.2
	Testability	3.8

Discussion

Principal Findings

The possibility of using ontology and semantic reasoning in public health decision making has been recognized in literature [58]. In this work, we adapt this idea and our previous experience in knowledge management in the pharmaceutical industry [59] to derive a detailed methodology on how to develop such a tool. We introduce the systems engineering–inspired ontology-driven framework for public health knowledge management. We demonstrate how complex and heterogeneous public health knowledge can be modeled and stored in an ontology. Previous work has focused on local

activities, such as activities within a health care network [60]. OntoPH extends the scope from local level to global/national level by focusing on general documents.

OntoPH's strength is threefold. First, it stores public health documents knowledge as classes, relations, and instances. Public health documents, including guidelines, procedures, and academic publications, are important sources of knowledge. Even though medical records, geographic information system data, and disease information have been studied and stored in ontologies [60,61], to our knowledge, there is no ontology for public health documents. OntoPH provides this missing piece of public health knowledge management. Second, we present a flexible knowledge management framework. OntoPH implements a modularized structure, which ensures its extensibility. For example, the space-time module can be extended using time ontologies [60,62] and World Wide Web Consortium spatial ontologies [63]. It is also possible to add new modules. If disease information is needed, we can create a new disease module, which inherits the disease ontology [61]. This modularized structure makes OntoPH a potential generic public health knowledge center. Third, OntoPH can manage the hierarchical complexity and heterogeneity of public health knowledge. Elements of knowledge are effectively organized by the teleological functions that highlight the means-end relations.

This framework is most useful in low- and middle-income countries (LMICs). Lack of resources and public health experts in LMICs usually makes a knowledge management system difficult to implement. Nonetheless, OntoPH's general knowledge is widely applicable. By expanding the data sources to include LMIC-specific knowledge [64] and connecting with other ontologies [61-63,65], OntoPH would become a useful tool to help LMICs respond to an outbreak quickly, both at the national and local levels.

Potentially, OntoPH can support decision making by answering user queries. For example, given an outbreak scenario, a user could list questions regarding disease identification, transmission prevention, disease control, and risk mitigation. With enough prestored knowledge, OntoPH could answer the list of questions by producing logical assertions with respect to each question.

Limitations

At this stage, however, there are some limitations. First, the training document corpus is relatively small. Only 5 general documents and 7 specific documents are prestored due to the manual annotation constraint. It will require a concerted effort to annotate and develop a more extensive public health knowledge base for widespread application. Nonetheless, the current corpus is comprehensive enough for proof of concept. Second, the selection of documents is subjective. When the corpus size is small, the accuracy of reasoning results is dependent on the document selection rather than the knowledge base. Increasing the size of the corpus and precise query statement will improve reasoning accuracy in general. In addition, rule-based reasoning has its intrinsic limitations—semantic rules are subjective. SWRL rules rarely allow ternary relations, and that limits the power of the SWRL representation. Third, the current framework is restricted to public health documents, which lack information from various data sources, such as geographic information system data, news articles, social media feeds, etc. This limits OntoPH's real-time usage. Moreover, current knowledge representation would not be able to capture knowledge in research articles that do not fit in the knowledge model. However, the basic and domain ontologies, such as space-time, resource, role, and agent modules, contain fundamental public health knowledge, therefore, making the knowledge framework extendable to cover research articles. This, of course, requires further study of new knowledge representation. Potentially, a research article knowledge expression module could be developed and incorporated into OntoPH.

Future Work

Future work will address the limitations and evaluate OntoPH's reasoning capacity. Adopting artificial intelligence techniques would significantly reduce the human effort, and, thus, get rid of many of the limitations. Specifically, a term extraction module implementing NLP techniques such as topic modeling would enable automated concept classification of public health documents, reducing the amount of work required for annotation. Enriching data sources will improve OntoPH's ability for real-time response. We plan to expand the corpus incorporating expert opinions. A survey for eliciting expert feedback on what to include in the corpus will be conducted. A systematic literature review on effectiveness of policy and interventions could help us determine what documents to include.

To evaluate this method, we will collect a list of general queries regarding general EID preparedness and response from public health experts and practitioners. Moreover, we will test OntoPH's reasoning capacity on hypothetical outbreaks. These full-scale case studies will provide us with valuable information on how to improve the usage and accuracy of OntoPH decision support.

Conclusion

In recent decades, many EID outbreaks and epidemics have resulted in considerable human disability and mortality, in part due to ineffective coordination or slow response at the start of the outbreak. Responding to EID outbreaks is intrinsically challenging due to the uncertainties associated with EIDs, specifically level of risk and potential for impact of its spread in a population. During an outbreak, evidence-based public health policies developed by public health authorities, legislators, and other government officials facilitate the implementation of a strong public health response. However, there are structural and political forces that prevent decision makers from making evidence-based policies in response to outbreaks. Therefore, it is necessary to have in place a mechanism to easily identify evidence in order to evaluate the consequences of public health or policy actions recommended to address these public health emergencies. An ontology framework for public health outbreak response will cut the time spent aggregating expert opinions during the initial stages of an outbreak. It would also assist public health administrators and government officials on next steps based on individual- and systems-level factors associated with the outbreak.

Our approach is a potentially effective methodology for EID preparedness and response. It manages complex knowledge via a function-based knowledge representation. It introduces a systematic way of storing, retrieving, and using public health knowledge. Accuracy and comprehensiveness of the ontology can be improved as more knowledge is stored. We advocate the public health community work toward the goal of developing a Gene Ontology-like [66] knowledge sharing standard. OntoPH demonstrates the possibility of knowledge management for EID emergency preparedness and response.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Ontology layer representation (Adapted from Cimiano [35]).

[PNG File, 225KB - resprot_v6i10e196_app1.png]

Multimedia Appendix 2

Ontology classes part 1.

[PNG File, 34KB - resprot_v6i10e196_app2.png]

Multimedia Appendix 3

Ontology classes part 2.

[PNG File, 25KB - resprot_v6i10e196_app3.png]

Multimedia Appendix 4

Ontology classes part 3.

[PNG File, 25KB - resprot_v6i10e196_app4.png]

Multimedia Appendix 5

Ontology classes part 4.

[PNG File, 26KB - resprot_v6i10e196_app5.png]

Multimedia Appendix 6

Ontology properties part 1.

[PNG File, 18KB - resprot_v6i10e196_app6.png]

Multimedia Appendix 7

Ontology properties part 2.

[PNG File, 16KB - resprot_v6i10e196_app7.png]

Multimedia Appendix 8

Ontology individuals (selected).

[PNG File, 30KB - resprot_v6i10e196_app8.png]

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Abbreviations

EID: emerging infectious disease
LKIF: Legal Knowledge Interchange Format
OntoPH: Public Health Document Ontology
OQuaRE: Ontology Quality Evaluation Framework
OWL: web ontology language
NLP: natural language processing
SWRL: semantic web rule language
WHO: World Health Organization
LMIC: low- and middle-income country

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Viewpoint

Studying Acute Coronary Syndrome Through the World Wide Web: Experiences and Lessons

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Abstract

This study details my viewpoint on the experiences, lessons, and assessments of conducting a national study on care-seeking behavior for heart attack in the United States utilizing the World Wide Web. The Yale Heart Study (YHS) was funded by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). Grounded on two prior studies, the YHS combined a Web-based interview survey instrument; ads placed on the Internet; flyers and posters in public libraries, senior centers, and rehabilitation centers; information on chat rooms; a viral marketing strategy; and print ads to attract potential participants to share their heart attack experiences. Along the way, the grant was transferred from Ohio State University (OSU) to Yale University, and significant administrative, information technology, and personnel challenges ensued that materially delayed the study's execution. Overall, the use of the Internet to collect data on care-seeking behavior is very time consuming and emergent. The cost of using the Web was approximately 31% less expensive than that of face-to-face interviews. However, the quality of the data may have suffered because of the absence of some data compared with interviewing participants. Yet the representativeness of the 1154 usable surveys appears good, with the exception of a dearth of African American participants.

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KEYWORDS

acute coronary syndrome; care-seeking; Internet study; Internet recruitment

Introduction

Several years ago, the idea of conducting a study on delay in seeking care for heart attack on the World Wide Web came to me when I began receiving invitations to complete various Web-based surveys. I had, at the time, been studying care-seeking behavior with regard to heart attack or acute coronary syndrome (ACS) for almost four decades. The goal in studying ACS delay is to improve health outcome by understanding why and how people get care during an ACS event where basically *time is muscle*; the longer it takes to get care, the less heart muscle survives, and more disability ensues. In the first hour, the risk of cardiac death is the highest. At present, delayed care-seeking behavior prevents individuals from obtaining the full therapeutic benefit of hospital-based reperfusion therapy that reduces the morbid and mortal consequences of an ACS.

In this study, I provide my viewpoint on the details of, and my perseverations on, my travails and triumphs and the lessons and liabilities of my journey in ultimately collecting 1154 usable Web-based interview surveys for analysis from 134,421 clicks to the study website and the 279,834,651 million ads displayed on social media and the unknown number of Yale Heart Study (YHS) flyers posted across the United States in public libraries, senior citizen centers, and cardiac rehabilitation centers. Although my viewpoint does reflect all the experiences common to conducting a Web-based behavioral study, I did experience a broad range of contingencies associated with conducting this study that may be useful to persons contemplating a Web-based study.

Study Description, Aims, and Background

The primary aim of the study I proposed was to increase our understanding of care-seeking behavior surrounding ACS by using an integrated self-regulatory care-seeking model (ISCM). The innovative part of this study was using a World Wide Web–based ISCM survey instrument. Prior studies on delays in seeking care for ACS generally rely on measures of time duration from acute symptom onset (ASO) to hospital emergency department (ED) arrival and measures of demographic and clinical variables extracted from emergency medical system (EMS) logs or ED charts and, at times, ACS registries. By relying on such limited data sources, these studies infrequently take into consideration the complexity of the social and behavioral processes by which individuals and their families and others make decisions to seek care for ACS symptoms. This study sought to extend my work and that of my colleagues from two communities: Silver Spring, Maryland and Columbus, Ohio, described below. I thought that by using the Web, we could overcome the limitations of one hospital, EMS, or community to obtain a more representative sample of ACS care-seeking experiences and to test the ISCM. I also considered additional influential factors in seeking care for ACS, for example, were ACS symptoms what the individual expected a heart attack to be like? [1] or how does cumulative adversity [2] and post-traumatic stress disorder (PTSD), if present, influence care-seeking behavior [3]?

What would eventually become the YHS was funded in a traditional manner by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). I applied for and received an RO1 level grant that was to run for 3 years with the aim of applying the ISCM to ACS care-seeking behavior and to delineate decision points and circumstances critical to producing care-seeking patterns that are efficient and expeditious or are protracted and delayed. The care-seeking process in the ISCM was viewed in terms of five analytic care-seeking phases from warning or premonitory symptoms to ED arrival. By noting the presence or absence of three central phases, the self, lay, and medical evaluation phases, it would be possible to distinguish care-seeking patterns and to record the duration of each care-seeking phase and the total duration of each care-seeking path to the ED. The ISCM fundamentally assumes that coping behaviors emerge over time and that initially care-seeking behaviors are constrained by demographic and structural influences. However, as the self-regulatory [4] and coping processes [5] emerge over the course of the ACS event, the influence of structural influences diminishes, and emergent ACS symptom evaluations, advice from others and health care providers, and emerging symptoms and emotions come to dominate the care-seeking process and directly predict the duration of ACS care-seeking. The goal was to capture the processes by which the study participants found their way to the ED and to delineate conditional care-seeking models and their predictors.

In the two earlier studies, interviews were conducted with hospitalized ACS patients either by myself or a physician—we were both US public health officers assigned to the NIH at the time—at a single hospital in Bethesda, or by a cadre of 6 “nurse epidemiologists” who interviewed patients hospitalized in one of 6 hospitals in Columbus. For the YHS, I took the interview schedules used in the two prior studies and extended the emphasis on emergent qualities of the ACS event noted above. The ISCM interview schedule was to be hosted on the Web, and potential participants who had experienced an ACS event would be asked to come to the YHS website to complete the YHS interview survey.

Having interviewed patients in the Bethesda study and supervised and reviewed interviews completed in Columbus, I thought we could successfully bring the YHS interview to the Web, and it could be easily found, downloaded, navigated, and completed. I also thought deep down that we would optimistically obtain a minimum of 10,000 study participants, even though we had calculated that a sample of only 2314 YHS participants was needed to test the ISMC model. I was dreadfully wrong, as will be made clear below. A warning: Doing a Web-based study is difficult and very time consuming, however, not as time consuming as doing face-to-face interviews. Whereas the intensity of the face-to-face interview comes from locating, asking permission, and interviewing potential participants, a Web-based study presents daily challenges centering on clicks to the study website, how many clicks to the site does it takes before someone signs up to participate, and whether that participant is going to complete the survey.

Research at the Ohio State University

The Survey Instrument

Over the years I had learned that to successfully win funding for research, you needed to complete some of the work for which you are requesting funding. With this in mind, and my prior work, I began to build the necessary survey instrument and to pilot-test it as a way of demonstrating the feasibility of a Web-based study of ACS events.

The YHS survey instrument, as noted, was derived from the two prior studies. Piloting the initial self-administered YHS survey instrument was accomplished using a paper-and-pencil version of the survey with 13 study participants who volunteered through an ad run in the Ohio State University (OSU) electronic staff newsletter. Volunteers sent me their name and address, and I sent them the questionnaire and a postage-paid return envelope. Interestingly enough, none of the volunteers who requested the questionnaire were the subjects, but they were going to give it to a family member or “friend” who was the potential participant. Although I had their postal addresses, all interviews were returned anonymously.

From the Bethesda study, it was obvious that there were patterns to ACS care-seeking behavior; not everyone reached the ED at the same time and used the same resources. Whereas an interviewer can skip nonrelevant questions, I also had to design a survey that could be self-administered and only asked relevant questions so as not to overburden participants. Therefore, I was extremely interested in the skip patterns presented in the paper-and-pencil format, which were the heart of a “self-tailoring” survey, and whether unique paths through the survey could be easily followed. The skip patterns, or

algorithms, made sense to pilot participants and became the basis of the self-tailored YHS survey instrument; for example, if the participants indicated that they did not consult a health care provider before ED arrival, a part of the survey covering prehospital provider contact was skipped over. To facilitate readability, a technical writing specialist had the survey read at the 5th to 6th grade level. Also, for terms that might need definition, participants only needed to hover their cursor over the term, and a pop-up balloon with a definition would appear derived from lay literature on health information derived from the National Library of Medicine or NHLBI websites where health terms are defined for lay audiences [6,7].

With this tested survey instrument in hand, I next looked for a means to bring it to the Web. I needed a Web-based, self-administered survey that had an efficient common gateway interface that allowed a potential study participant's computer to download and upload information quickly to facilitate survey progression, that was sensitive to a participant's connection speed, that allowed for participants to easily modify font size, and that required minimal computer skills.

Information Technology

I was basically a consumer of information technology (IT) relying on IT personnel and software programs with a user-friendly interface. So, I knew that I was not going to build the YHS survey instrument or the YHS website. I had a good working relationship with the IT staff in my department, and yet, the IT subculture surprised me from my initial approaches to having the YHS survey instrument designed by students in IT classes at the OSU to incompatibility issues not only between software and servers but also between the website designer and OSU IT graduate students maintaining the YHS website on a Yale server. Traversing the IT landscape at both OSU and Yale was instructive on many levels, yet, lessons learned came at a great price in terms of delaying the study's execution.

Shortly after piloting the survey instrument, I saw an email solicitation from an OSU IT faculty member needing faculty projects to work on for her class in system design architecture. Having no funding to produce a Web-based version of the survey, I wrote to her with my needs; she accepted me as her class project for the quarter. I was their class client; her class had five groups of 4 students, and each designed their version of the required system. I attended three classes; the first to tell the students what I thought I needed, with students asking me questions to obtain information they needed, and what decisions I needed to make for them to be efficient in their design. The next session was a progress report of what each group had produced to solve the design problems and, again, focused on more decisions to be made. At the final session, each group presented their final system design solution. The faculty member assessed which design was the best and that is what I carried away.

I then took this system design to another IT class in which my project was one of several being worked on by student groups. In this class, the actual code for YHS survey was written, and the instructor for that class became the IT consultant for the eventual YHS research proposal. Of the students who worked on the second stage, only one wished to continue with the project to the point of completing a final survey that could be pilot-tested to demonstrate the feasibility of collecting complex behavioral data using a Web-based survey instrument.

The student who volunteered to continue working on the study indicated that he would like to do this work in his spare time because he needed to work over the summer to support himself; I doubted this arrangement. Fortunately, OSU IT ran a summer intern program to facilitate student work with real-world projects, again drawing from faculty and the public who needed Web development services. We applied for the summer intern program and were accepted. He would receive a summer stipend and participate in enhanced IT seminars, and I would receive a functional Web survey that could be piloted to demonstrate feasibility to the NIH.

The Web-based survey developed at OSU was not entirely completed as, what I call it, the "black box," or data complier still needed to be built; the complier converted a click on the Web-based survey's radio button options into data points to be taken into statistical analysis programs such as Statistical Analysis System (SAS; SAS Institute Inc, North Carolina) or Statistical Package for the Social Sciences (SPSS; IBM Corporation, New York). However, the survey was functional enough in terms of collecting responses, and the preliminary output allowed me to demonstrate to NIH how many subjects participated in the Web-based pilot study and their demographic characteristics. The results looked very good in terms of hosting the survey instrument on an OSU server, having a functional instrument, and collecting a respectable demographic distribution of participants.

Pilot Study on Cape Cod

Where did our initial participants come from? For the initial survey pilot test I turned to Mended Hearts—a national heart attack self-help organization—to assist in locating members willing to share their ACS experiences. After considerable delay, a recurrent theme in this study, and administrative processing, the Mended Hearts national organization agreed to run a paragraph in their electronic newsletter, asking local chapters if they would consider running a solicitation notice in their local chapter newsletter. A chapter in the Cape Cod, Massachusetts (MA) area responded positively to our request, and many of the pilot participants came from that region. Whereas 27 pilot participants completed the Web-based survey, 18 partially completed the survey. This partial group, while not originally seen as prophetic, was, in fact, very telling as will be seen below.

The YHS server for the pilot study was housed in the Department of Sociology at OSU, my home department at the time. There was sufficient server space and personnel to support the website in the OSU environment. With pilot data collected and the grant proposal written and sent off, I waited to see the outcome. Lo and behold, several months later we were funded! At about the same time, my partner received an offer of a position at Yale University. Although it was actually my partner they wanted, because of the new grant, they would also take me as part of the package and provide a research scientist position, thus allowing me to complete the study.

Research at Yale University

Arriving at Yale

At Yale, and in particular the Yale School of Nursing (YSN), I would conduct the study and eventually begin to work on other projects, advise graduate students, assist faculty with grants, do guest lecturing, and, in general, participate in YSN's research and teaching missions. However, there was one difference in the two environments that either represented a true cultural difference or my lack of credibility as a newcomer. Having a research grant in hand is a great feeling, but moving it forward is an entirely different matter. I found myself in a new academic environment where considerable work had to be done just to bring the study to Yale and much more to get it up and running. Perhaps because I was a newcomer, I frequently felt as if I was being told what I had done wrong rather than someone helping me do it correctly in the first place. While at OSU, I had been accustomed to support colleagues that listened to what I needed to accomplish, and provided guidance within OSU's framework, offering resources and/or how to use a variance to accomplish a task.

Information Technology Surprises

Despite the move to Yale, I wanted to leave the survey instrument on the OSU server because it is where it was developed, and people were invested in the study. However, the subculture of IT intervened, and the IT director at the Department of Sociology, OSU, did not want Yale IT to have access to the OSU server because as you will recall, the survey's compiler was not complete and IT personnel from YSN were going to complete it as part of the transfer process. Therefore, I proposed transferring the entire study to Yale. This was not a bad idea but not a good one in practice. I was warned by my OSU grant officer that it was not a good thing to do, and it would take a long time to transfer the grant. Unfortunately, she was more than correct on both counts.

It took more than a year for the transfer to be completed. However, since I had no actual funds in hand when arriving at Yale, no one I needed services from wanted to invest much time in the study. More problematic were the changes in the expected support from the YSN IT unit. Furthermore, it was unbeknown to me at the time of our arrival at Yale that YSN was in the process of going from an autonomous IT unit to being folded into the larger Yale IT environment for economic and efficiency reasons. I was promised that YSN's IT would complete the survey's data complier, install it on YSN servers, and support it over the 2 years of data collection. However, the merging of YSN IT into the larger IT meant that I could not complete the survey instrument because Yale IT did not support the original PHP programming language used to build the survey. However, after the transition to central IT, PHP programs would probably be allowed to run in the larger IT environment. In the interim, however, no Yale IT personnel were allowed to write PHP code! Consequently, I would have to do one of two things, in addition to waiting—either have Yale IT rewrite the survey in compatible code or go outside of Yale to secure the services of a PHP programmer. However, I did have a third idea that I tried, which was going to the Yale's Department of Computer Science and engaging a graduate student programmer. I was told by a placement administrator that this would not work, because the department was not oriented toward applied endeavors. Yet, one student did respond to an ad posted on their placement system; the student was only peripherally familiar with PHP and wanted to work on the data complier at home abroad over the summer. I did not find this option appealing.

Thus, I decided, fatefully, to go outside Yale as I had already put so much time and effort into getting the survey instrument designed and implemented. Additionally, the cost of Yale rewriting the survey seemed absorbent, and there was no room in the budget to cover the costs of such a rewrite. However, in retrospect I did have adequate funding to accomplish this rewrite, despite Yale's overhead being greater than that of OSU's—thus, another misjudgment on my part.

Information Technology and Going Outside

Going outside the Yale IT environs proved very difficult. No one at Yale IT would officially, or unofficially, recommend a PHP programmer who could do the work; it was against Yale policy to recommend outside vendors. I finally tried the IT person at the Department of Sociology at Yale, who I thought should be familiar with surveys and survey hosting and thus might know of someone to assist me. I obtained a name, followed up, interviewed him, and we agreed on a price and a timeline. However, it took months to get his contract finalized with frequent conversation with contract specialists in Yale legal and the YSN business office. The programmer wanted partial payment up front, which was contrary to Yale contract policies. He said he had previously designed surveys, was doing contract work for a Yale department at the time, and he could have the project completed in 2 weeks' time.

At the time of hire, he was very confident, but he did not know enough about data compliers, and I found myself answering very basic questions about how to handle strings of variables and comma separated variable files. Eventually after months of frustration and some progress, I had to let him go, pay his total fee because he had spent so much time on the project, and return the survey to OSU to be completed by IT graduate students, where I should have left it in the first place.

How the Yale Heart Study (YHS) Site Worked and Where It Was Housed

When completed, the YHS survey instrument worked extremely well, it was stable, downloaded quickly, and collected data as designed. However, as mentioned above, the language it was written in was not compatible with Yale IT servers, and thus, it could not run on Yale central servers at the time. I had attended a Yale IT meeting where the migration of YSN IT to central Yale IT was the focus and asked when PHP programs would be allowed to reside on a Yale IT server. I had heard rumors that PHP would soon be allowed. Essentially, I was told it was not going to be in the near future and thus would be of no value to me when it occurred.

Fortunately, as it turned out, Yale also runs a special Yale research server where anything that does not violate the law and decency can be uploaded and run, but mostly faculty research projects were uploaded to this server. Why no one had

previously informed me about this option, I do not know. The server allowed PHP and was monitored, but it was not maintained by the Yale research server staff. Thus, I had OSU IT graduate students maintaining the YHS survey. The YHS website was only down for a brief period when a coding error was accidently introduced while updating a line of code; it was rectified in less than an hour.

Thus, with the YHS Web survey instrument hosted on the Yale research server, I thought we were ready to launch the YHS study onto the wider Web. However, a few more obstacles arose causing more delay.

The Security Design Review

One item that created a high degree of frustration and delay was the necessity of conducting a security design review (SDR) to ensure we were compliant with the Health Insurance Portability and Accountability Act (HIPPA) data protection regulations to safeguard personal health information of study participants. The YHS survey instrument was designed to be anonymous to facilitate participation and candid responses. However, my previous face-to-face interviews with ACS patients demonstrated that YHS participants may need an opportunity to return to their survey to make changes, to complete the survey if they ran out of time or were interrupted, or if after they completed the survey forgotten information came to mind. A way of allowing them to return to their survey needed to be designed and built. Because the survey contained medical history data, the log-in procedure, personal ID password system, and servers needed to be HIPPA compliant. If Yale IT had rewritten the survey, HIPPA compliance would have been written into the survey program, but because it was coming from an outside source, an SDR was needed, especially since the OSU IT graduate students writing the survey were not fully aware of HIPPA because they were not on the medical side of campus.

Yale IT charged a princely sum for the SDR. I did not feel that I should bear the cost of this review because the shift to central Yale IT was not anticipated or budgeted for. After intervention by the dean of YSN, I received assistance with the review without a fee. Thus, the YHS survey could be returned to by participants, was completely anonymous, was HIPPA compliant, and all data were deidentified in the event of a server security breach. No one breached the security of the YHS website.

However, checking to see if anyone returned, by monitoring a specific number of questionnaires for a given period, no one returned as far as we could determine. However, six surveys were begun and a similar, if not identical, personal code was close by in the sequence of identification numbers with one partially completed and the other completed. These participants had begun the survey with one passcode and forgotten it, and thus they had to start anew and complete the survey. In these instances, we accepted the survey that was most completed. Yet, we do not know how many participants wanted to finish and could not get back in and so did not complete their survey. Despite the multiple options available for contacting us, no one contacted us to indicate they could not return but wanted to.

YSN Graduate Research Assistants

Because I was anxious to get the YSN survey up and running, and Yale union hiring practices seemed an unfathomable mixture of rules and regulations, I decided to hire graduate research assistants (RAs) from the pool of graduate students at YSN and rely on available part-time RAs “floating” around YSN. Hiring YSN graduate students, I was warned, was not a good idea as the burden on the graduate entry program students (these students have a BA or BS degree and become both nurses and nurse practitioners in an accelerated program) was exceedingly high and, besides, no one would apply. Well, they were correct and also wrong. Yes, they were overburdened but still liked the idea of working part-time; they were limited to 9 hours per week (I had been accustomed at OSU to having plenty of graduate students wanting to work and being able to work 20 hours per week.) Although I was dealing with many of the issues mentioned above, I had 2 students begin to look for resources related to health websites and print ad recruitment strategies described below; this arrangement was not very productive, as students wanted to do all of their work off campus or on weekends, and I saw very little of them. Working this way did not help in the execution of the sampling strategy to recruit study participants. In general, YSN students were taking too much time off for exams, breaks, and holidays, and this was problematic in establishing a productive working rhythm.

A bit later in the study I also had 2 RAs who, as part of their PhD matriculation, were assigned to ongoing research projects. Rather than have them do something that an RA might do, they were given an independent task; one to run our YHS recruitment blog postings on heart disease and healthy behavioral changes, and the other to expand our outreach to potential African American participants.

Beginning to Collect Data

In the social and behavioral sciences, we like to have as much control over our sampling frame as possible to make certain that we are sampling the correct population and are not introducing systematic biases in data collection. To gain some semblance of control and to assess YHS’s representativeness, we turned to the National Health and Nutrition Examination Survey (NHANES) to estimate the size of our potential target population. We had, in 2004, a target population of 7.8 million individuals who had previously experienced an ACS event [8]. On the basis of the NHANES, we constructed sampling quotas stratified by sex, age, and race, white and African American, based on the prevalence of ACS events derived from the NHANES 1999-2000 [9] and 2001-2002 [10] studies. We would try to match the quotas in each category, thus providing a gauge of the representativeness of our sample. At the time the grant was prepared, the NIH had a policy of making certain researchers include African Americans, women, and older participants. The quotas developed around these three characteristics made us monitor our emerging sample and make modifications to our planned recruiting techniques as we progressed.

Oversampling African American Participants

My experience with the two prior ACS studies, described above, and the known difficulty in recruiting African American research participants [11], made me over sample African American by a factor of 2 to be certain that African Americans were adequately represented. We proposed recruiting 386 African American participants distributed by age and sex. We failed abysmally to recruit African American participants, with only 33 (8.5%) of the planned 386 being recruited. Of the 33 participants who completed the survey, only 27 provided usable time information and will be included in the analyses. I did not anticipate such a low level of African American participation. It is obvious that the digital divide has not been overcome as the literature [12] had led me to believe. I will detail our efforts to oversample African American participants as we proceed.

Recruitment Techniques

The Five Techniques

To fulfill the sampling quotas, we needed to attract potential participants who had experienced an ACS event. I did not believe that it should be too hard, as we only needed 2314 participants out of 7.8 million individuals in the United States who had experienced an ACS event. To reach the eyes and fingers of potential study participants, we devised five broad techniques to place ads: (1) on public social media websites; (2) on conventional public bulletin boards in public libraries, senior citizen centers, cardiac rehabilitation centers, and in African American churches; (3) in chat rooms, public forums, or electronic bulletin boards; (4) in the form of viral email marketing; and (5) in traditional print publications, for example, American Association of Retired Persons (AARP) or college alumni magazines. Ultimately, we spent most of our time and resources recruiting with paid Web ads on social media and contacting libraries and senior citizen centers to post our flyers on their community bulletin boards. Along the way, we devised additional techniques as we built upon the success of one method, while curtailing the emphasis placed on less successful ones, described below. The basic strategies were continually evolving and emerging over the 2 years, 4 months, and 16 days of actual data collection, excluding partial blackout periods described below. Each time we altered a technique or began a new one, we submitted an institutional review board (IRB) amendment; all were approved in a timely manner.

The Two Dominant Recruitment Techniques

Social Media Ads

We began our recruitment by running Internet ads on Facebook as well as Google and its family of websites. We added AOL and Yahoo or Bing a bit later, partially because they are known for being more popular among older potential participants, and we wanted to see if we could increase male participants who were not initially showing up to fill sampling quotas.

Bidding on YHS Ad Placement

Placing ads on social media is not a simple task. Knowing, as we all do, that we rarely go past the first page of our Google or Yahoo searches, we had to bid how much we were willing to pay for each click to the YHS website. The more you are willing to pay per click, the more likely your ad will appear on the first page of someone's search for information about the heart or heart disease. This also meant we had to select keywords and phrases that were likely to be searched by potential participants who had experienced an ACS event, for example, heart symptoms, I have chest pain, angina symptoms, heart attack women, or heartburn heart attack, to name a few of the 878 terms we used, including misspelled terms like "heart attach." So, when someone searched using one of our keywords, our ads would appear on the first page of their results, provided we bid high enough.

Having a budget for a given length of time, it was difficult to know how much to bid at first. It took time to overcome some frugal tendencies to bid against more well-funded pharmaceutical companies, purveyors of questionable heart disease nostrums, and university and for-profit health care systems. All Web providers allowed us to target potential participants by age and sex. Both Google and Facebook had the highest cost per click (CPC) ranging from US 50 cents to US $5 or more, whereas AOL and Yahoo or Bing were in the cents per click range. Additionally, we had to set weekly spend limits for each provider, whether US $50 or US $275 as we did near the end of our funding.

On average, we paid US 0.89 cents per click to the YHS website, meaning that each time someone clicked one of our ads and were taken to the YHS Web page, we paid the vendor or Web page owner our bid price. You never knew whether it was money well spent or not, but since we had so many clicks and so few participants, it is easy to suggest that it was not very efficient. It was also troubling to think of the possibility that students writing class papers about the heart or heart disease clicked on the site hoping to gain information, or that the ads never really ran because we could not have possibly monitored their display. However, one inquiry to Google about this possibility quickly brought back an image of our ad on a Web page as verification of ads' having been run.

Nonetheless, in bidding on the four social media hosts, we did not know whether the ads were being looked at by potential participants who were suspicious that they might be having an ACS event, those who were looking to see if they were at risk for a heart attack, someone wanting to prevent a heart attack, someone who wanted to know if someone they knew might be at risk or having an ACS event, or those who were searching post an ACS event and wanted to understand what had happened to them medically. In addition, some individuals may have been looking at the YHS website to help their friends, as in a Strauss "information provider" [13], which may have been the reason why we had so many individuals who registered on the YHS site but failed to progress beyond the first question; more on this point will be discussed below. In a compassionate manner, these information providers may have been trying to understand what a family member or friend may have gone through during an ACS event.

Although we wanted to avoid having our ads run on websites selling commercial products and questionable health nostrums, we, in fact, had little control over where our ads were placed.

However, judging from the sites that our YHS ads were clicked from, there was a wide variety of websites where our ads appeared; this was not a problem for Facebook as all ads were run on their site alone. A website from which a potential participant came was not an absolute indication of where they saw our ad, as they could have noted down our website URL from a site on which they happen to have been when they decided to check out the YHS site.

We did not use real-time bidding services to tweak our bidding; these had become more prominent after the study was designed. However, we did respond to contacts from the 4 social media vendors to have them evaluate our campaigns, and I generally found it beneficial but ultimately more expensive, as their specialists enviably recommended ways to increase our limit on spending or our CPC bid. They were most helpful in assessing our selection of keywords and how to target our ads to African Americans, men, and older potential participants. They also showed us newly added social media features and how to use them. Additionally, we paid extra, usually between US $5 and US $30, to promote our YHS Facebook page when our posts began trending upward.

Using the hit rate to the YHS site, our budget, the success of keywords and ads in securing Web page hits, adjusting our bids to be on the first page—someone new can come in at any moment and bid really high—and, of course, the need to monitor all 4 social media vendors, the recruitment by the Web is a very time-intensive activity.

Ultimately, in a very real sense, we were living and dying on the basis of our ability to run ads on the social media sites.

Public Libraries and Later Senior Citizen and Cardiac Rehabilitation Centers

Our second most intensive recruitment effort, in terms of personnel hours, was soliciting the cooperation of public libraries across the United States to post our advertising flyers on their community bulletin boards. A bit later, we began targeting senior citizen and cardiac rehabilitation centers to also post our flyers.

The Libraries

We contacted every public library in the United States that was listed on Public Libraries website [14] and for which we could locate an email address. We also used, when available, state lists of public libraries, as well as state listings for senior centers. There was considerable variability in the openness of access to contact information for library directors. The range of availability was from a picture of the library director on the library's Web page with an email address directly below to zero information on how to contact the library electronically, aside from a general telephone number for the library. If the city was relatively large and with multiple library branches, we directly contacted the central director rather than contacting each branch individually because in all probability branch directors would contact the central administrative office, and we did not wish to appear as if we wanted to circumvent them. Thus, it was an all-or-nothing approach in larger communities, for example, Los Angeles, California. Central directors frequently let us know whether they were sending out our materials to branch libraries because we had established a relationship with them, as additional materials were usually required for their approval.

The Senior Centers

In terms of senior centers, locating a list of centers for each state was the main task. In both public libraries and senior centers, no simple criteria were established in terms of how long to search on the Web to find an email contact. In the extreme, we would look for minutes of city council or governing board meetings because emails of city board members and significant directors would frequently be listed as part of the meeting minutes; websites of city managers would also have emails of directors, whereas the library website itself would not. We tended not to telephone libraries, as we initially thought it would not be efficient. We did relent, however, and telephoned using a standard script to request the name and email address of the director. Our request was never refused, and in very small libraries, the director was usually manning the telephone. At times we felt like quasi-spammers sending out hundreds of emails and stalkers when we went as far as checking on LinkedIn and Facebook for an email address.

Alternatively, we also used the "Contact Us" box for the library circulation desk or reference department and asked that our information be forwarded to the director. In these instances, we sent a modified cover letter with links to our download website, discussed below, because it was not possible to send our attachments through the Contact Us box. Reaching out to the city manager was also an effective way of contacting a small library or senior center director, especially those open for very limited hours

In many instances, contacting librarians, because we could not find an email address, proved beneficial as they made useful suggestions for advertising the study. The first time this occurred was when a librarian in California suggested that her patrons really liked bookmarks. So, we ultimately designed, printed, and mailed out hundreds of them each week to not only libraries but senior centers, cardiac rehabilitation centers, churches, and professional health care provider meetings willing to distribute them.

An additional suggestion by a librarian was that we translate our bulletin board flyer into Spanish. This was particularly useful in the West and Southwest. Due to the study design, and later, cost and time, we did not have a strategy to target Hispanic participants, and we did not have the YHS survey translated into Spanish.

We believe some libraries and senior centers opened our emails, went to the printer, and immediately posted our flyer, whereas others took considerable time processing our request through a committee or person who oversaw access to the public bulletin board. In cardiac rehabilitation offices, which were usually connected to hospitals, we also had to overcome the hurdle of an IRB or research committee review and approval process. In these instances, when requested, we responded with copies of Research Aims and Methods sections of our grant proposal and of our Yale IRB approval letter. In all instances where we were appraised of the approval process, we received approval. Also, each library, rehabilitation center, and other posting organization

had its own policy governing the length of time an announcement could remain posted. Thus, another important thing you lose is control over the exposure and sustaining power or half-life of your advertising efforts.

Multiple Web Pages for YHS

Originally, we sent libraries a cover letter soliciting their cooperation, including a PDF file of our IRB approval letter, a newsletter paragraph for use on their website or newsletter, a flyer with and without pull tabs they could print, and 2 box ads files for website posting. In some instances, these items were cumulatively too large to pass through email filters, and we subsequently reduced the size of our email package. We eventually developed an additional YHS download website from which librarians and others could download and print our materials or request that we send them our materials. This download site also meets the needs of a commercial email advertiser, discussed below, because they would not send out attachments in their email "blast," as they called their mass emailing. This download site served us well, as we had 701 download requests and mailed out hundreds of packages of bookmarks, posters, and flyers across the United States.

To avoid burdening librarians, we only asked for their email system to tell us that our email was received and not whether it was opened. Unfortunately, we received very few acknowledgments indicating that they would cooperate, but when they did, they did so enthusiastically noting that an ACS event had touched them personally or a family member. It was not unusual to be scrolling through a library' website or for a YHS team member to drop into a library while travelling and find our flyer or poster being displayed. After solicitations to libraries were ended, we began receiving notification that our email had been discarded without being opened; this reflected email systems clearing out unopened emails!

Chat Rooms and Changes in the Web Environment

In the original design of the YHS, I had proposed using chat rooms to disseminate information about the study and to post our YHS website URL link. During my initial exploration of these sites, in preparation for the grant proposal, all comers were welcome; information about products, services, and studies were relatively ubiquitous; and monitoring or restrictions were minimal. These websites had not yet been fully monetized and advertising seemed plentiful. By the time we returned to these sites, relatively strict rules and policies were in place. When we were ready to launch the YHS website and begin our advertising, we first read the prevalent "use agreement" of any site that appeared as a possible venue for YHS information and ads. Almost all websites that would have been useful now prohibited the "recruitment of research subjects." We did find a suite of sites, Daily Strength [15], which has numerous support groups covering a wide variety of chronic and acute health conditions. I reviewed their use agreement statement very carefully and noted that they did not prohibit the recruitment of research subjects, or so I thought. I uploaded one of our paragraphs describing the YHS and the URL of the YHS website to several support or self-help groups whose members might have had or be at risk for an ACS event; for example, I posted on their hypertension, diabetes, heart attack, cardiac arrest, women's heart health, and high cholesterol groups. We had a very good response, especially from women who could perhaps be described as having had a "microischemic" ACS event. One women had immediately signed up to participate in the YHS and then encouraged others participate; she was obviously a sociometric leader of the group of relatively young women. To facilitate participation, I responded to comments from group members who found the study useful and thanked them for participating.

The rapidly changing nature of Web information and the relatively short half-life of that information were driven home by the fact that engagement with the YHS lasted until another "hot" topic was posted. At that point, the presence of the YHS would be lost without a thread of comment. It was in going back to the support groups to remind them of the YHS that I was "caught" and told that research recruitment was not allowed. Consequently, all references to the YHS were removed from the entire suite of sites instantaneously. I pleaded my case indicating that no research recruitment prohibition was stated, but no response was forthcoming. However, I was subsequently informed that we could become a sponsor of the website and advertise with them as a site sponsor. I prepared an application to determine the cost of such sponsorship but never received a response. By this time, other pressing matters were confronting us, and we did not follow up with them.

Finally, early on we looked into running ads on WebMD, a very popular medical information website. At the time, they quoted US $20,000 to run our ads for 1 month. After some discussion, they were willing to sell us a 2-week period for just US $10,000. At the time, this seemed expensive and so we declined. I do not know just how much more successful we could have been had we gone with them for a 2-week period, but it would have been almost 10% of our original advertising budget.

Viral Marketing of the YHS

As part of the strategy to bring potential participants to the YHS site, we built in a viral marketing option for individuals who were either curious for someone they knew had experienced an ACS event or who happened upon the YHS site. What they needed to do was click on our "Visiting for Someone Else" button, and they were provided with a form to enter their first name, the first name of their friend, and their friend's email address. An invitation was sent to their friend describing the study and the fact that their friend was responsible for us sending the email. Email addresses were not collected, and a statement to that effect was present in the form and in the received email. A total of 163 invitations were sent out using this method. In general, I would not describe the method as effective, and we do not know how many of our final participants made a decision to participate based on receiving our email. We did not advertise the fact that we had this method available for individuals to send invitations to potential participants. We will assume that anyone finding us also had the option to send the YHS URL on their own to a potential participant.

Print Ads and Media Outlets

We never published a print ad, as I had proposed. We found that it was more expensive than I had originally estimated, and

there was considerable lag time from ad submission to publication, usually several months. In addition, a part of the expense that I did not anticipate was ad design. Newspaper ads were ultimately decided against because they were too local, and larger markets were too expensive.

At one point, we decided to place ads in university alumni magazines, especially those with a large alumni base, such as Michigan or Ohio State. But as we were not having problems recruiting educated participants, and if anything we were slightly biased in this regard, so we abandoned this plan as well. Instead, we were able to go onto the Facebook pages and Twitter feeds of various universities and alumni groups and friended and tweeted them our YHS link with a brief study description; we also friended and retweeted information from nationally well-known heart institutes and programs, for example, the Cleveland Clinic, Cleveland, Ohio, and the Texas Heart Institute, Houston, Texas. The overall assessment was that we probably received more interest from these Web-based efforts than print ads.

We did, nonetheless, have print coverage from various sources. The Office of Public Affairs at Yale University and the YSN both published studies covering the YHS. One of our RAs who had worked in the New York City media market had tried to obtain a spot for us on the Dr Oz and Oprah shows but was never able to obtain a firm commitment. However, she was also an occasional contributor to the *Huffington Post* and did publish a marathon of heart health–related editorial columns during Heart Month of 2012. We experienced an increase in website hits during this period.

We also focused on media outlets to cover the YHS as a news item. In this effort, I did two radio interviews, one email interview with questions provided for answering, and one newspaper interview with the *Wall Street Journal* (WSJ). After the WSJ study about ACS in general, we received a substantial bump in traffic to the YHS website. The WSJ was the most national coverage we received, and it was evident that advertising nationally is probably an efficient means of enhancing website traffic if funds are available.

New, Modified, and Emergent Recruiting Techniques

Email "Blasts" to African American Pastors

As noted above, the oversampling of African Americans was part of the study design, yet it yielded only 33 African American participants. To facilitate the oversampling of African American participants, we used three distinctive techniques. The first was a two-time email "blasts" by a proprietary emailing company to solicit the cooperation of African American pastors in communities throughout the United States. The company we used originally told us that their list included the names and email address of 1700 African American pastors, when in fact they provided only 1200 pastor addresses. We complained and were given an additional blast. Neither blast produced tangible evidence of success or increased spike in African American participation. However, we did receive two telephone calls that our materials would be disseminated to parishioners. Before this effort, I was to consult with a panel of African American pastors affiliated with the Yale Center for Clinical Investigations, a center that facilitates research with difficult-to-reach populations, but the meeting was canceled. However, I was able to consult with one pastor in the group who suggested my solicitation letter should be more compelling in terms of why a pastor should assist us. Apparently, I did not make the letter compelling enough.

Targeting Communities With High African American Populations

In addition to email blasts, we obtained from the US Census Bureau a listing of the 66 metropolitan areas and cities in the United States that reported 23.7% or more of the population being African American residents; for example, Detroit, Michigan; Memphis, Tennessee; and Jacksonville, Mississippi [16]. After our email solicitation techniques were finalized, we immediately targeted the public libraries and senior citizen centers in these 66 areas and cities.

The African American–Focused Health Website and Traditionally Black Colleges and Universities

Lastly, we contacted the most popular African American health bloggers and health websites to place ads with them. This was not successful both in terms of their response to our inquiries or the number of times we found our Web ads on their websites. African American health websites were notable for their lack of a direct focus on the prevalent health needs of African Americans and instead focus on physical appearance and lifestyle matters. It was rare to find among African American–focused sites information regarding health risks and behavior modification in prevention and treatment of high blood pressure (HBP), diabetes, or heart disease. I would assess their health information as "soft" at best.

As noted above, we "Liked" on Facebook and tweeted heart health information on university alumni sites, and we did the same for historically and predominantly black colleges and universities and their alumni groups.

Young Take Older to YHS Site

We approached youth-oriented websites to run our ads that encouraged more computer-literate high school students and young adults to take less computer-savvy family members, who had experienced an ACS, to the YHS website and assist them in completing the survey. I do not know how comfortable this was for older adults, but we assumed that for those who participated it was not an issue and this effort may have increased participation among the elderly. In addition, while working with state 4-H groups and the national organization of school librarians, we asked for their assistance in recruiting the young by displaying our posters. As an inducement for younger individuals, we provided a certificate for 1 hour of community service from YSN. We do not have complete records on this program to say how successful it was, but we did send out at least 100 certificates.

Walk With a Doc

We also spent a very nominal amount, US $50, for a national newsletter ad with Walk with a Doc (WWAD) [17]. WWAD is a national organization that promotes healthy physical activity among at-risk and chronically ill individuals. They sponsor

Saturday morning walks where interested parties can spend a couple of hours walking and talking with a physician who is willing to share his advice on health and well-being. Again, I have no idea how effective this effort was.

Avoid Your Own Backyard

In general, I tried to avoid recruiting in the environs of New Haven, Connecticut. I wanted to obtain a nationally representative sample of participants and to fill our sampling quotas. Despite the fact that RAs wanted to have more control over the sampling and wished to reach out to locally available participants, I resisted the temptation to pick the low hanging fruit. For this reason, I also resisted recruiting in the New England area, until we had been to other regions of the county with our library and senior center flyers.

Reward for Participation

As an appreciative gesture for participation, we maintained a Facebook page, Twitter feed, and YHS blog, providing a variety of health information links and studies related to heart health, heart disease prevention, diet, exercise, and other news items that might be of interest to study participants. We developed these information sources because we could not maintain anonymity and easily provide participation incentives. Also, these three social media platforms were also used to recruit participants to our study site, as we would periodically ask followers of these social media outlets to participate if they had an ACS event or knew someone who had had an ACS event; again a viral-type effort. Despite the study having ended some time ago, I still maintain the Facebook page and still post 2 to 4 items per week, depending on the number of people reached by the post—if it is something that is very popular at the moment and/or something that the individual can do to modify their heart health or risk, I may run it a full 7 days, but rarely does a Facebook posting have 7 day legs.

The Comments and "Other" Response Options

Whereas participation in the YHS was anonymous, some participants chose to provide us their email address in the event we needed more information or, surprisingly, if we wished to know the name of the hospital where they were treated to obtain their medical records. This offering was bittersweet, considering my effort to protect their anonymity and the SDR difficulties noted earlier. In the YHS, 271 participants left additional comments. In the Bethesda study, either my coinvestigator or I, or nurses in the Columbus study, had written detailed narratives for each study participant [18]. These were useful in understanding the behaviors and reasons for patient's actions as well as for developing the YHS survey instrument. The Comment section in the YHS survey and the "Other" response option in almost all questions provided useful information to supplement or clarify time calculations and event sequences.

How Did We Do in Recruitment, Final Yield of Participants, and Reasons for Noncompletion

Web Ad Stats

From June 1, 2011 to October 31, 2013, using Facebook, Google, AOL and Yahoo or Bing, and their families of websites, we displayed 279,834,651 impressions of YHS ads that generated, we believe, the vast majority of the 124,795 clicks to the YHS website since November 28, 2011, when we began tracking website hits; we tracked YHS Web activity for 1 year, 11 months, and 4 days or 704 days. During this tracked time, we averaged 177.3 hits per day to the YHS site. Over the total course of recruitment, which spanned 884 days, or 2 years and 5 months, we averaged 2.7 sign-ups per day to participate, meaning potential participants clicked to the YHS website, clicked on the button indicating they wanted to participate after reading our study description, consented to participate by clicking on an "Agree" radio button, read an instruction page detailing variations in page format and how to get definitions of medical terms, created a personal identification code, and progressed to the first question of the YHS survey. It was interesting that not unlike any Web vendor on the Internet, the YHS study had about the same ratio of clicks to the site for each completed survey as a vendor selling items on the Web.

There was one major 6-month interruption in data collection because of an administrative matter, discussed below, when no Web ads were run, and fewer library or senior center solicitations were sent out. During our two fully funded periods, we signed up 4.5 participants per day, in contrast to our unfunded period when sign-ups dwindled to 0.53 per day. There was a natural nonfunded period at the end of the study; because the YHS still had a presence in libraries, senior centers, rehabilitation clinics, and on blogger websites, the YHS website remained up for 184 days after funding had ceased to support RAs, printing, and Web ads. The IRB approval remained effective during this period. During this 184-day period, 81 additional participants or 0.44 participants signed up per day. What was curious was that during the periods when we posted no Web ads, the quality of the data actually improved, meaning that there were far fewer noncompleters than during fully funded advertising periods. We speculate that these participants were highly motivated and perhaps put off their actual participation until a later time, whereas during funded advertising periods, we attracted more persons just exploring our website.

What was obvious to us was that the most consistently productive recruitment method out of those we used was ads posted on Web on the four social media providers, Facebook, Google, AOL, and Yahoo or Bing. We spent US $112,303.98 in advertising on ads placed on these four providers. In constructing our social media ads, we found that the most effective ads were those that appealed to the "altruistic sense" of a potential participant. Our most successful ads, determined by how many clicks they received and the click-through rate—seeing the ad and then clicking through to the study website—had some variant of the following: title: Yale Heart Attack Study; ad text: Help Others by Sharing Your Heart

Attack Experiences; and a radio button to click to the YHS website. We tried many ads, even seasonal ones, but none worked better than those with an altruistic appeal.

This leads us to consider how many individuals actually completed the YHS survey and how many usable surveys were actually obtained. Of the 2381 who signed up on the YHS site, 1886 progressed beyond the sign-up and first question, "Before your most recent heart attack, had a doctor ever told you that you had heart problems?," and 1208 completed the survey by sharing their demographic characteristics at the end of the survey, which was our gold standard for completion. More importantly, 1154 provided sufficient information regarding the primary dependent variable of total time from acute symptom onset to ED arrival. The first cut of the 2381 participants was made at the first question that needed to be answered to progress in the survey, and thereafter, participants dropped out until the end of the questionnaire. Total time computations presented issues where participants would complete all of the survey but leave most time designations blank; participants who only provided certain time information but not enough to compute total time; and participants' whose time information did not allow for an accurate computation or was confusing with regard to the time of the day or the actual number of hours or days. The computation of total time was supplemented in 218 cases from information provided in the "Other" responses and "Comment" section. When none of these information supplements were available and a coherent timeline of events could not be constructed, participants were removed from the analysis.

Nine Reasons for YHS Survey Noncompletion

So why did we have a completion rate of just 48%, when it took quite a bit of diligence to sign up, which in turn should have made a potential participant feel committed to finish? There are several reasons why potential participants may have seemed committed to participating but failed to advance to the end of the survey.

First, it is possible that despite the fact that we say we are interested in people's heart attack care-seeking behavior, some people may have thought we were a study of the "heart" that might have some useful information for them about heart health, research findings, and the like.

Second, they are just curious about what might be behind the wall and registered only to find that the first question was about whether they have heart disease and stopped, although to get that far they must have seen what we were about from the study description, consent form, and navigation instructions.

Third, some people registered and decided they would complete the survey later only to forget their initial personal registration code. So, they reregistered, leaving us with one incomplete survey, as described above, and just did not feel motivated enough to do it all over again.

Fourth, they felt that being asked whether they had a heart disease was not a good way to begin a survey, and they stopped immediately because they found the question threatening, and/or the survey aroused feelings of PTSD that were still prevalent from the ACS event in question. In covering identical material in face-to-face interviews, I realized that at times it was difficult for patients to answer questions about a life-threatening experience; it was as if they were reliving it all over again.

Fifth, there may have been survey fatigue. It was a long survey for some participants, although the self-tailoring design did reduce fatigue somewhat. Furthermore, it was almost halfway through the YHS survey, after the medical history and ACS warning symptom sections, before they arrived at questions about the ACS event itself.

Sixth, although we carefully designed the YHS instrument to download and upload quickly, computers and connections may not have been fast or reliable enough to sustain a reasonable pace of progression, and participants may have become impatient or disconnected.

Seventh, in terms of care-seeking time entries, participants may have been unable to recall times for an event that may have occurred sometime before; some participants told us they became unconscious and were not aware of time, although there were some indications that in these circumstances participants had consulted with someone else to complete the survey. If no total time calculation could be discerned, participants were not included in the analyses.

Eighth, some individuals attracted to the YHS might not have been aware of what it means to participate in a research survey study and were not prepared for the experience in terms of the demands to recall a potentially life-threatening event, to read numerous questions, and to select among many answer options and checkboxes.

Finally, there may have been an "easy come, easy go" mentality. That is, potential participants found us, but they had no commitment to us. After all, we did not personally reach out to them, and they just as easily left us at the slightest distraction, interruption, discomfort, time pressure, or whatever deterrent broke their bond of connection to the screen reaching out to take their ACS experiences, even though they might have felt that they were helping others. The type of engagement that Web-based research creates maybe just too ephemeral to sustain without the existence of a personal bond between a participant and an interviewer. Web-based research efforts need to be aware of that balance between the comfortable security of anonymity and our investment in creating a bond strong enough to sustain them through to survey completion.

Distractions, Impediments, Delays, and Unsuccessful Recruiting Techniques

As already noted, there were many impediments to launching and to completing the study on time. Here are the most significant contributing factors for delays, some distractions that were unexpected, and some seemingly useful recruiting techniques that, in fact, failed.

The "No Cost Extensions"

Due to the many impediments and delays described above, it was necessary to apply for no-cost extensions (NCE) from NIH. This meant that my projected time to complete the study had

run out. We could do the study in 3 years, but at the end of 3 years, I was not finished collecting data; however, I still had funds to continue the study. So, one asks for an NCE to continue working. Rumor has it, and it was confirmed, that the first extension is easy, but the second extension is much more difficult. The rumors are true; the first one was merely a signature on a form. However, the second NCE required undertaking an extensive reapplication, and there was a full 2.5-month delay until it was finally approved. Interestingly, no one at YSN or Yale's Grants and Contracts office would approach NIH about the lost 2.5 months that were subtracted. Apparently, time being cut is just part of the process, especially on a second NCE request. Additionally, even more delay was experienced when I asked for the unprecedented third NCE.

The first NCE had no effect on data collection because it occurred before launching the YHS website. To some extent, the second NCE did not cause any disturbance in data collection either. Since there were sufficient funds remaining and the prospect of a second NCE was probable, we were lent the funds by Yale to continue data collection as we had just begun in June of 2011, and the approval was given in July of 2011.

We had built up full momentum by the end of the study's second NCE period. We were attracting potential participants to the YSN website, we had established a network of reciprocating websites and organizations whose focus was cardiovascular disease and heart health, we had a routine getting out our materials to libraries and senior centers, our Web ads were getting above-average hits for a noncommercial entity, and our efforts to reach out to other media, essentially health bloggers and organizations with target populations of interest, were successful and expanding.

As it is rare to obtain a third NCE, YSN was not going to front the YHS despite the remaining funds, and as NIH was going to lay a heavy penalty by delaying approval of the third NCE, we essentially closed for 6 months. Personnel were let go and one assistant was retained from funds from internal sources for 2.5 months, and I took over the outreach to senior centers. Emphasis on senior centers had an unanticipated benefit; we were in need of older participants, and during this 6-month period, we were able to raise the average age of study participants by 1 year.

As we did not have funding during the penalty period, I could not advertise for or interview an RA in anticipation of an approved third NCE application; funding needed to be in hand. The absence of Web ads during the NCE application period severely diminished the number of clicks to the YHS site. Enrollment continued but drastically reduced from 4.5 per day with funding to 0.53 without. I assume that these later enrollments were in response to flyers that were still posted in libraries, senior centers, and other places; Web-based banners and box ads; and from the followers on Facebook, Twitter, and the YHS blog. During the unfunded periods, I continued to respond to questions from various people who wanted information, responding to Facebook postings, and screening YHS blog comments that were mostly from companies trying to gain publicity by posting a comment, which usually did not have anything to do with the YHS blog content. We discontinued sending out requested materials because of a lack of funds for printing and postage.

After approval, when the third NCE finally came through, it took 2 weeks to regain prior enrollment rates. However, if there was any benefit from being unfunded, it derived from the ads appearing new to both new information seekers and to those who were previously ad fatigued, who may have seen ads anew when we started up again. Web providers must have a priority for taking on new advertisers, and we were placed at the end of the queue and had to work our way back by bidding above going rates to place our ads on the first Web search page.

I Want to Join Your Study

I do not know if this is a common occurrence in Web-based studies, but 3 physicians wanted to join the study and become an integral part of the team after coming across our YHS ads. Their entrance ticket was to be access to their population of patients who had experienced an ACS event. One wanted to be included in publications, and another was much more explicit in this request, needing publications for an upcoming tenure review. The more subtle approach merely mentioned collaboration and merging of datasets. My response ranged from "this is impossible as I already had a complete team, including a cardiology consultant," to "I can set up an alternative website to collect data and you can send your patients to the site, but I have no funds for your personnel to cull names from your medical records." Needless to say, no one followed up on my offer of another website and the use of their personnel to generate the list of potential participants.

Illness of a Research Assistant and Unions

The restrictions of union hiring were evident again when a key RA required emergency surgery shortly after being hired. She needed to recover for several weeks, and the process of hiring a new RA would have been almost as long as the projected recovery. Thus, for several weeks we were without any canvassing of public libraries. However, on the up side, the assistant became highly motivated and extremely productive upon returning; perhaps they were not feeling well during the period before their surgery. As a result of this increased productivity, we were able to meet our goal of sending to every public library in the country, for which we could locate an email address, our solicitation package.

The Evolving Internet Environment

The nature of Web advertising changed over the course of the study and when the YHS website was taken down. More tracking techniques became available; for example, if one currently entered on Google or AOL the term heart attack, for the next month everywhere you surfed on the Web, our ad would have appeared encouraging and soliciting participation in the YHS. We did not have the resources to pursue tracking techniques early on when they were developing. I do not know if currently people find these tracking techniques annoying enough to discourage participation in a Web study.

Unsuccessful Techniques

We tried contacting restaurant associations in each state to see if they would send out a newsletter item about the YHS and

whether members would be willing to post our materials on the bulletin boards one commonly sees filled with local tradesperson's business cards and flyers for pancake suppers. This did not prove to be effective as hardly anyone returned our calls and, of those who did, no one agreed to participate.

Modifying the YHS Instrument

Suggestions to modify the survey were met with much more consideration of scientific design and integrity; for example, adopted participants in closed adoptions could not answer whether they had heart disease in their family or if anyone had heart disease before the age of 50 years, which is a significant risk factor. Since genetics and lifestyle are both a part of risk, it is difficult to know what was ultimately more important a factor, family of orientation or birth family. As a compromise, a "Do not know" was added as an option. Also, one person wrote indicating they could not progress in the survey. I went to their survey and tried to determine why they were having the problem. As it happened, 2 questions back they may have entered an incorrect response by mistake, thus limiting access to where they thought they should be going given how they had answered prior questions; they had great insight into the logic of the self-tailoring algorithm. I wrote the participant with the solution but did not check to see if they followed up, as I wanted to maintain their anonymity as best I could.

No one in the Comments section commented on our advertising or suggested alternative approaches. Aside from 3 comments regarding questions in the survey, we received no criticism about the survey except that some sections seemed repetitious and they were as we wanted to know, for example, what did lay others advised in each care-seeking phase and we also wanted to know what self-treatments were used in all phases except the travel phase. In both cases, among others, all questions were identical, and if one experienced all care-seeking phases, the repetition was more than obvious. As noted above, fatigue may have set in, and repetition of questions may have encouraged discontinuation.

Spammers Effect on Web Studies

Cyber-war defenses to keep professional spammers from capturing names and email addresses from Web pages and Web page directories placed many barriers in our path. These efforts ranged from not posting vital emails to not allowing us to copy from websites vital information for contacting library and senior center directors. Thus, as noted, we sometimes relied on city managers among others as sources of information. As the cyber-wars have advanced, this type of study, with a national focus, may be more difficult to mount without major assistance from professional Web marketing organizations. However, noting that California had the most barriers to email access than any other region of the nation, it would seemingly be difficult to find one approach or technique that could sufficiently overcome a myriad of defensive barriers.

Personal Computers and Laptops, But No Mobile Phones

At the time I entered the Web ad world, ads on a mobile phone were just beginning to appear. I accessed our study website on a mobile phone and decided that the tiny image of our survey was far too small for our target audience to complete on a mobile phone. So, we only placed our ads on desktop and iPad-type devices. As mobile phone screens have increased in size and clarity, it may now be more appropriate to consider advertising on such devices and to modify a questionnaire to fit on mobile phone screens.

The End Was Near

As we neared the end of our final budgeted period, we calculated a spend rate that would provide one final bump in potential sign-ups. This was effective as website hits increased. However, the hits were not by persons likely to participate, and the noncompletion rate was higher than when no funding was available and potential participants were driven by flyers in libraries, senior centers, and rehabilitation centers. So, higher nonparticipant hits or noncompleters may indicate that broad advertising is not the most economical means of reaching a target audience. Obviously, access to lists of discharged ACS patients would be the most effective targeting. But such a focused list again has its own regional, hospital, medical practice, and EMS biases and limitations.

Lessons and Assessments and Final Comments

Are Web Surveys Worth the Cost?

In the prior ACS study [18] conducted in Columbus, Ohio, using 6 nurse interviewers, we obtained 1102 analyzable interviews from 1317 eligible hospitalized patients who were recruited to participate in an interview covering their ACS care-seeking experiences; 11 refused and the remainder died before the interview. Which is the better technique for studying ACS events, face-to-face interviews or the Web? It is very difficult to say, given the nearly equal yield of study participants—1154 in the YHS. However, the quality of the data may have been a bit better in the Columbus study because some questions in the YHS were not answered or left blank where the type of question asked should have yielded a response—not an unusual occurrence in Web-based studies [19]. It is much easier to disregard a Web-based question than resist an interviewer armed with alternative ways to ask a question and a look of disappointment when the participant does not answer. On the other hand, we do not know how much the desirability factor affected results in the Bethesda and Columbus studies. In terms of monetary costs and adjusting for inflation [20], the YHS was approximately 31% less expensive than the Columbus study.

Representativeness and Sampling Quotas

Overall, we did not achieve our sampling quotas derived from the NHANES, as described above. The sample we did collect, 1154 participants, differed from the NHANES-derived quotas, especially among elderly (>74 years), but the overall differences were not statistically significant in terms sex and age distributions from 2314 participants needed to test the ISCM.

In terms of African American representativeness, I do not believe an Internet-based study is an appropriate platform for their recruitment, despite opinions that the digital divide is closing regarding race and ethnicity [21].

Web Surveys Are Time Consuming to Develop and Complete

As noted, conducting a Web-based study can be very time consuming, especially the development of the survey instrument and having it hosted and supported. The YHS was relatively complex and long and required more time than what most participants are willing to spend on a Web-based survey, which is about 20 min [22]. Those who finished were probably more motivated and thus may represent a biased sample of individuals who have come to have a coherent story of what happened to them and are somewhat computer knowledgeable. More importantly, individuals who do not have a coherent sense of what happened to them or those for whom the structure of the YHS survey did not resonate with their personal experience of events were lost to us when they did not finish the survey.

Grant Transfer

I would not suggest transferring an NIH grant from one institution to another. I had the impression that the institution losing the grant was not pleased and neither was NIH with the extra administrative work. I probably should have appealed the decision of the IT director at the Department of Sociology and left the study website at OSU.

Libraries, Senior Citizen Centers, Cardiac Rehabilitation Centers, and Email "Blasts" and Upticks

In general, noting how only a few participants signed up to take the YHS survey when we were not running Web ads, our efforts to place flyers, posters, and bookmarks in various venues was probably not very efficient in terms of recruitment and personnel and material costs. Email blasts by private vendors may be effective if one can do repeated blasts with follow-up emails and have access to the recipient's demographics to know who is responding and who is not. But I am not certain it is cost-effective, given how much we paid for a single blast and how few responses were received. As Web-based surveys evolve, as they most certainly will, perhaps we will be able to obtain a more accurate sense of what is cost-effective recruitment.

Final Comments

A good deal of the delays and impediments described here may be the fact of just trying to conduct a Web-based study at the time I began. I was asking for a relatively conventional, and perhaps conservative, environment of YSN to accept a research design where the buying of Web ads was especially prominent, and I was an unknown entity to Yale. Given these issues, and the perspective at YSN that the grant was given to Yale to be managed and executed by them, with me as an employee, rather than the grant being given to me and the team to be conducted at Yale with their support and assistance, I guess things did not go too badly. My logs show that I contacted 35 separate individuals to finally get the study up and running. I do not know how less encumbered the YHS should have been. I only know that my two prior efforts in Bethesda and Columbus did not seem at the time as challenging. All totaled, it took 3 extra years to collect the YHS data.

Finally, from my viewpoint, I did learn a great deal in the execution of the YHS, and now as we begin to analyze the results, I hope to contribute to the ongoing discussion of why people delay in obtaining care for ACS events that have potential for both morbid and fatal consequences over a short period.

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Conflicts of Interest

None declared.

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Abbreviations

AARP: Association of Retired Persons
ACS: acute coronary syndrome
ASO: acute symptom onset
CPC: cost per click
ED: emergency department
EMS: emergency medical system
HBP: high blood pressure
HIPPA: Health Insurance Portability and Accountability Act
IRB: institutional review board
ISCM: integrated self-regulatory care-seeking model
IT: information technology
NCE: no-cost extensions
NHANES: National Health and Nutrition Examination Survey
NHLBI: National Heart, Lung, and Blood Institute
NIH: National Institutes of Health
OSU: Ohio State University
PTSD: posttraumatic stress disorder
RA: research assistant
SAS: Statistical Analysis System
SDR: security design review
SPSS: Statistical Package for the Social Sciences
WSJ: Wall Street Journal
WWAD: Walk with a Doc
YHS: Yale Heart Study
YSN: Yale School of Nursing

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Original Paper

Examining Factors of Engagement With Digital Interventions for Weight Management: Rapid Review

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Abstract

Background: Digital interventions for weight management provide a unique opportunity to target daily lifestyle choices and eating behaviors over a sustained period of time. However, recent evidence has demonstrated a lack of user engagement with digital health interventions, impacting on the levels of intervention effectiveness. Thus, it is critical to identify the factors that may facilitate user engagement with digital health interventions to encourage behavior change and weight management.

Objective: The aim of this study was to identify and synthesize the available evidence to gain insights about users' perspectives on factors that affect engagement with digital interventions for weight management.

Methods: A rapid review methodology was adopted. The search strategy was executed in the following databases: Web of Science, PsycINFO, and PubMed. Studies were eligible for inclusion if they investigated users' engagement with a digital weight management intervention and were published from 2000 onwards. A narrative synthesis of data was performed on all included studies.

Results: A total of 11 studies were included in the review. The studies were qualitative, mixed-methods, or randomized controlled trials. Some of the studies explored features influencing engagement when using a Web-based digital intervention, others specifically explored engagement when accessing a mobile phone app, and some looked at engagement after text message (short message service, SMS) reminders. Factors influencing engagement with digital weight management interventions were found to be both user-related (eg, perceived health benefits) and digital intervention–related (eg, ease of use and the provision of personalized information).

Conclusions: The findings highlight the importance of incorporating user perspectives during the digital intervention development process to encourage engagement. The review contributes to our understanding of what facilitates user engagement and points toward a coproduction approach for developing digital interventions for weight management. Particularly, it highlights the importance of thinking about user-related and digital tool–related factors from the very early stages of the intervention development process.

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KEYWORDS

weight loss; obesity; patient engagement; self-help devices; health technology; eHealth; mobile apps; patient adherence; review

Introduction

Weight Management and Digital Technology

Globally, 39% of the world's adult population is overweight, and 13% is obese [1]. These rates are increasing, and it is estimated that more than half of the adults will be affected by obesity by 2050 [2]. Obesity is most prevalent in westernized societies such as England, the United States, and Australia. For example, England has one of the highest rates of obesity, with an estimated 62% of the adult population being either overweight or obese [3]. It is well established that obesity is linked to the development of a range of health problems, including type 2 diabetes, coronary heart disease, musculoskeletal disorders, some cancers, and stroke [1,4]. In the United Kingdom alone, this costs the National Health Service in excess of £5 billion per annum [5], and costs arising from the impact of obesity on the wider UK economy (such as loss of productivity) are estimated to be up to £15.8 billion per year [6].

Although a number of interventions for obesity are available (eg, pharmacological treatments and bariatric surgery), these are effective for only a small proportion of the obese population [7]. In addition, these interventions are both costly and associated with a number of adverse physical and psychological effects, including kidney damage [7] and an increase in depression and anxiety [8]. Furthermore, these interventions fail to account for the complexity of eating behavior and the need to promote widespread changes in both diet and physical activity [9]. To initiate and maintain behavior change within overweight and obese populations, interventions must acknowledge the environmental, physiological, and motivational processes that regulate eating and physical activity behaviors [10-13]. However, reported interventions aimed at targeting obesity have had little or no effect on the mounting challenge [14]. Indeed, those who successfully lose weight are likely to regain one-third of the weight lost within the same year and often return to their baseline weight after 3 to 5 years [14,15]. Consequently, there is a clear need for interventions that are able to target daily lifestyle choices (including eating behavior and physical activity) over a sustained period of time.

The need to monitor behavior continuously is crucial for effective behavior change [16]. Therefore, interventions using digital technology may provide one mechanism by which healthy behaviors related to weight management can be targeted throughout a 24-hour period. A digital intervention is a program which aims to offer guidance, information, and support for a variety of physical or mental health programs via a digital platform [17]. Such platforms may take the form of websites, mobile phone apps, or text messages (short message service, SMS). Previously, digital interventions have been successfully developed to help with a number of health-related issues, including the self-management of long-term conditions such as diabetes [18,19], reducing alcohol intake [20], and promoting physical activity [21]. These tools have the potential to provide an attractive method of prompting users to not only change but maintain behaviors with minimal professional contact [22]. As such, digital health interventions are able to provide not only 24-hour availability to self-monitoring statistics, personalized information, and online social support networks but also great affordability, thus, affecting sustained significant change in both a cost- and time-effective manner [23].

Although there has been an increasing interest and investment in digital health interventions [24], their full potential is yet to be realized mainly because of their inability to engage the user into effective and sufficient use [25]. Although user engagement is arguably one of the most important factors in determining the success of an intervention, there are multiple definitions of the construct in the literature. For example, O'Brien et al [26] define user engagement as a quality of users' experience with technology that is characterized by attributes of challenge, aesthetic and sensory appeal, feedback, novelty, interactivity, perceived control and time, awareness, motivation, interest, and affect. Yardley et al [27], through a process of expert consensus, conceptualized engagement as a dynamic process that usually starts with a trigger (eg, health professional or peers' recommendations), followed by initial use, and then possibly followed by sustained engagement, disengagement, or shifting to a different intervention. As currently there are no agreed definitions nor validated theoretical models of engagement, for the purposes of this review we adopt a generalized approach that operationalizes engagement as the extent to which people use the digital intervention as intended [28]. The included studies in this review either do not provide information on or they use a variety of engagement definitions. In addition, it is quite often argued that effective engagement should be defined in relation to the purpose of the specific intervention and established empirically in the context of the intervention [27]. Thus, we feel that a more specific definition would be too restrictive for the purposes of this review.

Aim of the Review

It has been shown that a lack of user engagement with digital health interventions may result in low levels of effectiveness [29-31]. Therefore, improving user engagement with digital tools might result in more effective use and better health outcomes. Thus, it is critical to understand how to better engage potential users with digital health interventions. As different health behaviors are likely to require different engagement strategies [27], this review is focused on weight management and aims to examine users' perspectives on contributors that are likely to influence engagement with digital interventions and also encourage continued use. Overall, this rapid review aims to synthesize findings from published research to identify possible facilitators and barriers or inhibitors of engagement with digital weight management interventions.

Methods

Rapid Review

In recent years, there has been an emergence of rapid reviews within health technology assessments [32]. However, currently, there is no agreed guidance or methodology for rapid reviews. Rapid reviews tend to differ from systematic reviews, in that they are conducted within condensed timelines but follow the main principles of systematic reviews or preferred reporting items for systematic reviews and meta-analyses (PRISMA)

guidelines, such as an explicit and reproducible methodology, a systematic search, and a systematic presentation [33]. In the absence of clear guidance, the Cochrane Rapid Reviews Methods Group [34] has been formed to better inform rapid review methodology. Overall, rapid reviews tend to have the following characteristics: they are quicker than systematic reviews (approximately 6-8 weeks); the research question is specified a priori (may include broad PICO [population/patient, intervention/indicator, control/comparator, and outcomes] criteria); sources may be limited but sources or strategies made explicit; exclusion or inclusion criteria are defined either a priori and/or post hoc; they involve rigorous critical appraisal; they may include various depths of syntheses, for example, narrative synthesis and mapping or categorization of the data; and they involve cautious interpretation of the findings to answer the research question. The above methods have been framed based on a number of methodological reviews [35-37]. Given the lack of formal guidelines, this rapid review closely followed the above framework, incorporating when possible some of the established PRISMA guidelines for systematic reviews (eg, reproducible methodology, systematic search, and presentation) while maintaining the timely manner of rapid reviews.

The rationale for conducting a rapid review arises from a need to answer the specified research question rapidly and efficiently. Whereas systematic reviews may provide a comprehensive synthesis of the data, they are often time consuming and costly to produce. Furthermore, as the field of digital health is constantly evolving and because of the speedy technological advances [24], there is a clear need for rapid reviews to draw relatively rapid conclusions about a specific research question. This rapid review also forms part of the formative work for the development of a novel digital health intervention.

Search Strategy

An electronic literature search was performed using the following databases: Web of Science, PsycINFO, and PubMed. The search was limited to studies published from January 2000 to October 2015. Earlier papers are not deemed relevant to this review because of the rapidity of technological development. Due to limited time and resources available for translation, only articles published in English were included. For each database search, seven key terms (adherence, engagement, motivation, Web-based, mobile, weight, and intervention) were used to create search criteria by combining terms with either the “OR” or “AND” operator (ie, adherence OR engagement OR motivation AND Web-based OR mobile AND weight AND intervention). In addition to electronic searches, manual searches were conducted by screening reference lists of included studies.

Selection Criteria

Studies were eligible for inclusion if they investigated users’ perspectives on engagement with a digital weight management intervention. Studies with interventions, including digital components alongside nondigital components (eg, associated paper copies of toolkits) were included. Those examining intervention effectiveness but not investigating any aspect of engagement with the intervention were excluded from the review, as were articles where a full text or extractable summary could not be located. We focused on studies that drew their samples from Western societies for two main reasons. Cultural differences can affect individuals’ health beliefs and consequently their health care participation [38,39]. In addition, others have suggested that cultural differences may impact on digital engagement, and so, geographical and cultural differences need to be taken into consideration [40,41]. Finally, as age differences can impact on adoption of technology and user preferences [42,43], any studies using particularly young samples (16 years and under) were excluded.

Article Screening

One reviewer (ES) screened titles and abstracts using the inclusion and exclusion criteria. When there was uncertainty, a second reviewer (EK) was also consulted. The raters achieved 90% agreement [44]. Disagreements were discussed and resolved by consensus [45]. Full texts of potentially eligible studies were then screened by the first reviewer (ES) and verified by the second reviewer (EK).

Data Extraction and Synthesis

Data were extracted from relevant publications by one reviewer (ES) using a specially designed data extraction form that was developed according to the Centre for Reviews and Dissemination [45] guidance. The data extraction form collected information on the characteristics of each study, the results as reported by the authors, and key messages (focusing specifically on information relating to facilitators and barriers of engagement with digital weight management interventions). Data from each study were tabulated to compare and aggregate methods, sample characteristics, and research outcomes. Due to the variability in study designs, a narrative synthesis of the data were conducted.

Quality Assessment

For the purposes of this study, the short electronic health (eHealth)-specific Quality Assessment Checklist was used. The checklist was adapted for the requirements of the rapid review based on the eHealth-specific Quality Assessment Checklist that was originally developed by one of the authors for eHealth-related systematic reviews [46]. The eHealth-specific Quality Assessment Checklist followed the Centre for Reviews and Dissemination [45] guidance, with specific focus on publication-specific contextual, practical, and methodological issues associated with studies describing digital interventions or apps. Studies were assessed according to up to 8 criteria (depending on study design and focus): clear description of purpose, appropriateness of study design, primary methods, digital intervention development process, theoretical frameworks used, users’ description, access, and digital intervention description, including access requirements and intervention components (see Multimedia Appendix 1). No publications were excluded from the review based on quality. This form was independently tested by 2 reviewers (ES and EK) who achieved 91% agreement. Disagreements were discussed and resolved by consensus [45].

Results

Study Selection

Figure 1 shows the results of the screening process. Searching the electronic databases yielded a total of 362 records of which 10 articles met the inclusion criteria. One additional study was identified through reference list screening.

Quality Assessment

The quality of the papers included in this review varied (see Table 1). Although the majority of included papers investigate users' engagement with specific digital interventions for weight management, two examine general factors likely to influence engagement with digital weight management interventions [22,47]. Consequently, some of the quality assessment rating items were not applicable to these studies (eg, quality criteria relating to the development process and theoretical underpinning of specific interventions), and thus, they have a maximum quality rating of 4. All other included studies have a maximum quality rating of 8. No studies were excluded based on their quality score or their study design.

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of study selection process.

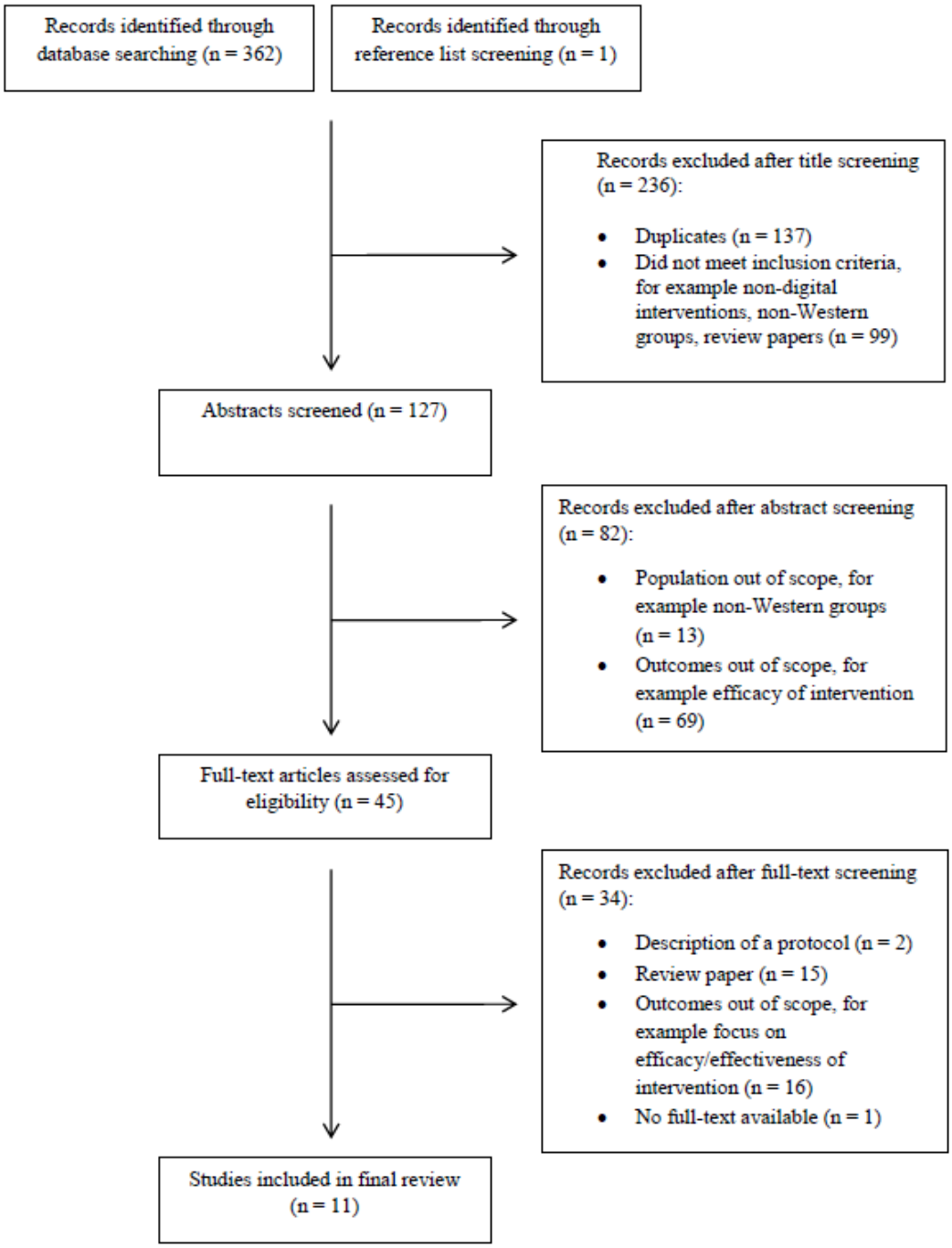

Table 1. Main characteristics and findings of included studies.

Study	Study design	Quality rating	Digital intervention	Sample	N	Main findings
Brindal et al, 2012 [50]	RCT[a]	7/8	Web-based total well-being diet; targets weight loss. 3 groups: 1. Information-based: dietary and activity-related information provided in a static noninteractive format. 2. Supportive: social interactive website (offers social support in addition to basic information). 3. Personalized-supportive: supportive version with a personalized meal planner.	Adults (18 years or over), BMI[b]>25	8112	Inclusion of social networking features and personalized meal planning did not promote user weight loss or retention but increased average number of user engagement days. In the supportive website, greater use of weight tracker tool led to greater weight loss.
Collins et al, 2013 [51]	RCT	7/8	12-week Web-based weight loss program: The Biggest Loser Club. 1. Basic program: targets self-efficacy, goal setting, self-monitoring, outcome expectations, and social support. 2. Enhanced program: includes all basic features plus personalized features (in response to a behavioral survey), weekly personalized feedback, and an escalating reminder schedule.	Adults (18-60 years), BMI 25 to 40	301	Personalized e-feedback in the enhanced program provided limited additional benefits compared with a standard Web-based weight loss program. However, it supported greater engagement or greater usage, which was related to weight loss.
Dennison et al, 2014 [54]	RCT	8/8	Web-based management intervention: POWeR. • Aims to empower users through the development of new self-regulation skills. • Coaching calls used to promote continued usage of the POWeR website and adherence to the recommendations within the website.	Adults, BMI>23	786	Usage of POWeR was poor. However, supplementing Web-based weight management with brief human support improved adherence and health outcomes.
Gorton et al, 2011 [47]	Mixed-methods study	4/4	Telephone survey (comprised questions exploring the nature or acceptability of any potential mobile weight loss program). Focus groups explored issues of acceptability.	Individuals over 16 years	306 survey, 54 in focus groups	Participants valued ready access to weight loss information, along with customized feedback and encouragement. Social support, tailored content, and practicality were also identified as features likely to predict engagement.
Lyden et al, 2013 [48]	Qualitative study	6/8	Web-based evidence-based lifestyle intervention.	Adults, BMI>25	50	Participants valued Web-based lifestyle coaching, self-monitoring tools, and structured lesson features. Moderated chat sessions and Web-based resources were rarely used.
McConnon et al, 2009 [55]	Questionnaire-based evaluation of an RCT	8/8	Web-based weight management intervention. • The website encourages healthy lifestyle changes, provides information, tools, and support on nutrition and physical activity, as well as behavioral components.	Adults (18-65 years), BMI>30	111	The support sections were used least often and rated most negatively by users. However, poor Internet access may have limited use, thereby reducing the support available to participants.

Study	Study design	Quality rating	Digital intervention	Sample	N	Main findings
Mhurchu et al, 2014 [56]	RCT	8/8	12-week weight management program. Comprised of 3 modules (designed to be integrated): 1. Text messaging: Participants sent an average of 2 texts per day over the intervention period. All messages were personalized or tailored toward specific needs (eg, whether they had children). 2. A hard copy toolkit: served as a source of detailed information (able to support personal plans and behavior monitoring). 3. Website: provided a blog to enable participants to share their stories and experiences.	Adults, BMI>25	36	Participants reported that they valued text messages; they found them motivational and liked their clear practical tips and reminders. However, others indicated that they found the messages impersonal, generic, or repetitive.
Morrison et al, 2014 [49]	Mixed-methods study	8/8	POWeR Tracker (weight management app) and POWeR (Web-based weight management intervention). Offers a flexible to foster autonomy and support users to adopt healthy behaviors.	Adults (18-52 years), BMI>23	13	Participants found it convenient to access information on-the-go via their mobiles compared with a computer. However, participants varied in their usage of the Web- versus app-based components.
Patrick et al, 2009 [53]	RCT	7/8	The intervention included personalized short message service and multimedia messaging service messages (sent 2-5 daily) and phone calls (monthly) from a health counselor.	Adults (25-55 years), BMI>25 to 39.9	65	Overall, satisfaction with the intervention was high. Specifically, users found texting their weight every week useful, as it "kept them focused."
Tang et al, 2015 [22]	Qualitative study	4/4	Semistructured interviews to explore participant experiences of using weight loss apps.	Adults (18-40 years)	19	Participants valued an attractive user interface. Structure, ease of use, personalized features, and accessibility (including dual phone-computer access) were important, and users indicated that continued use depended on these features.
Watson et al, 2015 [52]	RCT	7/8	Imperative health consists of a Web-based program. • Designed to assist with lifestyle change (specific focus on diet and nutrition, physical activity, and managing weight).	Adults (over 18 years), BMI 27 to 40	65	Interactivity was essential for engagement. Indeed, the authors argued that the provision of individualized support rather than automated feedback may have helped engagement levels.

[a]RCT: randomized controlled trial.

[b]BMI: body mass index.

Two of the included papers provide a qualitative investigation of specific factors leading to increased engagement [22,48]. Both articles achieved high quality assessment scores, with one achieving 6 out of 8 [44] and the other achieving 4 out of a possible 4 [22]. Two papers explore factors facilitating engagement using a mixed-methods approach [47,49], achieving scores of 4 out 4 [47] and 8 out of 8 [49]. The remaining seven papers are randomized controlled trials (RCTs) and achieved relatively high scores ranging from 7 to 8 out of a possible total score of 8. The average quality rating for studies exploring factors influencing engagement with a specific intervention was 7.33 (standard deviation [SD] 0.71). The mean quality score for studies investigating user engagement with a hypothetical digital weight management intervention was 4 (SD 0). Four out of nine papers lacked information about the intervention developmental process [48,50-52], and one paper lacked information about the theoretical underpinnings used to support the design of their digital intervention [53].

Characteristics of Included Studies

The characteristics of studies included are summarized in Table 2. Two studies provided a qualitative investigation of the factors that motivate use and encourage engagement with digital interventions for weight management [22,48]. Two studies carried out a mixed-methods investigation of the factors associated with user engagement [47,49]. The seven RCTs examined participant satisfaction and engagement after taking part in a weight management intervention [50-56]. Five of these studies explored engagement with Web-based weight management interventions, three examined participant engagement when using mobile phone weight loss apps, and three examined this when using text message reminders. All included studies were published from 2009 to 2015, with just under half of them (5/11) published on or after 2014 [52-56]. The studies were predominantly carried out in the United Kingdom (5/11) [22,49,52,54,55]. Participants in the included studies were predominately middle-aged, white, and female [47-51,53-56]. Two notable exceptions are the study carried out by Tang et al [22], which aimed to recruit young adults (aged 18-30 years) exclusively and the study conducted by Watson et al [52] in which equal numbers of males and females took part. Most participants in the included studies were in full-time employment [48,49,51,52,54,55]. However, not all the studies provided sufficient information to obtain a detailed educational or employment profile of the sample studied [22,47,50,53].

Main Findings

The findings are presented according to two key topic areas: factors that influence initial *motivation* to download and/ or use a digital intervention and those that influence subsequent *engagement* with a digital intervention. Table 3 summarizes the main findings.

Factors That Initially Motivate People to Download and Use Digital Weight Management Interventions

The review identified only one study [22] that explored why people decide to use a weight management digital intervention. Two main areas are highlighted by the study as important motivators.

Table 2. Characteristics of included studies (N=11).

Characteristics	n (%)
Type of study	
Randomized controlled trial	7 (64)
Qualitative study	2 (18)
Mixed-methods study	2 (18)
Type of intervention	
Web-based	5 (46)
Mobile phone app	3 (28)
Text message reminders	3 (28)
Country	
United Kingdom	5 (46)
Australia	2 (18)
New Zealand	2 (18)
United States	2 (18)

Table 3. Summary of the main findings.

Initial motivation factors for downloading and using digital weight management interventions	Subsequent engagement factors for enhancing use with digital weight management interventions
Perceptions of one's physical attractiveness	Personalization
Health outcomes	Social support
	Feedback and encouragement
	Ease of set-up and use
	Self-monitoring and prompts
	Accessibility of information/knowledge

Perceptions of One's Physical Attractiveness

Many users were motivated to use a digital intervention to lose weight to enhance their physical attractiveness, increase their confidence, or generally feel better about themselves [22]. In some cases, motivation to lose weight and download a digital weight loss intervention was prompted by an upcoming social situation or event for which participants wanted to look good

or fit into a specific piece of clothing. As expected, this goal-specific incentive to lose weight was linked to sustained digital intervention use and subsequent weight loss.

Health Outcomes

Improving health also appeared to be an important initial motivator for wanting to download and use a digital intervention. Specifically, several users identified concerns over health and fitness as the main reason for wanting to download and use a digital weight loss intervention [22]. The motivation to lose weight was particularly apparent if individuals saw themselves as being at an increased risk of health problems (such as diabetes or cardiovascular disorders) because of their weight or family history.

Factors That Subsequently Enhance User Engagement With Digital Weight Management Interventions

Personalization

The findings highlight the importance of *personalization* and the tailoring of interventions to individual needs and goals [47]. *Tailoring* has been described by Kreuter et al [57] as the attempt to reach one specific individual based on particular characteristics of a person that have been assessed or measured beforehand. Specifically, participants expressed a concern over digital interventions, fearing that the tool would be too impersonal. Indeed, when asked to provide follow-up details after completing a digital intervention for weight loss, the characteristics most disliked by participants centered on the generic nature and repetition of the feedback provided [56]. The personal tailoring of information given by digital interventions was also highly valued by users [22]. Interestingly, participants reported that nontailored digital interventions were difficult for them to integrate into their daily routine and expressed frustration at the lack of personal tailoring provided by most digital interventions. Finally, participants were shown to favor the use of personal targets (eg, weight loss, physical activity, and dietary targets) and found them both realistic and motivating [52].

Social Support

The importance of social support was emphasized by participants, with many suggesting that digital weight loss interventions should provide a communal aspect to enhance engagement [47]. Indeed, social comparisons may be particularly relevant for the younger adult sample studied [47]. Specifically, links to social networking, a group network, or buddy scheme were all identified as possible ways to incorporate elements of social support into an intervention. These users particularly valued the idea of being able to interact with or contact "someone in the same boat" as them. Furthermore, many participants stated that an awareness of being monitored by others also made them more likely to engage with a particular weight loss intervention [22]. For these users, social comparisons with peers increased their self-efficacy to achieve certain goals.

However, the use of social support within digital weight management interventions has generated mixed responses from participants [47]. For instance, some users reported positive experiences of chat rooms or forums, stating that talking to other users made them feel part of a bigger community, whereas others did not perceive their value. Many users felt chat sessions were not available at convenient times and cited problems with their usability (particularly if the user lacked experience using Web-based chat rooms). Indeed, some users believed that online forums or discussion boards were untrustworthy and felt that they were less likely to use or benefit from that particular feature [22]. The use of chat rooms to foster social support also received the lowest rating score by participants when asked to evaluate their experience of using a digital weight management intervention [55]. However, it is important to note that the use of the site was dependent on traffic to the website, which may have been limited by staggered recruitment into the trial. In this case, the peer support available relied on participants using the website to support each other, and when traffic on the site was low, the social support provided was minimal.

Feedback and Encouragement

Regular feedback (on both current behavior and outcomes) and encouragement has been found to be a particularly valued feature [47]. In particular, support from brief telephone coaching can enhance user engagement with digital interventions [54]. Similarly, immediate expert coach feedback has also been shown to be appreciated by many users [48]. In addition, participants were motivated to continue using digital interventions, as they hoped that the feedback provided would lead to effective and sustained weight loss. Specifically, features designed to provide daily encouragement were more likely to facilitate effective behavior change (eg, information regarding calorie intake [too high or low] and successful maintenance of weight goals) [22]. Furthermore, when asked to provide feedback after completing a digital intervention for weight loss, many participants stated that text messages were particularly motivating as they were able to provide clear, practical tips and reminders for changing their eating behavior [56]. However, as previously noted, one of the most common concerns raised regarding daily intervention feedback is that it can be perceived as impersonal, generic, or repetitive [56].

Ease of Set-Up and Use

The ability to download and navigate around the digital intervention easily was particularly important to users [22]. When the digital intervention did not seem straightforward to use, the users would describe it as "off-putting" and no longer use it. During follow-up interviews, users also stated that they valued the easiness of initial set-up and suggested that this promoted engagement [52]. Therefore, when digital tools were found to be time-consuming and burdensome, users were less inclined to persevere with the intervention. Specifically, participants noted that tasks that involved uploading and manually entering measurements were particularly tedious and were less likely to encourage adherence in the long term.

Self-Monitoring and Prompts

The provision of Web-based self-monitoring tools were particularly well received by users [48,50]. Specifically, daily feedback on eating behavior or weight loss monitoring in the form of graphs or pie charts was perceived as particularly

helpful. Self-monitoring was also valued by participants who rated this particular feature above all other components [55]. When asked to provide follow-up comments after completing a digital intervention, participants also acknowledged the importance of self-monitoring and found the use of reminders and daily weight texts especially beneficial [53]. Finally, users emphasized the usefulness of frequent notifications of reminders in facilitating effective behavior change [22]. These were reported to be particularly effective in motivating health behavior when sent as a personalized message to prompt action.

Accessibility of Information or Knowledge

Participants emphasized the need for a digital weight loss intervention to include relevant content with both practical and achievable messages [47]. They also highlighted the need for digital interventions to address the psychological aspects of weight loss, including the emotional and external factors associated with overeating. One of the main advantages participants described of using digital weight loss interventions was the fact that relevant information was "at your fingertips," and they particularly valued the flexible means by which this information could be accessed. Users also saw information about lifestyle change and behavior modification as a particularly useful feature within digital weight loss interventions [48]. Indeed, the provision of accessible links to reliable Web-based resources was one of the most highly rated features of the particular intervention.

Discussion

Summary of Results

This rapid review aimed to provide a brief synthesis of the factors that influence user engagement with digital weight management interventions. The papers included varied in design, with two providing a qualitative investigation, two utilizing a mixed-methods approach, and seven conducting an RCT. The findings revealed a distinction between the initial motivation to download and first use a digital intervention and the subsequent engagement with the digital intervention over time. According to our findings, different factors seem to influence the two phases of motivation and engagement. The first phase (motivation) where a potential user decides whether to use a digital intervention for the first time is influenced by user related characteristics (eg, self-perceptions of body and health outcomes). The second phase (engagement) where the user continues using, some or all, of the elements of the digital intervention is influenced predominately by characteristics related to the digital intervention (eg, ease of use and the provision of personalized information). Overall, the quality of the studies included in this review was high.

Factors Facilitating Initial Motivation

The findings emphasized the importance of user-related factors in an individual's initial motivation to download or visit a digital intervention with the aim of using it for weight management. In a Delphi experiment, Brouwer and colleagues [58] also found that user characteristics are important in this first phase of using a digital intervention. In the same way, recent research has demonstrated that an intrinsic motivation to better their health may encourage users to persist with a digital intervention [59]. Specifically, in this review, it was found that individuals were motivated to use a digital intervention to lose weight, improve their health, and/or enhance their perceived physical attractiveness. Expectedly, those who were motivated to lose weight were often the ones who were most successful in maintaining their weight loss [22]. As a result, it may be useful to incorporate motivational enhancement techniques to encourage use of weight interventions. Gauging participant views and attitudes beforehand may also help to predict those who are more likely to use the intervention. On the basis of the fact that the review identified only one study looking at motivation around using digital weight management interventions and as, according to the authors' knowledge, there are no related studies for other health behaviors, there is a clear need of further research to improve our understanding around motivation and its potential relationship with engagement.

Factors Facilitating Subsequent Engagement

In agreement with Brouwer et al [58], this review shows the importance of specific digital intervention features in facilitating an individual's engagement with a digital intervention. More specifically, the personalization of the digital intervention, such as providing individualized feedback and encouragement, was linked to higher levels of engagement across a range of studies [22,47,52,54,56]. This is consistent not only with more recent findings [59] but also with an earlier review suggesting that tailored advice and feedback improves user engagement with digital health interventions [60]. In addition, previous research emphasizes the association between the provision of personalized information and weight loss [61,62]. Therefore, providing participants with information specific to their individual circumstances and needs over and above the provision of generic, repetitive feedback may play a crucial role in facilitating effective behavior change. This may be achieved by obtaining detailed user information and gauging specific health and weight goals during set-up.

Access to social support (eg, peer groups) through the digital intervention was also highly valued by users across a range of studies [22,47,48]. Specifically, the availability of social support at any time and location was shown to promote engagement by making users feel valued and supported throughout the intervention [22]. The association between social support and user engagement in digital health interventions has been established in both the review by Brouwer [63] and Schubart's study [60] but not in Kelders et al's [28] review. However, it should be noted that in the review carried out by Kelders et al [28], social support referred to those interventions providing only the *opportunity* to contact others and did not measure how frequently this particular feature was used. In other words, where an intervention included a discussion board or forum, this was categorized as social facilitation, even when no posts were made. As such, not all offers of social support may have been taken up by users, which may help to explain the lack of positive association in this case. In addition, the link between social support and successful weight management is well established [64-66]. Thus, future digital interventions could benefit from incorporating a social support element into their design. Nevertheless, findings from this review revealed that social

support relies heavily on other users sharing similar views and experiences, and when the support provided from other users is minimal, its role in encouraging engagement is decreased [55]. It might be the case that the type of social support valued may differ depending on specific user characteristics. Therefore, designers may choose to make such features available but optional within future weight management interventions.

Self-monitoring features within digital weight management interventions were also associated with enhanced engagement [48,50,55]. Previously, research has demonstrated that eating behavior monitoring is necessary for effective behavior change [67,68]. However, constant self-monitoring can be monotonous and difficult to sustain. Using digital technology to prompt an individual to monitor or engage in a particular behavior may therefore provide an advantage over interventions that do not offer such features [22]. The importance of such features in encouraging continued use of a digital intervention [22,50,53] also highlights the key role of habituation in maintaining successful behavior change. In this way, daily prompts or reminders may increase the likelihood that a certain behavior becomes habitualized and incorporated into an individual user's daily routine [69]. This has also been supported by more recent research which highlights the role of prompts (specifically email reminders) in promoting continued user engagement with digital health interventions [70].

Finally, ease of using the digital interventions was found to be an important facilitator of enhanced engagement [22,52]. Notably, participants reported that they found non-user-friendly and nontailored digital interventions difficult to integrate into their daily routines [22]. Aesthetically attractive digital interventions that were easy to set up and use were among those rated most highly by users. Again, this closely aligns with recent work demonstrating a relationship between user-friendly technology and increased engagement with digital interventions for health [59]. Participants also found those that providing personal tailoring (ie, the opportunity to customize the digital intervention by changing colors and images, etc) to be more satisfying to use, and as a result, they were more likely to engage with these interventions for longer. This supports previous findings, which have emphasized the importance of personal tailoring in facilitating continued engagement with digital interventions [71]. Taken together, these findings suggest that future digital intervention designs should focus on key areas such as product functionality, user autonomy, and personalization.

Strengths and Limitations of the Review

To our knowledge, this is the first review to examine factors that may facilitate motivation to use and also further engagement with digital weight management interventions. The findings are summarized taking a user perspective and looking at the user's experiences and perceptions, thus providing useful recommendations for behavior change researchers and digital intervention developers. A key strength of this rapid review is the aim to minimize the risk of bias through the use of quality checklists and criteria (in line with PRISMA guidelines). Nevertheless, there are a few notable limitations. The review focuses predominately on samples living in Western societies, as cultural differences may influence health beliefs and engagement with one's health care and digital interventions [38-43]. Thus, even though this specific focus gives a clear picture for Western societies, the findings may be interpreted with caution to non-Western societies. The electronic literature search performed identified studies published until October 2015, so any studies published at a later date are not necessarily captured in the results of this review. However, we later performed an updated search in PsycINFO for any studies published until September 2017, and no additional studies were identified. Furthermore, as rapid reviewing is a relatively new methodology, currently, there are no agreed guidelines that may be followed. There is also a possibility that relevant literature may have been missed because of the rapidity of the search process, so a natural step following the findings of this review would be to conduct a comprehensive, systematic literature review. A framework based on relevant methodological reviews [35,37,72] is, however, available, and this rapid review closely followed this. Given the limited number of studies published in this area and the constant technological advancements, the rapid review method was deemed most appropriate. Indeed, the fast-paced nature of this review addresses a clear need to draw rapid conclusions about specific research questions within the constantly advancing field of digital health. In addition, it is worth noting that Watt et al [73] found that despite "axiomatic differences" between systematic and rapid reviews, "the essential conclusions of the rapid and full reviews did not differ extensively."

Research and Practical Implications

The findings of this rapid review clearly highlight the need for further research to better understand what motivates people in using digital weight management interventions and what makes them engage with such interventions over a sustained period of time. Such understanding will potentially come from focusing on specific groups of people because of the variety of unique characteristics and needs. For example, age—although not measured in the present review—might be a possible contributing factor warranting further research. Younger people tend to be more familiar with using technology in their everyday lives, and therefore, their needs, perceptions, and mastery levels may differ to those of older individuals who may not necessarily have integrated new technologies in their lives [39]. For this, exploratory studies using qualitative methods could be ideal in furthering our understanding in both motivational and engagement issues but also in the relationship between the two.

As currently, most digital weight management interventions fail to sustain user engagement and subsequently to achieve and maintain positive health behavior change, focus should be placed not only on effective behavior change techniques that are relevant to the health behavior of interest but also on how to enhance engagement with the intervention. The findings from this review should therefore be taken into consideration by incorporating specific features or components most valued by users when developing future digital weight management interventions. The development process could particularly benefit from an element of coproduction with key stakeholders and users and also of allowing for intervention personalization or tailoring.

Conclusions

Digital weight management interventions provide a unique opportunity to offer tailored help, support, and guidance for weight management; however, currently, the full potential of such interventions is hindered by a lack of user engagement. This review helps to further our understanding of the key issues around user engagement and points toward a coproduction approach for developing digital health interventions. Particularly, it highlights the importance of considering both user-related and digital tool–related factors from the early stages of the development process.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Quality assessment checklist.

[PDF File (Adobe PDF File), 34KB - resprot_v6i10e205_app1.pdf]

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Abbreviations

eHealth: electronic health
BMI: body mass index
PICO: population/ patient, intervention/ indicator, comparator/ control, outcome
PRISMA: preferred reporting items for systematic reviews and meta-analyses
RCT: randomized controlled trial
SD: standard deviation

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Original Paper

The Adoption of Social Media to Recruit Participants for the Cool Runnings Randomized Controlled Trial in Australia

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Abstract

Background: Using social media to recruit specific populations for research studies is gaining popularity. Given that mothers of young children are the most active on social media, and young children are the most at risk of preventable burn injuries, social media was used to recruit mothers of young children to a burn prevention intervention.

Objective: The aim of this paper was to describe the social media recruitment methods used to enroll mothers of young children to the app-based burn prevention intervention Cool Runnings.

Methods: Participants were recruited via paid Facebook and Instagram advertisements to a 2-group, parallel, single-blinded, randomized controlled trial (RCT). The advertisements were targeted at women 18 years and older, living in Queensland, Australia, with at least 1 child aged 5 to 12 months at the time of recruitment.

Results: Over the 30-day recruitment period from January to February 2016, Facebook and Instagram advertisements reached 65,268 people, generating 2573 link clicks, 1161 app downloads, and 498 enrolled participants to the Cool Runnings RCT. The cost per enrolled participant was Aus $13.08. Saturdays were the most effective day of the week for advertising results. The most popular time of day for enrolments was between 5 to 11 PM. This recruitment strategy campaign resulted in a broad reach of participants from regional, rural, and remote Queensland. Participants were representative of the population in regard to age and education levels.

Conclusions: To our knowledge, this is the first use of social media recruitment for an injury prevention campaign. This recruitment method resulted in the rapid and cost-effective recruitment of participants with social, geographic, and economic diversity that were largely representative of the population.

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KEYWORDS

social media; online recruitment; burn prevention; methods, randomized controlled trial

Introduction

More than half of the world's population now has access to the Internet, and 2.8 billion people actively use social media [1]. Social media has become an integral part of modern society. It is more than just a place for friends to connect socially; it is used for politics, education, entertainment, shopping, and health. While commercial companies were quick to see the potential of social media to reach and interact with large targeted populations, researchers were slow adopters. Increasingly, social media platforms, such as Facebook, are being used to recruit participants for health and medical research [2,3].

Facebook's ability to target advertising to specific demographics from its diversity of users offers researchers an opportunity to recruit populations that can be hard to access via traditional recruitment methods, including economically disadvantaged and geographically remote populations [3,4,5]. Globally, social media users have increased by 21% since January 2016 [1]. Facebook alone has 2 billion monthly users [6]. In Australia, approximately 70% of the population actively uses Facebook and the largest demographic are women aged 25 to 34 years [5]. Mothers with children under 5 years of age are the most active on social media [5,7].

Burns are the 5th most common cause of non-fatal childhood injuries globally [8]. Most burns to children under the age of 4 are scalds, predominantly from hot beverages [9-11]. In Australia, hot beverage scalds account for 1 in 5 burns to children—a figure that has remained the same for the past 15 years [9]. Added to this issue is the low use of correct burn first aid at the scene, despite strong evidence that burn first aid applied within 3 hours of the burn occurring provides pain relief and leads to less scarring, fewer surgical interventions, and shorter hospital stays [12]. Beyond the pain, itching, and scarring that can result from these injuries, there are also the long-term effects burns take on both the child and family. The frequent hospital visits/admissions for ongoing scar management, coping with changes in appearance, and people's reaction to the scar can lead to social and psychological problems. There are also financial costs both to the family when parents take time off work to care for the injured child and their continuing rehabilitation needs and the cost to the healthcare system. In the United Kingdom, they have reported the cost of treating a minor scald as £1850 (US $2400) [13]. In children, this figure is higher as scar management and surgical procedures continue until they stop growing.

The high physical, emotional, and financial burdens associated with hot beverage scalds make it an important public health issue. Increasing awareness regarding burn severity and frequency of hot beverage scalds, as well as correct burn first aid, is an important step in reducing the burden of this injury [14-16]. To date, public health interventions and injury prevention are areas where technology has been underutilized.

In light of the popularity of social media in mothers of young children and evidence of social media's broad reach, cost efficiencies, and capacity for targeting specific populations, social media was used to recruit mothers to the app-based burn prevention intervention Cool Runnings. The Cool Runnings app was used as the channel for delivering the 2-group, parallel, single-blinded, randomized controlled trial (RCT) over the 6-month intervention period (described in detail elsewhere). The purpose of this paper was to describe the use of social media as a tool for recruiting mothers of young children to this RCT.

Methods

Participants

Participants were recruited over a 30-day period for a 2-group, parallel, single-blinded RCT—Cool Runnings—aimed at changing knowledge about burn risks and correct burn first aid treatment in mothers of young children. The protocol for this study was published previously [17]. The inclusion criteria for this study were females aged 18 years and older with at least 1 child aged 5 to 12 months, who owned a mobile phone, and resided in the state of Queensland, Australia. Participants were recruited through Facebook and Instagram advertisements between January and February 2016. The state of Queensland is 1,852,642 km^2 (approximately 2½ times the size of Texas, or 3 times the size of France) with a population of 4.9 million.

Facebook Recruitment

Facebook and Instagram advertisements were directed to the target group described above. Facebook's Audience Insights tool was used to better understand the social and psychological triggers of the target group. Demographic filtering showed the audiences "liked" pages, lifestyle factors, education, job titles, and frequency of activities, and this information informed the approach, messaging, and strategies for recruitment on the 2 platforms. Targeted, persuasive ad copy was developed for the Facebook and Instagram advertisements. Ad sets used 2 message themes: incentive-based and emotive-based. The incentive-based messages leveraged the ability to earn rewards and win prizes to drive recruitment. An example of one of the incentive-based messages is shown in Figure 1. The emotive-based messages created an emotional response in potential participants and called out the "greater good" of participating in a study aimed at keeping children safe. An example of an emotive-based message is:

> *21 children die each week in Australia from preventable injuries! Thousands more are hospitalized. With your help we can reduce this. Download the Cool Runnings app and learn ways to protect your child and other children from preventable injuries.*

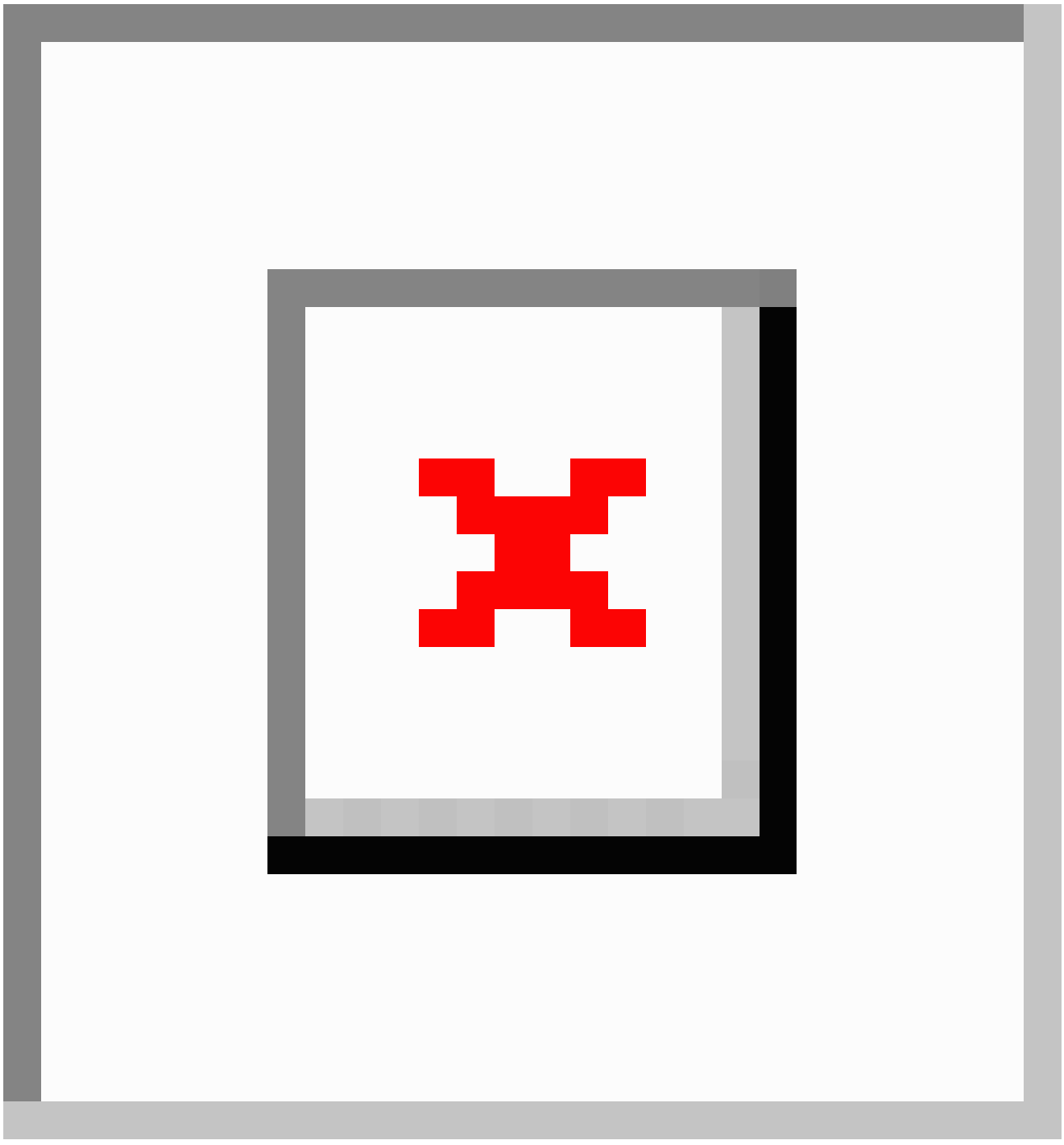
Altruistic and incentive-based messages are recognized as influential motivators in behavioral studies [18,19]. Messages that arouse emotions in potential participants and make an impact are more likely to get their attention and motivate them to take action [20]. These messages also aimed to raise mothers' awareness of the threat of injuries in young children, combined with an efficacy component to learn how to prevent these injuries. Messages that combine threat and self-efficacy components are more effective than just threat and/or fear based messages [21].

A total of 45 advertisement sets were developed, each containing different combinations (ie, device type, visual elements, message

theme, and ad placement). The variables tested were Apple (iOS) versus Android, video versus photo versus carouse, emotive versus incentive, and Facebook mobile newsfeed versus Instagram advertisement.

In total, 32 adaptations of the advertising copy were divided across the variables listed above. From the advertisements, interested individuals could click on an embedded link taking them directly to the Cool Runnings app in the Google Play or Apple App Store.

Figure 1. Example incentive-based recruitment advertisement used on Facebook.



Outcome Measures

Instagram is owned by Facebook, which allows the management of advertising campaigns and/or ad placement on both platforms from Facebook Ads Manager portal. This portal provides the following advertisement metrics: (1) impressions, number of times ads were shown; (2) reach, number of individual people who saw the ads; (3) link clicks, number of people who saw the ad and clicked through to download the app; (4) video views, number of times video viewed for 3 seconds or more; and (5) costs per 1000 impressions, per reach, per link click.

The number of Apple and Android app downloads resulting from the advertisement link clicks and the subsequent individuals who consented to participate in the study were calculated to determine the cost per participant.

Study Enrollment

Once the app was downloaded, individuals were provided with additional information about the study and given the opportunity to consent to participate. Participants completed a 19-item questionnaire detailing demographic factors (such as education level, age of youngest child, number of children, marital status, and smoking status) and level of child burn risk knowledge and burn first aid knowledge. Participants also recorded their postcode, which was later recoded using Accessibility/Remoteness Index in Australia (ARIA) 2011 data, developed by the National Center for the Social Applications of Geographic Information Systems into the categories major cities, inner/outer regional, and remote/very remote [22].

Ethics Approval

This study was approved by the University of Queensland Institutional Human Research Ethics Committee (approval number: 2015001652).

Results

During the 30-day recruitment period, 498 participants were recruited to the Cool Runnings study through Facebook and Instagram advertisements.

Participant Demographics

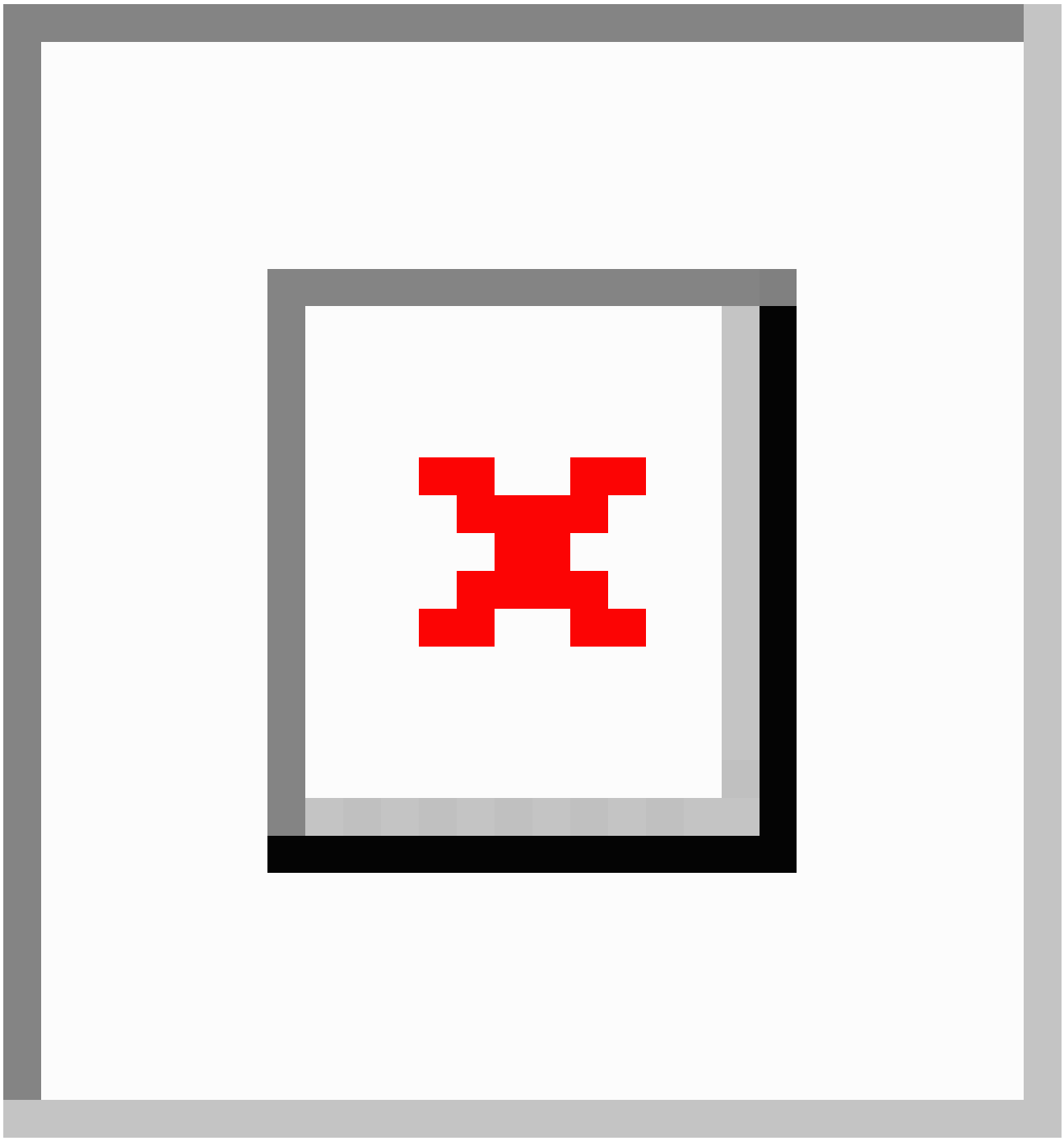
The demographic characteristics of recruited participants compared with mothers who birthed in Queensland in 2015 (the year the study was conducted), derived from the Queensland Perinatal Data Collection Report 2015 [23] is shown in Table 1. While statistical comparisons were not possible, these data indicated that participants recruited for this study were similar to the target population (mothers who gave birth in Queensland) on most characteristics (age group, marital status, country of birth, first-time mother), except smoking status. No comparable data were available for education level or ARIA. The location of usual residence was categorized using ARIA, developed by the National Center for the Social Applications of Geographic Information Systems. Each geographical area was allocated a score between 0 and 15, based on the (road) distance to nearby towns that provide services [24]. Scores were then allocated to the following categories: urban (major city: 0.0 to 0.2); peri-urban (inner regional: 0.2 to 2.4; outer regional: 2.4 to 5.92); and remote (remote: 5.92 to 10.53; very remote: 10.53 and greater). The broad reach of study participants is highlighted in Figure 2.

Table 1. Demographic characteristics of recruited participants (N=498) and Queensland population data for mothers in 2015.

Characteristic	Recruited participants, n (%)	Queensland mothers, n (%)
Age		
18-24 years	89 (17.9%)	20%
25-29 years	176 (35.4%)	28%
30-34 years	161 (32.3%)	32%
35-39 years	62 (12.4%)	16%
40+ years	10 (2.0%)	4%
First-time mothers	216 (43.4%)	41%
Marital status		
Married/defacto	416 (83. 5%)	84%
Single	67 (13.5%)	14%
Separated/divorced	13 (2.6%)	1.4%
Current smoker	97 (19.5%)	12%
Country of birth		
Australia	419 (84.1%)	74%
New Zealand	23 (4.6%)	5%
United Kingdom	23 (4.6%)	3%
Other	33 (6.6%)	18%
Highest education level		N/A
Less than Year 12	86 (17.3%)	
Year 12 completion	131 (26.3%)	
Advanced diploma/trade certificate	127 (25.5%)	
University degree	112 (22.5%)	
Post-graduate degree	42 (8.4%)	
ARIA[a]		N/A
Urban (major cities)	238 (47.8%)	
Peri-urban (inner/outer regional)	205 (41.2%)	
Remote/very remote	49 (9.8%)	

[a]ARIA: Accessibility/Remoteness Index of Australia.

Figure 2. Map of Queensland (area 1,852,642 km^2), Australia, showing the broad reach of study participants (marked by pins).



Facebook Recruitment Outcomes

Facebook and Instagram advertisements generated 420,402 impressions and reached 65,268 people, generating 2573 link clicks and 1161 app downloads. There were 291 post reactions (like, love, etc.), 61 comments, and 164 shares. The cost of advertisements (ads) per 1000 impressions was Aus $16.39, per 1000 people reached Aus $105.40, and per recruited participant Aus $13.08. The recruitment process from ad impressions through to recruited participant is shown in Figure 3. Based on data from App Annie (San Francisco, USA), an industry standard app ranking and analytics company [25], in February 2016 the Cool Runnings app ranked number 48 in Australia for all educational app downloads.

Of the 45 ad sets, 22 (49%, 22/45) were emotive-based (12 [55%, 12/22] videos, 6 [27%, 6/22] images, 4 [18%, 4/22] carousel), 16 (36%, 16/22) were incentive-based (6 [38%, 6/16] videos, 6 [38%, 6/16] images, 4 [25%, 4/16] carousel), and the remainder used mixed themes. Two emotive-based video ads were the most effective, resulting in 72.1% (359/498) of all participants recruited. Saturdays were the most effective day of the week for participant enrollment, and 5 to 11 PM was the most popular time of day with 55.0% (274/498) of enrollments occurring during these hours. The effect of advertisement optimization during each day of the recruitment period is shown in Figure 4. Once the advertisements started to be ineffective they were cut and the budget placed on the advertisements that were performing well.

Thirty-two adaptations of the ad copy were developed based on the variables listed earlier and split-tested. In the first 3 days of recruitment, 40 participants were recruited from 18 of the 32 adaptations. The advertisements that did not resonate with the targeted audience were removed and the budget reallocated to the advertisements that were performing well. This process was repeated until just 2 advertisements remained—both emotive-based videos on iOS and Android. The remaining budget was then allocated to these 2 advertisements. Individuals were removed from the advertising audience once they had been recruited. This saved advertising budget and stopped participants from continually seeing the recruitment messages. This ability to access Facebook's analytics and real-time reports on the effectiveness of different images, message themes, and message wording allowed more effective and efficient use of time and resources.

Figure 3. Flowchart of the recruitment process from Facebook impressions to recruited participants .

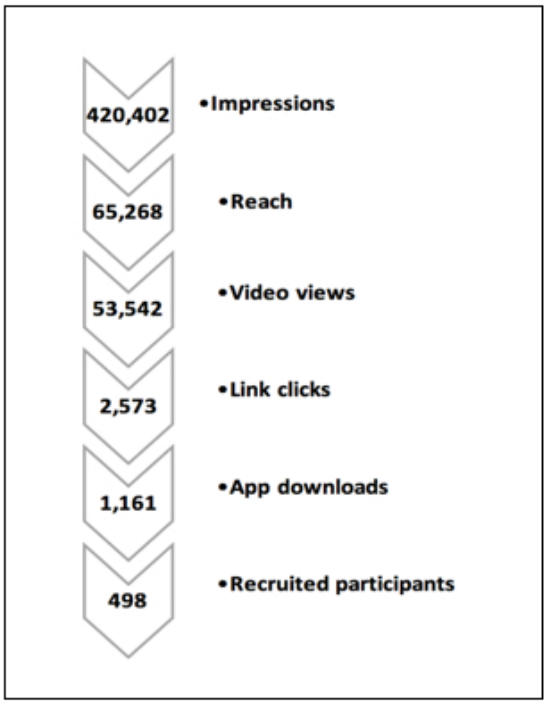
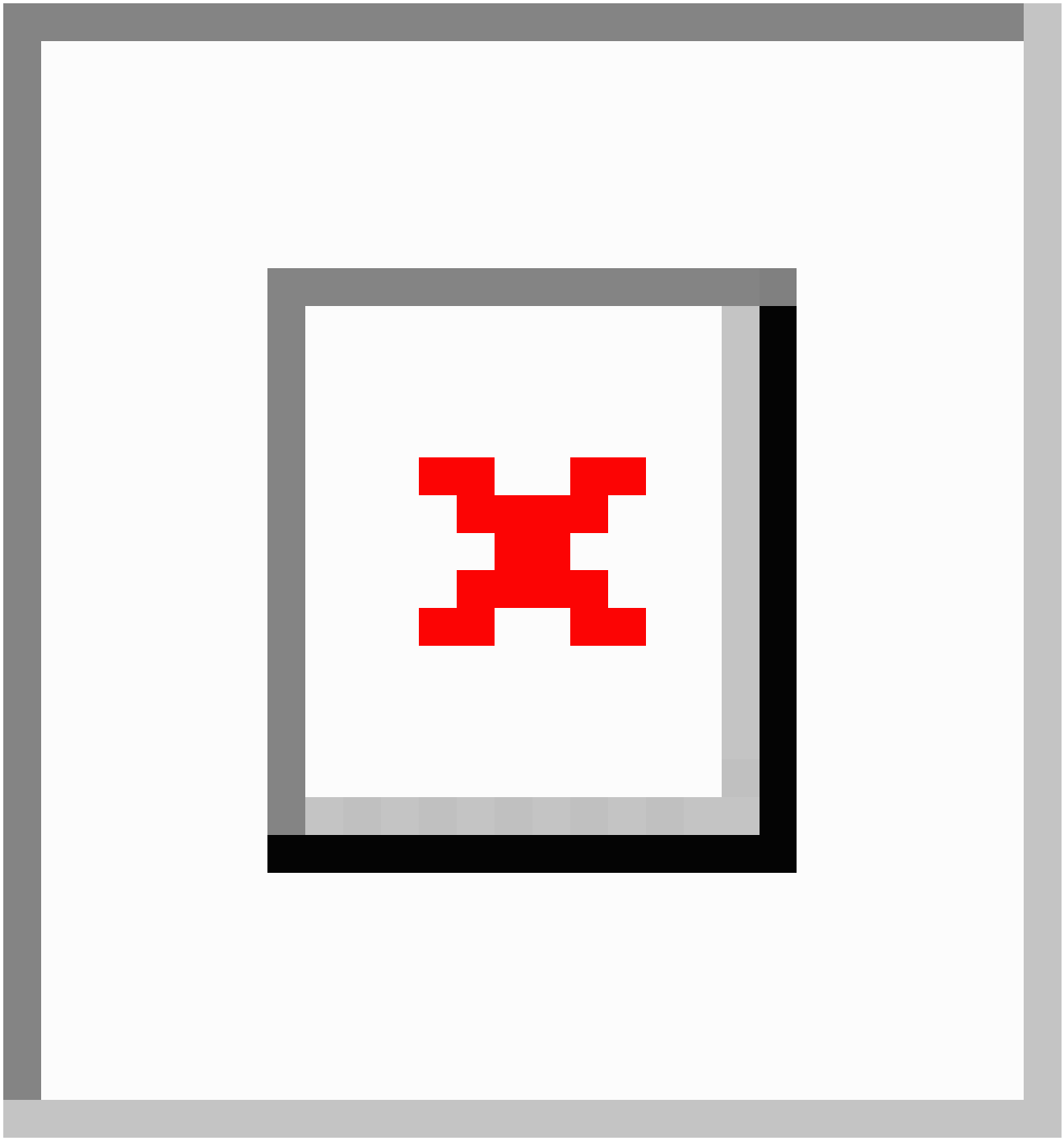


Figure 4. Number of participants enrolled each day of the 30-day recruitment period.



Discussion

Recruiting 498 eligible participants in 30-days for less than Aus $14 per participant demonstrated that recruiting using Facebook's targeted paid advertising on its 2 platforms (Facebook and Instagram) is an efficient and cost effective method for recruiting mothers of young children to public health research programs.

Targeted Advertisements

For this method of recruitment to be effective it is important to first understand how the targeted audience uses social media and what social media platforms are they using.

Facebook is the most widely used of the major social media platforms and its user base is most broadly representative of the population as a whole across age and gender [26,27]. However, it is important to note that some social media platforms are more popular among certain demographics. For example, in Australia Twitter is more popular among males and Pinterest is more popular among females; adults under 30 years prefer Instagram and Snapchat, while LinkedIn is more popular among older adults [28]. For targeting millennial mothers, Facebook and Instagram were an ideal choice given mothers active daily use on these platforms.

Reach, Representativeness, and Cost

Accessibility to Facebook and Instagram's large and diverse users address one of the challenges facing many research projects when it comes to recruiting—adequate size and representativeness of sample. The literature confirms targeted Facebook advertising has been effective in recruiting populations based on geographic location, age, and gender, but also specific, often hard-to-reach populations [29-31]. Mothers of young children were the focus of this recruitment strategy and are the most active users on Facebook [6,7]. The targeted advertisements for this study delivered participants from a variety of socio-economic, geographic, and educational backgrounds. There was good representation of mothers across the age groups and an almost equal split of premipara (first-time mothers) and multipara participants. These participants were largely representative of the target population (women who birthed in Queensland in 2015) with regard to age, marital status, being a first-time mother, and country of birth [23].

While the participants for this study were well represented on Facebook, Instagram, and many other social media platforms, it is important to note there are populations that are not so well represented on social media, such as older, economically disadvantaged, rural/remote, and less educated individuals [2]. However, research by the Pew Institute [32] shows these trends are changing. These issues and limitations also affect traditional recruitment samples.

A number of studies have compared social media recruitment with traditional recruitment methods in terms of cost and speed, with the majority showing social media to be more effective for both [2,33]. However, a review of 30 studies that compared social media with other recruitment methods reported only 12 (40%, 12/30) found social media to be the best recruitment method overall [3]. Social media recruitment is reported to be better for recruiting hard-to-reach populations. A systematic review by Thornton et al [2] reported the average cost per enrolled participant using Facebook recruitment was US $17 (range $1.36 to $110). Traditional recruitment methods can cost US $20 to $500 per participant, depending on the strategy and target population [34-36].

Limitations

This recruitment strategy had some limitations. The social nature of Facebook increases the likelihood of snowballing, with individuals sharing the study advertisements with their Facebook friends, potentially leading to sampling bias. Another limitation is relying on information individuals provide on their Facebook and/or Instagram profile, which may not be correct or up-to-date. Some interested individuals who received the targeted advertisements were not eligible for recruitment as they no longer lived in Queensland but had not updated their profile information. Because some of the baseline questions for Cool Runnings were to determine knowledge about burn risks to children, we were unable to mention burn prevention to children specifically in the advertisements. This may have led to confusion in interested individuals. Finally, the initial advertisement sets did not specify that participants had to have at least 1 child aged between 5 to 12 months. This led to some interested individuals downloading the app and then finding they were ineligible once they read the participant information/consent page. This issue was rectified in the second week of recruitment.

To our knowledge, this is the first use of social media recruitment for an injury prevention campaign. Based on the reach, representativeness, cost, and speed of social media recruitment for this study, and as reported in the literature, this recruitment method would be beneficial for recruiting targeted populations at risk of specific injuries. It also has great potential for public health campaigns that want to reach and engage large numbers of people, whether it is to promote healthy behaviors, prevent disease, or reduce injuries.

Conclusions

Recruiting via social media allowed a rapid and cost-effective recruitment of mothers of young children to an injury prevention campaign. The social, geographical, and economic diversity of the recruited participants demonstrates the power of social media recruitment as a positive option for studies needing to recruit hard-to-reach populations or representative study samples.

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Conflicts of Interest

None declared.

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Abbreviations

ARIA: Accessibility/Remoteness Index in Australia
RCT: randomized controlled trial

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